This paper described, for the first time, how diminished amounts of substances (such as adenosine diphosphate [ADP] and serotonin) that are ordinarily found in a special pool (the storage pool) located in platelet-dense granules could account for abnormalities of platelet function in patients with congenital bleeding disorders. It is an excellent example of how collaboration between scientists in two disciplines was used successfully to solve a problem in clinical medicine. The SCI/CSC indicates that this paper has been cited in over 170 publications.

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April 21, 1986

In the early 1960s a significant number of patients had bleeding disorders that were largely unexplained. Studies in New York by one of us (HJW) had demonstrated that the major deficiency in these patients was related to an impaired ability of the platelets to release substances (including ADP) upon stimulation by a variety of agonists, and further studies showed that these patients' platelets did not aggregate normally with collagen (which requires released platelet ADP), which led to the first description of bleeding disorders apparently due to deficient release of ADP. These studies provided the impetus for HJW to study the effect of aspirin on collagen-induced aggregation, since it was well known that aspirin also prolonged the bleeding time and resulted in the first demonstration that aspirin ingestion in normal subjects can also inhibit collagen-induced aggregation due to an impairment of the platelet-release reaction.

Simultaneously and independently, HH had been working in Oslo on basic mechanisms involved in agonist-induced platelet responses and had provided evidence that all substances released from platelets upon stimulation originated from subcellular storage organelles and were specifically discharged from the cells without loss of cytoplasmic constituents; the "platelet release reaction" was, in fact, an exocytotic event that should be called "platelet secretion." Of particular interest was the demonstration that the secretable ADP was stored in a special, nonmetabolic pool of adenine nucleotides (two-thirds of the platelets' total adenine nucleotides) within the dense granules of the platelet. HH had demonstrated the metabolic inactivity of this special pool of ADP by showing that it remained unlabeled during short-term incubation of the cells with radioactive phosphate, adenosine, or adenosine diphosphate. For this reason, it was termed "storage pool ADP." The findings by HJW that some of the patients with release defects had, in fact, a decreased amount of ADP in their platelets suggested that they might be deficient in storage pool ADP.

When HH moved to Philadelphia, the two authors soon discovered that they had several common interests. One of these was scientific and involved studies to determine whether any of the patients were, in fact, deficient in storage pool ADP. The other was musical; HH played the violin, HJW the viola, and both were avid chamber music players. The opportunity to pursue both interests was irresistible.

Having established that the family with deficient platelet ADP was, in fact, specifically deficient in storage pool ADP, we proceeded to examine the possibility that unrelated patients might also have the same abnormalities. This study resulted in the Classic article and showed that a deficiency of platelet storage pool ADP was the underlying basis for some types of bleeding disorders. Since these patients specifically lacked the storage pool of ADP, we termed the disease "storage pool disease."

Subsequently, this type of abnormality was found in several other groups of patients with congenital bleeding disorders, including Hermansky-Pudlak syndrome, myeloproliferative syndromes, disseminated intravascular coagulation, immune-mediated platelet injury, and others. Thus, the description of storage pool deficiency in patients with congenital bleeding disorders established a mechanism for explaining platelet-function defects that was more widely applicable in clinical medicine.

It might be added that the musical collaboration proved to be equally enjoyable, although we regret to say that our efforts in this area have never been cited as being particularly important.

For recent work by one of the authors (HJW), see reference 7.