HENRY FRIESEN AWARD LECTURE

Work, the clinician-scientist and human biochemical genetics

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The Henry Friesen Award

Cosponsored by Canadian Society for Clinical Investigation and the Royal College of Physicians and Surgeons of Canada, the Henry Friesen Award was created to recognize annually a distinguished Canadian researcher who has demonstrated leadership in developing biomedical research at local, national and international levels and who epitomizes the high standards and ideals of Dr. Henry Friesen. Dr. Friesen is currently Distinguished Professor Emeritus in the Department of Medicine, and Senior Fellow in the Center for the Advancement of Medicine, at the University of Manitoba.

Abstract

The pursuit of human biochemical genetics has allowed us to understand better how the person with the (genetic) disease differs from the disease the person has and to develop the concept that genetics belongs in all aspects of health care. It is a perspective that comes quite readily to the clinician-scientist, and the restoration of that “species” in the era of functional genomics is strongly recommended. Garrod, the initial founder of human “biochemical genetics” belonged to the clinician-scientist community.

Archibald Edward Garrod introduced a paradigm, new for its day, in medicine: biochemistry is dynamic and different from the static nature of organic chemistry. It led him to think about metabolic pathways and to recognize that variation in Mendelian heredity could explain an “inborn error of metabolism.” At the time, Garrod had no idea about the nature of a gene. Genes are now well understood; genomes are being described for one organism after another (including Homo sapiens) and it is understood that genomes “speak biochemistry (not phenotype).” Accordingly, in the era of genomics, biochemistry and physiology become the bases of functional genomics, and it is possible to appreciate why “nothing in biology makes sense without evolution” (and nothing in medicine will make sense without biology).

Mendelian, biochemical and molecular genetics together have revealed what lies behind the 4 canonical inborn errors described by Garrod (albinism, alkaptonuria, cystinuria and pentosuria). Both older and newer ideas in genetics, new tools for applying them (and renewed respect for the clinician-scientist) will enhance our understanding of the human biological variation that accounts for variant states of health and overt disease. A so-called monogenic phenotype (phenylketonuria) is used to illustrate, in some detail, that all disease phenotypes are, in one way or another, likely to be complex in nature. What can be known and what ought to be done, with knowledge about human genetics, to benefit individuals, families and communities (society), is both opportunity and challenge.

Résumé

Les recherches en génétique biochimique humaine nous ont permis de mieux comprendre la différence entre la
Introduction

Some forms of indebtedness

First, let me thank those who nominated and selected the Awardee for 2001. The Henry Friesen Award lecturer is likely to be recognized more for what has been done than for doing something remarkable in the present or for what may yet be done. Never mind; I am enjoying the honour, and what I am doing now or will be doing will not betray it or Henry Friesen. Yet, perspectives help. Someone said: “The older we get, the better we used to be”; and Stephen Sondheim — of course — had a somewhat different angle on it:

Charlie, nothing is the way it was.
I want it the way it was.
God knows, things were easier then.
Trouble is, Charlie,
That is what everyone does.
Blames the way it is.
On the way it was.
On the way it never, ever, was.
(Adapted with slight modification from Merrily We Roll Along.)

No further comment, except to remember that there are people who have made a difference in my life. They include my mentors, colleagues, students and fellows, all too numerous to name but they know who they are, and I thank each of you.

And then there is my family who, in its various ways, tolerated my addiction to medical science and to work, loving me nonetheless.

Reflections on work

An article by Richard Sennett 1 stimulated me to think about work and about my own in particular. I am an oddity in the predominant culture of work today in North America. I have been at only one institution and in only one “job” for the past 4 decades, and still counting. For all but a few of us, the conditions of work today are likely to be much more volatile and evanescent; we will score and move on. Where we work and for whom will change often, and the relationships between our colleagues and ourselves will be transient and superficial; friendships and loyalties become short term — a thing of the past. The old idea that self-discipline and stability in the present moment may actually be an investment in the future has much less currency when the investment has only a short shelf-life. Our families and other social relationships may even become a reflection of our work ethic and vice versa.

If the workplace is society’s primal scene, I have
had the benefit of stable relationships at my place of business. They were, and still are, mainly but not exclusively in the domain of science. They have endured under the recurring uncertainty of peer and institutional review. It is a way of life that some would consider bizarre. But for me, the uncertainty has been a leavening force — for autonomy, self-discipline and responsibility. Accordingly, I have had a unique form of freedom, with its own dignity, free of anxieties about corporate connections, the value of my stock options and the fictions of power — an anxiety that is rather new in my arena of science.

Has there been a driving force for my point of view, other than my own individuality? The answer is yes, and it lies in a belief that I was given opportunities to serve others. Believe me, there is nothing like the sustained pressure from below, even more than the pressure from above, to focus the mind, heart and spirit on what is really important. Patients, their families and the communities near and far where we live together are some of the forces from below; students are another. Meanwhile, as scientists, we serve knowledge and, yes, the unknowable. Together, these are the constant reminders that I serve, not only myself but also others. And beyond their immediate needs, I can also serve a mysterious calling. In its own way, I have experienced a form of socialism where there is dignity in my own labour; and the more communal the relationship, the greater the dignity. Of course it is a very old way of living and working. Long ago, one would speak about honouring a greater Life in which one could receive and share not only love of ourselves but also of others and of God. It is a form of work that will still fit within the measure of humankind, and it has always been within the reach of my own hands. It still suits me very well.

The clinician-scientist

A word about “us,” a nearly extinguished species.

A couple of centuries ago, many “scientists” were recognized primarily as medical persons.2 Perceptions and the balance of recognition have changed, and it is not so likely now that a medical person will achieve recognition as a scientist. The transition in Canada was catalyzed, in particular, by an article in a somewhat obscure journal,3 which proposed that “medical science” in Canada needed an intense infusion of molecular biology and genetics. Thereafter, medical science in Canada changed and nonphysician research initiatives became dominant. While this was happening, federal funding of medical research in Canada declined relative to elsewhere. The result was that the Canadian clinician-scientists faced not only competition for recognition among their peers but even stiffer competition for funds to do their kind of science. For this and other reasons, the selection pressure on the clinician-scientist became extreme, and our species faced near extinction.

The Canadian Institutes for Health Research (CIHR) have replaced the Medical Research Council of Canada model, and new policies are being initiated. If the funding of clinical research improves, it could rejuvenate the clinician-scientist in Canada. Remember, at one time we did rank second in the world in this area of “scientific wealth.”4 To be reminded of the loss of our prestige and reputation happens to be a source of some pain for the 2001 Henry Friesen lecturer. Restoring a role for the clinician-scientist will certainly serve the era of functional genomics as biochemistry, physiology and embryology, for example, flourish again, as proteomics transforms therapeutics and as the intact human organism, in all its complexity and wonder, returns as a valid focus of inquiry. In recognition that such a day is at hand, 2 great role models of the modern clinician-scientist have offered a prescription for the restoration (Table 15). I invite readers of this essay to read the original article by Goldstein and Brown.5

Genetics in health care

Genetics, the discipline (with uppercase G), and genetics, the practice (with lower case g) are pervasive

<table>
<thead>
<tr>
<th>Table 1: The clinical investigator or the patient-oriented scientist or how to retain the species: recommendations</th>
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<tbody>
<tr>
<td>• Reinvigorate the intellectual core of academic medicine (and endow it).</td>
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<tr>
<td>• Recognize the power of collaboration (and reward it).</td>
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<tr>
<td>• Train and support the “bridge builders” (between basic science, disease-oriented research and patient-oriented research).</td>
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influences, transforming how society can interrogate the biological interface between itself, its individuals and the experiences of life itself. Medicine, both the discipline and the practice, will also be invaded by concepts embedded in genetics. Medicine will be transformed, perhaps reluctantly because the Osler model has worked rather well, but transformed it will be; there will be reform with change in its language, its educational apparatus and its practice. In anticipation, the Science Council of Canada consulted widely in the late 1980s and produced Report No. 42, addressing issues arising from a potential revival of genetics in medicine; the report was published in 1991. Nothing happened following its presentation to the public and the government. It sank like a stone into the federal pond, and there were minimal ripples in the provincial bayous, yet everything that is emerging in the genome projects (see below), and most notably from the Human Genome Project itself, validates the insights, recommendations and content of the Science Council report. Accordingly, I will use this bully pulpit to urge you to visit the report, to respond to it and, on behalf of the health of Canadians, to begin the implementation of its ideas and recommendations. The insights that inform Report No. 42 are by no means new. Garrod, in his role as Osler’s successor at Oxford, recognized the influence of heredity in medicine. What better invitation, then, to have you join me in meeting Professor Garrod.

Study at the periphery discovers the core

Archibald Edward Garrod was born on Nov. 25, 1857; he died on Mar. 28, 1936. During his lifetime the natural sciences changed our view of the world, and genetics began its journey to the double helix. Garrod, an extraordinary physician-scientist, made premature discoveries and died long before we would appreciate fully the information, the knowledge and the wisdom he had passed on to us. This essay in part about his legacies, acknowledges my debt to yet another mentor.

During the past 500 years or so, Copernicus recognized that Man (and Woman) is not at the centre of the universe; Linnaeus, who had placed humankind on the top rung of the Systema Naturae, was overruled by Darwin who placed it on a minor twig of the great tree describing the evolution of species; and now I am told that who I am can be known (in part) from my DNA.

Meanwhile, among all the species on earth, mine, Homo sapiens sapiens, is the most mighty of those who intentionally modify experience — that other architect of our life. We are Homo modifcans. For example, during recent and present time, humankind has been using modifying technologies to make the 19th century one of steam, the 20th one of electricity (and electronics), and the 21st century perhaps one of DNA. Think, then, on the actual physical dimensions of the modern human experience. From the book Powers of Ten one learns that 8 orders of magnitude encompass our actual experience in space on and beyond planet Earth. And from out there, just beyond lunar distance, the true beauty and fragility of Earth is discerned in a way that was not accessible to Copernicus. In the era that began with discovery of the double-helical structure of DNA, 9 orders of magnitude take us from the familiar dimensions of the human organism, down to the nucleotide sequence of our DNA molecules. Thus, 17 tangible orders of magnitude span the dimensions that can be “me” in the year 2001. The realization that one is only a minute entity in this awesome dimension is one good reason for humility.

The images presented in the panorama of Powers of Ten are only new forms of earlier thoughts expressed by Blaise Pascal, the 17th century mathematician and philosopher. He recognized 2 infinities, one in the night sky, the other in the atoms in his body; one infinity above and around him, the other below and inside him. The thought provoked him to say: “Le silence éternel de ces espaces infinies m’effraie.” The space that frightened him more was the one he could not see.

Paradigms of biology

The complex reality of the life encoded in the DNA molecule collapses into a pair of paradigms (Fig. 1).
In one, there is *information transmittal* through time during some 3 billion years of evolution of life on Earth. Here, the bodies of organisms are mainly vehicles for copying and passing on genes. Fidelity of the copying process is maintained by an awesome editing mechanism, yet it is through the variety produced by *mutation* that evolution proceeds by selection and adaptation.

The other paradigm, *information utilization*, is linked to the former via the central dogma of molecular biology: DNA makes RNA makes protein (most of the time). The process of natural selection was recognized by Darwin, yet its mechanism (in genes) was not understood for more than a century after he proposed it. Whereas natural selection acts on the phenotype, the object selected is the gene. The second paradigm describes how the organism is made and how it works.

Yet how wild-type and mutant genes influence the health of the organism is not yet sufficiently understood, nor is the much more subtle feature of a living organism, namely its *emergent property*. Such ignorance is a peril because “nothing in biology makes sense without evolution” (implying the need to understand its process and consequence); to which one might add, “and nothing in medicine makes sense without biology” (implying that the profile of biology, and genetics, in medicine is still lower than desirable).

**Genome project(s)**

As the 20th century ended, many would have agreed that the Human Genome Project, or Projects because the one for the human genome embraces others that are about nonhuman organisms, was the greatest in the science of its time. Perhaps that is why the cover art for the annual issue of *Science* devoted to an aspect of the Genome Project, for many years linked genomics with a Vesalian image of the human body. Vesalius changed our approach to human anatomy and, as a consequence, influenced art, sculpture and culture. Now again, the genomic approach to biology is changing our view of life and of ourselves. A neo-Vesalian anatomy is underway. No surprise, then, that *The Economist* would dedicate its cover art for the issue of July 1, 2000, to a biochip image of humankind, while inside the maga-

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**Fig. 1: Two views (paradigms) of biology. In one there is information transmittal (via DNA) and mutation (speciation). In the other, information utilization is used to construct phenotype. The 2 are joined by the central dogma: DNA makes DNA makes protein (usually; sometimes only RNA is made).**

- **A. Evolution**
  - Information transmittal
  - DNA → RNA → Polypeptide → Phenotype

- **B. Gene expression**
  - Information utilization
  - DNA → RNA → Polypeptide → Phenotype

- **Fitness components**
  - no. of offspring
  - size of offspring
  - time of maturity
  - reproductive intervals
  - aging/death
zine there was a thoughtful editorial and a survey article\textsuperscript{15} that anticipated the impact of the genome projects on human society and its environment.

**Genomics**

Genomics is about the genomes of living organisms.\textsuperscript{26} In the evolutionary tree of eukaryotes for example, to unravel the genomes of \textit{Saccharomyces},\textsuperscript{28} \textit{Caenorhabditis elegans}\textsuperscript{29,30} and \textit{Drosophila}\textsuperscript{31} has provided milestones for humankind’s own evolutionary journey.\textsuperscript{10,32,33} Two core messages are already apparent. First, the biological program for energy metabolism was laid down long ago in single-cell eukaryotes, the genomic legacies of which have been retained by multicellular creatures and now make up a significant fraction of our own genome.\textsuperscript{10,30} Second, the genome required to become a particular multicellular organism, a human being, a fly or a worm, for example, is in itself particular and special;\textsuperscript{10,30,34} there are master genes such as \textit{PAX6} that point to pathways of development and there are genes that talk to each other during the regulation of gene expression,\textsuperscript{35} but what is said and how the message is received are the unique parts of speciation. Rather than see these “other organisms” (the mouse is a notable example\textsuperscript{36}), as so-called “models” unconnected to our own species, they are better seen as part of the whole of life on Earth; and from a point of view in Eastern philosophy,\textsuperscript{37}— even in physics (see also reference 38). As genetics acquires some of the attributes of a social science, along with those of biology and chemistry and physics, there is reason to acknowledge its other apparent attributes, including the concept of a “meme,”\textsuperscript{39,40} and the reality of cultural transmission.\textsuperscript{41} Hence my reference here to a long-held human spiritual awareness (i.e., Not One, Not Two) and to its echo in DNA: only one molecule encoding vast biological diversity.\textsuperscript{42} Finally, culture, tradition, myth-making — whatever — has a quality called bricollage or assemblage from odds and ends (Northrop Frye, reference 37, page xxi) that is not unlike the tinkering of biological evolution.\textsuperscript{43}

One product of the genome project is already with us: it is a series of OMES§ (Fig. 2); not quite the \textit{OM} of the Buddhist mantra but perhaps not so dissimilar in its implications. Colleagues now talk about the \textit{transcriptome} and the \textit{proteome}, the latter being at the core of functional individuality, and, since the living cell is a complex structure, there is a \textit{complexome}; all of the parts are connected ultimately with the \textit{metabolome}, and together these OMES house the \textit{phenome} which interacts with an \textit{environome}. Essays with titles such as “Evolvability”\textsuperscript{45} and “Molecular vitalism”\textsuperscript{23} invite the reader to consider the mechanisms by which organisms, cells and proteins are connected to information in the genome, and how “postgenomic” research will interpret the integrated biochemistry and physiology of cells and organisms.

**Genomes speak biochemistry — and physiology**

“Genomes speak biochemistry, not phenotype”\textsuperscript{46}; to which one might add, “they also speak physiology.” Whatever the case, a reunion of genomics, cellular biology, biochemistry and physiology is underway; for

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\textsuperscript{†}For other articles on genomics in other organisms, see references 10, 32 and 33.

\textsuperscript{‡}Northrop Frye\textsuperscript{37} comments on the relevance of oriental religion to contemporary Western modes of thought — even in physics (see also reference 38). As genetics acquires some of the attributes of a social science, along with those of biology and chemistry and physics, there is reason to acknowledge its other apparent attributes, including the concept of a “meme,”\textsuperscript{39,40} and the reality of cultural transmission.\textsuperscript{41} Hence my reference here to a long-held human spiritual awareness (i.e., Not One, Not Two) and to its echo in DNA: only one molecule encoding vast biological diversity.\textsuperscript{42} Finally, culture, tradition, myth-making — whatever — has a quality called bricollage or assemblage from odds and ends (Northrop Frye, reference 37, page xxi) that is not unlike the tinkering of biological evolution.\textsuperscript{43}

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\textsuperscript{§}I am grateful to William Gelbart and Daniel Hartl (both at Harvard University) for their views on OMES, and on the metabolome in particular, which were aired at a joint meeting of the genetics societies of America and Canada (June 11–14, 2000, Vancouver, BC).
example, there is a new awesome genomic strategy to identify the gene encoding any biochemical activity. According to molecular biology, we now have new tools to test hypotheses about living systems and to understand better how they came to have those mysterious emergent properties that are more than the sum of their parts. Mean-while, how can we better understand the effect of mutant alleles on structure, function and phenotype?

The problem of recessive and dominant phenotypes

In the era of “functional genomics” it would be wise to renew acquaintance with the work of Henrik Kacser, who used metabolic control theory to understand flux of metabolites along pathways at steady state, and to explain the recessive character of most inborn errors of metabolism and other dynamic relationships in cells and organs. An elegant essay makes reacquaintance easy and pleasurable. Kacser and colleagues were addressing an old problem in genetics: if mutations are important for evolution, how are their disadaptive effects buffered? The theme of buffering allelic variation is being addressed anew in elegant ways.

Simple equations describe the path and sensitivity coefficients and how they make up the summation property of a metabolome. In reality, the concepts advanced in a classic paper were addressing, through a metabolic angle of vision, a long-standing question in genetics. By what means is the effect of a mutant allele on phenotype either recessive or dominant in its expression?

An evolution-based line of reasoning, put forward initially by R.A. Fisher, went as follows: If mutation is essential for evolution, and the successful allele becomes the wild type, then it would become dominant. Hence, by invoking evolution through natural selection, Fisher thought he could explain dominance of the wild type allele. Sewall Wright, a physiological geneticist and a contemporary of Fisher, approached the problem from a different point of view. He noted that the web or chain of (physiological) events that link genotype with phenotype, in metabolism for example, had to involve fluxes of metabolites. Furthermore, if several unsaturated enzymes with equivalent activities mediated the flux through the system, a hyperbolic relationship would exist between enzyme activity and the rate of flux of metabolites through it. Wright argued that half-normal activity in a single enzyme, as would be the typical case in heterozygosity for a null allele at the corresponding locus, would likely have only a minor effect on flux through the total system, comprising several enzymes or pathways. Kacser and Burns extended this argument and showed the predicted effect in systems of one or many enzyme catalysts. Hence, the mutant allele would always be recessive in its effect on the measured phenotype of metabolite concentration in a complex metabolome. Incidentally, although this simple fact became a fundamental feature of the multicellular organism, it has become a problem for medical (and biochemical) geneticists who attempt to detect carriers of recessive traits by measuring a metrical trait such as the plasma concentration of the relevant metabolite. But that is another, enduring topic. Meanwhile, others are showing that as many as 173 different loci can be involved in an essential functional pathway in an organism; diploid redundancy, feedback regulation and allelic variance maintain homeostasis in the face of mutation. The phenomenon and relevance of redundancy in genomes and their products are now well appreciated.

From such reasoning, one could predict, or at least anticipate, that a dominantly inherited functional variant would have to involve something like a one-catalyst pathway (such as the relationship between a membrane receptor and its ligand), or conditions such as haplo-insufficiency; or a dominant-negative effect of the allele on a homopolymeric, or a gain-of-function effect. Moreover, the fact that many mendelian disorders of somatic development are so often dominantly inherited seems to imply that they are the result of deviant “one-step” components of pathways for development and differentiation in time and space.

Archibald E. Garrod: discoverer (1857–1936)

Garrod’s mentor in “biochemistry” (a new term at the time) was Gowland Hopkins, a proponent of physiological chemistry and also a student of pigment metabolism. The influence of Gowland Hop-
kins together with that of Bateson, and the rediscovery of mendelism in the early weeks of 1900, allowed Garrod to recognize an important biological message in 2 human disorders, hereditary albinism and alkaptonuria, both involving metabolism of a substance of colour. Garrod realized that the dynamic pathways of biochemistry were quite different from the static nature of organic chemistry; accordingly, the idea of metabolic pathways and how an “inborn error of metabolism” in one pathway or another might become manifest, seems to have come to him as a logical insight. Thus, when new technologies for the recognition of deviant metabolism became available in medicine, such as Charles Dent’s adaptation of partition chromatography and, later, the advent of gas chromatography and mass spectrometry, it was no surprise that novel metabolic phenotypes could be discovered in profusion. The current enthusiasm for tandem mass spectrometry to enhance metabolic medicine and screening is simply the next step on the path opened by Garrod.

Meanwhile, rare mendelian metabolic traits came to be seen by Garrod as only special forms of human inherited individuality, disorders that revealed specific components of metabolic homeostasis. Garrod knew nothing about genes, but he understood heredity, and he knew the significance of biochemistry. His perspectives were modified during the middle and end of his remarkable career to encompass what he called the “inborn factors in disease” or molecular groupings, thus blending his original insights with the other type of genetics described by Galton and Fisher: namely, the genetics of complex traits. Most variant human phenotypes are complex, and they are the result of OMES colliding, but because the sensitivity coefficient of each component in the system is likely to be small, approaches that are different from those serving mendelian traits are needed to find the corresponding genes and their phenotypes. Nonetheless, to recognize a mendelian form of a complex trait, for example autosomal dominant LDL receptor deficiency in coronary artery disease, is important because it highlights at least one important component of a homeostatic system; of course, one also recognizes that only one part of the complex trait has been exposed by the variant mendelian form of it.

The inborn errors of metabolism

Garrod was 42 years old when he posed for a photographic portrait in 1899 (Fig. 7 in reference 13). Nine years later he would publish the Croonian Lectures (Table 2), and a year later they would reappear in extended form as his first book, entitled Inborn Errors of Metabolism.

Four entities were documented in the Croonian Lectures: albinism, alkaptonuria, cystinuria and pentosuria. In the 1950s, Eugene Knox took a sabbatical leave from Harvard University’s Department of Biochemistry, and in the pleasant surroundings of the American University of Beirut he examined progress in the further understanding of Garrod’s canonical inborn errors. Knox published his findings in 4 elegant papers in the American Journal of Human Genetics (Table 2). In 2001, the 8th edition of The Metabolic and Molecular Bases of Inherited Disease (MMBID-8) contains a full chapter on each of Garrod’s inborn errors (Table 2). (The corresponding catalogue numbers in the Online version of

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**Table 2: A.E. Garrod’s Inborn Errors of Metabolism**

<table>
<thead>
<tr>
<th>OMIM*</th>
<th>Topic</th>
<th>A.E. Garrod (1908)†</th>
<th>W. G. Knox (1958)‡</th>
<th>C.R. Scriver et al§</th>
</tr>
</thead>
<tbody>
<tr>
<td>203100 (and others)</td>
<td>Albinism</td>
<td>1-7</td>
<td>249-266</td>
<td>220</td>
</tr>
<tr>
<td>203500</td>
<td>Alkaptonuria</td>
<td>73-79</td>
<td>95-124</td>
<td>92</td>
</tr>
<tr>
<td>220100</td>
<td>Cystinuria</td>
<td>142-148</td>
<td>3-32</td>
<td>191</td>
</tr>
<tr>
<td>260800</td>
<td>Pentosuria</td>
<td>214-220</td>
<td>385-397</td>
<td>73 (reprint)</td>
</tr>
</tbody>
</table>

† The Croonian Lectures were published in Lancet and republished with additions a year later as Inborn Errors of Metabolism.
‡ Knox assessed the impact of Garrod’s concepts by reviewing progress on the 4 canonical inborn errors of metabolism.
§ The Metabolic Basis of Inherited Disease (now The Metabolic and Molecular Bases of Inherited Disease) has contained chapters on the 4 topics in all its editions.

Mendelian Inheritance in Man (OMIM) are given and the entries can be retrieved from www.ncbi.nlm.nih.gov/Omim/.

Albinism

Albinism (many OMIM entries, e.g., 103470, 103500, 203200, 203280, 203310, 300500, 300600, 300650, 300700) was a natural attraction for Garrod because of his interest in pigment metabolism. It is a disorder of melanocytes involving both the biochemistry of melanin synthesis and the interaction of melanocytes with other cells. Albinism is a protean clinical trait, reflecting a group of inherited abnormalities presenting with congenital hypopigmentation that can involve the skin, hair and eyes in various combinations. When reports appeared noting that a child with normal pigmentation could be born to parents who were both affected with albinism, it was time to consider the possibility of locus heterogeneity and of allelic complementation. Accordingly, the albino trait described by Garrod a century earlier now requires a vast chapter in MM-BID-8 describing many genes and many cellular processes.66

Alkaptonuria

Alkaptonuria (OMIM 203500) was the disorder on which Garrod established his thesis of chemical individuality, the concept of an “inborn error of metabolism” and his novel view of disease in general (see chapter 2 in reference 25). The chapter in MM-BID-8 and those in its previous editions have all been authored by B.N. La Du, who first demonstrated deficient activity of homogentisate 1,2-dioxygenase (EC 1.13.11.5) in alkaptonuria.68 However, only at the end of the 20th century was it possible to isolate the human gene (symbol, HGO) for homogentisic acid oxidase and demonstrate that mutations in it map to the alkaptonuria (AKU) locus and cause the human disease. A commentary69 accompanying this landmark report described a long and slow “classical journey” covering the clinical, metabolic, enzymic and genetic facts about the disease between 1902 and 1994, followed by a very rapid “contemporary journey,” covered in half a decade, which revealed the HGO gene, the corresponding AKU locus on chromosome 3q2, the tissue-specific expression of HGO, the cosegregation of clinical phenotype with mutant genotype, confirmation of autosomal recessive inheritance, and an array of HGO mutations characterized by expression analysis. The AKU locus (HGO gene) was located by the powerful method of homozygosity mapping and required only 2 consanguineous pedigrees; the gene was then cloned and characterized by capitalizing on comparative genomics and knowledge about the gene in Aspergillus nidulans and mouse.70,71 The crystal structure of homogentisic acid oxidase (a dimeric structure of a homopolymeric trimer) has also been obtained to reveal how AKU missense mutations are likely to alter the structure and function of the HGO enzyme.72

Alkaptonuria, about which a great deal is now known, remains a disorder of the tyrosine pathway; unfortunately for the affected patient the progressive arthritic legacy of the disease still has no effective treatment. The triketone NTBC,73,74 an inhibitor of the preceding enzyme in the pathway and a dramatically effective therapeutic agent in hereditary tyrosinemia type 1,75 might turn harmful substrate excess into a harmless alternative and prevent disease in alkaptonuria.

Meanwhile, time has been kind to Garrod’s great paper on alkaptonuria.66 This relatively inaccessible paper is a classic in human and medical genetics; accordingly, it has been made available, in facsimile, on a Web site (www.SSIEM.org.uk/). Nominally a paper about a particular disease, it was far broader in its intent with its invitation: first to discover the relevance of mendelian genetics in medicine, then to accept the concept of biological and chemical individuality, and lastly to engage in the whole concept of inherited susceptibility (or resistance) to disease — the theme that would later reappear as the Huxley Lecture on “hereditary diathesis,”62 and fully in Garrod’s second book Inborn Factors in Disease.61,77

Cystinuria

Garrod’s understanding of cystinuria (OMIM 220100) was, in a minor sense, one of his few recog-
nizable errors; he thought it involved a pathway of metabolite conversion in the usual sense. Later enquiry revealed otherwise.

Cystinuria was identified as a familial cause of nephrolithiasis in the 1800s, but it was not until the mid-1900s that Dent’s group would show the disorder to be an inborn error of membrane transport involving a selective carrier for the amino acids cystine, arginine, lysine and ornithine. Cystinuria thus became the canonical “inborn error of membrane transport.” A high-affinity transporter located in the brush-border membrane of epithelial cells, both in the small intestine and in the pars recta of proximal renal tubule, is impaired by cystinuria-causing mutation. Harris and colleagues knew that cystinuria was genetically complex, having both completely (type I) and incompletely recessive (non-type I) forms, thus anticipating either locus or allelic heterogeneity for the disorder. A gene on chromosome 2p, which encodes the membrane transporter SLC3A1, has now been cloned, and the completely recessive (type I) alleles map to this locus. Non-type I alleles (so-called type II and type III incompletely recessive alleles) map to chromosome 19 encoding a different protein designated SLC7A9. It is presently believed the 2 proteins are part of a single transporter.

Pentosuria

Garrod’s fourth inborn error of metabolism was pentosuria (OMIM 260800). The metabolic disorder is the result of deficient L-xylulose reductase (EC 1.1.1.10) (xylitol-dehydrogenase) activity. MMBID-8 has reprinted its old chapter on this disorder because its author could find no substantive new literature about it. Nonetheless, pentosuria highlights 2 abiding themes in modern human genetics: first, the mutant alleles that modify this metabolic phenotype have no significance for personal health and to misunderstand this fact might well convert an otherwise healthy person into an “unpatient” concerned about his or her health for no good reason. Thus, pentosuria is a prototype in medicine, showing that caution is needed when interpreting a variant genotype or phenotype. Second, pentosuria illustrates the theme of individuality, not only in the person but also in an ethnic group: pentosuria is a trait of the Ashkenazim, and it shows that history of the gene and its alleles can also be the history of the population in which it is found; a theme that recurs in human and medical genetics with great relevance for counselling persons, families and communities about “their” particular problem.

Phenylketonuria: particular disease with general messages

Every inborn error of metabolism has both particular and general messages to convey. Those found in phenylketonuria (PKU, OMIM 261600), for example, have special interest for the scientist, but they also have transforming significance for the person with a mutant PKU-causing genotype. In my collection is a wedding photo (one that appears in at least 2 widely used textbooks and on the Web site [www2.mcgill.ca/pahdb]). The bride and her bridesmaid (the bride’s sister) share the same mutant genotype. The sister is profoundly impaired because of her untreated PKU, whereas the bride benefited from early diagnosis and treatment. Following her marriage, the bride dealt with the problem of maternal hyperphenylalaninemia and has given birth to a healthy daughter. From such private histories, the classic mendelian disease (PKU) with its solemn consequences for cognitive development became the prototype to show that treatment can modify the impact of a genetic disease—an achievement still awaited in many other genetic diseases.

Knowledge about PKU has been attained via 3 approaches (Fig. 3). On the mendelian route, phenotype pointed to a single locus and autosomal recessive inheritance. Lionel Penrose had already recognized in PKU the potential for treatment of a chemical cause of mental retardation; he brought the discovery of this new inborn error of metabolism to the attention of Garrod who then wrote to Asbjorn Folling, its discoverer. The Norwegian replied: “I am very proud that the author of Inborn Errors of

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**The differences between expectations and achievements in the treatment of genetic disease were the subject of a millennium essay; the starting points for the author were the hopes and the actual experience with PKU.

††The anecdote is described in Bearn’s biography of Garrod (page 145).
Metabolism likes to have a reprint of every paper on phenylpyruvic imbecility. For the time being, I have collected 16 cases of the disease in this country.

Folling lived to receive the Kennedy medal in 1962 for his achievements. Garrod died in 1936, never to know the recognition he would later receive from Beadle in his Nobel address.

Biochemical studies revealed the metabolic pathways used by phenylalanine during its disposal, conversion and catabolism. The major outflow pathway is initiated by parahydroxylation of phenylalanine to form tyrosine. When the function of phenylalanine hydroxylase (PAH) (EC 1.14.16.1) is impaired, there is overflow of phenylalanine into a minor pathway and the formation of phenylpyruvic acid and derivatives. Current evidence suggests that none of these alternative derivatives is significant in the pathogenesis of impaired cognitive development in PKU; the chief villain appears to be the phenylalanine molecule itself.

PKU shows the predicted gene dosage effects when PAH enzyme and phenylalanine flux activities are correctly measured; at the same time, PKU is fully recessive at the level of its measured metabolic phenotype — the plasma phenylalanine concentration. Thus, whereas the enzyme phenotype in PKU fits expectations for an autosomal trait, the corresponding metrical metabolic phenotype is fully recessive as predicted.

PAH enzyme requires tetrahydrobiopterin cofactor in catalytic amounts and metabolic homeostasis of this pterin requires enzymes for both its biosynthesis and recycling. Mutations in the corresponding genes (www.bh4.org) produce forms of hyperphenylalaninemia (HPA) that do not respond to classical dietary treatment. A theme of locus heterogeneity was revealed, and its particular relevance penetrated into every newborn screening program for PKU. About 1% of newborns with persistent HPA have a disorder of tetrahydrobiopterin homeostasis and they must receive the correct diagnosis for its treatment to be effective. Yet another general message is apparent here: detailed knowledge of the relevant biochemistry is needed to understand phenotype and help the patient.

Molecular genetics joins gene to protein to metabolome to clinical phenotype (Fig. 3). The human PAH gene is on chromosome 12q23.4; it harbours at least 28 polymorphic or silent alleles, and over 400 phenotype-modifying alleles (ww2.mcgill.ca/pahdb/). Half of all known disease-causing alleles in the human genome are missense mutations, and over 60% of PAH alleles are missense; only a few of the latter affect critical residues in the catalytic domain of PAH enzyme. The major effect of PAH missense alleles seems to be on PAH protein stability, a finding that has started a new paradigm — that defective folding and degradation of mutant proteins is a common pathogenic mechanism for genetic disease — and from this particular evidence emerges a broader question: If most human missense alleles affect protein folding and stability primarily, could an intervention that stabilizes the protein (by means of “micromolecular or chemical chaperones”) be a new direction for treatment of some, perhaps many, genetic diseases? Evidence is appearing to support this hypothesis.

Crystal structures are now known for many proteins; the corresponding homotetrameric structure of PAH enzyme is among them. A dimeric PAH structure is necessary for the catalytic reaction, but tetramerization of the dimer is required for the subtle regulation and control of phenylalanine hydroxylation. The PAH monomer has regulatory, catalytic and tetramerization domains, and the potential effect
of the PAH mutation can be better understood by knowing the domain and the residue(s) affected.

PKU alleles have also yielded interesting information about the evolution and diaspora of modern human beings and the nature of locus-specific mutation events. Although there are hundreds of PKU-causing mutations, only a half dozen account for two-thirds or more of their relative frequencies in any human population; the remainder are rare or even private. This finding at the PAH locus is being echoed at almost every other human locus examined so far: a few alleles are prevalent, most are rare in the population. This biological perspective has important implications for medicine: diagnosis and counselling based solely on mutation analysis will have serious limitations until comprehensive methods for total mutation analysis at any given locus are available.

There is an interesting historical message buried in the PAH allelic variation of PKU. PAH alleles appear to document the “out-of-Africa” scenario for Homo sapiens, with their independent emergence in Oriental and Caucasian populations. The subsequent distribution of alleles through demic expansion, human migration and genetic drift, and during the past 500 years through range expansion out of Europe, explains their appearance in Old World and New World human populations. The PKU story, at the PAH locus, like many other variant human phenotypes derived from locus-specific mutations, is clearly telling us that the history of a population is also a history of its mutations.

When molecular genetics came to medicine in the last decade of the 20th century there was a widely held belief, or at least a hope, that to know genotype at the particular locus would predict the corresponding phenotype and assist counselling of compliance with treatment. It was, of course, a naïve belief. For example, Penrose knew in 1946 that a PKU genotype did not necessarily predict IQ yet we ignored his observation. Some form of biological variation, perhaps polymorphic in nature, has now been recognized to act at the blood–brain barrier in some individuals to keep phenylalanine out of the brain when its concentration in blood is pathologically high and could play a role in the pathogenesis of cognitive dysfunction in PKU. Through specific expression in these individuals the genome protects their brain from phenylalanine toxicity. Here is an example of a modifier effect on phenotype, and it implies that PKU, the mendelian disorder, is also a “complex trait.”

PKU thus illustrates several general messages in human genetics: allelic heterogeneity is the norm; locus heterogeneity underlies many phenotypes; the phenotype can reflect both nature and nurture and is thus multifactorial; the variant phenotype at its various levels is complex. Accordingly, one is inclined to say that monogenic traits are probably never “simple,” and when that can be said, it is time indeed to read Garrod’s second book. In some ways, it has all been said before. But that was then and this is now, and we have too little time for then.

**MMBID-8: a repository of information in the “post-Garrod” era**

In 1960, the McGraw-Hill Book Co. published the first edition of a book which, through 7 subsequent editions, has become a repository for all that could be known about many hundred so-called “inborn errors” and “orphan diseases.” With time, the book gained mightily in stature, not only in the number of authors and topics but also in pages and heft. MMBID-8 now has 7 editors and over 500 authors, and it was published in early 2001 in 4 volumes with some 7000 pages of suffocating weight should you take it all to bed. The current editors see MMBID as an appropriate repository for what will emerge in the post-genome era of “functional genomics” wherever mutation affects adaptive health and is a contribution to the cause of disease. It has also become a valuable resource for the physician-scientist — a class to which Garrod belonged with distinction and for that matter for any physician involved with genetic disease, and which physician is not?

Because the new knowledge is likely to accumulate exponentially, MMBID will appear on the Internet and will become a dynamic online book, permitting new topics to appear as required, existing ones to be updated, and with links and accessory features not feasible in the print version. It is the only way to keep pace now that over 1000 human genes are known to harbour at least one disease-causing allele.
or significant polymorphism. The information will serve a cumulative caseload of the prevalent inborn errors of metabolism alone, where the incidence of these correctly classified orphan diseases‡‡ in Western societies, is approximately 40 cases per 100 000 births.112

Where next?

If science is an assault on ignorance113 and if through it our knowledge expands, then society as the ultimate patron of science will anticipate returns on its investment in the form of concepts, databases and technologies. Harold Varmus reflected on the likely course of the biological sciences in the near future (Table 3). For someone training today for a career in biology and medicine, the 7 areas listed in the table offer opportunities beyond anything Garrod could have imagined. Moreover, each area of enquiry enlarges the interface between our own science and the interests of the patients whom we ultimately serve. The prospects are impressive.

Concluding thoughts

A declared goal of the Human Genome Project was to understand better the DNA code behind the phenotype and how mutations in it might undermine health. Accordingly, the medical initiative in the genome enterprise was to link phenotype, pathogenesis and cause (Fig. 4), which embraces a pair of questions:7,25 i) What is the disease this patient has? (an Oslerian question); ii) Why does this particular person have this disease now (a Garrodian question)?

No organism is an island unto itself; always there is interaction with an environment, with an experience. Accordingly, Homo modificans desires to control experience. This can help the PKU patient, for example. On the other hand, millions of nominally healthy citizens in Europe and the Americas, Asia and the Orient do it every day by tailoring experience through Holistic, Ayurvedic or Chinese medicine to fit experience to their private phenotypes and needs.7 Both extremes of adaptation reflect Garrod’s insight into human individuality.

The genome projects give us genes that harbour alleles; mutation analysis will reveal them and databases will record them. Some persons will deny that to know about alleles is useful facts or has much to do with health and disease, but those people are wrong: genes, mutations and the discipline of genet-ics have each penetrated medicine irrevocably and have validated Garrod’s thesis about our biological individuality.

### Table 3: Seven emerging sectors in biomedical science (and their related technologies)‡*

1. Genomics (structural; function ...)
2. Large gene sets/families (expression maps; chips ...)
3. Bioinformatics (accession, distribution, interpretation ...)
4. Complexity (homeostasis, signalling pathways ...)
5. Molecular genetics “in the clinic” (susceptibility testing, risk assessment ...)
6. “Proteomics” (combinatorial drug design ...)
7. Cellular plasticity (stem cells, development, cloning ...)

*Taken from a speech (“New themes in medical science”) given by Harold Varmus at the 40th anniversary of the Gairdner Foundation International Awards (Toronto, Oct. 22, 1999).

‡‡Orphan diseases are a challenge to society: too few affected persons for any particular entity to recruit much interest except that of the affected population itself. However 1000 or more different orphan diseases constitute a very large, albeit disparate, community. In the interest of such citizens in need, a group of companies (www.swedishorphan.com, www.orphanusa.com and www.orphan.com.au) has begun to address their needs for new therapeutic agents and enabling food and drug-type regulations.

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**Fig. 4:** A diagram relating cause and pathogenesis with cause of a genetic disease, where the environmental (extrinsic) and biologic (intrinsic) components of cause are both necessary and sufficient and imply opportunities for (genetic) screening and testing and treatment; opportunities to prevent or avoid disease provoked by intrinsic causes are among the features that genetics brings to medicine.
With these developments in genetics come new opportunities to develop tests for population screening and testing of individuals, new ways to treat genetic disease and, better still, to prevent some or many of them. It won’t be Utopia; bad things will happen en route, but by the year 2036, the centenary of Garrod’s death, medicine will be different and better because of genetics, if the opportunities are used wisely.

Members of the genetics communities (human, medical and others) are also likely to be different in ways unfamiliar to Garrod; we will have loyalties significantly divided between academe and industry. One part of our community will connect with the private sector to be involved with new technologies, corporate ethics, patents, profits and — forgive us — secrecy; the other will remain in the more open community of academic science. How the divided loyalties and pressures will affect science and society has yet to be discovered.114

The major commodity for the community of science will always be knowledge. I recognize 5 types of knowledge. Some of it is unknowable, whereas the stuff of science is the unknown. When a thing is known, we use it (technology). Sometimes the knowledge itself worries us (genetics worries a lot of people) and so we hide away from it (the I-don’t-want-to-know type of knowledge). And then there is forbidden knowledge, a very harmful form (censored information).

What we do with data, information and knowledge becomes either a challenge or an opportunity, depending on the wisdom involved. Humankind has long wrestled with challenges and the opportunities attached to knowledge, hoping to arrive at Wisdom. T.S. Eliot recognized the problem when he asked: “Where is the wisdom we have lost in knowledge? Where is the knowledge we have lost in information?” Isaiah Berlin recognized another problem, namely that in every choice there is an irrevocable loss. Immanuel Kant encapsulated these existential struggles in 2 rhetorical questions: What can I know? With that knowledge, what ought I do? These 2 questions are good mantras for every geneticist (and physician) and I hope we will reiterate them during every day of our professional lives. Like DNA, they are transforming entities, and they can make us wiser.

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