2007 ASHG AWARD FOR EXCELLENCE IN HUMAN GENETICS EDUCATION
Introductory Speech for Robert C. Elston*

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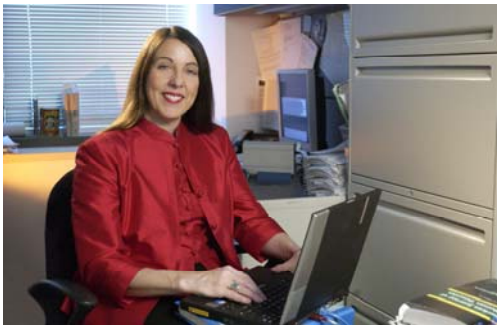

It is my great honor and pleasure to introduce Dr. Robert C. Elston as the recipient of the 2007 ASHG Award for Excellence in Human Genetics Education. Robert is one of the founding fathers of modern statistical genetics and a teacher and mentor extraordinare. He was born February 4, 1932 in London, England and received his B.A. and M.A. in Natural Sciences with a diploma in Agriculture from Cambridge University in 1956, followed by his PhD. in Animal Breeding from Cornell University in 1959, and postdoctoral training in statistics at University of North Carolina from 1959-1960. Robert joined the faculty of University of North Carolina in 1960, rising to the rank of Professor by 1969. In 1979, Robert moved to New Orleans to become Professor and Head of the Department of Biometry, which he later changed to the Department of Biometry and Genetics. In 1995, he took his current position as Professor of Epidemiology & Biostatistics and the Director, Division of Genetic and Molecular Epidemiology at Case Western Reserve University

Robert's scientific accomplishments are many, with the most well-known being the Elston-Stewart algorithm [Elston RC, Stewart J. A General Model for the Genetic Analysis of Pedigree Data. Hum Hered 21:523-534.] which was a landmark in the field of statistical genetics, providing a unifying computational approach to evaluation of data from families. His achievements have been recognized by many different awards, including the Hoch Award from the American Psychopathological Association in 1992, the Wick R. Williams Memorial Award from the Fox Chase Cancer Center in 1994, the Leadership Award from the International Genetic Epidemiology Society in 1995, the William Allan Award from American Society of Human Genetics in 1996, and the Marvin Zelen Leadership Award for Statistical Science from the School of Public Health, Harvard University for outstanding achievement in statistical science in 2004. He is also an elected Fellow of the American Statistical Association, an elected Fellow of the Institute of Mathematical Statistics, a John Simon Guggenheim Fellow and a Fellow of the Ohio Academy of Science. He has made important contributions in every area of statistical genetics with 567 per-reviewed papers covering segregation analysis, linkage analysis, association analysis, genome wide association studies and other diverse topics. Lest you think Robert might be slowing down, note that 27 of these papers were published or in press in 2007 and one of his papers won the "Best Paper Of 2006" award from the journal *Genetic Epidemiology* [Wang T, Elston RC (2005). The bias introduced by population stratification in IBD based linkage analysis. Hum Hered; 60: 134-142].

However, today we are here to recognize Robert's outstanding talents as a teacher and mentor. Those students lucky enough to take classes from Robert have always been amazed by his ability to make even the most complex concepts understandable. He is widely sought after as a lecturer and is always willing to mentor students, even when they are not his own students! He has often been known to spend hours at scientific meetings helping students from other institutions to understand his statistical methods. Robert has trained many students in his career. In 2002, the International

Genetic Epidemiology Society Chris Amos and several of Robert's other ex-trainees set out to collect data on the scientific 'offspring' of Robert Elston. At the time, Robert had over 70 students and post-doctoral fellows that he had personally trained, but his influence stretched to their trainees as his more distant scientific "descendants". The "pedigree" spanned 5 generations and included 382 individuals. There were 73 in the first generation, 209, 47, 42 and 11 in the second through fifth generations, respectively. The pedigree quickly became out of date since Robert and his trainees all continue to train more scientists! Robert has personally trained 8 more students and postdoctoral fellows since 2002, bringing his current total number of trainees to 81! Robert's trainees come from a wide range of backgrounds and disciplines, including statisticians, geneticists, biologists, M.D.'s, epidemiologists, and computer scientists. Robert's trainees and his scientific "descendants" make up a sizeable proportion of the scientists actively working in statistical genetics and genetic epidemiology today.

In addition to the traditional training of graduate students and postdoctoral fellows, Robert has taught many other scientists through his distribution of the well-documented statistical analysis software page, S.A.G.E., and the training courses that are held regularly in the use of these methods. Several S.A.G.E. courses are held each year at locations all over the world with 25-80 attendees at each session. Recent sites have included Leuven, Belgium, Seoul, Korea, Charlottesville, VA and Cleveland, Ohio. Robert's invited lectures are too numerous to list here, but through these he continues to educate a new generation of scientists all over the world.

When I was preparing this introduction, I polled many of Robert's previous trainees for comments and opinions, and heard the same things over and over: "Robert was the best teacher and boss I ever had." "He always took time to explain." "He spent time helping you even if you weren't his student." I must add my own opinion that he truly is a teacher and mentor extraordinaire. It is for all these reasons that the American Society of Human Genetics presents you with this year's Education Award. Thank you Robert for all you have done for so many of us!

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They blame the wrong thing

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I am very honored to receive this award for excellence in human genetics education and can hardly thank enough the committee for choosing me to receive it. As you might imagine from the kind of things I do, on receiving it I performed a quick statistical analysis. The mean age of past recipients of this award is 74, and their median age lies between 74 and 75. As I am 75, it would appear that I am typical, and this is an award that comes with old age. Now my primary field of specialization as a schoolboy in England, more because it was expected of me than anything else, was classics – Latin and Greek. So my mind immediately went back to Cicero's "De Senectute" (On Old Age), a book Cicero wrote when he was 62 years old, a year before he died.

I was not terribly good at Latin and Greek – I was a β student rather than an α student, occasionally rising to a β+ (even once to β++). Every week we had to write a Latin prose composition, a Latin verse composition, a Greek prose composition and a Greek verse composition. We had to do things like translate Churchill into Cicero or Shakespeare into Sophocles. I did enjoy Greek verse composition, because in Greek you can add particles here and there to help make the verses scan, and it was perfectly acceptable to make up new words – after all, it was fairly obvious that the Greek poets did. Latin prose, on the other hand, was another matter. We read Cicero, Caesar, Livy and Tacitus, but had to be very careful whose style we imitated in our prose compositions. Cicero and Caesar were good, Livy was O.K., but Tacitus (for reasons I didn't really appreciate) was a no-no.

I remember how one of us once asked our schoolmaster, Mr. Freeman, how he knew Cicero would have said something one way rather than another. So Mr. Freeman made a pact with us. Provided we promised not to look back, he would translate into English something of Cicero's we had read the previous year and set it as our prose composition for the week. I remember that prose composition well. There was one thing that none of us knew how to put into Latin: "they blame the wrong thing". Cicero was talking about how his contemporaries were not only upset about being denied the sensual pleasures without which they thought life was not worth living, but also the fact that on account of their old age nobody listened to them any more. Cicero had written "mihi non id videbantur accusare, quod esset accusandum" (literally, "it didn't seem to me that they were blaming that which ought to be blamed"). Mr. Freeman defended himself against our objections that he had not translated Cicero accurately, pointing out that no one would never say in English "they were not blaming that which ought to be blamed".

Now why do I tell this story? Cicero goes on to point out that there can surely be no greater pleasure than the pleasures of the mind, and that the fruit of old age is the memory of abundant blessings previously acquired. So this book, written as a conversation between the aging Cato and his young friends Scipio and Laelius, points out that the blame lies with a person's character, not old age. (Incidentally, he also talks of his love of agriculture, which was my field of study in college after studying natural sciences for two years).The important thing, said Cato, is to have a long and busy career and pass on as much wisdom as one can to the next generation. This is something I have always tried to do. In Cicero's (Cato's) words: "For just as I approve of the young man

in whom there is a touch of age, so I approve of the old man in whom there is some flavor of youth"[1].

[1] As translated by W.A. Falconer, Loeb classical library.

There is another reason why I quote this from Cicero. So often in statistical genetics, I see the wrong thing being blamed. I won't mention any names, but I have seen epistasis confused with pleiotropy, interaction confused with (additive) joint action, and joint probability confused with conditional probability. (Perhaps it is all right for me to mention the names of the two authors who confused joint probability with conditional probability – I am thinking of a paper by Elston and Stewart (1971)). There are those who make the distinction between Haseman-Elston (1971) regression and "the" variance component method of linkage analysis, when both methods are variance component methods. The distinction they should be making is between least squares and maximum likelihood under certain distributional assumptions. To be sure this is a technical statistical distinction, but how can one understand the strengths and weaknesses of a particular analysis without understanding the assumptions that underlie it?

Every two years there is a Genetic Analysis Workshop ("GAW", to the cognoscenti) at which those who develop statistical methods for genetic analysis try out their new methods on common sets of data. There are always two types of data available, real data and simulated data. So how do we evaluate our various methods of analysis? Now that our interest is in the commoner, complex disease, we are usually far from 100% sure of the true mode of inheritance when we analyze real data. So if a method uncovers a new gene or gene-gene interaction, we cannot know whether this is due to the method

being more powerful or simply to type 1 error. It might therefore seem reasonable to compare the different methods of analysis on simulated data, for which the true mode of inheritance is known. But then how do we know that our simulated data are realistic? It occurred to me that perhaps one day we would be able to repeat Mr. Freeman's experiment. Someone would have to have a set of real data in which a complex disease has been so thoroughly studied that every detail of the genetic and environmental causes of the disease is known, and then that dataset would be made available (changing the name of the disease, of course) to the participants of the Genetic Analysis Workshop. That would provide a real test of the various methods of analysis.

I have myself been blessed with many mentors. Mr. Whale, who taught me mathematics when I was a schoolboy, was always quoting the Oxford mathematician Charles Dodgson (more commonly known as Lewis Carroll). Two of my favorites are:

From Alice in Wonderland -

"Cheshire-Puss," began Alice, rather timidly, "would you please tell me which way I ought to go from here?" "That all depends on where you want to get to," Mr. Whale would answer.

From Through the Looking Glass -

"When *I* use a word," Humpty Dumpty said in rather a scornful tone, "it means just what I choose it to mean - neither more nor less."

"The question is," said Alice, "whether you CAN make words mean so many different things."

"The question is," said Humpty Dumpty, "which is to be master- that's all."

Many are the students who have heard me say that a careful reading of "Alice in Wonderland" and "Through the Looking Glass" is a prerequisite for any course I teach. And then, while still a schoolboy, I remember being told something by the speaker when I attended my last speech day (something vaguely like high school graduation in the US). He told us he thought that across the top of the blackboard in every classroom there should be printed in gold letters: "The teacher may be wrong". I try to remember to say this at the beginning of every class I teach, and that has led me to learn many things. First, there are only three important things when teaching: clarity, clarity and clarity – clarity of purpose, clarity of method, and clarity of result. Second, I have learned that students are wonderful mentors. I thank them all, both for all the things they have taught me and for proposing me for this award, which I shall cherish. And once again, I thank the Society and the Awards Committee for choosing me to receive it.

Elston RC, Stewart J (1971) A general model for the genetic analysis of pedigree data. Hum Hered 21:523-42

Elston RC, Haseman JK (1972) The investigation of linkage between a quantitative trait and a marker locus. Behav Genet 2:3-19