Production of plasma-derived medicinal products: ethical implications for blood donation and donors

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Introduction

It is not only useless, but probably also tactless to remind a meeting of haematology experts of the importance of blood. But its relevance is such that a reminder is nonetheless useful. Two definitions of blood significantly reveal a glaring contrast: blood "*est synonyme de vie, de force, de santé, de noblesse, de descendance*", while at the same time blood "*représente la maladie, la mort e la guerre, les maladies héréditaires, l'étranger et la haine raciste*"[1]. Another of the numerous examples of this contrast is to be found in the laws relating to "*limpieza de sangre*" enacted in Spain between the fifteenth and sixteenth centuries and so well described by David Biale, Professor of Jewish history, in "Blood and belief: the circulation of a symbol between Jews and Christians"[2].

Even when it is not directly paid for, a complex global network of trade in biological material ensures that the donation of blood involves the movement of large sums of money, albeit not for profit. Some authors have likened this material to a sort of "corporeal currency". Roberto Esposito, for example, coined the expression "immunitary paradigm" in which immunity has become the basis of a "bioeconomic flow, circulation and exchange"[3]. It is also worth recalling that the words "*immunitas*" and "*communitas*", while having profoundly different meanings, nonetheless share a common etymological root, "*munus*", meaning both "gift" and "obligation". "*Communitas*" means sharing, reciprocity, while "*immunitas*", whether used in biomedical or in legal contexts, means closure, a resistance to reciprocity, protection against sharing. For the purposes of the present considerations, both can refer to the notion of "gift relationship" coined by Richard Titmuss[4]. The donation of umbilical cord blood is a demonstration of altruism that could perhaps restore some kind of harmony between the two concepts[5].

In the specific case of plasma-derived products, on the 12th April, 2012, the Italian Ministry for Health enacted four new decrees regarding: the processing of plasma collected in Italy; the import and export of human blood and blood-derived products; the marketing of products derived from human plasma, and the presentation and assessment of applications for registration as centres or companies authorised to enter into agreements with local governments for the processing of plasma[6-9].

As with many bioethical issues, it is helpful to address the question using a triangular approach.

The first -and perhaps most important- side of the triangle is represented by technical-scientific data. "Bad science, bad ethics": the first requisite for ethics is a sound scientific base.

The second side of the triangle is represented by the values at stake; and the third side by the ethical evaluation that springs from the first two.

The first consideration will be omitted here: it is not the bioethicist's job to illustrate the technical-scientific aspects of blood to an audience of experienced haematologists. Instead, I shall consider the second and third sides of the triangle.

The values at stake

An incomplete list of the many and varied issues of ethical significance would include considerations regarding mainly the recipients of plasma-derived medicines (availability, access, safety, efficacy, etc.), considerations regarding the donor (respect for the dignity of the individual, voluntariness, remunerated or non-remunerated donation, safety, information, consent, respect for rights, etc.) and considerations regarding the system (remuneration, organisation, cooperation, relations with industry, regulations, etc.).

This report primarily addresses the issues regarding donors, which are nonetheless inextricably bound to those of the other parties involved. For a meticulous examination of the problem it is helpful to refer to documents published by authoritative organisations, two of the most important of which are the "Expert Consensus Statement on achieving self-sufficiency in safe blood and blood products, based on voluntary non-remunerated blood donation (VNRBD)"[10] approved and adopted by a group of WHO experts, and the "Dublin Consensus Statement"[11,12].

The WHO "Expert Consensus Statement" focuses particularly on the criteria for attaining and maintaining self-sufficiency in safe blood and blood products (meaning "that national needs of patients for safe blood and blood products, as assessed within the framework of the national health system, are met in a timely manner, that patients have equitable access to transfusion services

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and blood products, and that these products are obtained from VNRBD of national, and where needed, of regional [such as neighbouring countries] origin").

The Dublin Consensus Statement indicates basic commonly-held principles that aim to ensure the protection of patients and donors, cooperation, and the worldwide availability of donated plasma.

One of the more controversial aspects is whether blood should be donated voluntarily or paid for. The expression "paid donation" is widely used in the literature. The 1924 publication of Marcel Mauss's "*Essai sur le don*"[13] generated a flood of literature from renowned scholars on the sociological aspects of giving that continues to the present day[14]. There is no need, however, to appeal to gift sociology to recognise that the expression "paid donation" is an oxymoron. The problem is controversial: when the World Health Organisation examined practices adopted in 162 nations it was found that truly unpaid donations were the rule in only 57 of them: the remainder all envisaged some form of remuneration for the donor[15]. Although these forms of remuneration generally comprised reimbursements to cover expenses or discomfort, the border between reimbursement and actual payment was often blurred. Another particularly thorny aspect of the problem is that over 50% of the roughly 92 million blood units donated each year come from economically developed countries, which account for only 15% of the global population[10]. The problem is to find means of increasing donations where the need is greatest. In many quarters it is held that this could be achieved by paying so-called "donors", a claim that is well known to those who work in the sector and which has been widely debated. The problems (regarding ethics, public health and sustainability, etc.) are complicated not only by considerations intrinsic to any so-called "paid donation" but also by their many implications. For example, remuneration would certainly lead to an increase in the number of donors from economically weaker sectors of the community, in whom the possible risks of transmitting disease are potentially higher; payment might discourage altruistic donations; so-called paid "donors" could too easily be exploited[16-18]. For various reasons the problem is often aired in public, as for example when Victor Grifols, president of the multinational Grifols S.A., which markets plasma-derived drugs in several countries, championed the need to pay blood "donors"[19].

In addressing the problems associated with donation, as well as with possible payment, together with documents published by authoritative organisations it is also useful to consult the opinions expressed by national bioethics committees. For the present purposes the opinions of the National Bioethics Committees of 27 EU nations were consulted, alongside those of other Council of Europe member countries. No documents dealing specifically with the preparation of plasma-derived products are available. However, the European Commission's European Group on Ethics in Science and New Technologies has expressed an opinion on the matter[20], although it dates from 12th March, 1993. It is significant that the European Group decided to include plasma-derived products among the first issues they addressed: the document bears the number 2. This decision may have been influenced by the entry into force on 1st January, 1992 of Directive 89/38/EEC[21], which triggered a lively debate[22]. In contrast, the matter has received little attention from national committees in the subsequent 20 years.

In 2011 the Nuffield Council on Bioethics published two reports -"Solidarity: reflections on an emerging concept in bioethics"[23] and "Human bodies: donation for medicine and research"[24]- which do not specifically deal with the issue of blood-derived products but are nonetheless interesting. Both documents are long, being 127 and 272 pages respectively. They are the fruit of lengthy preparation by a working group composed of respected experts, who also consulted professionals and ordinary members of the public. The second of the two reports is of greater interest in this specific case, and makes a crucially important point: the Nuffield Council proposes shifting the attention away from the paid/unpaid donation dilemma and towards a distinction between altruistic and non-altruistic donation. I personally, as a bioethicist, am convinced that donation should be free and unpaid. However, the British report includes some interesting proposals, three of which are particularly significant: the relationship between availability and demand; reference criteria; a distinction between altruist-focused and non-altruist-focused interventions, together with practical proposals.

Supply and demand

The first proposal regards the relationship between supply and demand. It is as well to remember that even when we use impersonal terms such as "demand" and "supply", we are really talking about human lives.

According to the Report, demand "is not simply a matter of the quantity of a particular type of material being available, but also its qualities: in organ, blood and bone marrow donation, for example, donated material has to be "matched" immunologically to its potential recipient". Likewise, supply depends not only on the donor's motivations: the central roles of "organisations, organisational procedures and intermediary professionals" are crucial. The Council applies the concepts of "supply" and "demand" to every part of the human body that can be donated: blood, organs for transplantation, tissues, cells. Moreover, most of the Council's proposals apply also to products derived from these parts of the human body.

The relationships between demand and supply are complex. Demand is elastic: developments in scientific knowledge offer the prospect of new opportunities and alternative therapies, often increasing demand and certainly not reducing it. The case of plasma-derived products is emblematic: Edwin Cohn's albumin[25] was joined in the 1970s by factor VIII and later by immunoglobulins[26].

The Nuffield Council points out that there is often a tendency to make a direct link between the two sides of the demand-availability equation: if something is scarce, then its availability must be increased. The Nuffield Council instead proposes addressing the problem of scarcity in part by acting on demand. In doing this the Council does not wish in any way to underestimate the needs of patients whose health depends on the availability of donors, but rather to improve management and avoid waste. The avoidance of waste is also an ethical imperative.

Where the specific preparation of plasma-derived products is concerned, the relationship between demand and supply inevitably involves the relationship between the public and private/commercial sectors. The Nuffield Council suggests that the two sectors should not be considered as in opposition but as complementary, even overlapping at times. Research by commercial organisations can lead, for example, to the development of medicines of great value to the public sector, just as research in the public sector can have a commercial spin-off.

One significant example of this is cord blood donated for altruistic purposes to be stored and circulated in the international networks for use in transplants, but which is found to be unsuitable for storage or transplantation. Although the Nuffield Council does not address this question explicitly, it does point out how the preparation of blood products also enables precious donated resources that would otherwise be discarded to be used. The very strict and selective criteria applied to the preservation and storage of cord blood[27] lead, as is known, to roughly 90% of donated blood being discarded[28]. This blood can be used for research, or it can also be used to prepare blood-derived products such as platelet gel[29]. Using this blood in the preparation of platelet gel, in a non-commercial setting, means not only that this precious biological material is not wasted, but that it can be put to good use. Naturally, this and other possible uses should be clearly indicated in the information given to donors prior to obtaining informed consent.

This example also shows that while the preservation of biological samples is regulated by different rules and procedures according to whether the samples are being stored for therapeutic or for research purposes, the boundaries between the two types of donation may become blurred. The Nuffield Council report rightly points out that "donation for research purposes may differ in important ways from donation for treatment purposes", but cord blood donated for storage in a biobank for transplantation purposes and that is instead used (because it is not suitable for transplantation) to produce platelet gel or for research shows us how the two types of biobank often come together.

Ethical framework

The second point to consider is that in such a complex scenario it is absolutely necessary to have some kind of framework of reference values, as emphasised by the British report referred to above.

A key aspect for reflection from the ethical point of view is the peculiarity of a situation in which a sample that is taken from one person is then used to benefit other persons. This undermines the principle of beneficence, one of the cornerstones of bioethics, and inevitably gives rise to conflicts between values.

The Nuffield Council lists a series of values commonly invoked to address this problem -altruism, autonomy, dignity, justice, maximising health and welfare, reciprocity, solidarity- to which it adds "professional values, such as respect, honesty, and the exercise of the duties of care and confidentiality", as well as "positive values inherent in interpersonal relations, including love, generosity, compassion and trust". The Council points out that traditional emphasis on the importance of the gift is questioned by those who maintain that recourse to donations alone is not sufficient to meet demand, or even that donations may be used to conceal unacceptable situations of coercion or exploitation.

The Council considers that the inevitable conflicts between values necessarily call for mediation and consensus, though some principles should remain intact, in particular: "the role of the state with respect to donation should be understood as one of stewardship, actively promoting measures that will improve general health" and "altruism, long promulgated as the only ethical basis for donation of bodily material, should continue to play a central role in ethical thinking in this field". At this point the Council hazards a bold interpretation: "An altruistic basis for donation does not necessarily exclude other approaches: systems based on altruism and systems involving some form of payment are not mutually exclusive". This does not in any way imply that the Nuffield Council is in favour of commercialisation. The report clearly states: "We do reject the concept of the purchase of bodily material, where money exchanges hands in direct return for body parts. We distinguish such purchase clearly from the use of money or other means to reward or recompense donors".

The protection of donors from possible risks is of particular importance. Discussions of the ethics of donation and the use of biological material often concentrate on the rules governing consent, the protection of personal data and various legal aspects, while relatively little attention is devoted to the physical risks for individuals. Although we are not talking about actual interventions on individuals of the kind implied in drug testing trials or other clinical experiments, the possible physical risks for those involved, including from the ethical viewpoint, should not be overlooked and should be constantly monitored. There are times when physical risks require a higher level of vigilance than other types of risk that, albeit significant, do not pose a physical risk.

Altruistic and non-altruistic interventions

The distinction made by the Nuffield Council between two types of intervention, "altruistic" and "non-altruistic", has already been referred to, particularly in regard to the "ethical framework".

The Nuffield Council also identifies three different possible levels of payment, which it defines precisely. These are: purchase (for a thing), reward (to a person for donating) and recompense (of a person for losses incurred). The third category is further divided into: reimbursement (for a financial loss) and compensation (for non-financial losses, such as discomfort). There are those who consider that all kinds of "incentive" pose an ethical problem because they alter the perception of the risks and benefits associated with donation. Instead, the Council invites reflection on the fact that the term "incentive" can be interpreted in the broadest sense (as something that motivates or encourages somebody to perform a specific action) or more narrowly, which the Council calls "non-altruist-focused intervention", where the incentive is the primary motivation for the action.

The Council propounds the view that a purchase model would be inappropriate, both because there are currently no grounds for believing that it works and because it would pose fundamental questions regarding the welfare of donors and the potential erosion of common values. A "purchase model" is defined as a system in which the guiding principle is a transaction between a seller and a buyer where there is a direct exchange between biological material and money. However, the Council suggests that the mere presence of money in the transaction does not necessarily imply a purchase-based model.

The Council proposes a ladder with six levels of intervention to encourage donations.

The lower four rungs of the ladder are "altruistic" interventions, while the top two rungs are "non-altruistic-focused". They are as follows:

- *Rung 1*: information about the need for the donation of bodily material for others' treatment or for medical research;
- *Rung 2*: recognition of, and gratitude for, altruistic donation, through whatever methods are appropriate both to the form of donation and the donor concerned;
- *Rung 3*: interventions to remove barriers and disincentives to donation experienced by those disposed to donate;
- *Rung 4*: interventions as an extra prompt or encouragement for those already disposed to donate for altruistic reasons.

The non-altruistic-focused interventions are:

- *Rung 5*: interventions offering associated benefits in kind to encourage those who would not otherwise have contemplated donating to consider doing so;
- *Rung 6*: financial incentives that leave the donor in a better financial position as a result of donating.

The approach illustrated by the Nuffield Council can usefully be taken as the basis for an ethical evaluation.

An ethical evaluation

The Nuffield Council proposes that where a healthcare need cannot be satisfied through altruistic interventions, the possibility of non-altruistic-focused interventions should be considered. In order to evaluate the potential harmful effects of such an approach, the Council recommends that the following aspects should be closely scrutinised: the welfare of the donor and of the other persons involved, the potential harm to the common good, the responsibilities of the professionals involved, the strength of the evidence regarding all these factors.

The first of these elements, the welfare of the donor, is paramount. Several documents on the subject of blood donation and the preparation of blood products (for example, the "Dublin Consensus Statement[12]), cite the precautionary principle. In purely formal terms, recourse to the precautionary principle is not wholly appropriate: in the healthcare sector the so-called "principle of caution" has a very precise definition[30] that refers to situations in which there is uncertainty as to the frequency and/or entity of the potential risks, either because there is a lack of scientific data, or because the available data are contradictory. In the case of blood products the risks are essentially known and data are not lacking, so that it might be more appropriate to refer to the "cautionary criterion" and to avoid using the word "principle", which is decidedly weighty, whether used in an ethical, philosophical or legal context.

The other factors cited in the Nuffield Council report refer more or less directly to the notion of "gift", which is still much debated. Although the rationale for free and voluntary donation propounded by Richard Titmuss in his seminal work "The gift relationship"[31] is contested by some[32,33], it is nonetheless regarded as a point of reference on the subject by the majority[34].

The Nuffield Council report notes that the notion of gift evokes two different images. The first is of a complete transfer, in which the donor gives up any right in the gift: the second involves the circulation of gifts within a network of interpersonal relationships in which there is the recognition of an obligation generated by a gift and the possibility of receiving something in return. This can also be the case with anonymous donations, where it is not possible to reciprocate directly, but where the recipient can in turn become a donor, thereby offering the benefit received to another person. However, a donation may have less positive connotations: dependence on donations may not be sufficient to satisfy demand, it might raise problems of equity in a system where compensation is allowed, and it might even become a rhetorical cover for out-and-out commercialisation. As is known, the principle of the non-commercialisation of the human body is enshrined in numerous authoritative documents. Article 3 of the Charter of Fundamental Rights of the European Union includes a "prohibition on making the human body and its parts as such a source of financial gain"[35]. Of particular significance is Article 21 of the "Convention on Human Rights and Biomedicine"[36]. The Convention was adopted by the Committee of Ministers on 19 November 1996. It was opened for signature on 4 April 1997, then signed by 35 member states and ratified by 29 member states, but all the relative documents agree regarding the prohibition of any form of payment for "donations". Notwithstanding this, the levels of intervention proposed by the Nuffield Council merit consideration. The ethical issues they raise can be analysed from various angles:

- utilitarian: this consequentialist view assesses actions on the basis of their usefulness;
- ethical: founded on respect for certain moral rules and principles;
- community: the focus is on the specific peculiarities of the different communities that comprise a population;
- contractual: centred on negotiation;
- egalitarian: the emphasis is on equity of access to goods;
- liberal: based on equal access to rights and a free market;
- individualist: focuses on free choice for the individual;
- personalist: centred on the person and seeks to build the common good by protecting and promoting the good of the individual. If the person is placed at the centre a meeting point can be found between social utility and individual solidarity.

Altruism, to which personalism attributes maximum importance, has been present throughout the history of humankind.

Altruism and respect for the intrinsic dignity of each individual are thus fundamental values in the ethics of donation and, as is the case with the other values at stake, have to be transformed into operational criteria. The general principles set out in various documents by the Nuffield Council, as well as some of their prompts, however controversial, are of great help in identifying general criteria. Below, to conclude, are a few.

The donation of blood is a voluntary, free gesture and, in accordance with the principle that the human body cannot become a source of financial gain, is not remunerated. The fact that it is free does not preclude some form of reimbursement for the donor, but this should not be of such a kind as to distort the nature of the action, which must remain a donation and a gesture of altruism. The regulations governing this sector should therefore both recognise and encourage these acts, as well as ensure that the donor receive the respect due to him or her.

From the ethical viewpoint, the physical risk for those involved is a priority consideration and every effort must be made to safeguard the donor's safety. The donor should receive exhaustive and precise information concerning the risks before he or she consents to the donation.

Informed consent is an indispensable requisite for donations, as for any medical intervention. The donor should also receive information concerning the possible uses of his or her blood, the potential beneficiaries and the procedures involved. The principle of non-commercialisation of the human body and its parts should not exclude the possibility that donated blood or tissues be used in the preparation of products that subsequently enter the commercial circuit. The donor has the right to receive accurate and unambiguous information regarding this possibility. Appropriate measures should also be taken to ensure the protection of personal data and confidentiality: this obviously implies that the facility and the healthcare personnel involved should be of a standard to guarantee these requisites.

The above criteria should not, however, be allowed to slip into a purely legalistic observation of rules.

By paying due attention to altruism when considering the numerous problems connected with the donation of blood, it should be possible to overcome the legalistic approach, which risks reducing the problems to obtaining informed consent, respecting commercial rules, and stipulating intra- and international agreements. Respect for the rules is paramount, but should not be allowed to obscure the overriding goal: the good of patients and donors.

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