The very youngest science

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Next April sees the 50th anniversary of the publication of "Molecular structure of nucleic acids: a structure for deoxyribose nucleic acid,"[1] in which the elegant and revelatory structure of DNA was laid out by James Watson and Francis Crick. Watson, Crick and Maurice Wilkins shared the Nobel Prize in 1962; the fourth major contributor to the work, Rosalind Franklin, died in 1958.

Molecular biologists date the start of molecular biology from that paper. There are other dates that might be chosen for the birthdate of molecular medicine, that emerging branch of medicine unified by the understanding of the human genome. Perhaps molecular medicine began with Charles Darwin's and Alfred Russel Wallace's theory of natural selection (1858), or Gregor Mendel's publication of the results of his experiments on inherited traits in pea plants (1866), or the isolation of "nuclein" (DNA) from the white cells in pus-stained bandages by Swiss physician Johann Friedrich Miescher (1869) or, closer to Watson and Crick, the discovery of "the transforming principle," which established that DNA, not protein, was the source of genetic information, by Oswald Avery, Colin MacLeod and Maclyn McCarty (1944).[2,3] Avery began his career as a physician in the pre-antibiotics era and entered research when he saw how many patients he could not help with the medical knowledge of his time.

And then, of course, there is another milestone associated with James Watson's name, the human genome project, which was declared to be all finished but for the tidying up in February 2001.[3]

Lewis Thomas dubbed medicine "the youngest science."[4] Molecular medicine is younger still. The last major paradigm shift in the theory and practice of medicine was the germ theory of disease in the 19th century. We are sufficiently removed from the initial impact of that shift to appreciate only its benefits. Life expectancy in Canada is presently 76 years for men and 81 years for women, while a century and a half ago the average life expectancy in Liverpool, England, in the heartland of the industrial revolution, was a mere 25 years. Much of that mortality was caused by infectious disease, and much of the progress can be attributed to public health measures, which were based on empirical observation of the transmissibility of disease and given authority by scientific understanding, as well as to the antibiotics and vaccinations developed from scientific theory.

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There are 2 significant differences between the 19th century germ theory of disease and the genomic theory of disease. Genomic medicine predicts the risk of disease in the individual, whether as a high likelihood in the case of some of the well-established single gene disorders, or in terms of an increased susceptibility likely to be mitigated by environmental factors. There is hope that molecular medicine, properly applied, should make preventive medicine more powerful and treatment more specific to the individual, allowing tailoring of investigations and treatments to an individual's genetic susceptibilities, or to a tumour's or infectious agent's characteristics. But we must grapple with the consequences of replacing "healthy" with "at risk" in both our practice and our thinking, as the experience of people screened for genetic disease has shown.[5,6] And, more controversially and further down the road, understanding of genetics and genomics raises the possibility of the genetic engineering of complex traits, "improving" on human norms of intelligence, disease resistance and lifespan — the dream of the early eugenicists whose work expressed not only their ideals for humanity, but also their judgements on others' race, sex, lifestyles and intrinsic worth.

However, the social context of Western society in the 21st century is different from that of the 19th. Individuality has flourished, the influence of religion has diminished, and class, race and social inequalities have eroded, though have by no means vanished. There is greater awareness of the potential abuse of knowledge, and of the misuse of medical and institutional authority, and there is wider public education and access to information, with greater potential for public participation in the future development of medicine.

What can physicians do to help that potential be realized? We have 2 major responsibilities. The first is to individual patients and families who are immediately affected by

the unfolding knowledge, those who might, or wonder if they might, have a disorder with a genetic basis. Much of popular coverage of genetics is in the language of absolutes — absolute knowledge and absolute determination. Genes "cause" disease; tests tell you whether or not you will get a disease. The reality is one of relative risks and uncertainty. As with all tests, genetic tests are most meaningful when ordered appropriately. And when the tests are ordered, physicians must be able to communicate what they are, what they mean, what they can tell a patient and what they cannot.

The second responsibility physicians have is our responsibility as educated members of society. As a society, we must soon make significant decisions about the ownership and use of genetic information, and about the acceptable extent of genetic manipulation, whether of humans or other species. To do so, we must discuss science, ethics, uncertainty, morality, health, birth, death, and our hopes and fears for the future. This is all familiar territory for physicians, for all that the vocabulary of genetics and genomics is a new one; our contribution, and our leadership, in the choices before us, will be invaluable.

CMAJ has previously published papers on the subject of molecular methods applied to infectious diseases,[7] fluorescence in situ hybridization (FISH),[8] genetics and ethics,[9] and the implications of genetic testing for Canadian medicine and society.[10] With this issue, we begin a new short series focusing on aspects of medical genetics, starting with the embryo and the fetus and the risk of teratogenic exposures (page 265),[11] followed by a description of the specialist approach to the child whose appearance, behaviour and development might suggest a genetic abnormality, and then a review of how a primary care physician might approach an adult with a genetic disorder. In short companion papers, Alison Sinclair describes some of the laboratory methods currently used in the diagnosis of genetic disease, starting with both current methods of studying the chromosomal changes that underlie inherited and acquired disease and a new technique using DNA microarrays or "chips" (page 275).[12] Inevitably, given the current pace of development, these papers will be rapidly outdated, but for the moment they present a snapshot of today's genetic diagnostic methods, an introduction to the language of DNA and a summary of the principles that will underlie the methods of tomorrow.

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References

1. Watson JD, Crick FHC. Molecular structure of nucleic acids: a structure for deoxyribose nucleic acid. *Nature* 1953;171:737-8.
2. Avery OT, MacLeod CM, McCarty M. Induction of transformation by a desoxyribonucleic acid fraction isolated from pneumococcus type III. *J Exp Med* 1944;137-58.
3. International Human Genome Consortium. Initial sequencing and analysis of the human genome. *Nature* 2001;409:860-921.
4. Thomas L. *The youngest science: notes of a medicine watcher*. Oxford: Oxford University Press; 1984.
5. Marteau TM, Lerman C. Genetic risk and behavioural change. *BMJ* 2001; 332:1056-9.
6. Di Prospero L, Seminsky M, Honeyford J, Doan B, Franssen E, Meschino W, et al. Psychosocial issues following a positive result of genetic testing for BRCA1 and BRCA2 mutations: finding from a focus group and a needs-assessment survey. *CMAJ* 2000;164(7):1005-9.
7. Louie M, Louie L, Simon AE. The role of DNA amplification technology in the diagnosis of infectious diseases. *CMAJ* 2000;163(3):301-9.
8. Demetrick DJ. Gone FISHin' for genes. *CMAJ* 1999;161(9):1138.
9. Burgess MM, Laberge CM, Knoppers BM. Bioethics for clinicians: 14. Ethics and genetics in medicine. *CMAJ* 1998;158(10):1309-13.
10. Caulfield T. Gene testing in the biotech century: Are physicians ready? *CMAJ* 1999;161(9):1122-4.
11. Polifka JE, Friedman JM. Medical genetics: 1. Clinical teratology in the age of genomics. *CMAJ* 2002;167(3):265-73.
12. Sinclair A. Genetics 101: detecting mutations in human genes. *CMAJ* 2002;167(3):275-9.

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