Obituary: Hans Jürg Schatzmann (1924–2021)

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The most dangerous result in science is the one you were hoping for because you declare victory and become lazy.

W. G. Kaelin Jr., Noble Laureate 2019

Hans Jürg Schatzmann, a pioneer in the analysis of cation transport mechanisms across the cell membrane, died on the 2nd of October 2021 at the age of 97. He held the position as Professor and Chairman of Pharmacology at the Faculty for Veterinary Medicine (today Vetsuisse Faculty) at the University of Bern, Switzerland, until his retirement in 1989. Hans Jürg Schatzmann was born in Bern in 1924 as the eldest son of a medical doctor. Except for a 2-year stay (1956–1958) in the USA, he remained loyal to his hometown throughout his education and professional career. In 1951, after graduating from Medical School and finishing

a doctoral thesis in Internal Medicine, he joined the Institute of Pharmacology. He became an assistant to Walter Wilbrandt, one of the pioneers in the quantitative analysis of membrane transport mechanisms, whose work and thinking made a lasting impression on the young scientist. Nevertheless, still undecided, he left the institute after 2 years for another stint in clinical medicine prior to moving to the States. There he worked first at the Department of Pharmacology at the University of California in San Francisco and then in the Biophysical Laboratory of Harvard Medical School in Boston under the supervision of A. K. Solomon. In 1958, he returned to the Pharmacological Institute in Bern. He obtained his ‘habilitation’ for Pharmacology in 1964, and 1 year later, he was elected as Professor of Pharmacology to head a newly established institute at the Faculty of Veterinary Science. Prior to his arrival, instruction on drugs and drug treatment played a relatively minor role in the lectures of the various clinicians. The new institute was small and had only very limited financial and human resources. Nonetheless, Schatzmann preferred to manage very carefully and economically rather than to spend his time on administration and on the writing of major grant applications. He remained in this position until his retirement in 1989.

Schatzmann has gained international reputation as a scientist, especially through two important discoveries. Both concerned active cation transport mechanisms in the cell membrane which he studied using human erythrocytes as a model system. This system is particularly useful because, as shown in 1952 by a Hungarian group, solute concentrations can be controlled on both sides of the membrane via reversal of haemolysis. Schatzmann’s results have been part of the general knowledge for so long that young pharmacologists or physiologists may have trouble to link his name with his findings. Thus, for example, the use of the term ‘Na⁺/K⁺-ATPase inhibitor’ as a general designator for cardiac glycosides (Seifert and Schirmer 2021) is based on Schatzmann’s experimental results 68 years ago.

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In 1953, as a young assistant of Wilbrandt, Schatzmann observed a highly specific inhibition of the red cell 'Na⁺-pump', the active (uphill) transmembrane movement of Na⁺- and K⁺- ions, by ouabain, a cardiac glycoside (Schatzmann 1953). At the time, very little was known about the mechanisms of this transport system. Neither was it clear whether Na⁺ and K⁺ movements were coupled nor whether they required ATP. A hypothesis suggested that mineralocorticoids (MC) might be involved in the regulation of membrane transports. Schatzmann reported in his very readable autobiographical essay (Schatzmann 1995) that he, initially, was not aware that the stereochemistry of cardiac glycosides differs greatly from the one of cholesterol-derived steroid hormones. Therefore, he expected some kind of competitive interaction between MC and ouabain and was surprised that its inhibitory action was completely unaffected by MC.

In spite of these false starts, Schatzmann persisted and later made significant contributions to the clarification of the kinetics of the membrane Na⁺/K⁺-ATPase and its detailed interactions with specific inhibitors in human and cattle red cells (Schatzmann 1965; 1967; 1974). This enzyme had first been described in 1957 by Skou in nerve microsomes, but only after it turned out to be specifically inhibited by ouabain was it identified as the membrane transport protein.

Thirteen years after his first important discovery, in 1966, Schatzmann was the first to characterize, in red cells, an active, ATP-dependent uphill transport of Ca²⁺ ions from the cytosol across the cell membrane into the extracellular space (Schatzmann 1966; Schatzmann and Vincenzi 1969). At the time, it was already known that the intracellular Ca²⁺ concentration of erythrocytes was much lower than the one in blood serum. Moreover, muscle cells had been shown to contain a Ca²⁺-activated transport ATPase that seemed to be associated with muscle relaxation and to be located in intracellular vesicles (Hasselbach and Makinose 1961). However, no association between an ATPase activity and Ca²⁺ movements across the surface membrane of cells had been observed.

As with the Na⁺/K⁺-ATPase inhibition, Schatzmann's observations on the membrane 'Ca²⁺-pump' were confirmed in many other kinds of cells. They provided a starting point for a host of studies not only on the kinetics and the biochemical and molecular properties of the ATP-dependent transport proteins, but also on the more general regulation of intracellular ion concentrations. In addition to Schatzmann and his co-workers, many international research groups have contributed to improve our understanding of these life-sustaining ion transport systems. Schatzmann focussed on the mechanisms enabling cells to maintain nanomolar intracellular Ca²⁺ concentrations in the presence of millimolar extracellular concentrations. He contributed crucial studies to establish the stoichiometry of the transport system (Schatzmann 1973). Together with Ben Roelofsen, a guest researcher from Utrecht in his lab, he studied the lipid

requirements of the ATPase (Roelofsen and Schatzmann 1977). Already in 1962, Schatzmann had provided evidence for the lipoprotein nature of both the Na⁺/K⁺-ATPase and the Ca²⁺-ATPase in the red cell membrane (Schatzmann 1962). Frank Vincenzi, a former guest researcher from Seattle, who had contributed to the early calcium pump studies (Schatzmann and Vincenzi 1969), later went on to describe the interaction of the pump with Ca-calmodulin. However, it would take a few more years before it could be shown unequivocally by the Group of Carafoli in Zürich that the pump indeed catalyses a Ca²⁺-H⁺ exchange (Schatzmann 1988).

In many cell types, especially excitable cells like neuronal or myocardial cells, the intracellular Ca²⁺ concentration is closely linked to cellular signal transduction, cell movement or muscular contractility. It is also coupled to the regulation of transport systems for Na⁺ and K⁺. In addition to the Ca²⁺-pump, excitable cells express a transport system that uses the inwardly directed electrochemical gradient for Na⁺ as driving force for the outward (uphill) transport of Ca²⁺, mediating the electrogenic exchange of one Ca²⁺- versus three Na⁺- ions. This transmembrane Na⁺/Ca²⁺ exchange, first described by Reuter and Seitz (1968) for the myocard and by Baker et al. (1969) for the squid axon, later allowed to explain the positive inotropic effect of ouabain via its inhibitory effect on the Na⁺/K⁺-ATPase, described by Schatzmann (1953), and the resulting increase in the cellular Na⁺-level. Due to the activity of the Na⁺/Ca²⁺ exchanger, any increase in the cellular Na⁺-concentration entails a decrease in the efflux of Ca²⁺ through the cell membrane. The resulting increase in the cellular Ca²⁺-level will enhance myocardial contractility. It was a major advantage that human red cells, Schatzmann's favourite model system, do not express the Na⁺/Ca²⁺ exchanger and hence, allow an analysis of the Ca²⁺-pump in isolation. In excitable cells, the bulk of transmembrane Ca²⁺-movements is handled by the exchanger. Therefore, the simultaneous presence of an ATP-dependent Ca²⁺-transporter in the cell membrane, responsible for the fine tuning of cellular calcium levels, was overlooked initially. It required a targeted search on the basis of Schatzmann's earlier results (Caroni and Carafoli 1980).

Prior to embarking on his successful work with the red cell Ca²⁺-ATPase, during and after his stint in the States, Schatzmann had ventured into renal and smooth muscle membrane physiology. In A. K. Solomons Laboratory in Harvard, he had worked with Erich Windhager and Guillermo Whittembury on renal water and sodium movements in perfusion experiments with single amphibian proximal tubules (Schatzmann et al. 1958). Together they established the presence of an active sodium transport and a passive reabsorption of water. Back in Bern, he started a project in smooth muscle physiology using electro-physiological methods and calcium flux measurements in the guinea pig taenia coli preparation (Schatzmann 1964). In retrospect, he

felt that overall, compared to red cells, both of these model systems were too difficult to control and too prone to artefacts and hence resulting in his work leading to dead ends.

In addition to his research in membrane physiology, Schatzmann took his role as veterinary pharmacologist very seriously. His lectures were very well received by the students. Since a short textbook on Veterinary Pharmacology was lacking, he carefully elaborated a suitable text (236 pages). It was printed and bound by the University printing office for the exclusive use by Bernese Veterinary students. Twenty-nine gifted undergraduates were motivated to start a doctoral thesis by doing experimental work within the small team in his laboratory. Part of their work resulted in important pharmacokinetic studies in farm animals and horses at a time when such studies were still rare, and the lack of pharmacokinetic information quite frequently resulted in more or less severe dosing errors. Other projects were concerned with measuring fermentation rates in the ruminal fluid or with the handling of cations in cattle red cells. In erythrocytes from most, but not all, animals, the activity of both the Na^+/K^+ - and the Ca^{2+} -transport ATPases decreases from high levels at birth to low levels in adults (Schatzmann 1974).

Outside of these veterinary research interests, he also played an important role in the Swiss drug control authority as president of the section for veterinary drugs.

He was keen to give his students the experience of how much effort and (self-) critical analysis need to be invested into even rather small steps towards scientific progress. He was convinced that deep and original thinking prior to performing experiments was immensely more efficient than doing experiments with a fuzzy concept and hoping for some interesting result due to serendipity. He remained suspicious towards complicated apparatuses, complex computer programs, or ready-made reaction mixtures whose functioning was beyond the step-by-step control through the experimenter. One of the idiosyncrasies in Schatzmann's personality was his conviction that for a serious researcher, the only trustworthy experiment was the one that he had performed himself and that he had completely understood. Hence, it was surprisingly difficult for him to accept, for prolonged periods, in his lab self-reliant co-workers following their own ideas.

In almost all of his original papers, he shared a significant part of the experimental work and about a third of them he authored alone. Of course, this ambition contributed to limiting the total number of his publications to about 70. In the age of impact factors, it might seem surprising that Schatzmann's early papers were published in German in relatively modest Swiss Journals. Still, the ouabain paper from 1953 in *Helvetica Physiologica et Pharmacologica Acta* remained his most cited work collecting, up to now, 845 citations. It is also the only paper that still maintains (after 68 years!) a constant citation rate of 4–7 per year. One might suspect that most authors pick it up from Schatzmann's later publications

in English. Second on the list, with 525 citations, is the first detailed Ca^{2+} -pump study by Schatzmann and Vicenzi in the *Journal of Physiology* (1969). By contrast, the first description of the pump in 1966 (in *Experientia*, albeit in English) lags behind with 361 citations. After 1969 *The Journal of Physiology* became his preferred, though not exclusive, platform, for the publication of his best work.

Schatzmann disliked to put himself or his work into the lime-light. Nevertheless, he was proud to perform successful research with relatively simple techniques and a low budget. In any case, he gratefully appreciated the recognition of his achievements by his numerous scientific colleagues and in particular by the award of honorary doctorates by the Universities of Ulm and Vienna.

As scientist as well as privately, Schatzmann was an impressive personality, highly original, keen minded, witty, widely interested and always prepared to challenge established views. Unmarried, he lived alone without television and without internet access but with a large library in the chalet-style house with a garden built by his grandfather near the centre of Bern. He stayed there even after the surrounding family houses were gradually replaced by apartment buildings, and he was offered large sums for his property. What is more, he was a dedicated cello player, and he pursued this musical interest in a long-standing Trio where he played chamber music together with two colleagues from other university institutes. He ran his own household until 2 years before his death when he entered a home for aged members of old-established Bernese families. In spite of his bodily frailness, he kept his admirably clear and lucid mind as well as his pleasure in discussions on philosophy and history of science. He loved books treating such topics. To thank someone for a loaned book, he would occasionally send a long, handwritten letter containing a review that was always pointed, thoughtful, critical and almost ready for press.

His relatives, friends and scientific colleagues mourn the loss of an unforgettable personality, a resourceful, humorous friend and a highly esteemed scientist and teacher.

Schatzmann in his laboratory

References

- Baker PF et al (1969) The influence of calcium on sodium efflux in squid axons. *J Physiol* 200:431–458
- Caroni P, Carafoli E (1980) An ATP-dependent Ca^{2+} transport system in dog heart sarcolemma. *Nature* 283:765–767
- Hasselbach W, Makinose M (1961) Die Calcium-pumpe der Erschlaffungsgrana des Muskels und ihre Abhängigkeit von der ATP Spaltung. *Biochem Zeitschr* 333:518–528
- Reuter H, Seitz N (1968) The dependence of calcium efflux from cardiac muscle on temperature and external ion composition. *J Physiol* 195:451–470
- Roelofsen B, Schatzmann HJ (1977) The lipid requirement of the $(\text{Ca}^{2+}+\text{Mg}^{2+})$ -ATPase in the human erythrocyte membrane, as studied by various highly purified phospholipases. *Biochim Biophys Acta* 464:17–36
- Schatzmann HJ (1953) Herzglykoside als Hemmstoffe für den aktiven Kalium- und Natriumtransport durch die Erythrozytenmembran. *Helv Physiol Pharmacol Acta* 11:346–354
- Schatzmann HJ (1962) Lipoprotein nature of red cell adenosine triphosphatase. *Nature* 196:677
- Schatzmann HJ (1964) Erregung und Kontraktion glatter Vertebratenmuskeln. *Erg Physiol Biol Chem Exp Pharmacol* 55:29–130
- Schatzmann HJ (1965) The role of Na^{+} and K^{+} in the ouabain-inhibition of the $\text{Na}^{+}+\text{K}^{+}$ -activated membrane adenosine triphosphatase. *Biochim Biophys Acta* 94:89–96
- Schatzmann HJ (1966) ATP-dependent Ca^{2+} -extrusion from human red cells. *Experientia* 22:364–368
- Schatzmann HJ (1967) Effects of cardiac glycosides on active Na-K -transport. *Protoplasma* 63:136–142
- Schatzmann HJ (1973) Dependence on calcium concentration and stoichiometry of the calcium pump in human red cells. *J Physiol* 235:551–569
- Schatzmann HJ (1974) Correlations between $(\text{Na}+\text{K})$ -ATPase, Ca-ATPase and cellular potassium concentration in cattle red cells. *Nature* 248:58–60
- Schatzmann HJ (1988) The calcium pump of the surface membrane and of the sarcoplasmic reticulum. *Annu Rev Physiol* 51:473–485
- Schatzmann HJ (1995) Amarcord. *Annu Rev Physiol* 57:1–18
- Schatzmann HJ, Vincenzi FF (1969) Calcium movements across the membrane of human red cells. *J Physiol* 201:369–395
- Schatzmann HJ et al (1958) Single proximal tubules of the *Necturus* kidney. II Effect of 2,4-dinitrophenol and ouabain on water reabsorption. *Am J Physiol* 195:570–574
- Seifert R, Schirmer B (2021) Why Naunyn-Schmiedeberg's Arch Pharmacol abandons traditional names of drug classes (Editorial). *Naunyn-Schmiedeberg's Arch Pharmacol* 394:1321–1325
- Skou JCh (1957) The influence of some cations on an adenosine triphosphatase from peripheral nerves. *Biochim Biophys Acta* 23:394–401

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