mission of resistant organisms by providing and using adequate isolation facilities in hospitals, for example; educate patients not to expect an antibiotic for everything; to ensure that low dose short-period regimens are avoided; and to make determined efforts to persuade the pharmaceutical firms and the Government to get into useful cooperation with each other and with the veterinary and medical professions to prolong the useful life of antibiotics. Failure to build constructively on the recommendations of the Swann Committee on the use of antibiotics in agriculture³ may prove in the long term to be as serious an error as it was judged to be in the leading article in the *BMJ* on the subject.⁴ Dr Tyrrell rightly says that we are likely to succeed in containing the spread of antibiotic resistant bacteria only if we use all the tactics open to us—there is no one simple and easy way out and no hope of getting away from the problem if we say that no real problem exists and that in due course if we carry on as we are doing all the difficulties will go away.

Valuable new drugs are on the horizon: the antivirals and human interferon, now made more readily available by genetic engineering. It is equally important that we are careful enough in our use of them to ensure that they remain of value for a long time. Genetic engineering should be encouraged with reasonable but not exaggerated safeguards. The prospective dividends are very rich indeed and seem to include the possibility of making safer and more effective synthetic vaccines with a few amino acids instead of a whole microbe. On the general question of laboratory safety the way forward, as Tyrrell wisely sees it, is to resolve differences of opinion and conflicts of interest by relying upon scientific evidence, based on specific and quantitative data wherever possible; by proper consideration of risks in relation to routes of infection; by leaving some matters unsettled pending epidemiological study; and by avoiding attitudes which promote confrontation and mistrust. The problems are real and have to be faced but they must not be exaggerated. The law and common sense demand only what is reasonably practicable and demonstrably necessary.

Organisation and training must be re-examined if we are to develop adequate strategies for the control of infectious diseases. Adequate supplies of pure water and clean food, together with better treatment, more immunisation, better housing, and better isolation facilities, have done much for advanced countries but we may not take these things for granted. The pipework of some sewage collection systems already needs replacement; and the few simple rules of kitchen hygiene necessary for the safe cooking of frozen chickens are often not even dimly understood. Isolation facilities, although better than they were, need to be made still better and be more often and more intelligently used.

Above all, the organisation of our preventive efforts and the training of infectious disease physicians need to be radically upgraded around the general theme of better provision of basic preventive care. There is little drama in preventing infection (indeed often no real evidence to prove success) and certainly no grateful patients. Worst of all there is little esteem from one's fellow doctors. What is required for the best practice and research in infectious diseases is a substantial effort to build up a structure beyond what is needed for the competent practice of a general physician or other specialist—a structure that includes bacteriology, virology, and epidemiology on the one hand and immunology and pathogenesis on the other as well as a detailed understanding of the pharmacokinetics, toxicology, and the antimicrobial range of antibiotics. In Tyrrell's view, that means providing an infectious disease unit in a general hospital. There are various directions in which changes would

have to be made in existing training and staffing procedures, but clearly academic esteem, at present lacking, should be built up, as it has been in the United States. Staff and students must come to understand that the study of infections is not a matter of past history or present routine but a subject of growing knowledge and interest. He says in plain words that we must not allow academic cuts and lengthy programmes for specialist accreditation to deprive us of that small number of clinician scientists we need and can support. Alas, there is a rumour that a university chair of infectious diseases may remain unfilled after the retirement of its present occupant within the next year. Dr Tyrrell's clear challenge deserves full discussion and an adequate response.

JAMES HOWIE

¹ Higgins P. Enteroviral conjunctivitis and its neurological complications. *Arch Virol* (in press).

² The Rock Carling Fellowship Lecture. *The abolition of infection. Hope or illusion?* D A J Tyrrell. London: The Nuffield Provincial Hospitals Trust, 1982.

³ Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine. London: HMSO, 1969, 12.16 and 12.17. (Cmnd 4190; Swann Report.)

⁴ Anonymous. Death of a quango. *Br Med J* 1981;282:1413-4.

Monoamine oxidase inhibitors in depression

Depression is a universal experience—and one which in most cases is self-limiting, often psychologically beneficial, and (apart from a little help from our friends) best managed without the intervention of specialists or the use of drugs. Depressive illness or disorder is a very different matter, for here we are dealing with a condition of high morbidity and a substantial mortality—a cause of much suffering and misery to patients and their families.

Unfortunately, depressive illness is not a single entity but a heterogeneous group of disorders and the difficulties are increased by confused terminology. The depressed phase of affective psychoses (ICD, ninth revision),¹ major affective disorders (American Psychiatric Association criteria),² endogenous depression, and major or primary depressive disorders³ all broadly correspond to the same entity characterised by severe depression, retardation or agitation, diurnal variation of mood, and other biological features. These conditions give high scores on various depressive indices, and patients usually show a good response to tricyclic antidepressants or electric convulsion therapy.⁴

Smiling, masked, covert, or hidden depression; atypical facial or other pain; alcohol abuse; and shoplifting or other atypical behaviours are often described as depressive equivalents. Though such terms may help to increase our awareness of the difficulties of diagnosis of primary depressive disorders, there is no justification for treating the disorders described as independent entities. Careful history taking and examination should result in a proper diagnosis, and soon more help may be available from the laboratory in doubtful cases.⁵

Patients who give low scores on depressive indices and respond poorly to tricyclic antidepressants or electric convulsion therapy present real difficulties and suffer much distress. They are often labelled as having atypical depression, the term used by West and Dally in 1959⁶ to describe a group of patients who showed a preferential response to monoamine

oxidase inhibitors. A recent review⁴ confirms the existence of such patients but urges that they should be included in the same category as depressive disorder—especially now that the American Psychiatric Association uses “atypical depression” as a residual category.²

In practical terms, symptom profiles can be more useful in predicting response to monoamine oxidase inhibitors. “Non-endogenicity” is the salient feature. Responders tend to be women more than men and under the age of 40, mood is depressed but retains its reactivity, somatic anxiety features are common, and psychomotor retardation is absent. The patients have lost interest and energy, then show irritability and hypersomnia or initial rather than late insomnia, they have evening worsening of mood, and often they overeat. They do not show guilt, delusional ideas, severe loss of weight, or suicidal intent, and these patients are not usually admitted to hospital. In one subgroup the prominent features are phobias, panic attacks, and depersonalisation.

Clearly these characteristics of the group of patients responsive to monoamine oxidase inhibitors place them at the end of any endogenous-neurotic continuum. The danger is that all that is not psychotic will be treated with these drugs. Careful selection and matching of drug and patient profiles are important if treatment is to be successful.

One further question remains. Even if a group of responders to monoamine oxidase inhibitors can be identified, given that the risk of suicide or hospital admission is low and that disability tends to be a result of chronicity rather than of severity, should these dangerous drugs be used? A formidable list of food and drug incompatibilities must be provided for the patient, and foods with a high tyramine content must be avoided even if these produce no symptoms.⁷ The risk of hypertensive crisis is five times higher with tranylcypromine than with phenelzine, and since tranylcypromine is partly metabolised to amphetamine it should never be followed by another monoamine oxidase inhibitor without a washout period.

Given reasonable caution, however, the risk of serious side effects is low, so that the use of monoamine oxidase inhibitor drugs is justifiable in patients with substantial disability who fulfil the diagnostic criteria. Recent work⁸ suggests that the simultaneous prescription of amitriptyline may significantly reduce sensitivity to tyramine, and such combined antidepressant treatment may prove both safe and effective in patients otherwise resistant to treatment.

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¹ World Health Organisation. Mental disorders. In: *International classification of diseases. 9th revision, 1975*. Geneva: WHO, 1978.

² American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 3rd edn. Washington DC: American Psychiatric Association, 1980.

³ Andreasen NC. Concepts, diagnosis and classification. In: Paykel ES, ed. *Handbook of affective disorders*. Edinburgh: Churchill Livingstone, 1982: 24-44.

⁴ Davidson JRT, Miller RD, Turnbull CD, Sullivan JL. Atypical depression. *Arch Gen Psychiatry* 1982;39:527-34.

⁵ Anonymous. The new psychiatry. *Br Med J* 1981;283:513-4.

⁶ West ED, Dally PJ. Effects of iproniazid in depressive syndromes. *Br Med J* 1959;ii:1491-4.

⁷ Nies A, Robinson DS. Monoamine oxidase inhibitors. In: Paykel ES, ed. *Handbook of affective disorders*. Edinburgh: Churchill Livingstone, 1982: 246-61.

⁸ Pare CMB, Kline N, Hallstrom C, Cooper TB. Will amitriptyline prevent the “cheese” reaction of monoamine-oxidase inhibitors? *Lancet* 1982; ii:183-6.

Haematuria and exercise-related haematuria

In clinical practice microscopic and macroscopic haematuria are regarded as evidence of underlying urinary tract disease until proved otherwise.¹ The standard advice is that no matter how trivial the bleeding a complete investigation is mandatory.² Investigation may include a formidable array of invasive procedures such as intravenous and perhaps retrograde pyelography, cystoscopy, renal biopsy, and renal arteriography.

Behind this aggressive policy lies the fear of missing a malignant lesion. Since, however, the routine use of dipstick methods has increased the frequency of detection of microscopic haematuria, we need fresh guidance in selecting patients for full investigation. One particular current problem is the number of athletes who develop transient haematuria after running long distances. Glomerulonephritis, present in some 1% of the community, is probably the most frequent cause of asymptomatic haematuria. By contrast, only about one in 10 000 people in middle age have tumours of the bladder and kidney.^{3 4} The prevalence of microscopic haematuria has been documented better in children than in adults. One of the best studies reported microscopic haematuria in 4% of children. Renal biopsies were done in 23 of the 27 children in whom microscopic haematuria persisted, and 13 were found to have clinically significant lesions.⁵ Larcom and Carter⁶ found more than two erythrocytes per high-power field in 1.2% of 3000 young men, and a study from Singapore reported more than five erythrocytes per high-power field in 1.5% of 67 695 Army recruits.⁷ This study emphasised the frequency of glomerulonephritis, which was detected in 93% of the 121 recruits who consented to renal biopsy. Eight of these developed renal failure in only three years—glomerulonephritis may prove as “malignant” as cancer.⁸

In 1979 Birch and Fairley⁹ described a method for examining erythrocytes in the urine and differentiating those coming from the glomerulus from those produced by non-glomerular disease. More recently, they have illustrated the changes in more detail¹⁰ and carried out a blind evaluation of urine findings in 112 patients with haematuria.¹¹ This analysis shows a high degree of sensitivity (99%) and specificity (93%) for diagnosing glomerular bleeding. In non-glomerular bleeding the sensitivity of the test was 100% and the specificity 90%; in other words, no tumours would have been missed.

These studies show that simple observations of the morphological features of erythrocytes in urine permit the expert to diagnose the site of urinary bleeding with a high degree of accuracy. One of the beauties of the method is its simplicity. It requires only a urine specimen, a phase-contrast microscope, and a counting chamber, and must be preferred to invasive procedures claimed to distinguish upper-tract from lower-tract bleeding.¹² Erythrocytes that arise from glomeruli show great variation in size, shape, and haemoglobin content, whereas those coming from lesions such as infection, calculi, tumours, and other non-glomerular sources are uniform in size and shape and usually retain a high haemoglobin content (except when the urine is strongly acid).

It is surprising that the importance of these changes has been overlooked for so long. Addis noted fragmented and partially lysed cells but did not conclude that such cells indicated a glomerular lesion.^{13 14} Larcom and Carter⁶ stained fragmented cells to define them better but also failed to recognise their significance. The crucial innovation may have been the recognition that phase-contrast microscopy is