EDITORIAL

Clinical molecular medicine has finally arrived

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About a hundred years ago spectacular changes in medicine were occurring. The discovery of hormones and the understanding of clinical endocrinology, the development of antibiotics, early application of radiation for diagnosis and treatment of various diseases, identification of blood groups and initiation of transfusion medicine, and many other new advances rapidly changed the face of medicine. The famous physician William Osler wrote in 1902: '*Never has the outlook of the profession been brighter. Everywhere the physician is better trained and better equipped than he was 25 years ago. Disease is understood more thoroughly, studied more carefully, and treated more skilfully. The average sum of human suffering has been reduced in a way to make the angels rejoice. Diseases familiar to our fathers and grandfathers have disappeared, the death rate from others is falling to vanishing point, and public health measures have lessened the sorrows and brightened the lives of millions.*'[1]

It is fair to say that medicine is in a similar situation of very rapid progress in the present era. Advances in technology present us with a fascinating imaging potential that is improving every few months. Similarly, minimally invasive interventions are swiftly developing and getting better each year. Simultaneously, the dazzling elucidation of molecular genetics is supposed to provide medicine with a similar boost. Indeed, the exponential increase in knowledge about genes, DNA variants, polymorphisms and mutations, as well as transcription regulation, gene-environment interaction and epigenetics, has certainly been translated into mounting knowledge about biology and disease.

However, clinical medicine has derived very few advantages from the genetic revolution in biomedicine so far, even for relatively simple genetic disorders such as sickle cell disease, which affects hundreds of thousands of people worldwide. The genetic mutation of this monogenetic disorder was elucidated more than 50 years ago,[2] yet this very precise molecular knowledge has had no effect at all on clinical management. In fact, despite all genetic preciseness patients with painful sickle cell crises are managed with intravenous fluids and painkillers.[3] Similarly, patients with primary haemochromatosis due to a precisely defined gain of function mutations in genes involved in iron absorption are managed by blood letting, a therapy that has been with us since the Middle Ages.[4] Another clear example is the genetics of thrombophilia. Factor V Leiden was discovered in 1994 as the genetic defect responsible for activated protein C resistance, leading to a prothrombotic state and an increased risk of thrombosis.[5] However, almost 20 years later we do not have a clue how to provide adequate differential primary or secondary prophylaxis for affected individuals or how to precisely handle common thrombotic complications in patients with factor V Leiden or similar genetic thrombophilic defects.[6] Apparently, the gap between the discovery of the genetic base of a disease and the consequences for clinical management is large and it takes a lot of additional research and time before this gap can be bridged. And the examples given all represent monogenetic and relatively simple diseases, let alone the clinical consequences in terms of management of multigenetic disease, such as atherosclerosis and cancer.

Nevertheless, and despite the tardiness of the translation of molecular genetic knowledge to clinically applicable improvements, the first changes are visible. In the field of Internal Medicine, this may be most clear in clinical haematology. Indeed, the discovery of the Philadelphia chromosome as the underlying genetic disorder of chronic myeloid leukaemia (CML) stems from more than 50 years ago,[7] but in the last few years this knowledge has indeed translated into a cure for affected patients. In this issue of the *Netherlands Journal of Medicine*, Thielen and colleagues extensively review the further improvement in the management of patients with CML based on new insights into the molecular genetics of this disease.[8] But also in the management of chronic lymphatic leukaemia molecular insights form the basis for further improvement in clinical management, including better treatment strategies, as reviewed in the guideline

paper by Kater *et al.* in this issue of the Journal.[9] And in other forms of malignant haematological disease genetic insights are now starting to translate into improved management strategies or even better treatment options for these disorders.[10,11] It seems that precise molecular characterisation of malignancies does not only provide more insight into the pathogenesis of disease but can also be of use to stratify patients as high- or low-risk for recurrence and adverse outcome. But ultimately, the goal is that this knowledge translates into a better treatment outcome and it seems that this is happening now in clinical haematology. It is clear that other disciplines within oncology will follow soon, as previous publications in this journal indicate.[12,13] But also many other fields in medicine, such as rheumatology, have entered the phase in which incisive knowledge on molecular mechanisms will translate into better management options for patients.[14]

It may be fair to say that the 'genetic revolution' will indeed change the face of clinical medicine but that these changes take a lot of time and research effort. Fundamental research is crucial for further development of our insight into normal biology and disease but translational research to bring these results to practical solutions for patients is at least as critical and may require major investment. Nevertheless, it seems that we are at the threshold of reaping the rewards of molecular genetics and that Osler's statement from 110 years ago is by the same token applicable to the present era.

REFERENCES

1. Bliss M. William Osler: A life in medicine. New York: Oxford University Press; 1999.
2. Barkhan P. Genetics of haemoglobin. Guys Hosp Rep. 1967;116(3):307-22.
3. Rees DC, Olujohungbe AD, Parker NE, Stephens AD, Telfer P, Wright J. Guidelines for the management of the acute painful crisis in sickle cell disease. Br J Haematol. 2003;120(5):744-52.
4. Wheeler CJ, Kowdley KV. Hereditary hemochromatosis: a review of the genetics, mechanism, diagnosis, and treatment of iron overload. Compr Ther. 2006;32(1):10-6.
5. Bertina RM, Koeleman BP, Koster T, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature. 1994;369(6475):64-7.
6. Middeldorp S, Levi M. Thrombophilia: an update. Semin Thromb Hemost. 2007;33(6):563-72.
7. Freie E, Tjio jH, Whang J, Carbone PP. Studies of the Philadelphia chromosome in patients with chronic myelogenous leukemia. Ann N Y Acad Sci. 1964;113:1073-80.
8. Thielen N, Ossenkoppele GJ, Schuurhuis GJ, Janssen J. New insights into the pathogenesis of chronic myeloid leukemia: towards a path to cure. Neth J Med. 2011;431-41.
9. Kater AP, Wittebol S, Chamuleau M, van Gelder M, van Oers MH. Guidelines for diagnosis and treatment of chronic lymphocytic leukemia 2011. Neth J Med. 2011;423-30.
10. de Jonge HJ, Huls G, de Bont ES. Gene expression profiling in acute myeloid leukaemia. Neth J Med. 2011;69(4):167-76.
11. Minnema MC, van der Spek E, van de Donk NW, Lokhorst HM. New developments in the treatment of patients with multiple myeloma. Neth J Med. 2010;68(1):24-32.
12. de Wijkerslooth TR, Bossuyt PM, Dekker E. Strategies in screening for colon carcinoma. Neth J Med. 2011;69(3):112-9.
13. Kroep JR, Linn SC, Boven E, et al. Lapatinib: clinical benefit in patients with HER 2-positive advanced breast cancer. Neth J Med. 2010;68(9):371-6.
14. Verweij CL. Transcript profiling towards personalised medicine in rheumatoid arthritis. Neth J Med. 2009;67(11):364-71.