Obituary

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Alfred Hässig

1921–1999

Prof. Dr. med. Alfred Hässig, an internationally respected pioneer in the field of blood transfusion and blood products, died on November 14, 1999, after several months of illness. His life was dedicated to building up and developing the Swiss Red Cross (SRC) Blood Transfusion Service and its Central Laboratory (ZLB). He strongly influenced immuno-haematology and other fields of medicine in Switzerland and abroad.

As a young physician, Alfred Hässig joined the ZLB in 1949. The mission of this small division of the SRC included the production of lyophilized plasma for hospitals, blood group serology, the recruitment of blood donors, and the manufacture of transfusion equipment. In 1955 Alfred Hässig became head of this enterprise.

Lyophilized plasma, which was at that time the only stable blood product, was manufactured from pooled plasma obtained from whole blood of 30–70 donors. It soon became evident that recipients of this product occasionally developed hepatitis. Although transfusion-transmitted hepatitis was well known at that time, the striking association with dried plasma of this otherwise rare event was worrying. Alfred Hässig realized that by the pooling process, entire production batches became contaminated with hepatitis agents from a single donation. As a consequence, he started production of lyophilized plasma from single donations. By this measure, the risk of hepatitis decreased to the level observed after whole blood transfusions. Reduction of the infectious risk of blood products by using individual donations or the smallest possible donor pools became a dogma for Alfred Hässig.

Another important principle in Alfred Hässig's professional life was the non-remunerated nature of blood donations, an idea which was not, at the time, taken for granted in many countries, including Switzerland. Following this principle, the ZLB recruited unpaid blood donors and made them available to hospital blood banks, on condition that they became members of the SRC Blood Transfusion Service and no longer relied on paid donations. Within a few years, non-remunerated blood donation had been introduced throughout the country. As a representative of Switzerland in the Council of Europe and the World Health Organization, Alfred Hässig successfully helped to promote unpaid blood donation in other countries. In the 1950s and 1960s, the recommendations of these international bodies were mainly based on ethical considerations. However, the introduction of routine blood screening tests in 1970 provided evidence that paid donors were more frequently infected with transfusion-transmissible infectious pathogens than unpaid donors, and that products from paid plasma sources thus carried a greater risk. His international engage-

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ment in support of unpaid blood donation was met with considerable animosity from the emerging plasma product industry, which depended on paid plasmapheresis donors.

As early as in the 1950s, Alfred Hässig rallied a group of dynamic young scientists in the areas of protein chemistry, cell biology, experimental surgery, and immunology. Together, they developed the ZLB into a centre of excellence in plasma fractionation and transfusion medicine. In addition to the risk of hepatitis, the production of lyophilized plasma was hampered by the fact that a substantial proportion of donations had to be discarded due to high titres of haemolysins. How could this waste be avoided? An effective solution was plasma fractionation. Based on the technique developed by E.A. Cohn at Harvard University, H. Nitschmann, an alumnus of Cohn's group and P. Kistler, introduced their modified method of plasma fractionation at the ZLB, which today is still used there and at other European non-profit fractionation facilities. The first plasma product, pasteurized plasma protein PPL, became available in 1954. This product was a virtually pure 4% albumin solution, and was successfully used in hospitals in Switzerland for many years. PPL was later replaced by the current 5% albumin and supplemented by 20% albumin solution.

In 1956, the ZLB produced a lyophilized Cohn fraction I, aimed at the prevention of bleeding in haemophiliacs and other patients with a bleeding tendency. In order to keep the infectious risk as low as possible, the product contained plasma from just 2 donors. When in the mid-1960s J.G. Pool and coworkers discovered that the coagulation factor VIII precipitated in the cold and could be harvested as cryoprecipitate, many blood transfusion services including the ZLB took this up. To minimize transmission of hepatitis, Alfred Hässig supplied the Swiss haemophiliacs with a lyophilized cryoprecipitate made from 2 donations for paediatric patients and 8 donations for adults. The appearance in 1970 of coagulation factor concentrates made from pooled plasma of thousands of paid donors confronted the ZLB product with serious competition, since the concentrates were well tolerated and suitable for home treatment. The disadvantage of the concentrates, i.e. the increased risk of viral hepatitis, was accepted by many doctors and patients as an unavoidable hazard of treatment. At the instigation of the Swiss Haemophilia Association, Alfred Hässig started to produce concentrates from pooled unpaid domestic plasma, but continued to advocate treatment of haemophiliacs with cryoprecipitate from small donor pools. The introduction of virus inactivation steps came too late to prevent the AIDS tragedy in the haemophilia community.

In the early years of the ZLB, the team working with Alfred Hässig gained its first experience with immunoglobulins. It was known that this plasma fraction contained antibodies against infectious pathogens, and intramuscular injections of immunoglobulins were used clinically to prevent or mitigate viral diseases such as measles and hepatitis. The observation that certain patients with severe susceptibility to infection were unable to produce immunoglobulins gave rise to the term agammaglobulinaemia, or antibody deficiency syndrome. Intramuscular injections of immunoglobulins resulted in a clear reduction in the susceptibility of such patients to infection. Swiss investigators at the Universities of Bern and Zürich recognized the great therapeutic potential of immunoglobulins produced by plasma fractionation. The painful and volume-limited intramuscular injections were not suitable for adequate treatment. However, intravenous substitution of the missing antibodies was impossible because of severe intolerance reactions. After years of clinical and experimental studies, Alfred Hässig's group gradually overcame these difficulties and developed a safe intravenous immunoglobulin preparation. Thanks to the cooperation of the ZLB with Sandoz and later with Novartis, this product has since 1980 developed into one of the leading intravenous immunoglobulins. Its use in the early years was limited to antibody deficiency states, but the work of P. Imbach and his colleagues at the Children's Hospital of Bern and of many other clinical investigators has broadened the range of indications to include autoimmune and chronic inflammatory disorders.

Until about 1970, only whole blood transfusions were given to anaemic patients. When Alfred Hässig realized that red blood cells were therapeutically employed in Eastern Europe, he encouraged clinical studies in Switzerland. Plasma-depleted concentrated red blood cells proved to be clinically superior to whole blood. This was the birth of component therapy, formulated by Hässig's friend and colleague P. Lundsgaard-Hansen. In this widely recognized therapeutic approach, whole blood was replaced by its components, i.e. red blood cell and platelet concentrates, fresh frozen plasma, and plasma derivatives including albumin, coagulation factors, and immunoglobulins. It permits treatment based on the needs of the individual patient and optimizes the use of donated blood.

How could the ZLB use its surplus red blood cell concentrates sensibly, without threatening the existence of regional transfusion centres economically dependent on these components? Alfred Hässig found a suitable partner in A. Kellner, the head of the New York Blood Center, which was suffering from a permanent shortage of donors. In 1973 the Euroblood Program was started, in which the ZLB and other European Red Cross blood transfusion services sent their surplus units of red blood cells to the New York Blood Cen-

ter. A smaller programme involving the ZLB and the Greek Ministry of Health helped cover the high demand for red cells of Greek thalassaemia patients.

For the employees of the ZLB, Alfred Hässig was an appreciated and popular father figure; nowadays, his style of leadership would probably be described as patriarchal. His comprehensive and detailed knowledge of transfusion medicine and related topics was impressive, and his voluminous memory never let him down. At his retirement in 1986, Alfred Hässig left his successor H.J. Heiniger a flourishing and internationally recognized company with around 500 employees. The planning for a major expansion of the building and production facilities was already underway. Alfred Hässig liked anecdotes, bons mots and jokes, and had a remarkable talent of relaxing tense discussions by an amusing story told at the right time. This gift may have often helped him to successfully reach agreement in difficult negotiations. With his lively perception of interesting new ideas he generously supported external research groups, especially in the field of immunology. His expertise in transfusion medicine and blood products was in great demand internationally: as a guest and consultant, Alfred Hässig visited blood transfusion services and non-profit fractionation centres all over the world. Between 1960 and 1968, he served as adviser to the World Health Organization, the Federation of the Red Cross and Red Crescent Societies, and the Council of Europe. From 1974 to 1978, he was president of the German Society of Transfusion Medicine and Immunohaematology, and from 1982 to 1984 he presided over the International Society of Blood Transfusion. In 1962 Alfred Hässig was awarded the Marcel Benoist Prize. Since 1966 he was professor of immunopathology, transfusion medicine, and forensic serology at the University of Bern.

During his retirement Alfred Hässig and his newly created study group on alimentation and immunity were devoted to fundamental questions relating to the influence of nutrition on atheromatosis and arthrosis, as well as on immunity and cancer. He also developed a number of – sometimes provocative – hypotheses on the development of AIDS. Unfortunately, these years were overshadowed by legal proceedings in Geneva, in which he was accused of negligence in the production of coagulation factors. As has been known since 1986, the AIDS catastrophe has not spared haemophiliacs in Switzerland, although the number of patients affected is low in comparison with other countries – not least due to the preferential use of domestic small donor pool cryoprecipitates. The case brought against him by HIV-positive haemophiliacs hit hard. The reduction in the infectious risk, particularly of coagulation products, had been one of his central lifelong concerns, and these accusations caused a personal tragedy.

With Alfred Hässig we have lost an extraordinary person. We miss his profound knowledge, his anecdotes, and his witty conversations. His life's work deserves our recognition and respectful thanks.

Andreas Morell