Blood Transfusion Services in the wake of the humanitarian and health crisis following multiple detonations of nuclear weapons

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Medact *is a global health charity tackling issues at the centre of international policy debates. Led by its health professional membership it undertakes education, research and advocacy on the health implications of conflict, development and environmental change.*

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Contents

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Introduction

The nuclear detonations in August 1945 at Hiroshima and Nagasaki (at 16 and 21 Kt equivalent respectively) killed at least 110,000 citizens immediately: an estimated further 130,000 died by the end of 1945. It is possible that some survivors of the immediate blast and radiation damage but who died in the following weeks may have been saved with the help of an effective supply of blood products for transfusion.

This paper explores the possibilities and challenges which would face the organisations involved in transfusing blood or blood products as part of the clinical management of survivors of a hostile detonation of multiple nuclear weapons, such as described by Helfand (2012)[1]. Since 1945 transfusion services have become much more sophisticated in their science and practice; it may be that current organisations could give a better response in the 21st century than their predecessors in the mid-20th century.

However, the reality is that in the face of the challenges of a nuclear conflict and consequent famine over wide areas, a complete breakdown of the provision of safe blood and blood products for transfusion must be expected. Indeed, there can be no adequate global medical response to even a regional nuclear war. So prevention is key and diplomatic efforts to secure a nuclear weapon free world as soon as possible are paramount and must start in a meaningful way without delay.

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Donor selection; donation collection, testing, processing and storage

A typical donation involves the collection of a fixed volume of blood (commonly a 'pint' or about 500ml, but in Japan 200 or 400ml) into a solution of pharmaceutical grade anticoagulant (citrate) and nutrient (glucose). Such 'whole blood' can be stored for 4, 5 or 6 weeks and is the 'raw material' for further processing, as described below.

The following features influence WHO recommended standards for blood transfusion services. 1) donor selection and testing; 2) processing donated blood into *products*; 3) patient (recipient) identification and testing; and 4) clinical indications for transfusion. Although developed in advanced societies, these are for global application and for deviations to lead to legal liability. But they are not wholly appropriate for developing societies[2] and applying them to humanitarian crises needs re-evaluation.

Accepted ethical principles of blood donor selection

- Altruistic voluntary unremunerated adult donors of either gender.
- Written and aural questionnaires concerning current health, weight*, and health and lifestyle histories, including travel and residence overseas and current medications: *this is to detect risk factors for transfusion-transmitted diseases, and also to protect donor health.*
- Encouraging repeat donation after a suitable time interval. Repeat donors who have already 'passed' an initial selection process are usually processed more efficiently on later donations; and experience adverse reactions such as fainting less commonly. *This optimises collection from "low-risk" individuals.*
- On-session tests for 'anaemia': *this avoids bleeding anaemic donors or causing 'donation-induced iron deficiency'.*
- Off-session tests for markers of infectious diseases which could be transmitted by transfusion: *to detect specific high-risk transfusion-transmissible infections.*

** Usually a standard volume of blood (commonly 500ml but varying across jurisdictions) is taken into a fixed volume of anticoagulant. Based on work over 50 years old, the maximum tolerable blood loss is taken as 13% of a donor's circulating blood volume (estimated as 7% of the body weight). Hence the minimum weight of a donor bled 500ml is 55Kg although 50Kg (110lb or 8 stone (UK) is often accepted. These recommendations still apply as re-investigating the '13% rule' would be difficult ethically. Even in developed societies many women weigh less than 50Kg so are more affected than men when the rule is applied to a 500ml donation.*

Desirable systems for collecting donations

- conducted under optimal conditions and with minimum donor discomfort
- by skilled and trained operators
- a secure system of donor identification and donation labelling*
- over an adequate time period at the session
- in repeat donors, after an adequate interval from the previous donation - this may vary according to gender, and other factors including donor weight

** This is crucial, but recipients rarely have direct access to donor identity although the Collection Service responsible for donor care must be told if there is an adverse reaction so that they can check the donor. Anonymity protects the donor from unjustified liability claims and maintains confidence within the donating community.*

Recommended donation procedures and testing

- with adequate care for the donor
    - allowing adequate preparation and post-donation recovery times
    - pre-donation drink of water (optional)
    - intra- and post-donation adverse event management and reporting system, including retrospective recognition of delayed events
    - post-donation refreshments to optimise recovery
- testing for blood group antigens and antibodies
    - Mandatory world-wide for ABO status
    - In most parts of the world, mandatory for Rh types and subtypes
    - Other clinically significant groups as indicated by
        - Specific patient needs - patients possessing significant antibodies to rarer blood group antigens
        - ethnic and demographic origins of the affected societies
- testing to minimise the risk of transfusion-transmitted infection
    - system for reporting very recent donor exposure to infections unrecognised at the time of donation
    - The most frequent infections - about 1 in 2000 platelet packs and 1 in a million red cell packs - are from skin bacteria contaminating the donation during needle insertion in spite of rigorous skin cleansing, etc; but risks are reduced by any of the following
        - a system of detecting bacteria in the pack after rapid culture
        - adding photo-activateable platelet-sparing antimicrobial chemicals to the pack
        - collecting the first 20ml into a diversion pouch (and using such blood for the tests - see below).
    - Tests on donated blood are mandatory for
        - retroviruses including HIV/AIDS
        - viral hepatidides - B and C
        - syphilis
    - Discretionary tests are indicated by recent exposure risks, patient categories, travel etc
        - CMV and some other herpes-related viruses
        - viruses such as West Nile Virus, dengue, etc
        - malaria
        - Other micro-organisms including trypanosomes, etc

Donation processing and storage

Donated blood is collected directly into a pharmaceutical grade anticoagulant/ preservative mix usually of citrate and glucose. Optimal formulae were developed during World War 2 and subsequently refined. As the collection packs already contain a fixed volume of the mix, the volume of blood to be added has to be within a defined range - usually between 5 and 8 volumes of blood to 1 of the mix. These allow red cells in whole blood kept strictly at 4^0C to remain viable for 4, 5 or even 6 weeks.

Although unprocessed "whole blood" is still used in many parts of the world, being cheaper to prepare, there are considerable economic and efficiency advantages in separating out the cellular components from the plasma (processing into '*products'*) either for direct therapeutic use (as for example red cells or platelets, or as fresh plasma) or using the plasma as a source of '*fractions*' - clotting factors, etc (see below).

All therapeutic blood products require careful storage as they become unviable outside the body. Granulocytes die within 24 hours even when stored optimally (at 22^0C). Platelets can last for several days at 22^0C, and up to 80% of red cells stored strictly at 4^0C can last for several weeks when there are adequate supplies of glucose. Techniques for freezing and preserving red cells below -80^oC were developed during the Vietnam War: these allow storage for years or decades but are very expensive and any storage failure or faulty thawing processes lead to unviable cells. Frozen storage is a 'niche' for very rare cell types. Plasma for clinical use can be maintained more cheaply at minus 20^0C for 2 years or more.

Blood processing includes;-

- A short period of post-donation cooling during which the inevitable traces of bacteria are destroyed by the auto-antiseptic qualities of healthy fresh blood
- Filtration to deplete leucocytes and prions (not universal)
- Separation of cellular and plasma components by centrifugation
- Resuspending cells in plasma or in glucose-saline crystalloid solutions

Blood products include

- Red cell concentrates (partial removal of plasma) usually for neonates, each donation being processed into several low-volume packs for multiple use
- Red cells resuspended in preservative media (sugar/salt solutions)
- Platelets suspended in plasma or crystalloid (for therapeutic platelet concentrates)
- Granulocytes (for therapeutic granulocyte concentrates)
- Plasma products
    - Freshly frozen plasma ('FFP')
        - 'cryoprecipitate' - a precipitate rich in fibrinogen, fibronectin, 'Willebrand factor' and factor VIII separated from FFP
    - 'Fractionation' into specific therapeutic fractions
        - Immunoglobulin solutions for intramuscular or intravenous use
        - Albumin concentrates (5 to 20%) for intravenous infusion
        - Various plasma-derived clotting factor concentrates, especially but not exclusively factors II, VII, VIII, IX and X).

Fractionation is an industrial scale activity conducted by national and commercial enterprises. Biosynthetic pharmaceutical grade (non-blood derived) factors also exist, including specific 'monoclonal antibodies' which are refined immunoglobulins.

Other services from Transfusion Centres

In addition to the 'traditional' collections of whole blood which are then processed there has been an increase in the number of 'apheresis' donations of either red cells, platelets or (in countries other than the UK) plasma. These are collected by automated devices which - on the principal initially developed in dairies to separate cream from milk - separate the wanted component (red cell, platelets or plasma) from the whole donation and return the remaining bulk to the donor. Anticoagulation is achieved by infusing a constant proportion of sodium citrate to the blood as it flows from the donor's vein. This allows a more constant blood/anticoagulant ratio and better quality (less damaged) cells. The complete collecting time is little more than an hour during which the donor is never disconnected from the device. Apheresis allows frequent collection of high quality platelet concentrates (up to 20 times a year) and - particularly from larger male donors (80Kg or more) on iron-rich diets - up to ten or more units'-worth of red cells a year (a 'unit' being derived from the equivalent of about a pint, or 500ml, of standard donated blood).

Current Regional and National 'Transfusion Centres' in many countries now offer extended services - for example: testing antenatal maternal blood for antibodies; procurement and/or testing of stem cells (including from umbilical cord blood), services related to the procurement of tissues and solid organs (e.g. kidneys) for transplantation; diagnostic services (laboratory testing) for immunological and microbiological conditions; forensic analyses, etc; and even special veterinary services related to animal 'immunohaematology'. Many Centres also have active academic biomedical research programmes, some of which are arguably remote from the 'core' traditional transfusion services (for humans). As pressures for diversification progress, the costs of a Centre's 'core' activity (collecting, testing and distributing blood, and specialist diagnostic services for patients with rare blood group antigens or antibodies) may constitute less than two-thirds of its total budget.

Recipients of blood products

In the UK and many developed societies, blood donation services are organised separately from clinical services to patients. Donation collections are organised from regional 'Centres' where the processing and testing of donated blood is conducted in high-capacity laboratories; and from where the blood products are distributed to the hospitals. The other half of the total service is organised from and largely conducted in hospitals where the patients are tested and compatible products selected and transfused. In the UK there are over 450 hospitals where transfusion of blood products to specific patients is organised. The costs of these much more diffuse hospital services - which are of necessity integrated into the whole patient care - is similar to the total costs from the collecting, processing and testing Centres. Specialised testing services for patients with unusual immunological complications are also offered by the Regional Centres. These aspects are discussed in more detail below.

Further remarks

In the early 20th century the two main obstacles to safe transfusion practice were identified, and a third one shortly thereafter. These were the immunological markers of inherited 'blood groups' (ABO, etc); the intrinsic property of shed blood to clot (for instance during donation); and the risk of transfusion-transmissible infections such as syphilis or hepatitis. The first obstacle could be avoided by selecting blood of an immunologically compatible group (either the same - 'A' for 'A', 'B' for 'B' etc, or more simply by only using blood from group 'O' donations as these were regarded as 'Universal' (i.e. such blood could be given to anyone, a rule which, however, is not absolute). The second was overcome during World War I by adding safe chemical anticoagulants such as sodium citrate salts to the blood: the third (and most subtle) required selection of infection-free donations, although this could be difficult in the early days as infected donors often exhibited no symptoms and young men especially were often reluctant to admit any risk (such as sexual activity).

During the First World War transfusions of whole blood undoubtedly saved lives - sometimes very dramatically. The ABO groups and the dangers of incompatibility were recognised. However donor recruitment systems or panels were not well developed and difficulties of ensuring 'same-group' transfusions often meant that even in 1945 people of group O were favoured as donors. In mid-20th century 'battlefield' practice this was not unreasonable but would be avoided today.

The clinically important non-ABO system 'Rh' was only discovered in the early 1940's and not taken into general consideration in 1945. Fewer than 1 in 200 Japanese (and Chinese) are Rh D negative compared with about 35 in 200 Britons. However there are over 20 other inherited blood group systems, and several hundred different antigens the frequency distribution of which often differ by ethnicity. Although most are clinically insignificant, several can cause occasional problems; so practitioners have to be alert to unexpected immunologically-mediated incompatible reactions.

Current reagents and testing methods for ABO status are very reliable. The occasional 'weak' reactions are nearly always due to genetically determined variations in blood group 'antigen' expression on otherwise normal blood cells, rather than 'error' or poor reagent quality. Cheap and reliable 'micro-array' systems can detect most non-ABO blood groups: however in order to maintain maximum reliability, reagents and 'kits' need cold storage (c 4^0C) in documented well-maintained refrigerators, and reliable analysis requires high standards of performance by skilled staff.

In 1945, donation-processing was most advanced in the USA where it had been developed largely to produce stocks of freeze-dried plasma (much under a specific program destined altruistically for Britain*). Under ambient conditions these stocks could be transported across continents and reconstituted in sterile water immediately before use to any patient as they could restore the blood volume of a traumatised bleeding patient - albeit transiently. For efficiency, plasma donations were pooled prior to freeze-drying: this had the unfortunate effect of increasing very significantly the risk of transmitting viral hepatitis to recipients, resulting in significant fatality.

From 1960 disposable flexible plastic containers started replacing glass bottles to contain blood, allowing far safer separation of products, and are now almost universal.

**Sadly, although well-meant this was somewhat misguided, not really needed, and transmitted several cases of hepatitis.*

Alternatives to blood for transfusion

The fact that all blood for transfusing to humans has to be from humans was established before the confirmation of the ABO blood groups in 1900: indeed occasional ‘accidents’ accompanying transfusion at that time had already led to the use of intravenous, or even subcutaneous, immunologically inert saline (solutions of sodium chloride at approximately physiological concentrations) for people suffering acute blood loss. The results could be encouraging. However, although still a ‘front-line’ replacement fluid for acute blood loss, saline lacks the essential components for longer-term fluid retention; water rapidly enters the tissues which become waterlogged (‘oedematous’). The most essential component for fluid retention is the plasma protein albumin which, due to its ‘colloidal’ nature, helps retain plasma inside the blood vessels because albumin imparts an osmotic force. However for patients with severe burns, physiological saline solutions (such as ‘Ringer lactate’ or RL) are often preferred - indeed specifically indicated - as the mechanisms of fluid loss are complicated: FFP (formerly favoured) is not now used, and albumin but rarely.

From the 1950’s solutions of artificial colloids for replacing lost blood and mimicking albumin (mostly starch-like substances such as ‘dextran’) became available: refined preparations are still used. But there are no clotting factors in artificial colloid or albumin solutions so bleeding may continue unabated. Some clotting factors are lost from plasma during blood processing and none of the solutions supply the cellular elements essential for carrying oxygen (red cells) or stopping bleeding (platelets).

In spite of much research no established alternative to red cells and platelets have been developed although advances in protein bio-synthesis have resulted in the commercial availability of some clotting proteins (see above). Solutions of modified haemoglobin combining colloidal plasma-fluid-retention characteristics with oxygen carriage have been developed but are too toxic for clinical use. Although cell culture techniques are steadily improving, the provision of red cells from culture media is more likely to prove another ‘niche’ market rather than a more general source for many decades yet. Hence there is still no alternative to donated red cells and platelets - or indeed granulocytes which, although with difficulty, can be made available by donor services for certain patients with acute intractable sepsis.

Increasing use of ‘blood conservation’ during surgery has been accompanied by reduced clinical use of blood. This usually involves use of the patient’s own blood in planned surgery, either by pre-operative donation in the weeks prior to surgery (which now is less common) or by intra-operative recycling of the patient’s own shed blood (after washing free of operative debris).

Direct transfusion of fresh blood

Blood taken into citrate allows storage and transport prior to transfusion. Until WW1 the rare transfusion was usually directly from donor vein (or artery) to recipient vein. Undeniably, the freshness of such blood maximises its contribution to stopping traumatic or surgical bleeding; but citrated blood is much easier to use. Nevertheless ‘fresh’ whole citrated blood could be transfused shortly after collection (although the ‘virtues’ of freshness start to decline within hours) and advocacy for such use gets revived from time to time. Currently, the UK Armed Forces ban the use of such blood although collection from off-duty service personnel is allowable in emergencies so long as the standards of processing and testing (which may take a day) are maintained.

Transfusion transmitted diseases

Infections

It is mandatory for all services to exclude blood for transfusion which is found to have markers of certain infections - particularly syphilis, HIV/AIDS and related viruses, and viral hepatitis. Tests for other infections (CMV, malaria, etc) are conducted when indicated by demography. These tests are very sophisticated but can be conducted by very simple 'kit' technology although their reliability is affected by poor storage of the kits. But no test can be 100% accurate and 100% reliable. False positives and negatives due to 'biological variability' are inevitable even in the absence of 'operator error'. Reagents and test systems for high-throughput low-reactivity circumstances (such as populations screening and for multiple blood donations) may need a different design from systems for low-throughput high-reactivity systems (such as in clinics for specific infections) - not least because of cost and efficiency considerations.

Transmission of non-infectious disease

These include transmission of immune factors (sensitising antibodies) and medications in the donated blood which may affect vulnerable patients - including the fetuses of pregnant women. Such circumstances are very unusual and cause adverse clinical reactions very rarely. However neonates are more vulnerable to some aspects of adult transfusion practice (including fluid volume overload and donor lymphocyte engraftment; both of which can be fatal) so extra care and vigilance may be needed

Donor health

Current services require that blood for transfusion be collected only from 'healthy' donors, free from obvious disease and with no recent medical history. These include recent foreign travel, vaccinations, exposures to infected individuals (such as children with recent intercurrent viral infections), pregnancies, etc. Lifestyle questions - to elicit risks of silent disease carriage - can be quite intrusive. The strategy of most modern services is to encourage repeat donations from unremunerated and well-attested volunteers in order to reduce transfusion-transmitted infections. Donor health *per se* is of fundamental importance - ethically and practically. Donor care is a fundamental aspect of modern blood collection practices and encourages repeat donation - but only after suitable intervals to allow regeneration of the blood.

However donation sessions should not be used - by staff or donors - as opportunities to screen for clinical disorders (apart from anaemia). Activities such as taking blood pressure readings, testing blood for additional markers such as cholesterol or glucose, should ideally not be conducted, not least because they complicate donor motivation and might lead to donation by someone who has an underlying disease which could affect donation quality. Similarly, people should not be encouraged to donate because of the availability of a 'free AIDS test' or similar (often unjustified) assurance of clinical fitness, or even to determine their blood group if, for example, they are about to undertake a hazardous activity (either occupationally or recreationally). Donors sometimes attend on the apparently simple basis that '*if they accept me I must be fit*' largely in ignorance of the limited nature of the screening process, and that the services - and especially the patients receiving blood - rely on donor honesty.

Service organisation; costs

Session team skills (local)

It should be apparent that good donation-collection teams need highly skilled members, each knowing their role and being able to respond to unexpected developments. Sessions are designed to optimise the number of successful collections in the shortest feasible times - a good 'mobile' team of, say, 16 people in various roles coming to a community site some distant from a 'Centre' (one hours' or so travelling time) should be able to collect at least 120 donations in 5 hours of session time (during a total shift of 8 hours, including setting-up and closing down times). Such a session may well include up to a fifth of the donors being first-timers for whom more time (at all stages) may be needed. Unexpected occurrences such as donor faints and even misunderstandings can lead to unwarranted delays. Donor misunderstandings have to be managed sensitively, especially for donors who are deferred or rejected. All people have a right to be considered for donation, but there is no automatic right for anyone to donate and donors may be deferred or rejected permanently if there are reasonable grounds for suspecting that either the donor or any recipient is at risk as a result of the donation. The donor has a right to a clear and honest explanation of the deferral or rejection: even if he or she does not accept any such reason the collection team is not obligated to take a donation - indeed it may be unethical to do so as the priority is *patient* care.

Regional/National organisation and administrative responsibilities

Recruitment and training

In order to function optimally, all donor team staff must undergo continuous training, evaluation and regular revalidation - from the most senior to the most junior and across all professions. Staff recruitment procedures at all levels must accord to legislation such as equality and competence. However, it is important for 'administration' not to become too draconian: the skills of experienced professionals must be respected especially during planned re-organisations.

Regional and national dimensions

Most advanced societies collect about 30,000 units (500ml whole blood) a year per million population. In the UK for many decades there have up to 2 million donations annually: this has declined slightly of late, mainly because the clinical use of blood has become more efficient - for example, in open heart surgery.

The close co-ordination and large-scale management of national transfusion services requires sophisticated computing records - at every step from donor recruitment through to each patient and every transfusion episode (in detail), of which there are at least a million each year in the UK.

Costs

Although transfusion services require a very small proportion of the national health budget of most countries (about 0.5% in the UK), they are essential for emergency services after trauma; supporting cancer chemotherapy and major cardiovascular surgery; and occasionally for premature infants and obstetric complications. Some people with inherited conditions such as thalassaemia are transfusion-dependent.

In 2001-2, the UK governments spent about £400 million a year on their transfusion services: an additional £500 million or so was spent by the hospitals on the comprehensive requirements of transfusion[3], as they have to test the patients for blood groups etc, administer the blood (under close nursing supervision) and manage the related consequences of transfusion. Improved efficiency in the last decade may well have held, if not lowered, these costs, and the charge to English hospitals for a red cell unit (single processed donation) fell by 11% between 2008 and 2010 (to £125): but the 2001-2 figures indicate the order of magnitude for overall annual costs of transfusion in a nation of just over 60 million inhabitants although these findings may not be typical.

The UK services are unique in that they continue to be affected by the impact of 'Mad Cow Disease' which was detected in the UK in the 1980's and recognised as a human disorder in the 1990's. The causative 'organism' is a 'prion', a protein capable of replication in lymphoid tissues and mammalian brain, and is spread by exchanges of bodily fluids (sheep), bovine-protein-rich cattle feed (cattle), beef offal (humans) and blood transfusions (demonstrated in sheep and in humans). The consequences of infection are severe. Humans nearly always die of neurological disorder within two years and there is no effective treatment: particularly poignant is the fact that most victims are in their 20's. There is a genetic pre-disposition which may render up to half the population susceptible. It is very difficult to inactivate prions *in vitro* and *in vivo*, and there is as yet (in spite of over 10 years' research) no working diagnostic blood test (although in symptomatic people brain biopsies are diagnostic). Although the UK has been effectively prion-free since 1997, people who have lived in the UK before then are frequently excluded from blood donation overseas due to a perceived high-risk of transfusion-transmissible prion disease. Within the UK, attempts to reduce prion transfusion risk (by leukocyte depletion and specific prion filtration) have added about 5% to the costs of transfusion. The ethical implications of an acceptably high standard specific blood test for human prion disease are profound but beyond the scope of this discussion.

Clinical uses of blood

In advanced societies the mean age of transfusion recipients is about 70 although there are smaller 'peaks' for newborns and for women with obstetric complications. Transfused newborns usually have complications of prematurity or congenital defects - mainly of the heart.[4]

The main illnesses among adults in such societies are cardiovascular diseases and cancers; these are also behind the main indications for transfusion. People with leukaemias and similar diseases, particularly if treated by stem-cell transplantation, also require frequent transfusion (and are the main consumers of platelets) as do people with chronic anaemias, many of whom have inherited disorders such as thalassaemia and sickle-cell disease. In countries on the Mediterranean littoral and in the Middle East, including Pakistan and India, people with beta thalassaemia major are significant consumers of red cells: alpha thalassaemia disorders (which in general are less severe clinically, as homozygous embryos die *in utero*) are endemic in SE Asian; and sickle-cell disorders among Afro-American and Caribbean communities. Globalisation is leading to the birth of many children with genetic combinations of these disorders, particularly in the Americas and Caribbean, many of whom become transfusion dependent.[5]

In less developed societies, transfusion needs are more for victims of trauma - particularly road traffic accidents and war - and for women suffering complications of childbirth where maternal mortality is often very high. Among the children needing transfusion are those with severe malaria (for whom it is life-saving). In developing societies where there is a significant middle class, the appearance of 'diseases of affluence' (non-communicable diseases) which include type 2 diabetes and its cardiovascular complications, and cancers, is also impacting on their transfusion needs.

It is possible to transfuse too much blood in one episode: this can cause serious 'hypervolaemic' congestive heart failure. Therefore constant monitoring before and during transfusion is part of the skills of the 'good nursing routine'.

Transfusion Services in the immediate aftermath of a nuclear exchange

The lessons from Hiroshima and Nagasaki in 1945 indicate that survivors in the affected areas may suffer in three broad ways: immediate physical trauma from the shockwaves (blast injuries); burns to exposed skin from the atomic flash and subsequent fire-storms; and radiation sickness which can be acute (within minutes) or chronic (lasting months or even years), or combined. Furthermore, those apparently recovering from radiation sickness have an increased incidence of leukaemias and solid cancers: the incidence of leukaemias in those affected at Hiroshima and Nagasaki peaked at eight years after; the increased risk (raised incidence) of solid cancers was life-long - even for decades. Furthermore, most hospitals in Hiroshima and Nagasaki were severely damaged, if not completely destroyed, large numbers of medical and nursing staff killed, and clinical services rendered non-existent (a particularly severe war crime).

All these conditions have implications for blood transfusion services. Injuries from blast or other trauma (falling buildings, etc) require blood to combat the clinical shock. It was this feature which impressed surgeons on both sides in the 1914-18 War such as Geoffrey Keynes and Leo Eloesser[6] and remains a fundamental principle of surgical management of shock. The traditional responses of communities in many countries coming forward to donate blood in the aftermath of disasters such as earthquakes illustrate this: - indeed, the floods of such volunteers can cause profound organisational challenges to recovery services.

The degree of a patient's radiation sickness is influenced by the distance from the nuclear detonation, the amount of shielding from the flash (hills, buildings, shelters, etc) and by radioactive fallout over subsequent days (many coming to the aid of Hiroshima and Nagasaki got radiation sickness from the fallout - with some fatalities).

Flash burns cause skin blistering over extensive areas. Quite apart from the pain and vulnerability to infections, there is extensive and life-threatening loss of fluid from the body which can only be treated by replacement. Even if potable water is available, radiation sickness to the gut can impair absorption; so replacement is only practical by injection or, preferably, by intravenous infusion. Saline or 'Ringer-lactate' solutions offer significant relief and are the first choice, but in severe burns with complications of shock, colloids, preferably plasma albumin may be indicated: but the amount infused to each patient must be carefully limited to avoid heart failure from fluid overload, as fluid excretion may be impaired because of renal failure induced by shock and crush injury.

Radiation sickness affects all organs, particularly the fast growing such as skin, gut and bone marrow. Symptoms from affected gut include vomiting, diarrhoea and malabsorption; and from the marrow, anaemia and immune suppression causing vulnerability to infections. Teeth and hair may fall out; and high doses can directly damage the brain. General tiredness and malaise are also prominent. Recovery is aided by rest, nursing in a clean environment, and by fluid, vitamin and calorie replacement. Mortality rates are high but can be reduced by appropriate care. Radiation sickness is a feature of radiotherapy and of stem-cell transplantation regimes the management of which includes the use of anti-nausea drugs. These would also be indicated in people affected by radiation sickness induced by nuclear war.

A brief account of the medical effects of nuclear war and the subsequent famine - implications for transfusion services

It is highly likely that - along with many clinical services - a famine such as that described by Helfand[1] would follow a hostile exchange of nuclear weapon detonations and disrupt transfusion services locally and globally. In many cases supplies of blood products and even saline would rapidly become exhausted and not be replaced for a very long time. Procurement of materiel, including supplies of the basic disposable blood collection packs, would likely force a significant compromise in standards of medical practice, including transfusion. Reduced access to the required professional and technical skills may further diminish the provision of a service which should accord to current standards, as would any disruption to computing and other electronic services.

A particular concern, even for those societies not involved with the immediate consequences of a nuclear exchange, is the demand for energy and transportation. Blood transfusion services are energy-intensive, requiring high-quality temperature control including refrigeration, and complex technical and computing demands, transport requirements, and capital maintenance. The impact of disruption on ambulances and other transport systems would also be very severe - on donor (and team) attendance at session venues; communications to the testing Centre; and the supply of blood from Centres to hospitals (see below).

Clinical needs

Short term ‘local’ effects (weeks)

One ‘airburst’ detonation of a single 100Kt nuclear weapon at 2800 ft altitude would produce a blast of over 12 psi (pounds per square inch) in a radius of 1.5 miles: this would cause very extensive damage, firestorms and 98% of people would be killed. Up to 1.85 miles away the blast would be up to 5 psi which would destroy houses: a firestorm is quite possible; and up to 50% of the people killed and 45% severely injured. Up to 3.2 miles the blast of 2 psi would damage most houses beyond repair, and kill 5% of people with 45% injured. Even at 1 psi (up to nearly five miles away) many would suffer second degree burns and flash-blindness (which may be permanent)

A detonation of several nuclear weapons aimed 5 or so miles apart from each other would greatly exacerbate the tragedy, even if the targets were mostly military and away from non-militarised cities (although ports may well be targeted). For affected survivors of the initial exchange the main short-term needs would be to combat clinical shock and to control excess bleeding. A nuclear exchange of the degree envisaged by Helfand[1] would involve many people - possibly millions - over a wider zone of damage and radioactive contamination. Furthermore, many such people would be among the poorest and most disadvantaged in those communities, and more vulnerable to the clinical and societal sequelae.

It is difficult to offer a realistic assessment of clinical needs for the immediate but injured survivors, but the likely clinical demand - for intravenous fluids, plasma, whole blood, clotting factors etc, even with an effective triage - would rapidly overwhelm the supply of services, including blood. In the UK, where burns services have received much attention and been greatly improved in the last decade, there are usually only a dozen or so ‘burns beds’ for adults and a similar number for children in

each Region (around 600 beds in the whole UK at any one time, many of which are occupied). Given that city centres may have several hundred thousand residents and many weekend visitors, the national supply of burns beds may easily be overwhelmed by a bomb on a city centre, even if only a tenth of the people are affected. Even though patients with severe burns principally require crystalloid fluid replacement, rather than blood product, associated injuries (crush, fractures, etc) may well require transfusion. Under such circumstances any attempts at triage would be largely ineffective, complicated further as it would be by major hospital destruction and vastly reduced bed availability, if not complete loss.

Following a major exchange of nuclear weapons (several dozen or so) there would be large swathes of destruction and contamination across urban and rural (and military) sites, including medical facilities: this may make even basic medical care unavailable. For transfusion, even if apparently well people further afield responded by giving blood, the capacity for collecting, processing and testing would be compromised, as would storage, refrigeration, record-keeping (particularly if paper-work had to replace computerised records) and indeed hospital capacity and available medical personnel.

Unprocessed donations collected for use as ‘whole blood’ may well become compromised for patient safety (for example by inadequate storage) - possibly significantly and seriously so. However, in such emergencies compromises in safety standards may be necessary - for example, applying shorter storage times which may anyway be less significant in the face of high demand. But involved staff - and, wherever possible, patients - should be aware and take whatever precautions are feasible. However, if and when a new blood donation collection system becomes operative, many staff would likely be recruited rapidly from inexperienced personnel and volunteers; and the principles of blood collection may be over-simplified and delegated unwisely to less thoroughly trained staff. Managers should be organisationally adaptable, inventive, and thoroughly and comprehensively aware of the intricate nature of transfusion procurement and practice. Such experience may allow more educated decisions on appropriate compromises and adjustments.

Mid-term effects (months) on the local population

Sadly, many local short term survivors - even if suffering lightly from blast injuries - will succumb to impaired healing and immune suppression due to radiation-induced anaemia and reduced white cell function, aggravated by poor nutrition and malabsorption (due to radiation damage to the gut), chronic infections and societal stress. Careful re-hydration and antibiotics when indicated may mitigate the effects but may well be out of reach of most affected people. It is possible to make only very approximate guesses of the scale of casualties but in countries such as India and Pakistan they could run into millions.

Mid-term effects generally and globally - refugees

Societies further from the swathes of destruction will also be affected. Even if there is a fully effective transfusion service away from those swathes, and even if some hospital services remain in the more directly affected regions, the demands will likely divert large quantities of donations to them - perhaps causing further inter-societal tension. Such developments would be further compromised by large numbers of refugees fleeing to relatively unaffected areas - possibly to relatives. These refugees

would include many suffering from blast injuries and significant radiation sickness which would in turn affect medical (and transfusion) services in the receiving areas.

During the first year or so there would be a sympathetic response from more distant countries, and blood and products shipped to the areas of demand. However effective use requires local storage and patient testing facilities, and patient care may remain severely compromised in the most affected areas. Furthermore, refugees are likely to attempt to reach 'havens' in more distant parts of the globe - with attendant health challenges and problems.

The plight of people with transfusion-dependent conditions such as thalassaemia may become serious. In India and Pakistan, where the thalassaemia carrier rate is up to 10% of the population (about 5 to 6.5% in Punjab), one in four children in affected families have the 'major' condition which is treatable only by regular (monthly) red cell transfusions: many thousands of such children are born each year across SE Asia.[5] Currently, the global burden of thalassaemias is gradually falling because of increased access to services including testing and genetic counselling, but these would be put at risk by a nuclear famine, yet alone access to regular high quality transfusion.

Long-term, general and global

As the nuclear famine developed into its second and subsequent years, global access to transfusion services may well deteriorate further. Possible factors include

- Disruption to transport
    - For donors
    - For service staff and equipment
    - For supplying blood and products to hospitals
- Increased population mobility
    - Donors searching for work and security
    - Donors are best recruited from stable populations
- Deteriorating health of donors
    - Nutrition
    - Epidemics of infectious diseases
- Disrupted IT, record-keeping and communications
- Loss of expertise
    - Reagent preparation
    - Standards and quality control
- Industrial disruption of supplies
    - Reagents
    - Diagnostic kits
    - Materiel - blood packs and delivery sets.etc

As global conditions deteriorate there will be increasing difficulties in maintaining all health services, including transfusion. Retrograde developments such as increased reliance on 'commercial' blood donors, reduced use of blood component therapy, reduced leucocyte depletion of blood products, less sensitive tests for transfusion-transmitted infections, etc may be needed in order to maintain any sort of blood supply. Similarly, a reduction in the efficiency and clinical applications of blood use may lower standards which, however, may be countered by an awareness of blood shortages encouraging increased blood conservation and alternative methods of clinical management of disorders traditionally associated with transfusion therapy.

Requirements for patients with cancer

An increased incidence of malignant disorders - especially acute leukaemias - is to be expected among ‘local’ survivors during a nuclear famine of ten years or so, particularly from about 4 years after the nuclear detonations. These may strike at all ages (in contrast to the statistically significant but much lower incidences of childhood leukaemia associated with some families residing within 5Km of a normally-operating nuclear power plant). This was found in Hiroshima and Nagasaki even in people who had not apparently suffered from acute radiation sickness.

Whereas treatments for leukaemia in 1945 were largely ineffective, options - and the consequent prognosis - are now vastly improved, especially in children of who up to 90% are cured (and most of the remainder have favourable responses which can last for decades). However, the disease remains highly distressing - particularly for the parents - and can carry life-long sequelae even for those who are cured by modern therapy and have become biological parents of healthy offspring. The mainstay of treatment is chemotherapy, sometimes (ironically) with radiotherapy. However, a common complication of such therapy is temporary bone marrow failure for which blood transfusion is indicated. Platelet concentrate prepared from blood donations are frequently required, sometimes from many donors (double-figures being not infrequent). Such requirements would add a substantial challenge globally to services already hard-pressed during a nuclear famine.

Stem cell transplantation (formerly known commonly as ‘bone marrow transplantation’) is now an established and effective treatment for severe or relapsing leukaemias - and also for thalassaemia major. Techniques for procuring stem cells were developed largely by transfusion services, and these are still involved in routine procurement for patients - either from ‘allogeneic’ donors (somebody else of the same tissue type who is often a sibling but may be an unrelated donor from a registered panel) or, in the absence of any suitable donor, ‘autologous’ - i.e. the patient him- or her-self. As part of the preparation of the patient is to ablate their own bone marrow stem cells (which leads inevitably to a period of marrow failure and transfusion dependency) transfusion services are essential while the transplanted stem cells ‘take root’, which can take two or three weeks.

Transfusion support is less often needed in most other cancers, including childhood (and adult) thyroid cancers (which can also follow fallout of radio-iodine).

Possible remedial actions

A steady global supply of trained expert professionals - clinicians, biomedical scientists, nurses, informatics, management, etc - should be maintained and academic research into improved transfusion techniques (including alternatives to donated blood and clinical practice) sustained and further developed. Similarly, rapid sensitive and accurate diagnostic techniques and reagents - including micro-array systems - must continue to be developed; and supplies of well-attested diagnostic materials and kits must be maintained in secure sites. This would at least prepare for severe but remediable situations.

Nevertheless, it could be wrong to aim to re-create transfusion services on the current 'Western' model. For example although altruism is an admirable human characteristic, a wide practice of voluntary unremunerated blood donation is usually associated with relatively well-developed stable societies. (Intriguingly, it has been observed that as societies become highly developed the motivation for altruistic blood donation seems to wane and donor recruitment, especially among young adults, becomes more difficult.) In the aftermath of a 'limited' nuclear war, local surviving populations - particularly from less developed societies - may not have a tradition of voluntary blood donation, so reliance on donations from family members may have to be accepted, along lines referred to by Ala *et al.*[2] This would still require skilled application of high organisational and medical standards.

However, in the face of the challenges of a widespread nuclear famine a complete breakdown of the provision of safe blood and blood products for transfusion must be expected. The maintenance of high-quality global services have become key, not only for emergencies accompanying the huge-scale of trauma to be expected from even a 'limited' exchange of one or two nuclear weapons, but also in the aftermath.

The above considerations indicate that there can be no adequate global medical response to a regional nuclear war. So prevention is key and diplomatic efforts to secure a nuclear weapon free world as soon as possible are paramount and must start in a meaningful way without delay.

Specific considerations for the city of Manchester, UK

In 1996 a 1.5Kt semtex bomb was exploded by Irish terrorists in central Manchester. The mushroom cloud rose to 1000 feet, and flying glass and masonry was flung up to half a mile away. The police, who were forewarned, succeeded in evacuating shoppers etc up to a quarter of a mile away, in spite of which there were 212 casualties (but no fatalities) and £1bn damage (2013 values) was caused to property.

Reference was made above to the effects of a 100Kt airburst. Taking Manchester as an example, the City has about 500,000 residents of whom about 70,000 are students; Greater Manchester Region has about 2.7 million. The City Centre area is about 300 hectares, the city council covers 11,000 hectares and Greater Manchester about 130,000 hectares. A detonation over the Centre at 2800 ft would cause very extensive damage and firestorms over a radius of 1.5 miles, and 98% of people would be killed. Up to 1.85 miles away, houses would be destroyed and a firestorm is quite possible, with up to 50% of the people killed and 45% severely injured. Up to 3.2 miles most houses would be damaged beyond repair, and 5% of people killed with 45% injured. There would be a high risk of radiation sickness among the 50% survivors, especially those caught in the open who would also receive severe burns from the flash. Even up to nearly five miles away many would suffer second degree burns and flash-blindness (which may be permanent)

The major Manchester University teaching hospital complex (Manchester Royal Infirmary and Royal Manchester Children's Hospital, where there are about 12 paediatric burns beds) is sited just over a mile from Piccadilly Station and would fall under the 12 psi blast from a 100 Kt device. Although constructed of modern materials, like many new hospitals in the UK there is extensive use of reinforced glass. In the wake of terrorist attacks, there has been much research into reinforcing glass and reducing the shatter effects (so that instead of sharp shards, smaller less sharp fragments result from nearby explosions); but as one advertiser states 'there is no such thing as blast-proof glass".[7] No glass could resist the blast effects of a thermo-nuclear nuclear explosion resulting in 12 psi blast pressure.

The Manchester regional centre for treating burns in adults is at Wythenshawe hospital, where there are 12 designated burns beds. At 8 miles south of central Manchester this is far away enough to be less affected by a 100Kt detonation over the Centre, but within range of damage and severe burns from a Megatonne bomb. Even if the hospital continued to operate (staff availability, intact electricity supplies, tele-communications and IT systems which may be vulnerable to the Electro-magnetic pulse effect, etc) it would likely be overwhelmed by the scale of casualties in the first day: referrals to other regions, (Liverpool, Birmingham, nationwide) would be needed and even then many might die who could have been saved by intensive care.

Although radiation is only about 10% of a nuclear bomb's released energy (half as acute radiation, half as fallout), the high intensity flash would cause rapidly fatal acute radiation sickness in all exposed people up to 2 miles away, but shielding by buildings or cellars would mitigate this. A plume of radioactive fallout and 'black rain' over the neighbouring countryside would affect nearby communities, especially to the north-east (Oldham at 13 miles, Leeds at 40 miles, etc). Survivors of the acute exposure (who would nevertheless experience months of ill-health) and those exposed to fallout are liable to long-term cancer complications of which leukaemias, with their characteristic rise and fall of annual incidences with time, are the most predictable.

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