Transsexualism observed

"Vive la différence" might well be the mating call of the lusty, masculine male, a male, that is, who is not only biologically masculine but whose gender identity is the same. A very few biological males exist, however, whose gender identity is decidedly feminine and who regard "la différence" as an abomination. They see themselves unequivocally as women, a belief which reaches near-delusional proportions—and one which may be reinforced by narrowing the gap between fantasy and reality by the surgical removal of the offending male sexual organs and the substitution of simulated female ones. Such grossly aberrant men are true transsexuals (the condition occurs less often in women) and are to be differentiated from transvestites, who obtain a degree of sexual excitement from cross-dressing, or homosexuals, who know themselves to be men but obtain sexual gratification mainly or exclusively from other men. The three conditions can, however, overlap to some extent.

With modern hormonal procedures coupled with advances in the technique of plastic surgery the operation demanded by male transsexuals is now available—sex reassignment surgery. From time to time the names of alleged successes hit the headlines as, for example, those of Christine Jorgensen, Roberta Cowell, Jan Morris, and, a relatively recent addition to the list, that of the six-foot-tall top model Tula.

Of particular importance is the case of April Ashley, née George Jamieson, not so much because George Jamieson was transformed into what Judge Ormrod had occasion subsequently to term "a convincing feminine pastiche" but because of the autobiographical account¹ of her case just published. Marred as it is by a good deal of literary candyfloss and unnecessary revelations of the goings on among the somewhat rancid social crème de la crème with whom she mixed, the book is, nevertheless, an excellent account of male transsexualism and one which should commend itself to anyone interested in this intriguing but sad human condition.

April Ashley fulfils almost all the criteria needed to establish a diagnosis of the syndrome. The environmental setting was right. She despised her father, who was a cook in the Royal Navy and not often at home and whom she describes in no uncertain terms as a scoundrel and a boozier. She was, therefore, driven into a dependence on and preference for her mother. Her psychosexual development was right; at the age of 15 she said of herself: "I was taunted for being like a girl and, yes, I wanted to be one." This preoccupation with her gender identity grew: "I was convinced a monstrous mistake had been made and only my being a woman would correct it." After one of several suicide attempts she was admitted to a mental hospital, where heroic attempts were made to alter her determination. She was subjected to ether and thiopentone abreactions and to electric convulsion therapy and given male hormones. It all ended in dismal failure. She told her doctor, "No matter what you do you'll never be able to change my mind."

Finally, there was her obsessive determination to have the sex operation. She was asked by Dr Burou, a surgeon in Casablanca who specialises in "the operation," "Are you absolutely sure you want this operation?" "Yes," she replied, and added "because I'll kill myself if I don't."

Was April Ashley's (and other transsexuals') serious, mutilating operation, rendered more hazardous by the danger of serious after-effects, really necessary? The question has been asked by Lothstein² in a critical review of sex reassignment

surgery. His major conclusion is that: "To date the evidence suggests that many patients who would have otherwise undergone sex reassignment surgery may adjust to a non-surgical solution through psychotherapy . . . and that surgery should be considered only for a highly select group of diagnosed gender dysphoric patients." There can be no doubt that April Ashley would be included in this group. But the tragedy, says Lothstein, is that the demand for the operation has grown inordinately and that certain hospitals or clinics in the United States make surgery available on a fee-for-service basis. It is from this group of heterogeneous and frequently misdiagnosed patients that the real disasters stem.

Virtually the same conclusions were reached in an equally important and complementary paper³ by J R B Ball, whose interest in sexual dysphoria began in Britain and continued after his move to Australia. Though at one time he had grave doubts about the use of surgery in any circumstances, he has, in the light of 30 years' experience, changed his mind. He writes: "In the main the conservative attitude, thorough screening, ruthless exclusion of doubtful cases, and prolonged presurgery observation, led to successful results with excellent individual, social, and sexual adjustment."

What is implicit in both these papers is that sexually dysphoric patients have a high incidence of other forms of psychiatric disorders, including anxiety, recurrent depression, suicidal attempts, drug abuse, and alcoholism. Clearly these disorders need treatment, including psychotherapy. What shines out like a beacon in all the relevant literature, however, is that transsexualism is a no-man's land whose denizens, with or without sex reassignment surgery, with or without psychotherapy, can, unhappily, never experience biological or emotional fulfilment.

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Immune guided missiles

The hope of using the immune system in the battle against cancer is an old one. The tried and trusty weapons in the oncological armoury—surgery, chemotherapy, and radiotherapy—have proved inadequate against a widely dispersed enemy apt to lurk in impregnable strongholds. What is needed is a guided missile programmed to seek and destroy the target wherever it may be.

Early attempts to recruit immunology as the guidance system have been scathingly dismissed¹; there was confusion between tumour antigens and transplantation antigens. Even as late as 1977 a review of over 200 attempts at the passive serotherapy of cancer² concluded that results in animals were disappointing; it could find "no convincing evidence that immune serum from any source had had a beneficial effect on the course of malignant disease in man." The reasons for these failures include the difficulty of preparing sufficient quantities of antisera that react with the tumours but not with normal tissue; the fear of administering large amounts of foreign

protein to patients; the lack of a molecularly defined antigen at which to aim the missile; and insufficient knowledge of events at the cell surface, particularly the ways in which cancer cells might defend themselves from attack.

Recent reports³⁻⁸ on the use of passive antibody against lymphoid malignancies have given us a greater understanding of how an immune attack might be pressed home. They have shown that some of the objections to this treatment are not well founded. No immune response to the foreign protein occurs—possibly because these patients with lymphoid malignancies are immunocompromised, or because given intravenously in an aggregate-free form the antiserum induces immunological tolerance.⁹ Furthermore, biopsy specimens of bone marrow⁵ and lymph node⁸ after injection of the antibody have shown that it can reach its target in the tissue. Nevertheless, the damage inflicted by the antibody attack has usually been minor⁴; and immediately after an attack the tumour enjoys a period of immunity from further damage and is soon back in full production.

One barrier to a more successful outcome is the presence of free antigen in the serum. Such blocking factors were first recognised by the Hellströms in laboratory studies,¹⁰ and even tumours that apparently do not actively secrete antigen release enough of it to be a problem.¹¹ Immune lysis of tumour cells may release large quantities of the target antigen,³ making further attacks with antibody futile. This extracellular barrier may be circumvented by plasmapheresis⁴ or by so grading and spacing the attacks as to avoid releasing more antigen than can be easily overcome.⁷

Choice of an antigen that is truly tumour specific is extremely difficult. The "c ALL" antigen chosen by Schlossman's group⁵ is present on the leukaemic cells of most patients with acute lymphoblastic leukaemia, but is also found on a few normal marrow cells¹² and in the kidney,¹³ whereas the target chosen by Levy^{6,7} was a differentiation antigen of a normal T cell. For B-cell lymphomas, however, the determinants of the surface immunoglobulin are effectively tumour specific¹⁴ in that the loss of the odd normal lymphocyte that might bear the antigen would do the patient no harm. Unfortunately, the very idiosyncrasy of this target makes it necessary to raise a fresh antibody for each patient—no easy task for an antigen in such short supply. Nevertheless, two groups have adopted this approach using different methods. The more elegant technique of cell hybridisation to rescue the immunoglobulin from the patient's non-secreting lymphoma cells and the production of monoclonal antibody against this protein, as used by Levy,¹⁵ seems less certain to be successful than Stevenson's more conventional technique¹⁶ of raising polyclonal antibody against idiotypic antigen digested from the lymphoma cell surface.

Whatever antigen is chosen there is a theoretical risk that it will not be possessed by all tumour cells and, in particular, by a proliferating pool of primitive cells. Hence a population of cells lacking the antigen might grow through the immune attack. Recent experiments by Krolick *et al*¹⁷ have suggested that, at least for the murine prolymphocytic leukaemia BCL₁, no such population exists; with luck, the same may be true for similar human tumours. In any case, such immunoselection does not seem to be the cause of the tumour resistance encountered in practice. The explanation for the appearance of antigen-negative cells after treatment is the phenomenon of "antigenic modulation." This effect, first noted by Boyse and Old in a murine thymic leukaemia,¹⁸ is brought about by the formation of a complex between surface antigen and serum antibody; this leads to a rearrangement of the antigen-antibody complex on the surface of the cell and eventually it is absorbed

into the inside of the cell. When the antibody disappears from the surrounding environment the cell re-expresses the antigen. Such antigenic modulation has been observed for c ALL antigen, thymic antigens,^{6,7} and surface immunoglobulin.¹⁹

How antibody on the surface of the cell might bring about the death of that cell has also been studied. The polyclonal anti-idiotypic used by Hamblin *et al*⁴ to treat a case of prolymphocytic leukaemia fixed complement and was able to cause lysis of the tumour cells in the laboratory. Complement consumption was evident clinically, as shown by fever, rigors, and bronchospasm in the patient. Nevertheless, monoclonal antibodies seldom behave in this way and mechanisms other than the need for complement have been postulated for their clinical effects—such as K cell killing or destruction of cells coated with antibody⁷ or C3⁵ in the reticuloendothelial system.

Any mechanism that depends on the fixing of antibody to the cell surface may be defeated by antigenic modulation. One way of overcoming this is to arm the missile so that lethal effects occur before there is time for the antigen to be rearranged. A nuclear warhead such as radioactive iodine would seem ideal. Nevertheless, iodine binds to the amino-acid tyrosine, which is well represented in the antibody-combining site and therefore interferes with the antigen binding.²⁰ A chemical warhead might be tried. Chlorambucil non-covalently linked to antibody enjoyed a vogue in the 1970s.²¹ Unfortunately, the link comes apart when the complex is given to patients.²² Biological warheads such as diphtheria toxin²³ and ricin¹⁷ have their advocates, though they have yet to be tried in man.

A more elegant solution to the problem is the use of univalent antibody. Antibody molecules are normally divalent; they are shaped like two-pronged dinner forks. The rearrangement of antigen at the cell surface is caused by each prong reacting with adjacent antigenic molecules and in the process drawing them together. Glennie and Stevenson²⁴ have produced univalent antibody by cutting off one of the prongs with the enzyme papain, and they have shown that this molecule does not induce antigenic modulation. In the laboratory it is better able to kill cells from the guinea-pig prelymphocytic leukaemia L₂C than whole immunoglobulin and is far more effective at prolonging the lives of guinea-pigs affected by the disease.

This method of construction of univalent antibodies is appropriate only for rabbit immunoglobulin, but other chemical manoeuvres are applicable to antibodies from other species and hold out hope for the more effective use of mouse monoclonals.

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Neuroleptics and abnormal movements

As soon as drugs such as chlorpromazine and haloperidol came into clinical use they were found to have considerable effects on involuntary movements. The neurological syndromes associated with antipsychotics or neuroleptic drugs are acute dystonias, akathisia, Parkinsonism, and akinetic mutism—all reversible if treatment is stopped—and tardive dyskinesia, which in some cases may persist.

On the other hand, neuroleptic drugs have also proved useful in the management of spontaneously occurring movement disorders. For example, Huntington's disease is characterised by chorea, mental deterioration, and behavioural changes. The patient is clumsy, restless, and fidgety, and in the later stages the dementia becomes more profound and the chorea more grotesque, all parts of the body writhing, twisting, and turning in incessant uncontrollable movements. In the past, reserpine, which depletes nerve endings of dopamine, was used in treatment, but now neuroleptics are generally used.¹ Fahn² reported that the chorea was helped by perphenazine, and Whittier and Korenyi³ found that 43 of 65 patients with Huntington's chorea improved with fluphenazine.

Neuroleptics have been more systematically evaluated in Gilles de la Tourette's syndrome. This rare, strange condition develops in childhood or early adolescence and has a prolonged course, with motor tics affecting the head and body together with verbal ejaculations—grunts, sounds, words, or phrases that may be obscene. Treatment with neuroleptics is the only

drug regimen that consistently ameliorates the symptoms.⁴ In a controlled study, 6 mg diazepam a day was no better than placebo in treating four patients, but haloperidol was appreciably superior.⁵ Bruun and her co-workers⁶ treated 59 patients, finding that an average dose of 13 mg haloperidol a day improved symptoms by 80%. The dose required is extremely variable and treatment should include continuous monitoring. As the duration of treatment increases the effectiveness of haloperidol seems to improve, so that some diminution in dosage may be possible in time. Dosage may need to be increased during exacerbations. Akinesia, sometimes misinterpreted as clinical depression, is the commonest unwanted effect and is especially apparent in patients having doses above 5 mg haloperidol a day. Phenothiazines seem consistently less effective than haloperidol, though no controlled comparisons have been published. Some patients have responded only marginally to high doses of phenothiazines but remitted almost completely with low doses of haloperidol.

Stuttering is another motor disorder for which haloperidol has been found useful. In one study the drug diminished the amount of time the eight patients were dysfluent but not the number of dysfluencies a minute.⁷ The hesitation and phonemic stoppage of the severe stutterer may be helped, and the facial contortions accompanying stuttering may almost completely disappear. Low dosages (about 3 mg haloperidol a day in divided doses) are recommended, but even so some young patients find the extrapyramidal side effects intolerable.

Intractable hiccups have long been known to respond to neuroleptics. The early observations related to chlorpromazine, and there are no controlled data concerning haloperidol, which, to extrapolate from the responsiveness of patients with Tourette's syndrome, might be more effective. Another repetitive paroxysm is uncontrollable sneezing. Davison⁸ has described a 60-year-old woman referred for psychiatric advice for severe, intractable sneezing. On the reasonable hypothesis that repetitive sneezing might be related to other forms of repetitive involuntary movements oral haloperidol was prescribed, with complete remission.

Does the response of repetitive abnormal motor conditions to haloperidol and other neuroleptics tell us anything about the pathogenesis of these curious conditions? Neuroleptics block dopamine receptors, varying among themselves with respect to their potency on receptors in various parts of the brain. Cholinergic pathways and gamma-aminobutyric acid seem abnormal in patients with Huntington's chorea,⁹ and perhaps 5-hydroxytryptamine in Tourette's syndrome^{10 11}—but it would be premature to conclude that dopaminergic neurones are implicated in the pathogenesis of all the movement disorders described above. The long-term effects of haloperidol differ from its acute effects—for example, the turnover of acetylcholine in the rat striatum reverts to normal with repeated administration of haloperidol.¹² The only common factor in all these conditions may be that the abnormal movements are mediated via a final common pathway under dopaminergic control.

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