A century of transfusion medicine

In 1914, Olav Hanssen defended the first Norwegian PhD thesis on a topic related to transfusion medicine. At the time transfusion was almost unknown as a treatment. In 2014, it is a fundamental procedure with many functions, performed in all general hospitals and dependent both on volunteer blood donors and an international industry worth billions. Alternatives to transfusion are on their way, but the health service of 2114 will probably also be reliant on the ability to transfuse blood and plasma products from donors.

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In 1914, Olav Hanssen (1878–1965) of Rikshospitalet defended a monograph on transfusion in anaemia (1) (Figure 1). Transfusion was at the time almost unknown as a treatment in Norway, and knowledge of anaemia diagnosis and pathophysiology was fairly limited. It was believed that heavy metals could stimulate the formation of erythrocytes, and arsenic was often administered in chronic anaemia. The question at the heart of Hanssen's work was whether transfusion could stimulate the formation of new blood, but he was also interested in side effects and the practical implementation of this new treatment method.

Healthy colleagues and a small number of patients were used as donors, and blood was collected from arteries. Anticoagulants were not available, so the blood was defibrinated and filtered through cotton before intravenous infusion in an open system (Figure 2). It was recognised that many patients possess antibodies (isoagglutinins) against other people's erythrocytes, but Hanssen doubted that they were of relevance to transfusions. He made no reference to the concept of blood types, even though Landsteiner and colleagues had described the ABO system more than ten years earlier (2, 3). This lack of understanding of the importance of blood types is typical of the period. Landsteiner himself was preoccupied with whether isoagglutinins had a role in defence against infection, and in his article «Über Agglutinationserscheinungen menschlichen Blutes», for which he was later awarded the Nobel Prize, he mentioned only briefly that isoagglutinins and blood types could have relevance for transfusions (2).

Hanssen did perform pre-transfusion compatibility testing, but blood was given whether the result was negative or positive. Patients with positive tests often developed dyspnoea and back pain, and signs of haemolysis. In one patient haematuria was observed for 14 days following a transfusion. Hanssen concluded correctly that the isoagglutinins that gave rise to positive compatibility tests caused the haemolysis. Chills and fevers occurred frequently, even when compatibility tests were negative.

Hanssen found no evidence that transfusion could stimulate the formation of new blood. He understood that transfusion is purely a form of treatment by substitution and that its effects are time-limited. For chronic cases of anaemia, he therefore recommended transfusion only if other treatments had no effect. The main indication for transfusion should be acute blood loss for which neither physiological mechanisms nor saline infusion can compensate. Here he followed the lead of von Ott, who as early as 1883 claimed that blood loss can largely be replaced with saline (4). Hanssen also suggested that transfusion could be used to stop haemorrhaging in haemophilia.

The thesis did not lead to a breakthrough for clinical transfusion in Norway: the technology and organisation necessary for this were still many years off. It was only in 1948 that the first Norwegian blood bank was established, at Ullevål hospital (5). Nevertheless, the centenary of the thesis is still worth marking, both because it is the first academic work on transfusion in Norway and because, despite primitive technology and a somewhat confusing background literature, it reached conclusions that still hold true today.

Transfusion in the year 2014

Each year, about 200,000 erythrocyte concentrates are administered to between 50,000 and 60,000 patients in Norwegian hospitals (6, 7). The majority of patients are elderly individuals with anaemia due to neoplastic or other chronic diseases (6). In 2012, a total of 24,508 platelet concentrates were transfused (7), the majority probably in association with myelosuppressive chemotherapy. At Oslo University Hospital, 1,525 patients received 8,871 platelet concentrates in 2012 (unpublished data), and it can therefore be assumed that 4,000–5,000 patients received platelet concentrates nationwide. The number of patients who receive plasma products has not been studied, but haemorrhagic conditions and immune disorders probably represent the largest diagnostic groups in need of such treatment.

Based on product prices at the Oslo Blood Bank in 2013, products from Norwegian blood banks are worth an estimated 600–700 million NOK per year. The international industry supplying products and services related to transfusion is worth many billions (8). Globally, more than 100 million units of 450 ml whole blood are collected (9) and approximately 40,000 tons of plasma are fractionated (G. Zerlauth, Baxter GmbH, personal communication,


TRANSFUSION UND ANÄMIE

EINE KLINISCHE STUDIE AUF GRUNDLAGE VON 74 TRANSFUSIONEN BEI 29 FÄLLEN VON ANÄMIE

VON

OLAV HANSSEN

(MIT 82 TEXTFIGUREN, 2 TABELLEN UND 7 TAFELN)

(VIDENSKAPSSELSKAPETS SKRIFTER. I. MAT.-NATURV. KLASSE. 1913. No. 15)

KRISTIANIA
IN KOMMISSION BEI JACOB DYBWAD
1914

Figure 1 *Title page of Olav Hanssen's monograph*

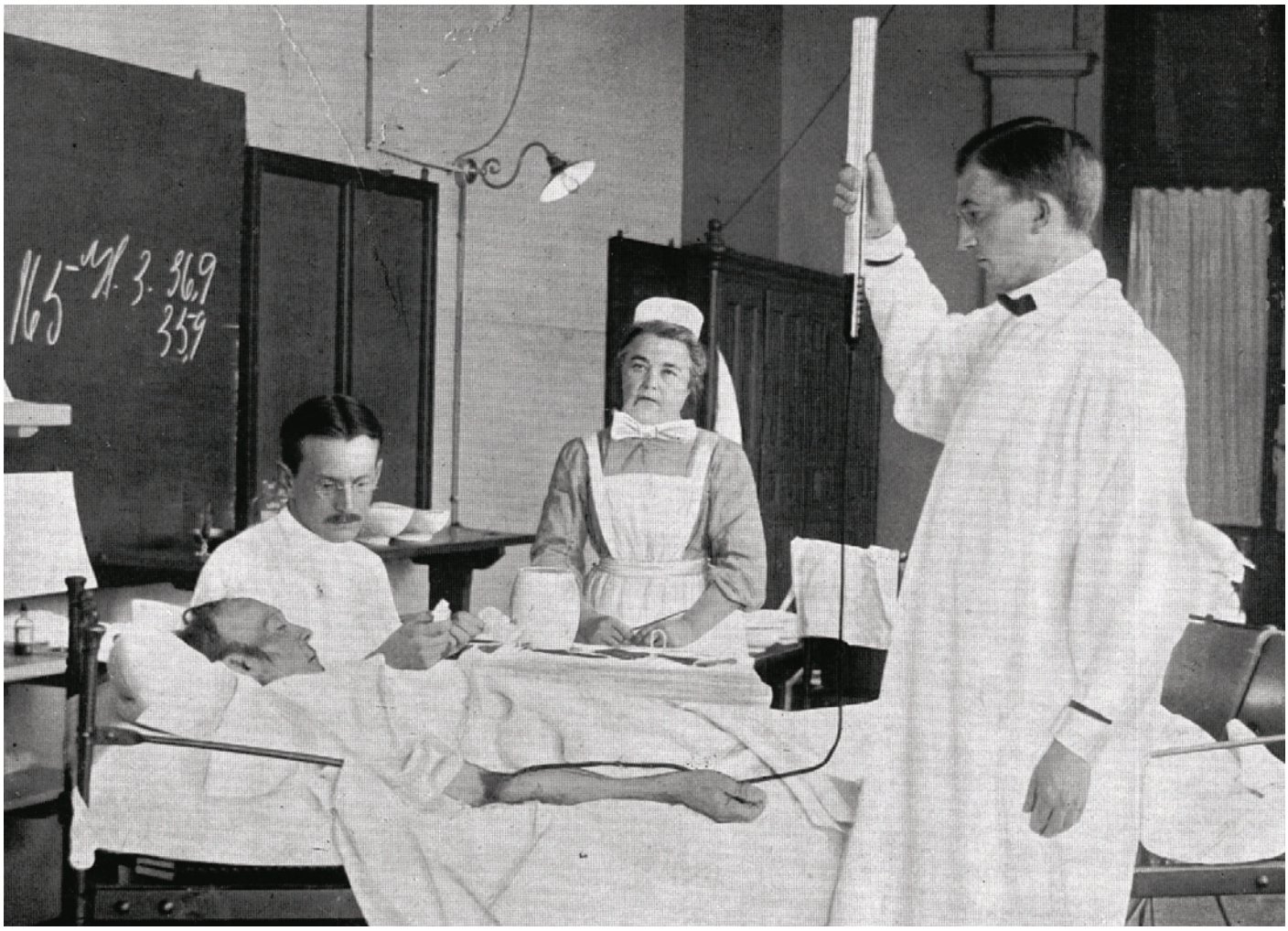

Figure 2 *Transfusion at Rikshospitalet circa 1912. The blood is defibrinated and administered from a measuring cylinder in an open system. Note the camphor bottle that one doctor is holding ready in case of complications. From Hanssen (1)*

2011). The transfusion service has become an important global player.

Blood banks meet clinician-defined needs, but often the indications for and results of transfusions are not documented in a satisfactory manner (6). This may suggest that the decision to transfuse is not always adequately thought through. This is not new; as early as 1985, Heistø suggested (10) that the clinical use of blood products often occurred on insufficient grounds.

This assumption is supported by the significant differences in transfusion practices seen between comparable countries and hospitals (11–13). Among the Nordic countries, Norway has the lowest use of erythrocytes for transfusion in relation to population size, but has long had higher levels of use than, for example, the Netherlands, which has moreover reduced its use by more than 20 % since the turn of the millennium (14). In Norway, a continuous increase in use has now turned into a slight decrease (7), despite an ageing population.

High dose intravenous immunoglobulin (IVIG) can alter, or «modulate», an unwanted immune response, and is attempted as a treatment for many otherwise intractable conditions. While for certain disorders this treatment must now be considered established, the evidence base is often weak (16). In Norway and other Western countries, use of IVIG increased greatly after the start of the millennium. By 2009, use had reached levels beyond what could be achieved with plasma collected domestically. Norway's system of self-sufficiency for plasma products had to be discontinued. Instead, Norwegian plasma is now sold to the European commercial plasma industry, which then delivers desired products back in accordance with contracts with regional health authorities (17). This also includes plasma from paid donors.

Norway has approximately 100,000 volunteer, unpaid blood donors. These individuals satisfy what are probably the world's most stringent selection criteria, and safety for patients is excellent (18). Voluntary, unpaid blood donation began in the Allied countries during World War II as a way for the civilian population to support the fight for a free society (8). Donating blood voluntarily and without pay is a reflection of socio-ethical values (19). A secondary rationale is that volunteer, unpaid blood donors may be less susceptible to blood-transmissible infections than paid donors (20), although such differences are not always evident (21). International organisations advise member states to remain self-sufficient in blood and plasma products with the help of volunteer, unpaid donors (17), also to prevent the commercialisation of human tissue (22). The Norwegian transfusion service is working to restore the balance between blood donation and blood use with the help of such volunteer, unpaid donors (17).

Back to self-sufficiency

A donation of whole blood provides approximately 250 ml of plasma. If the use of

erythrocyte concentrates were reduced, donors could be transferred from whole blood donation to plasmapheresis, in which each donation provides 600 ml of plasma. Over time, it would then be possible to restore the balance between supply and demand, and return to national self-sufficiency based on volunteer, unpaid donors (17).

Patient blood management (PBM) is an approach aimed at the optimisation of erythrocyte transfusion in elective surgery. The idea is to boost and make best use of the patient's own blood resources and ability to tolerate anaemia, and to use transfusions only to secure good treatment results and prevent complications. The PBM concept encompasses three main points: 1) detection and treatment of preoperative anaemia, 2) blood-saving surgical and anaesthetic techniques, including securing biological haemostasis and 3) improvement of the patient's ability to tolerate anaemia. PBM programmes can provide significant savings in the use of erythrocyte concentrates (23–25). Norwegian anaesthesiologists accepted lower Hb values as a transfusion threshold in 2002 than in 1996. Younger anaesthesiologists accepted lower thresholds than their older colleagues (26). PBM-like ways of thinking seem to be making their way into Norwegian hospitals and are probably part of the reason for the decline in the country's erythrocyte use. The PBM concept is also of interest for the management of chronic anaemia and in palliative contexts. About half of erythrocyte use is for non-surgical indications (6), and well-founded algorithms for these conditions will also help to optimise transfusion practice.

Outlook for 2114

There will always be anaemias that require provision of oxygen-carrying substances. *Ex vivo* production of blood cells for transfusion seems too costly for routine use (27). Artificial oxygen carriers are unlikely to serve as anything but niche products (27). If the number of circulating erythrocytes falls too low, biological haemostasis becomes suboptimal due to a reduction in the forces pressing platelets against the walls of small arteries (28). In bone marrow failure, transfusion of both erythrocytes and platelets will remain essential for the patient's survival.

Possibilities for manipulating the formation of new blood will probably improve. So too will methods for monitoring oxygenation and haemostasis, and for defining treatment needs (29, 30). Immunoregulatory drugs will take over from much of the use of IVIG. In 2114, there will still be a need for donor blood for transfusion, but its use in Norway will have decreased. Hopefully, the balance between Norwegian blood donation and use will be restored and will be based on voluntary, unpaid donations.

The global challenges are extensive. The WHO estimates, for example, that approximately 800 women die in childbirth every day (31), and that bleeding is the cause of death in 25–30 % of cases (32). In 2014, many countries have an inadequate transfusion service. In 2114, no one should die from lack of blood for transfusion. This requires conscious political and economic reforms in addition to good research (31, 33).

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