of insertion, which may decrease as clinicians gain experience, but the incidence of difficulty is unknown. A reasonable starting point is the review by Brantigen and Grow, who performed 655 surgical cricothyroidotomies as an alternative to tracheostomy but with a larger indwelling intratracheal tube than that in the current kit.[19] They reported an overall complication rate of about 6%, which is lower than for tracheostomy.

The technique recommended is blind and requires some guesswork to insert the cannula. This has led some authors to suggest that the tissues should be dissected on to the cricothyroid membrane and the cannula inserted under direct vision, but that approach would need to be done in an operating theatre or intensive treatment unit. Another approach has been to suggest that the safety of the procedure would be enhanced if a Seldinger technique was used for insertion[20,21]; use of a guarded needle to puncture the cricothyroid membrane and dilators passed over a guide wire to make a channel would much reduce the chance of damage to blood vessels and of incorrect placement. Aspiration of air with a syringe filled with saline on entering the trachea is a sensible test for correct placement.

Current clinical knowledge suggests that minitracheotomy has a part to play in treating patients with retention of sputum, particularly when repeated suction and active intervention are needed to arrest the downhill course to tracheostomy. The technique may be used prophylactically after extubation and as a temporary access port after removal of a tracheostomy tube in anticipation of suction difficulties. Safe placement requires some experience and skill, and supervision is essential, therefore, for clinicians learning the technique. The procedure should not be used in patients with a bleeding diathesis nor in those who are unable to protect their airway, and it should be used with considerable caution in those needing high frequency jet ventilation.

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Single domain antibodies

A simpler and possibly better alternative to monoclonal antibodies in diagnosis and treatment

Antibodies are back in the news again with a report that genetically engineered fragments of an antibody molecule have many of the properties of specificity and binding of more complete immunoglobulin chains.[1] Dogma had it that antigen recognition and binding depend on the presence of segments or domains of both light and heavy chains; or at least their terminal domains. These were the segments with the variability in amino acid sequences that gave each antibody its unique specificity for one particular antigen. Now a group of workers in the Medical Research Council Molecular Biology Laboratory at Cambridge have shown that single domains are sufficient to ensure specific binding—albeit at rather lower affinities than those observed when both light and heavy chain domains are present.

The commentary in *Nature* on the implications of this exciting discovery made the point that this time the Medical Research Council has tied up the patient,[2] avoiding the expensive mistake made by the National Research and Development Council in the late 1970s when Kohler and Milstein first discovered the technique for making monoclonal antibodies in the test tube. This replaced the tedious and unreliable animal immunisation methods previously used,[3] but the council decided then that there were "no immediate practical implications of commercial value."

In fact, the discovery by Kohler and Milstein was undoubtedly one of the most useful advances in immunology in the past 10 years, and commercial firms have not been slow to exploit it. The method produces monoclonal antibodies in tissue culture (that is, antibodies that are effectively the product of a line or clone of identical cells) by using hybrids that are the fusion product of immortal mouse myeloma cells and splenic B lymphocytes. The lymphocytes contain all the necessary genetic information needed to programme the myeloma cells to produce unending quantities of specific antibody in continuous culture in vivo or in vitro with inbred strains of mice as the source of cells.[1] Within months every scientist who wanted to use antibodies was beavering away making hybridomas and selecting antibodies for the task in hand. Endless possibilities were envisaged for the application of such reagents in diagnosis—both in the laboratory and as tools for imaging tumours and other deep seated lesions—and for treatment either alone—for example, to remove excess digoxin—or coupled to bacterial or plant toxins to target their toxic effects on specific cells in tumours or in the marrow.[4,5]

Many diagnostic test kits were soon designed that used monoclonal antibodies, but the therapeutic and in vivo diagnostic uses were not so successful. The snags became obvious only with time: the need for expensive large volume tissue cultures to produce the quantities required, the chance that the chosen hybrid might shed the necessary chromosomes for immunoglobulin production, the problems of using mouse immunoglobulin in humans (where it is treated as a

foreign protein), and the seeming impossibility of finding a human fusion hybridoma to replace the murine model.

The new single domain antibody molecules are produced by an ingenious combination of producing hybridomas, cloning the DNA sequences from the hybridomas, amplifying this DNA by using the polymerase chain reaction, and placing the DNA fragments by transfection by using plasmids into the usual work horse of the genetic engineers—*Escherichia coli*. The bacteria then express and secrete the single heavy chain domains.[6] Not only does this method permit the prior selection of the desired specificity it also avoids all of the recognised problems associated with the inability of prokaryotic cells to secrete large fragments of immunoglobulin containing both heavy and light chains in the folded, tertiary form—previously believed to be essential for antigen recognition and binding.

The discovery that single domain antibodies have adequate specificity has altered our thinking about the methods to be used for production of therapeutic antibodies, and these "dAbs" (as opposed to "mAbs") may well avoid the hypersensitivity problems of murine antibodies. It may prove easier to couple other molecules such as toxins and chemotherapeutic agents to dAbs without distorting their antigen-combining sites. The lower affinity shown by the first dAbs may mean that there will be limitations to their use. But, provided that they are present in sufficient amounts, they may well be just as effective as whole antibodies in blocking antigenic sites that feature in the virulence properties of micro-organisms, such as adhesion molecules and toxins. Clearly the Medical Research Council must be grateful that this is one fish that didn't get away; it may well prove to be a valuable catch if its potential can be realised.

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The toxic shock syndrome

Many cases are not associated with menstruation

The development of acute illness with fever, hypotension, blotchy erythema, myalgia, diarrhoea, and vomiting at the time of menstruation in a young woman using tampons would lead to the expectation of a toxin-producing *Staphylococcus aureus* being isolated from a vaginal swab. The same staphylococcus can grow—and allow absorption and dissemination of toxin—from any site of infection in either sex at any age, however, and diagnostic acumen of a higher order is required to consider the toxic shock syndrome in an acutely ill man with conjunctivitis, an elderly woman with influenza, or a child with a burn. In the United States, where cases meeting strictly defined criteria have been reported since 1980, almost half those reported from 1986 to 1988 were not associated with menstruation.[1] Reported sites of infection include surgical wounds (even when minor), burns, abscesses, and sinuses and areas affected by postinfluenzal bronchopneumonia, tracheitis, and empyema.

The pattern of clinical illness is the same wherever the toxin is produced.[2] The definition criteria of the toxic shock syndrome require: a fever of at least 38·9°C; a macular erythema (like sunburn) that may be generalised, patchy, or localised; and hypotension with a systolic blood pressure of 90 mm Hg or less (or below the fifth centile by age for children) or a postural drop of diastolic pressure of at least 15 mm Hg, postural syncope, or dizziness. Toxic action on at least three systems needs to be shown by either diarrhoea or vomiting; myalgia or raised creatine kinase activity; reddened conjunctivas, oropharynx, or vagina; raised creatinine or urea concentrations to at least twice normal; thrombocytopenia below 100×10^9/l; or confusion or drowsiness without focal neurological signs when the fever and hypotension have been corrected.

Of all these features I have found that the one sign that most specifically triggers my personal diagnostic process in assessing the patients presenting with acute illness is the hypotension. I can usually think of several options for the other signs and symptoms present, but when I consider "Why such hypotension as well?" the reply is, "Could it be toxic shock?"

S aureus is usually readily isolated from the site of infection (and sometimes from the blood), and toxin production can then be confirmed. In most cases the cause is the toxic shock syndrome toxin-1 (TSST-1), though other staphylococcal toxins may also cause the same pattern of illness. A rise in antitoxin antibodies provides further diagnostic support, but the test is not widely available in Britain. The diagnostic criteria finally require there to be no serological evidence of leptospirosis, measles, or Rocky Mountain spotted fever and negative results (except for *S aureus*) from cultures of blood, cerebrospinal fluid, and throat swabs, if performed. Severe streptococcal infection may present similarly.[3]

Treatment requires preventing any further production or absorption of toxin, and this may mean the removal of tampons or packing, wound debridement, and drainage of abscesses. Parenteral antibiotics should be given and the effects of the toxin countered by fluid replacement with crystalloid solutions rather than colloid solutions. Measures such as inotropic support with dopamine or dobutamine may be indicated by appropriate intensive monitoring. Steroids may be helpful.[4] Whether treatment with antitoxin is useful has not yet been determined.

The mortality is about 3%, but this should improve further as more patients benefit from prompt diagnosis.

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