motivation.⁵ Alternatively, media publicity or telephone or group contact may provide enough added support.⁶⁻⁸ Likewise, the addition of minimal contact with a therapist seems to enhance the effectiveness of weight loss manuals, but competitive incentives are of particular benefit.⁹

Most intervention studies are short term, focusing on reducing symptoms. Other self direction manuals have broader aims. A "heart manual," for example, covered education, an exercise programme, stress management techniques, and the self treatment of common postoperative psychological problems. At one year follow up the people using the manual were significantly less psychologically disturbed, three times less likely to die, and significantly less likely to have another infarction over the next five years than those given only stress management training.¹⁰

Similar techniques have been used to treat emotional disorders such as depression,^{11 12} anxiety,^{13 14} phobias,¹⁵⁻¹⁷ panics,¹⁸ and eating disorders.¹⁹ Patients report being as satisfied with this form of treatment as they are with conventional treatment with a therapist.²⁰ The effects of self directed treatment seem to be long lasting, with improvements maintained for several years.^{12-18 21} Teaching the partners of psychiatric patients can also have benefits, increasing their understanding of the illness and strengthening core relationships.²²

What are the critical elements in successful self directed treatment? Simply giving general advice and information alone is insufficient, although it may lead the reader to seek help. There is plenty of evidence that self directed treatment manuals that teach users key techniques for overcoming problems give more successful results than simple education leaflets.^{10 23 24} But the order of delivery of components may be important. For example, problem drinkers given strategies for self regulation first and then education had a significantly greater reduction of alcohol intake than a group who received these components in the reverse order.²⁵ No differences have yet been found between competing therapeutic rationales such as behavioural and cognitive treatment.¹⁰

Self directed treatments thus seem to be effective in a variety of conditions. Most of the research so far has tested written materials. Computers have the potential to add "therapeutic interactions" which printed materials cannot,²⁶ and television interventions may also have potential. Self directed interventions are attractive because they allow the possibility of many more patients being treated closer to home and because they allow patients to play an important part in their own treatment. These interventions are unlikely to do specialists out of a job; instead, integration of these approaches

into practice will free clinicians' time and skill to focus on the problems of the more severely ill patients.

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Apheresis in the 1990s

Technological innovations are opening up new therapeutic vistas

Apheresis is the removal of selected components from the blood by using cell separators. Medical technology has not yet, however, reached the future as envisaged by Professor Edwin J Cohn of Harvard Medical School in the late 1940s. This great pioneer protein fractionator believed that ultimately it should be possible to separate out all the formed elements of the blood immediately after its withdrawal from the donor. Forty years on this vision of the future has not yet been realised, but enormous progress has been made on both the cellular and humoral fronts.

Plasmapheresis was first used in 1914 in experiments on

dogs.¹ In 1944 Co Tui and his coworkers showed that frequent plasmapheresis of donors could meet the demand for plasma to cope with wartime emergencies.² Plasmapheresis was first used therapeutically in 1952, when it was tried as a means of controlling hyperviscosity in multiple myeloma.³ Once Judith Pool had described cryoprecipitated factor VIII concentrate commercial companies were quick to seize the plasmapheresis initiative by introducing paid plasma donation as a means of obtaining large quantities of fresh frozen plasma for fractionation.⁴ In the same year, 1965, a collaborative effort between the IBM Corporation and the National Cancer

Institute gave birth to the first continuous flow cell separator.⁵

Initially, cell separators were used to collect granulocytes and platelets from single donors for supportive treatment for immunosuppressed patients with cancer. In the mid-1970s plasma exchange began to be used as a therapeutic modality, and there were soon reports of its dramatic effectiveness in Goodpasture's disease and in myasthenia gravis.^{6,7} For the next few years plasma exchange was tried in over 90 different diseases—almost any disorder with an immune component. Research studies using controlled clinical trials have now defined some of the disease categories in which therapeutic plasma exchange is of proved benefit.⁸

The next development came in the early 1980s, when Britain decided to attempt to achieve national self sufficiency in blood and blood products by using voluntary unpaid donors. The demand for plasma outstripped the demand for red cells, and the shortfall was met by the introduction of automated apheresis machine donation programmes. Transfusion services are now—at least potentially—flexible enough to respond to whatever demands are placed on them for plasma, platelets, or red cells, through use of the multicomponent donor apheresis collection machines currently undergoing clinical trials. Specific protein donation is still being developed.

Advances are also being made in therapeutic apheresis. Secondary cascade filtration and various adsorption columns (some using monoclonal technology) are being investigated in the hope of removing the causative agent of the disease rather than the relatively crude “remove all” approach of plasma exchange. Equally interesting developments are occurring in leukapheresis. The range of cells that can now be collected include killer cells, macrophage-monocyte cells, and myeloid stem cells. These developments began with the advent of interleukin 2 and the generation and retransfusion of lymphocyte activated killer cells in the treatment of patients with cancer.⁹ Next came extracorporeal photoactivation for the immune modulation of mononuclear cells in the successful

management of cutaneous T cell lymphoma. This technique may possibly also be useful in certain other aberrant T cell disorders, including graft v host disease.⁹ The development of effective monoclonal haemopoietic cytokines has made it possible to collect peripheral stem cells for bone marrow grafting—and this may eventually prove a better method of achieving marrow engraftment. The use of separation procedures such as electrophoresis and cell adhesion may further improve the efficiency, speed, and specificity of cell separation and collection.

The most exciting development to date is the management of immune deficiency syndromes with gene modified peripheral blood mononuclear cells.¹⁰ The interdisciplinary cooperation that these innovative developments require may need to come from transfusion medicine, where expertise in cell separation and purification technology, cell component support, development and use of recombinant human growth factors, and transplant immunology are all needed to provide the necessary catalytic environment for dramatic developments in haemapheresis for the 1990s.

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Leukaemia: a genetic disorder of haemopoietic cells

Understanding the mechanism can help management and may one day improve treatment

The change of a cell from normal to malignant is generally accepted to be a multistep process. Interestingly, the first evidence for this came not from high tech laboratory research but from an imaginative use of epidemiology when it was noted that the overall frequency of tumours as a function of age fits a straight line on a log-log plot,¹ suggesting to the mathematically minded that the probability of developing a tumour behaves like the result of a cumulative succession of random events.

The best candidate for a random event that can change permanently the behaviour of a cell and its progeny is a somatic mutation; the progeny of the cell in which the mutation has taken place is a mutated clone. Again we do not need sophisticated tools to visualise these processes. A pigmented naevus is a visible clone of an epidermal cell that makes more melanin than the cells around it; freckles accumulate on our skin as we get older and give us a tangible impression of the rate of somatic mutation. If we extrapolate from these considerations to the pathogenesis of leukaemia then the notion that this consists of one or more somatic mutations arising in a haemopoietic cell seems the only

sensible model. But what evidence do we have that it is true?

If we look back at textbooks of some 50 years ago we find different “theories” of leukaemogenesis²: the viral theory, corroborated by animal experiments; the physical agents theory, documented by the victims of leukaemia in Hiroshima; and the chemical agents theory, supported by the development of leukaemia after exposure to benzene or cytotoxic agents. Today we know that retroviruses can integrate into the host cell genome and that radiation and alkylating agents are mutagens. Thus the various theories are not in conflict: on the contrary, the somatic mutations model reconciles them all.

Molecular analysis of leukaemic cells has allowed us to identify some of these somatic mutations. The first example came from the study of Burkitt's lymphoma and from the related form of acute lymphoblastic leukaemia called L3. Here the gene c-myc, encoding a nuclear DNA binding protein, is brought by a t(8;14) chromosomal translocation to be juxtaposed to an immunoglobulin gene. Subsequently, another well known translocation, the t(9;22), giving rise to the Philadelphia chromosome of chronic myeloid leukaemia, proved to be the first example of what we now call a chimeric