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 Bizzozero [1] and others drew attention to their unique role in hemostasis and thrombosis. For Morawitz, when he wrote his classical review [3] 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 Roskam [4] and Macfarlane [2] 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 synthetizing 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 atherogenesis [5], mainly because they release mitogenic factors acting on cells of the vascular wall; however, doubt has been cast on their dominant role [6] 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.

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Platelet abnormalities and the pathophysiology of essential hypertension

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Summary. The mechanisms whereby intracellular calcium concentration is controlled are briefly reviewed. With the current knowledge of both calcium homeostasis and the function and properties of cellular Ca^{2+}-target proteins/signal transduction systems, a dysfunction of cellular calcium metabolism is considered in relation to the pathogenesis of hypertension. Although the enhanced peripheral vascular resistance characteristic of hypertension is ultimately a function of Ca^{2+} availability for smooth muscle cell contraction, the platelet possesses many parallel biochemical and physiological properties. Therefore, we have utilized the platelet as the cell-model for investigating the role of Ca^{2+} in hypertension disorders. An overview of Ca^{2+}-linked platelet processes altered in essential hypertension is presented, and an attempt is made to integrate these multiple aberrations in a fundamental membrane lesion.
Key words. Platelets; intracellular calcium concentration; essential hypertension; cyclic nucleotides.

Regulation of cellular Ca^{2+}-concentrations

Calcium is a fundamental regulator of cellular function. An understanding of the general principles of cellular Ca^{2+}-regulation is crucial to the pathophysiology of hypertension and its effective treatment because the heart, adrenal glomerulosa, neural synapses, juxtaglomerular apparatus, platelets and smooth muscle cells use Ca^{2+} as a positive intracellular messenger.

Intracellular calcium concentrations ($[Ca^{2+}]_i$) are regulated by a complex array of transport mechanisms at various membrane and intracellular locations. The entry of Ca^{2+} from the extracellular space is mediated by voltage sensitive Ca^{2+}-channels and other putative mechanisms including release of Ca^{2+} bound to membrane surfaces, entry through receptor-mediated channels, or nondefined passive leaks across the membrane. Ca^{2+} is also released from internal endoplasmic reticulum and from mitochondria. In resting cells, $[Ca^{2+}]_i$ is maintained at $\sim 10^{-7}$ M which is considerably lower than millimolar extracellular free Ca^{2+}. In stimulated cells $[Ca^{2+}]_i$ does not generally exceed 10^{-5} M. Therefore, under both conditions, internal calcium levels are necessarily maintained by the action of active transport mechanisms that remove Ca^{2+} from the cytosol, including the plasma membrane ATP-dependent Ca^{2+}-pump, the plasma membrane $Na^+ - Ca^{2+}$-exchanger, the endoplasmic reticulum ATP-dependent Ca^{2+}-pump and the mitochondria Ca^{2+}-pump. The net result of the operation of all these Ca^{2+}-translocating mechanisms is the imbalance of Ca^{2+}-concentrations within the cells, which are therefore primed for Ca^{2+}-signaling events to permit a rapid and large increase in cytosolic Ca^{2+} [14, 36].

Essential hypertension, platelets and calcium

In the pathophysiology of essential hypertension several factors have been proposed including enhanced sympathetic nervous system activity, reduced renin-angiotensin-aldosterone axis endocrine control, dietary salt and genetic factor(s). Direct clinical corollaries for an integrative contributory role for Ca^{2+} in the pathophysiology of essential hypertension are that patients with essential hypertension (EHT) exhibit excess calcium-influx-dependent vasoconstriction, and that blood pressure in these patients is normalized following therapy with calcium antagonists [6, 7, 31]. A key characteristic of essential hypertension is elevated peripheral vascular resistance, which is ultimately mediated by enhanced vascular contractility. An altered state of vascular reactivity can result from alterations in either cellular calcium metabolism or the sensitivity of response elements to the actions of Ca^{2+}. Investigations in search of support for the hypothesis that perturbation of calcium metabolism is a fundamental lesion in essential hypertension have been carried out on a wide variety of tissue and cell types including myocardium, smooth muscle, erythrocytes, adipocytes, hepatocytes, synaptosomes and platelets in both human and animal models of hypertension [15, 34, 35, 41].

A specific role for platelets in the pathophysiology of hypertension should be considered since these cells are mediators of thrombotic complications, vectors for vascular tone and promoters of atherosclerosis. There are many similarities between platelets and smooth muscle cells. Both platelets and smooth muscle cells have an adenylate cyclase system that can be activated by adrenaline via alpha-2 adrenoceptors and inhibited by prostaglandins with attendant changes in calcium [11]. Calcium can be selectively stimulated via angiotensin II receptors [30] and calcium entry can be blocked by slow calcium channel inhibitors [37]. There are similar calcium-dependent contractile systems and similar pools for regulation of intracellular calcium (the dense tubular system in platelets and the sarcoplasmic reticulum in smooth muscle cells) [36]. There are comparable calcium-dependent physiological functions: shape change, aggregation and secretion in platelets and contraction in smooth muscle cells. Hormone receptor activation leads to parallel alterations in the clinical setting of essential hypertension: increased sensitivity, shape change and aggregation of platelets and increased vascular resistance of resistance vessels. These corollaries together with easy clinical accessibility and preparative cellular homogeneity of platelets focused our investigations on the human platelet as a model reflecting events occurring in smooth muscle cells.

It is the purpose of this paper to present a summary of present findings with respect to cellular Ca^{2+}-handling in platelets from patients with essential hypertension in search