

The platelet in pathophysiological research

Introductory remarks

The idea of a special review in EXPERIENTIA on the platelet in pathophysiology arose from the consideration of how to celebrate two anniversaries, namely the 70th birthday of Professor Alfred Pletscher and the first ten years of the Department of Research of the University Hospital of Basel for which he was one of the most eminent promoters and which he directed during its first decade. The Department, which is located in the Center for Teaching and Research (Zentrum für Lehre und Forschung, ZLF) and brings together the research laboratories of the different university clinics, has become a unique center for basic and applied medical research within the medical faculty.

Since Alfred Pletscher has devoted most of his scientific career to research into neurotransmitters, using the platelet as a model for investigating the mechanisms of transmitter function, we felt it appropriate to organize a meeting on the platelet as a model in neurobiological and cardiovascular research. Distinguished scientists from various countries gathered at the ZLF on March 20/21, 1987, to honor Alfred Pletscher and to review the state of research in this field. In

addition, members from the Department of Research presented some highlights of their own research. The meeting was also a tribute to the centennial of the National Institutes of Health in Bethesda with which Alfred Pletscher has been long connected.

Since EXPERIENTIA and Alfred Pletscher have been closely associated in the last decade, EXPERIENTIA is the journal of choice for the publication of this meeting. The proceedings are grouped into three sections: 1) The Platelet in Cardiovascular Research, introduced by E. F. Lüscher, Bern; 2) The Platelet in Neurobiological Research, introduced by G. A. Born, London, and 3) Current Activities of the Department of Research. In his closing remarks on the perspectives of the platelet in neurotransmitter research, Alfred Pletscher demonstrates that this model is still very attractive for future research.

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Alfred Pletscher completed the seventh decade of his life on 5 March 1987. He did not consider this to be an occasion for contemplation. It was a day like any other, perhaps with a pause for breath, but only with the aim of 'reculer pour mieux sauter'.

Alfred Pletscher has always been able to make rapid decisions and has never been tempted to ponder too extensively over his actions as time was too valuable for him. His intuition and experience rarely let him down.

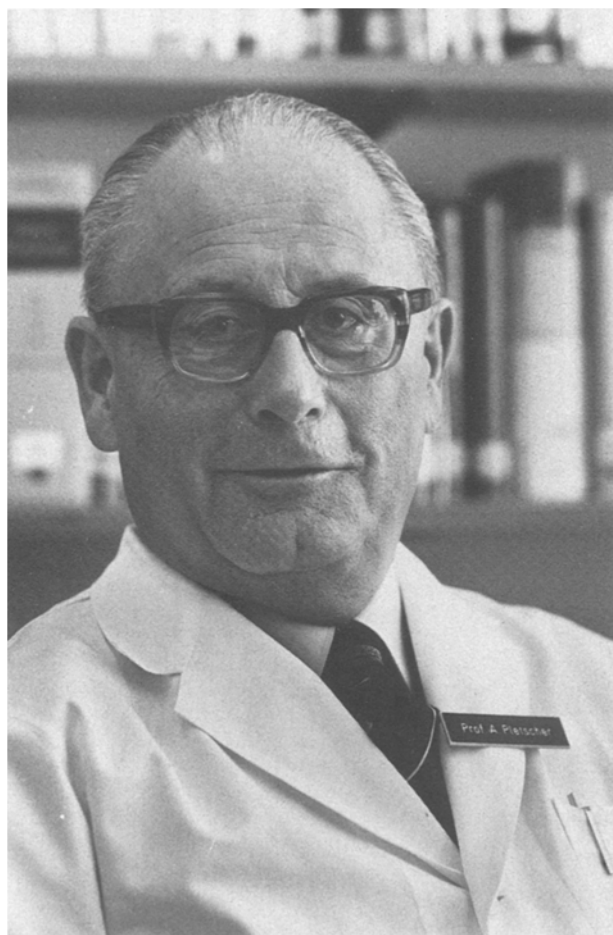
It may sound strange, but Alfred Pletscher is actually a Rhinelander, although a genuine Swiss one being a citizen of Schleitheim near Schaffhausen on the Rhine. He was born and grew up in Altstätten, in the part of the Rhine valley belonging to the canton of St. Gallen where the river is still young and only dreams of its later importance. Basel, the city on the Rhine, finally became his second home.

Alfred Pletscher has always had a special relationship with nature. It is rational rather than idealistic and it influenced his future as a scientist. He first studied medicine in Zürich, Geneva and Rome between 1935 and 1942. However, he

found the subject matter too narrow, conventional and empirical, and therefore, after qualifying as an MD and spending two years doing clinical work, he turned to chemistry. Paul Karrer, the famous bioorganic chemist and Nobel laureate in Zürich, became his teacher and supervised his Ph.D. thesis.

Thinking and working in chemical terms fulfilled his need for order and synopsis. The studies of simple natural products made the young physician realize the complexity of biomedical questions and the difficulties involved in answering them. He not only wanted to treat patients but, even more, to understand the biochemical patterns behind the disease. From the very first his main guiding principle was to follow the changes brought about by natural or synthetic substances in specific cell and organ models.

In 1948 Alfred Pletscher came to Basel and joined the University Medical Clinic where he found a teacher tailored to his needs – Hans Staub – who was exceptional both as a clinician and clinical pharmacologist. He was given time and money for clinical and experimental investigations, mainly in



the field of carbohydrate metabolism and toxicology. He was among the first to discover that fructose is metabolized differently from glucose and that it accelerates the disappearance of glucose from the blood. Also, together with F. Übelin, he was one of the first to describe that β -naphthylamine and benzidine but not aniline were the causative agents for the high incidence of bladder carcinoma in dye workers. On the basis of these studies he became 'Privatdozent' and head of the clinical research laboratories. Could it be that he was already then playing with the idea of an independent research department within the medical faculty which was actually realized 30 years later?

He was the favorite pupil of Prof. Staub who would have liked him to be his successor as head of the clinic. However, in 1954 Pletscher went to work with Bernard B. Brodie at the Heart Institute of the NIH in Bethesda, USA, and many of his later research projects originated from this stay. This period was perhaps the most significant experience in his scientific life. The discovery made together with Shore and Brodie that the psychotropic agent reserpine depleted brain 5-hydroxytryptamine was an important breakthrough which had a major impact on the development of the then new field of biochemical neuropsychopharmacology.

In 1955 Alfred Pletscher was appointed director of biomedical research at Hoffmann-La Roche in Basel and later became also the first Professor of Pathophysiology of the University of Basel. In 1967 he was promoted to head all research of the whole Roche group, first in conjunction with Prof. Pl. A. Plattner. At the same time he became a member of the executive management.

He was the first medical scientist to be trusted with the entire research of a large Swiss chemical firm. Even his tremendous obligations as head of a research department with over 1000 employees and as professor at the University did not make him give up his own laboratory work. He does not deny that he was lucky and greatly helped by the favorable climate for scientific research at Roche which, at that time, possessed a degree of autonomy and coherence which was the envy of scientists in other chemical companies.

After his stay in Bethesda, Pletscher's scientific interests concentrated mainly on biogenic amines – a research direction which had interested Marcus Guggenheim in Roche decades earlier. The entry of Pletscher revived the activities of the firm in this field. Together with his colleagues, he published many papers on biogenic amines, especially on their diversity and manifold functions as neurotransmitters in both the nervous and circulatory systems. He also introduced the blood platelet as a practical model for the investigation of the modes of action of these amines at the cellular and subcellular levels. These research activities brought new insights into the pathophysiology of various diseases of the central nervous and circulatory systems and led to the development of new drugs against mental depression and disorders of movement, e.g. in Parkinson's syndrome and choreoathetosis. He has been awarded honorary degrees by the Universities of Geneva, Paris, Lausanne and Vienna for his scientific achievements and he received the Science Prize of the City of Basel.

During his time at Roche, Pletscher set his own priorities in research directions, not only opening up new fields, but also sacrificing one or the other research project. Even an industrial research director with a high degree of freedom has to set preferences and observe certain boundaries.

Pletscher has always had a touch of the autocratic and has never been an easy superior. Someone who disagrees with him has to have concise and cogent reasons for doing so. He does not like prolonged arguments. Basically, he is also too much of an individualist to be cut out for teamwork. However, over the years the gifted 'soloist' has gradually changed into a many-sided conductor of the 'orchestra'.

As a result of his professional experience, he found the necessary detachment and insight to convert his concept of science policy into reality also on a general basis. In the 1960s he began to be involved in the management of several public and semiprivate research institutes, such as the Institut Suisse des Recherches Expérimentales sur le Cancer (ISREC) at Lausanne and the Biocenter of the University of Basel of which he was one of its most prominent initiators. He was also mainly responsible for the foundation of both the Roche-sponsored basic research institutes, namely the now famous Basel Institute of Immunology and the Roche Institute of Molecular Biology in Nutley, New Jersey.

It was therefore not surprising that Pletscher was elected to the Research Council in 1968, which is the executive body of the Swiss National Science Foundation (SNSF). As a member of its Division of Biology and Medicine, he continued to encourage Swiss scientists working abroad to return to research institutes in Switzerland, thus contributing to the establishment of a number of centers of excellence in this country. With the limited funds available to a small country, Pletscher did not avoid the dilemma between supporting a few elite research groups (priority areas) and ensuring broad competition. He realized that more reliable methods for the evaluation of projects and applicants as well as the rating of results had to be the answer.

In 1976 he was elected to be the head of the division of the newly created National Research Programmes (NRP) within the SNSF. This politically motivated venture was established in order to promote an interdisciplinary approach to research and to stress its more practical needs. Pletscher had

been accustomed to acting along similar lines for many years so that he understood the problems and could avoid programs that would merely lead to wishful thinking. The SNSF which had formerly only supported basic research was now forced to tackle a task which was delicate because of the social and political pressures involved. Perhaps this was the first of Pletscher's jobs which did not cause any envy. As usual the challenge inspired him, and under his guidance the proposal was shaped and made tangible. The NRP came gradually into being and finally found their place within the SNSF. It was only logical therefore that the Council of the SNSF elected Pletscher as President of its Research Council in 1980.

In the meantime Pletscher had left Roche because of changes and new strategies in management including new concepts of research which did not conform to his ideas of scientific planning. Both his entry into Roche and his departure from the company were under a lucky star; was it 'chance or necessity'?

The Medical Faculty of the University of Basel had been considering transferring all the scientific activities from its various clinics and institutes to one Department of Research for a long time. As Professor of Pathophysiology, Pletscher took part in the preliminary planning with the idea of allowing qualified scientists to work in small groups in stimulating surroundings with a good research infrastructure. The themes had to be clinically orientated and of immediate interest to the practitioner. The head not only coordinates the groups but also follows his own research interests, like any other member of the Department.

A center of biomedical research was a novelty in Switzerland at that time. It became a reality in 1977, finding a home in the newly constructed Center for Teaching and Research (Zentrum für Lehre und Forschung) at the University Hospital. Pletscher was invited to become its first head in 1978 and has since then built it up to its present high standard. The Department of Research which unmistakably bears Pletscher's signature also forms a link between the University Clinics and the Biocenter, which concentrates on basic research. The circumstances which led Pletscher to decide to part from Roche might have been a 'necessity' but the timing was 'chance'.

For all who have known Alfred Pletscher for decades and have had the privilege to work with him or had the opportunity to follow his career, he is a stringent personality, strictly factual in his ways of thinking and nevertheless anything but insensible to human concerns and needs. It is because of these particular features that we hope to see him in the coming years, not only as an elder statesman of the scientific community but also as a mediator between science and society since, in spite of the right to information now generally acknowledged, more and more people know less and less about the essentials of science and nature. This is in fact a human problem as culture is also communication, as Jeanne Hersch once said. Would this not be a new challenge to Alfred Pletscher? May he continue to pursue his objectives and, together with Mrs Pletscher, enjoy the time to come.

Platelets and cardiovascular research: An introduction

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Platelets have a rather intriguing history: first described in 1842 by Donné, it took 40 years until Bizzozero¹ and others drew attention to their unique role in hemostasis and thrombosis. For Morawitz, when he wrote his classical review³ in 1905, blood coagulation started out from damaged platelets. It is amazing that during the following 50 years, platelet research was almost totally neglected and we owe it to Roskam⁴ and Macfarlane² and their schools that research workers again became aware of the essential role of the platelets in hemostasis and of their actual function in the blood clotting system. However, what finally caused platelet research to expand in an almost dramatic way, was the realization that platelet aggregation ever so often initiates arterial thrombosis and therefore is a primary pathogenetic factor in myocardial infarction and stroke.

Within the last 40 years we have come a long way in recognizing the platelet as a metabolically highly active cell capable of synthesizing prostaglandins, of releasing from storage organelles an amazing variety of substances, of responding to a vast spectrum of agonists which trigger the most complex intracellular machinery involving G-proteins, calcium- and phospholipid metabolism, and an intricately controlled contractile system, to mention only a few highlights among

the many findings which we owe to a still increasing number of workers in this field.

Platelets have also been implicated in atherogenesis⁵, mainly because they release mitogenic factors acting on cells of the vascular wall; however, doubt has been cast on their dominant role⁶ and more work is required in order to elucidate the highly complex process of the formation of an atherosclerotic lesion.

There is of course another reason why platelets have become such a preferred object of research: It is relatively simple to isolate them in pure and viable form and they react to stimuli in a well-defined, easy to follow way. No wonder that platelet research is no longer the domain of hematologists alone; however, as useful as the platelet may be as a model for many aspects of cellular activity, its involvement in cardiovascular diseases will continue to stand in the foreground of interest and it is this aspect which will dominate the first part of this symposium.

1 Bizzozero, J., Über einen neuen Formbestandteil des Blutes und dessen Rolle bei der Thrombose und der Blutstillung. *Virchows Arch. Path. Anat. Physiol.* 90 (1882) 265–332.