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Prediction of recovery from post-traumatic vegetative state

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The value of neurophysiological assessments for the diagnosis of the vegetative state has been widely discussed, and the general view is that they are supportive rather than diagnostic. Neurophysiological tests that can accurately predict the outcome for patients in the vegetative state would be welcome, to assist in discussions with the family, to help plan the treatment programme, to inform decisions about allocation of resources, and to assist in major decisions about withholding or withdrawal of treatment.

In today's *Lancet* Andreas Kampfl and colleagues report on their investigation of the value of magnetic resonance imaging (MRI) in predicting recovery from a post-traumatic vegetative state. For the purpose of this commentary the diagnosis of the vegetative state at the various stages of the study is assumed to be correct. The investigators base their prediction on MRI scans done 6–8 weeks after the brain injury. The prediction of recovery is thus not being made in the acute phase, the time when life-and-death decisions are usually made in the intensive-care unit. By 6 weeks, the patients were presumably medically stable.

So what are the potentially important findings of the study? First, those who remained vegetative had more lesions than did those who recovered (mean 10·4 [range 5–19] *vs* mean 7·9 [3–18]). Although the difference may be statistically significant, the ranges for the groups are so similar and so broad that they can be of no help in decisions about individual patients. Second, 98% of those remaining vegetative had corpus-callosum lesions, but so did 24% of those who recovered (ie, 18% of those with corpus-callosum lesions). The overlap is even greater with corona-radiata lesions—57% of those remaining vegetative had these lesions, compared with 26% of those who recovered (ie, 29% of those with corona-radiata lesions). Similarly, 76% of those remaining vegetative and 26% of those recovering had lesions in the dorsolateral upper brainstem. Again, although the difference between groups may be very statistically significant, the overlap is too high to help in the management of the individual.

Will the findings assist in discussions with relatives? To some extent they will, in that anything that helps to put the chances of recovery into context is valuable. However, relatives usually grasp at the chance that there may be some recovery, no matter how small. An 18–29% chance of recovery depending on the site of damage is too great a a range to dampen high expectations.

Do the figures help in decisions about the type of programme to be followed? No, but the study was not designed for this purpose.

Will the finding affect referral for rehabilitation programmes? Sadly, in countries where there is a strong purchaser-provider model of allocation of resources, the finding might encourage the refusal of funding for rehabilitation programmes when there are lesions in the corpus callosum, corona radiata, or the dorsolateral upper brainstem, or when more than eight lesions have been identified. The high proportion of patients with these lesions who recovered might be ignored by health purchasers.

Similarly, there is a risk that the findings may result in decisions to withhold treatment for infections or other acute episodes to the detriment of those who might otherwise have recovered. The decision on withdrawing augmented nutrition and hydration is unlikely to be affected quite so much. Withdrawal of tube-feeding is generally not accepted in much of Europe, and UK guidelines require the vegetative state to have been present for a year and the case to be referred to the Family Division of the High Court for a declaration on the acceptability of withdrawing tube-feeding.

Any test that helps in decision-making is valuable. The findings of this study, however, do not help because they are not precise enough for day-to-day practice in dealing with individuals. Until neurophysiological tests can give precise results, their role in this complex neurological disorder remains supportive rather than diagnostic.

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Patients' records on the Internet: a boost for evidence-based medicine

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The concept of evidence-based medicine has emerged as one of the fundamental elements in western-style clinical medicine. Two essential components of that concept are the patient's record and the clinical knowledge base.

The way information in the patient's record is generated, handled, and presented has been transformed by advances in modern information technology, starting with the dictaphone and the electric typewriter and culminating in present-day computer-based systems. Tedious, inefficient, and continuously space-demanding medical records offices are being replaced by "listening" computer terminals linked to a central patient register via a local area network (LAN). The required information, nicely presented, becomes obtainable at the touch of a button or with a simple voice command.

Similar systems are being used for the dissemination of clinical information among health institutions in a district or even an entire region. In their letter published today, H I Goldberg and colleagues describe the system linked to the University of Washington Medical Centers in Seattle for electronic transmission of a vast range of clinical, administrative, and financial information. Similar systems operate elsewhere. In Hong Kong, for instance, public hospitals are linked by a fast Ethernet-based LAN,[1] which allows transmission of clinical and administrative information among more than 3000 physicians and 19 000 nurses. Although cost-effectiveness has not been assessed, costs should be very reasonable if calculated per patient event.

The second element in evidence-based medicine is a continuously updated medical knowledge base. The Internet, with all its library functions, contains much more information than any traditional library, and elegant search routines enable the relevant "case-oriented" information to turn up within seconds.

It is therefore natural, as Goldberg and colleagues have

attempted, to combine the transmission of patients' details and library information within the same system and to extend the system beyond Seattle. The choice of an Internet instead of a LAN system was easy since most physicians are familiar with the Internet, and its cost is very acceptable, even for low-frequency use. As with databases linked by a LAN, confidentiality of patients' details transmitted over the Internet can be safeguarded by encoded transmission in the secure-socket layer. This precaution makes transmission of information about patients as safe as electronic transmission of any other type of information (eg, banking) and certainly safer than in paper-based systems.

The potential of the proposed Internet-based system for supporting evidence-based medicine is substantial. Correct clinical information at the right time can be provided, especially when the information is most needed—for example, when a patient is discharged from hospital to the care of the general practitioner, and in an emergency, when the patient is unknown to the attending doctor. For similar reasons, access to patients' records and medical databases could, long term and with patients' consent, be extended to other groups of health professionals. It could ultimately extend to the patients themselves, in support of providing them with individualised, affordable, health-education programmes.

New procedures intended for use in clinical practice must be assessed. So should new applications of information technology. Thus the hope is that Goldberg and colleagues will do a randomised controlled trial comparing traditional and Internet-based access to patients' records, with clinical, temporal, and fiscal outcome variables. Moreover, with so many medical records in the system, many important hypotheses could be tested and verified by solid statistical evidence.

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How many neutrophils are enough?

About 30 years ago, Crosby wrote a commentary entitled "How Many 'Polys' are Enough?", in response to an article on chronic idiopathic neutropenia by Kyle and Linman a few months earlier.[1,2] Crosby described sharply contrasting events in two patients with no circulating neutrophils—one patient did well despite severe neutropenia, whereas the other had raging infections. His commentary emphasised that the risk and outcome of bacterial infections depend on an individual's ability to respond to infection by delivering neutrophils to tissues, rather than the actual number of neutrophils in the peripheral blood. "Look for pus", was his advice. Stain a sample of opportunistic body secretions and look for neutrophils. If they are missing, the patient is truly neutropenic and susceptible to infections.

Despite Crosby's wise advice, the problem of understanding neutropenia on a clinical, physiological, or molecular basis persists. Recently, H R Koene and colleagues reported a new method for assessment of susceptibility to infection in patients with chronic idiopathic neutropenia.[3] They examined plasma concentrations of one of the receptors for the Fc component of IgG, which is normally expressed on neutrophils, and correlated these concentrations with the susceptibility to infection in a group of patients with chronic idiopathic neutropenia. The patients were similar to those who provoked Crosby's commentary. For several years, this excellent research group led by Albert E G Kr von dem Borne in Amsterdam has investigated this receptor, called Fcγ RIII or CD16. CD16 can be shed as a soluble receptor (sCD16) by neutrophils, and plasma concentrations of sCD16 are directly proportional to the total-body neutrophil mass.[4,5] Stimulation of neutrophil production seems to increase concentrations, which are lower when neutrophil production is suppressed. CD16 is expressed predominantly on mature neutrophils and is lost from the surface as the cells age and undergo apoptosis.[6] Thus, the concentration of sCD16 in plasma seems to correlate physiologically with overall neutrophil production and turnover.[4-7] The report by Koene and colleagues is important in that it shows that patients with neutropenia and frequent infection have low plasma sCD16, whereas other patients with equally low neutrophil counts but raised concentrations of sCD16 fare far better. Consistent with Crosby's concepts, these findings suggest that patients who produce more neutrophils but turn them over rapidly experience fewer infectious complications than those in whom neutrophil production is more severely suppressed.

Fewer than 5% of the total number of neutrophils in the body normally circulate in the peripheral blood. Although severe neutropenia (<500/μL) correlates with the incidence of serious bacterial infections, the risk of infections in patients with mild-to-moderate neutropenia (500–1500/μL) has been difficult to predict. Over the years, various other tests have been used to estimate neutrophil production and susceptibility to infection. These tests include direct examination of the marrow (marrow aspirates and biopsies), measurement of the marrow neutrophil reserve (by use of endotoxin, etiocholanolone, or glucocorticosteroids), assay for plasma concentrations of neutrophil granule components (eg, muramidase, lysozyme, and vitamin-B12 binding proteins), and various measurements of neutrophil accumulation during an acute inflammatory response. In general, none of these tests has proved very useful clinically when applied to the individual patient because of substantial overlap of test results between normal and neutropenic patients. This criticism can also be applied to the measurement of sCD16. These tests further expand our understanding of disease processes in general, rather than indicate the severity of disease in any individual patient.

For the general clinician, the report by Koene and colleagues is important for its insights into the role of neutrophils in host defence against the multitude of potential bacterial pathogens that reside on all mucosal surfaces. The study focuses on CD16 (Fcγ RI), a low-affinity receptor for the Fc moiety of monomeric IgG. As recently summarised by McKenzie and Schreiber,[8] CD16 on both neutrophils and monocytes may play a crucial part in facilitating phagocytosis of IgG-opsonised microorganisms and in the triggering of the release of inflammatory mediators. Dissecting apart the biological function of Fc receptors on phagocytes is currently a very active area of investigation.[9,10]