The clinical implications of gene amplification fall into two main categories—prognosis and therapy. There are now three human tumour types in which proto-oncogene amplification correlates with a poor prognosis:

(1) Neuroblastoma, in which N-*myc* amplification correlates with tumour stage[14] and is the best predictor of survival time.[15]

(2) Small-cell lung cancer, in which c-*myc*, N-*myc*, and L-*myc* may be amplified.[16-18] Originally c-*myc* amplification was reported to be associated with an aggressive histological subtype,[16] but this finding has lately been disputed.[18]

(3) Breast cancer, in which *neu* amplification correlates both with time to relapse and with overall survival.[19] Amplification of this proto-oncogene is more important in prognosis than patient age, tumour size, or hormonal receptor status and it is independent of axillary lymph node infiltration.[19]

This type of molecular analysis may lead to prognostic refinement sufficient to allow the early use of intensive treatment in selected high-risk patients.

An understanding of the molecular mechanisms of drug resistance is of obvious relevance to the rational use of chemotherapy. Debulking operations, high-dose cytotoxic regimens, and combination chemotherapy all seem reasonable strategies to combat small subclones of pre-existing resistant cells.[20] It may also be possible to exploit the mechanism of collateral sensitivity by which cells with the MDR phenotype exhibit a paradoxical increased sensitivity to other cytotoxic agents.[21] However, perhaps the major therapeutic importance of gene amplification lies in the attention it focuses on cellular genes involved in drug resistance and tumorigenesis. Once the products of such genes are recognised, and their functions understood, it should be possible to devise pharmacological or immunological ways of preventing drug resistance or even of reversing the malignant phenotype. Unfortunately, it is unlikely that these approaches will be tumour-specific in their toxicity, and so major difficulties with targeting will need to be overcome.

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Diagnosis: Logic and Psycho-logic

"The three main tasks of the clinician . . . are diagnosis, prognosis and treatment. Of these diagnosis is by far the most important, for upon it the success of the other two depends."—RYLE J. A. *The Natural History of Disease* 2nd ed. Oxford: Oxford University Press, 1948.

ACCURATE diagnosis is the keystone of good medical practice: not only must diagnostic categories be valid (so that nosologically unacceptable conditions such as "nephroptosis",[1,2] the floating kidney, can be eliminated), but also practitioners must be able to place patients correctly within those categories. As the third medical revolution—of genetic engineering[3]—begins, following closely behind the second revolution of powerful, effective drugs, so it becomes clear that the first revolution—the 18th century emphasis on the pivotal role of precise and correct diagnosis—is little understood as a psychological process. Large textbooks of medicine typically contain no description of diagnosis as a skill, or how to acquire it, while undergraduate courses usually ignore the subject completely, treating it like adolescent sex education thirty years ago—best acquired from the confused or erroneous hints of peers who claim marginally greater experience.

The past decade or so has witnessed studies of diagnosis as a process,[4,5] of the psychological nature of diagnosis,[6] and of statistical[7] and artificial intelligence based[8,9] approaches to computer diagnosis, all of which have been illuminating. There have also been novel textbooks devoted to diagnosis itself.[10,11] Cognitive science (psychology, linguistics, computing, and artificial intelligence) has shown that many seemingly trivial problems, such as an experienced radiologist looking at a chest radiograph and saying "TB", almost without hesitation, are deep in a strict sense, the test for profundity being the impossibility of programming a general-purpose computer to make such a judgment. Despite this apparently superior behaviour of the human mind, studies of clinical performance have also confirmed the findings of cognitive psychology in general—[12,13]

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that humans are often illogical and inefficient in using information, frequently make wrong deductions, ignore evidence, overemphasise irrelevancies, and are inconsistent, both with others and with themselves. In short, it is now realised that logic is not the same as "psycho-logic", the actual way in which humans process information.

In this issue (p 849) Professor Campbell argues not only that cognitive science can improve understanding of diagnosis, but also that such insights should modify teaching of the subject. With its emphasis on the hypothetico-deductive method as the central form of problem solving, this approach contrasts with the views of Professor McCormick that we published a few months ago.[14] McCormick argued that the hypothetico-deductive method was merely a fashionable piece of mystification and obscurantism for the commonsense process of looking and recognising: "Recognition is not hypothesis generation", he maintained, thereby flying in the face of most modern work on perception,[15] and contradicting Popper who argues against the existence of theory-free observation.[16] The long medical tradition of instantaneous recognition, seen in numerous volumes entitled "spot diagnosis", the ubiquitous short cases in exams, or the advice of Sir Thomas Lewis to recognise murmurs "as one learns to know a dog's bark", neither explains how the process is possible, nor the slowness or difficulty of acquiring this "treasury of pictures",[17] nor even the frequency of diagnostic errors.[18,19] David Marr's[20] fundamental contribution to the understanding of such visual processes as recognition was his insight that the otherwise insoluble equations linking the three-dimensional world to the two dimensions of retinal images can be solved (that is, can be programmed into a computer) only if assumptions (hypotheses) are made about the nature of the world—eg, that objects do not move randomly or continually fragment. With more complex recognition, in which "top-down" influences of expectations and likelihoods modulate perceptions, then hypothesis testing becomes more apparent. All perception tests hypotheses against sensory data, but the process may not be conscious and can be very fast—hence the apparent ease when the task is well learnt.

Popular accounts[21] of such medical mysteries as the "Epping jaundice"[22] make clear the similarity of complex diagnosis to the detective fiction of Conan Doyle, with the continual testing, refutation, and reformulation of elaborate hypotheses. Published accounts of clinico-pathological conferences typify the process par excellence. But do they represent an idealised practice, remote from the routine of outpatients or of general practice, with its diagnoses of "fibrositis", "gastric flu", and 'there's a lot of it about'?[23] Probably not, since such diagnoses can still be regarded as testable hypotheses for explaining the mild, poorly structured symptoms and few physical signs of familiar and common patterns of self-limiting disease (and such diagnoses are at least as refined as the supposedly more scientific idiopathic disorders that are frequently mere redescriptions of symptoms or signs). In each case the diagnosis acts as a provisional programme for action, albeit with continuing awareness that new evidence might necessitate a reformulation of the hypothesis.

Why is diagnosis seldom found in conventional medical school curricula? It is undoubtedly the principal intellectual skill of medicine, and its neglect as a research topic is slowly being rectified (possibly because the intrinsic cost-effectiveness of accurate diagnosis[24] is now recognised). Nevertheless, medical schools continue to emphasise the rote learning of a myriad of facts, all somehow felt to be fundamental to subsequent diagnostic practice, but without serious attempts at teaching the manipulation of such information. Medical students should not merely memorise lists of causes for particular symptoms—they must be taught to practice medical *thinking*, using evidence to reject unacceptable diagnoses. That is what problem-based learning attempts.[25]

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FORGOTTEN SYMPTOMS AND PRIMITIVE SIGNS

NEUROLOGY, according to one of its devotees, is "the Queen of Medicine which embraces in its scope the neurotropic virus and the human mind". The jewel in the neurological crown has always been the clinical examination. A modern (and excellent) Edinburgh textbook goes as far as to claim that "no other clinical discipline than neurology offers so exemplary an illustration of the logical and scientific foundations on which medicine is based . . . where possible, the precise anatomical site of lesion is determined . . . there are no short cuts".[1] By comparison, other disciplines may be wrongly felt to lack breadth or depth, and psychiatry, following the remark of Dupré, is left to the poets: "Voulez-vous pénétrer les secrets de la psychiatrie? Lisez les poètes et les romanciers".[2]

Last century, neurological examination in many clinics consisted of a haphazard hunt for various so-called

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