The Journal of Laryngology & Otology
July 2000, Vol. **114,** pp. 491–493

The Future of ORL-HNS and Associated Specialties Series

The future of pathology

Justin Weir, B.Sc., M.D., F.R.C.S., Ketan Shah, M.R.C.Path.*

It was said in the latter quarter of the last millenium that electron microscopy would revolutionize our understanding of disease. Now those monolithic microscopes lie abandoned and are rarely used. Immunohistochemistry was then championed as the ultimate diagnostic tool but again its light has faded and is used now to clarify and classify rather than diagnose. Molecular pathology is the latest beacon. For how long and to what degree remains to be seen. But behind all these advances lies a technique that has changed little in the last hundred years, namely: the haematoxylin and eosin (H&E) stain. So against a background of futuristic technology the standard H & E slide will remain for the foreseeable future the bedrock of diagnostic histopathology.[1] However, it is also evident that the Human Genome Project and information technology, in particular the management and application of information to our understanding of health and disease, will have a major impact on the way medicine is practised.

Bioinformatics and telemedicine

Cyberspace has allowed an unparalleled global access to information. Pathology recognizes that this provides an arena for distance surgical specimen reporting and there are many advocates for 'telepathology'. Coupled with automated surgical specimen handling, off site reporting using a 'robotic interactive system' that allows the pathologist to see the slides in real time, and manipulate the slides from afar, may be commonplace.[2] Basic systems are currently used in Norway[3] and prototype systems are in use in Germany and the United States. Technological improvements in image quality, speed of transmission, security and tele-conferencing will come in time. That telemedicine will become such an important feature of 21st century healthcare follows from President Clinton's State of the Union address in 1998 in which he pledged enormous investment in this field. Virtual reality environments and real time interaction could become the norm. Digitization of the analogue source will allow for compact storage of data, rapid recall and infinite reproducibility. The educational benefits from such a virtual database would be enormous.

Alongside telepathology will be advances in microscopy. The light microscopy has enabled substantial advances to be made in histopathology. The next generation of microscopes will be atomic-force microscopes that will enable the visualization of shapes and structures down to the atom. By imaging DNA and individual proteins, normal and abnormal protein-DNA interactions can be seen in real-time under physiological conditions. The limits to this technique remain unknown.[4]

Human genome project

Biology's holy grail:- the sequencing of all three billion base pairs of the human genome is within reach and perhaps by the time this article is published the first full consensus sequence of the human genome will be known. It will be a remarkable feat to the start of the new millenium. However, its immediate impact remains dubious in so far as a single consensus sequence represents a collection of different fragments assembled together, so there is no information about the genetic differences that may explain who gets which disease and why.[5] The critical question for clinicians is: 'what are the sequence differences?' rather than knowing the consensus sequence. Only with this in mind will advances be made in the area of determining who is more likely to acquire a particular disease. Just recently sequence variability has been formally included in the project's goals.[6]

Identification of genetic factors affecting prognosis of disease is likely to be of the most clinical importance. Genetic dissection of complex traits will continue to yield specific genes,[7] whilst most progress will be made in understanding the genetic contribution to the intermediate phenotypes linking genes and disease. In any given gene conferring disease susceptibility there are generally multiple alleles that affect disease risk to different degrees.

From the Department of Pathology, Bristol Royal Infirmary, Bristol, and the Department of Cellular Pathology*, Northwick Park and St Mark's Hospitals, Harrow, Middlesex, UK.

For example, the cystic fibrosis gene has over 800 mutations associated with the disease. Indeed, a decade of research has indicated that the genotype poorly predicts phenotype.[8] Such multiplicity of mutations and disease-associated alleles tends to be more the rule than the exception.[9] Thus progress in finding and establishing susceptibility genes will be slow. However, progress in Iceland is being made with deCODE genetics, which combines information about genealogy, medical records, and genetic information on the entire population.[10]

Molecular diagnostics carries with it high expectations that will not necessarily be realised unless further improvements are made in developing diagnostic technologies that are fast, cheap and can be applied to common as well as rare diseases.[11] Assuming this is possible, we may well revisit an area of research that is much chastised in our evidence based culture; namely the 'non-hypothesis driven' field of expression profiling. Comparisons between genes of different organisms, variants of the same gene in different populations, and genes in health and disease, will yield enormous data on patterns. From pattern recognition can new hypotheses be tested. A technology that is currently in use for research purposes but will play a leading role in expression profiling is the 'DNA chip' (Affymetrix, Santa Clara, CA, USA). These gene chips are high-density microarrays, which can scan for mutated sequences at a phenomenal speed enabling expression levels from hundreds of thousands of genes to be evaluated in normal and diseased states. This technique will not only provide a strong boost to the study of more complex genotype-phenotype correlations, but will also elucidate the events between primary mutation and dysfunction of the cell or organism. Thus a disease state will have a particular gene expression pattern which may help to define the stage of the disease and the prognosis. Coupled with this will be the introduction of gene product assays to determine the structural, developmental or immunological defects caused by the mutations.

The much vaunted although currently disappointing field of gene therapy will be one beneficiary of genome technology. Our understanding of our genetic and physical constitution will allow for the development of more effective therapies to order. These will be a combination of gene therapy strategies and pharmacological treatments that will bypass or block defective systems. Eventually, there will be a paradigm shift from diagnosis and treatment to one of prevention. The question of tomorrow will be not 'which disease does this person have' but rather 'which person may get this disease'.[11] Is this what we as individuals will want to know? Each one of us will have our tailor-made treatments and lifestyles regimens to ensure a healthy life, knowing the consequences of non-compliance against a background of pressure from a society forever decreeing the importance of the 'healthy physic'. Undoubtedly, we will face many difficult ethical judgments that few will be capable of understanding and that we as doctors will be expected to dissimulate to the public.

Molecular pathology

Tumour classification will need substantial change in certain fields. Chromosomal and molecular amendments are already commonplace to classify lymphomas, soft-tissue sarcomas and paediatric tumours (e.g. acute myelogenous leukaemia (AML), lymphoblastic leukaemia/lymphomas, Ewing's sarcoma)[4] where identification of a certain translocation defines the type of tumour and thus its therapy. However, for the more common tumours work on mismatch repair has revealed another genetic mechanism leading to carcinogenesis[12] and further different mechanisms of causation are likely to be identified resulting in specific approaches to treatment.

Increasing antimicrobial resistance remains one of the great fears. However, the tighter control of antibiotic prescription and effective infection control (especially hand-washing) practices will prevent further resistance.[13] The issue of antimicrobial resistance was addressed by the European Union (Microbial Threat Conference, Denmark, 1998), which listed seven recommendations, and we must ensure that the future of healthcare is not blighted by the spectre of the invincible microbe. Advances in the sequencing of bacterial genomes will yield information about antibiotic sensitivity and resistance and, furthermore, we will be in a position to determine the patient's predisposition and resistance to a bacterium. For example, work has shown that certain HLA types such as B27 may be more susceptible to intracellular infectious agents,[14] HIV progression is affected by HLA type,[15] and polymorphisms in interleukins or other cytokines may effect the efficiency of the immune response.[16]

The pathologist and the otorhinolaryngologist

The interaction between a surgeon and pathologist must be both interactive and proactive if the very best standards of care are to be reached. The use of minimum data sets[17] particularly for cancer will be mandatory as will the treatment of cancer in regional 'Calman' centres. Guidelines are there to ensure so called best practice but equally they are not unchangeable and all parties must be responsive to change driven by patient expectations, resources, technology, etc. Open communication will remain the most important facet of any multi-disciplinary teamwork.

The importance of fine needle aspiration (FNA) in establishing a diagnosis with the minimum of invasion is well appreciated and there is an argument to be made for creating one-stop FNA clinics as for breast surgery for the rapid diagnosis of head and neck tumours. Coupled with the ability to perform genetic analysis on single cells[18] such parameters as chemosensitivity status on metastatic deposits may become routine.

In terms of working practice, the need for communication, transparency and competency is of fundamental importance to the future of medicine. Whatever the means are of assessing these factors, we will, as humans, remain fallible. The challenge will be to deliver a safe and effective service that incorporates support systems, which will provide a diagnostic practice that is not only fail-safe but will also include error trapping as a formal part of our work.[19] Other practices may involve the use of 'near patient testing/point of care testing' as a means of delivering faster turn around times.[20] Continuous non-invasive monitoring in the form of transcutaneous biosensors are available which obviate the need for blood collection, whilst near infra-red spectroscopy may allow the continuous monitoring of more than one analyte.[20] Indeed this technology could be used in the home setting by the patient and is no more in essence than an extension to the current widely used practice of pregnancy home test kits.

Conclusion

We are on the verge of a period of radical change in our understanding of disease. How we handle the enormous amount of information that we well be presented with remains a challenge. Although H & E morphology remains the cornerstone of surgical pathology, it is routinely supplemented by immunohistochemistry to provide a more accurate diagnosis. Similarly, the role of new technology in clinical management needs to be clarified, generating a vast potential for clinicopathological research. But as Edmund Burke[1] remarked over 200 years ago, 'to conceive extravagant hopes of the future is a common disposition of the greatest part of mankind'. Thus we have to critically assess new developments and old hypotheses against an ever-expanding knowledge to arrive at robust diagnostic and prognostic indicators, always aware that we must be flexible and willing to change.

References

1 Fox H. Is H & E morphology coming to an end? *J Clin Pathol* 2000;**53**:38–40
2 Wolf G, Petersen D, Dietel M, Petersen I. Telemicroscopy via the internet. *Nature* 1998;**391**:613–4
3 Nordrum I, Engum B, Rindle E, Finseth A, Ericsson H, Kearney M, *et al*. Remote frozen section service: A telepathology project in Northern Norway. *Human Pathol* 1991;**22**:514–8
4 Quirke P, Mapstone N. The new biology: histopathology. *Lancet* 1999;**354** (suppl 1):26–31
5 Cardon LR, Watkin H. Waiting for the working draft from the human genome project. *Br Med J* 2000;**320**:1223–4
6 Collins FS, Patrinos A, Jordan E, Chakravarti A, Gesteland R, Walters L. New goals for the US human genome project: 1998–2003. *Science* 1998;**282**:682–9
7 Kapiro J. Genetic epidemiology. *Br Med J* 2000;**320**:1257–9
8 Geddes DM, Alton EW. The CF gene: 10 years on. *Thorax* 1999;**54**:1052–4
9 Terwilliger JD, Weiss KM. Linkage disequilibrium mapping of complex disease: fantasy or reality? *Curr Opin Biotechnol* 1998;**9**:578–94
10 Gulcher J, Stefansson K. An Icelandic saga on a centralized healthcare database and democratic decision making. *Nat Biotechnol* 1999;**17**:620
11 Van Ommen GJB, Bakker E, den Dunnen JT. The human genome project and the future of diagnostics, treatment, and prevention. *Lancet* 1999;**354** (suppl 1):5–10
12 Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW *et al*. A National Cancer Institute Workshop on microsatellite instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Res* 1998;**58**:5248–57
13 Cookson B. Infection and antimicrobial prescribing control in the new millenium: nightmare or nirvana? *J Clin Pathol* 2000;**53**:66–70
14 Ikeda M, Yu DT. The pathogenesis of HLA-B27 arthritis: role of HLA-B27 in bacterial defense. *Am J Med Sci* 1998;**316**:257–63
15 Roger M. Influencee of host genes on HIV-1 disease progression. *FASEB J* 1998;**12**:625–32
16 Hurme M, Lahdenpohja N, Santtila S. Gene polymorphism of interleukins 1 and 10 in infections and autoimmune diseases. *Ann Med* 1998;**30**:469–73
17 Helliwell TR, Woolgar JA. Minimum data set for head and neck carcinoma histopathology reports. *R Coll Pathologists* 1998
18 Findley I, Frazier R, Taylor A, Quirke P, Urquhart A. Single cell DNA fingerprinting for forensic applications. *Nature* 1997;**389**:355–6
19 Kirkham N. The pathologist in the 21st century – generalist or specialist? *J Clin Pathol* 2000;**53**:7–9
20 Crook MA. Near patient testing and pathology in the new millenium. *J Clin Pathol* 2000;**53**:27–30

Address for correspondence:
Dr J. Weir,
Department of Pathology,
Bristol Royal Infirmary
Marlborough St,
Bristol BS2 8HW, UK.