AUSTRALASIAN SOCIETY OF BLOOD TRANSFUSION INC

Annual Scientific Meeting

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MALARIA SYMPOSIUM

Dr. Beverley-Ann Biggs, The University of Melbourne

Malaria remains a major health threat to mankind, with more than half the world's population still living in endemic areas and 1-2 million deaths in children each year. Our genetic makeup has changed in many different ways during the evolutionary period that we have been exposed to malaria. These adaptions are not restricted to haemoglobin and other proteins in the RBC but also involve the immune system and probably many other gene groups. In this presentation I will discuss the range and variety of host mechanisms that modify susceptibility to malaria, and will touch briefly on some aspects of malaria genetics that play an important role in this interaction.

VIRUSES AND LYMPHOPROLIFERATION

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Viruses may cause acute lymphadenopathy or chronic lymphoproliferation leading to lymphoma. Acute generalised lymphadenopathy, presenting pathologically as reactive lymphadenitis, is a feature of EBV and CMV mononucleosis syndromes, the acute seroconversion illness caused by HIV, occasionally Hepatitis B and rubella and rarely acute toxoplasmosis.

The chronic lymphoproliferative diseases have only two main viral causes, Epstein Barr virus and Human Herpesvirus, Type 8. EBV causes Burkitt's Lymphoma (in Africa and Papua New Guinea) and nasopharyngeal carcinoma and is strongly associated with 50% of Hodgkin's Disease. EBV associated lymphoproliferative diseases and lymphoma are quite commonly associated with immunosuppression following transplantation and AIDS. Post transplant lymphoproliferative disease occurs in 1-20% of patients within months to 20 years after transplantation and presents as a diffuse or local proliferation or true lymphoma. Diffuse lymphoproliferative disease especially follows primary EBV infection and is commonest in young cardiac transplant patients. The development of true lymphoma is associated with monoclonality and mutations in oncogenes and anti oncogenes. The treatment consists of reduction in immunosuppression or, most recently, the ex vivo expansion of EBV specific cytotoxic T lymphocytes and reinfusion,, either as prophylaxis or therapy. This therapy is still confined to highly specialised laboratories. EBV associated primary cerebral lymphoma is quite a common malignancy in advanced HIV infection. Human Herpesvirus type 8 causes the rare multicentric Castleman's Disease and also Primary Effusion Lymphoma in addition to Kaposi's Sarcoma in patients with AIDS and other forms of immunosuppression.

PLENARY SESSION: HEALTH CARE—EXPECTATIONS AND REALITIES

Presentation by Peter Dwyer

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The law imposes on the medical and other health care professions, a duty to exercise *reasonable* care and skill in the provision of professional advice and treatment. The duty is a single and comprehensive one covering all the ways in which the practitioner is called upon to exercise his or her skill and judgment. In any given case it is necessary to give *content* to this duty.

In Australia the *standard* of care is not determined solely, or even primarily, by reference to a practice followed (at the relevant time) by a particular profession. The ultimate question is whether a practitioner's conduct (acts or omissions) conforms to the standard of *reasonable* care demanded by the law.

In Australia, litigation against medical practitioners is reported to be increasing. Reasons include consumers' increased awareness of their rights and greater preparedness to exercise them. Advances in medical / related technology and knowledge (often announced in the general media) may add to the standard of care expected of practitioners but can result in patients' having unrealistic expectations.

Application of *evidence based medicine* principles and techniques including *clinical practice guidelines* may assist the attainment of optimal standards of care, improve patient outcomes and perhaps reduce litigation.

Effective communication between health care professionals and their patients is critical in addressing these issues of concern. Adequate systems where appropriate, need to be developed and implemented, to ensure best patient care. These require regular review using best available and current, evidence.

The health and welfare of patients remain the paramount objectives of the health care professions. The message seems clear.

THALASSAEMIA AND GREEK SOCIETY

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The purpose of this discussion is to provide an understanding of how thalassaemia as a genetic disease with a long history in the community has affected Greek society. In Greece, thalassaemia is commonly referred to as "Mediterranean Anemia", and unfortunately this compounds the myth that it only affects persons of Mediterranean ancestry. In Australia, thalassaemia is seen as an "ethnic" disease. These misunderstandings add to the sense of stigma associated with a genetic disease. The interwoven nature of faith and culture in Greek society also place a heavy burden on those diagnosed with thalassaemia. Does individual or community behaviour change with knowledge of genetic predisposition? What is the role of faith and culture in genetic counselling? What rights does a society give to the unborn?

CORD BLOOD BANKING AND THE ROLE OF REGULATION

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The development of cord blood banks in a number of countries has raised a number of issues as to the place of Quality Systems, Good Manufacturing Practice and regulation in this area. In Australia, other tissue banks are already licensed by the Therapeutic Goods Administration (TGA) according to a code of GMP, on the basis that these products are collected and stored in a controlled manner and that GMP can therefore assure that the product meets the highest quality and safety standards. Moves are also underway to regulate aspects of the handling, storage and manipulation of haemopoietic stem cells harvested from bone marrow, peripheral blood or cord blood. Most peripheral blood or marrow stem cell collections are directed to a particular recipient (autologous or allogeneic), and the collections are therefore irreplaceable. There is a thus a limit to the degree to which some aspects of GMP can be applied (such as rejection of non-conforming product), though it is clearly important to ensure that all processes are of the highest quality. Cord blood, like many other tissues, is usually banked as an allogeneic product for general use and the applicability of the principles of GMP is therefore greater. However, the potential for extensive product manipulation (such as ex vivo expansion) after selection of a matched cord blood has more in common with other forms of stem cell collection in that the product is directed and irreplaceable. In this setting there is the potential for the requirements of GMP and the needs of the patient recipient to be in conflict.

Other issues currently being debated include the need for 6 month follow up for virology testing and the potential role of follow up medical questionnaires or examination of the donor to exclude transmissable inherited disorders. These and other issues arising out of the potential regulation of cord blood banking will be discussed.

Nucleic Acid Testing (NAT) Experience at the American Red Cross (ARC)

Susan L. Stramer, Ph.D.

HIV-1 and HCV NAT has been implemented under “investigational use” labeling at US blood centers to detect infectious “window period” donations. Linked NAT at the ARC began on March 3, 1999. ARC is using the Gen-Probe HIV-1/HCV Assay (Transcription Mediated Amplification, TMA) in a phase I study involving pool sizes of 128. Testing occurs in a single centralized laboratory using samples collected in EDTA to preserve viral RNA (Becton-Dickinson, Plasma Preparation Tubes, PPT). During the phase I study, HIV-1 and HCV seroreactives are removed prior to pooling to decrease the testing viral burden. The turnaround time involved in releasing NAT results is approximately 2 days following receipt of samples. This necessitates the release of cellular components based on serologic results; in this program, only plasma is managed on the basis of NAT results. In order to release all products based on NAT (phase II), smaller pools will have to be tested (16 donations per pool) in which the serologic reactives are included (so that all testing occurs simultaneously). Test results to date using the Gen-Probe test have yielded excellent specificity. During the Phase I study (to June 21, 1999) approximately 1,000,000 donations have been pooled and tested; there have been 14 reactive 128-member pools that have not resolved to single donation (reactive rate of 0.16%). These are referred to as “false positive” since the reactivity cannot be reproduced during the resolution algorithm. During this testing, there have been three true positives detected (HCV RNA). True positivity in this study is defined as reactivity that resolves to a single donation, that can be identified as either HIV-1 or HCV by discriminatory testing and that is reactive by a NAT method of a different type (PCR). The first HCV reactive donation contained approximately 60 million copies per mL of genotype 2B; testing is being completed for the other two HCV RNA positive, seronegative donations.

Sensitivity data indicate that NAT using pooled donations (of 128 to 500 donations per pool) will close the HCV window by 50 to 98% (or 40 days of a 57-day infectious or RNA-positive window period). However, to date there are no HCV RNA-containing seronegative samples that can be identified that would not be detected using a pool size of 16. Sensitivity data for HIV-1 indicate window-period closure of 30 to 50% using pooled NAT (or 3 to 4 days of a 6 to 10-day infectious window period). In contrast to HCV, a small number of HIV-1 RNA-positive samples may be identified that would not be detected using pooled NAT, even if small pools (containing 16 donations) were to be tested. However, the frequency of this event in the US using the HIV-1 p24 antigen testing experience as a model would predict that an HIV-1 RNA-positive donation using a pool size of 16 would be missed once every 2.68 years.