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The Years in Mainz – III

Hans Mislin's angio-cardiological studies

R. Schipp

Institut für Allgemeine und Spezielle Zoologie, Justus-Liebig-Universität, Stephanstr. 24, D-35390 Giessen (Germany)

Dr. Rudolf Schipp is Professor of Zoology at the Institute of Zoology of the Justus Liebig University in Giessen (Germany).

The special fascination with rhythmical phenomena in biological systems, their phasal dynamics, constantly retreating into themselves and forever reappearing, the 'eadem mutata resurgo' symbolised in the Bernoulli spiral, was also destined to determine the biological life-work of Hans Mislin.

Even when working on his thesis in Basel about 'The biology of nutrition of the Rhine river salmon' he was especially interested in the rhythm of the changing phases, and the connections between physiological starvation and changes of the blood depots, especially of the spleen. These investigations also roused his great interest in the circulatory system. Thus it comes as no surprise that in 1939, when he began to work as an assistant at the Physiological Institute in Bern under the tutorship of A. von Muralt, he continued his scientific work with studies on the contractile veins in the bat wing.

It had already been known for about one hundred years that the veins within the patagium of Chiroptera show an active pulse[29,41]. Mislin, however, managed to register the activity of these vessels in situ in *Myotis myotis* by photoelectrical methods and to document the differing temperature dependency in wakeful and hibernating animals[5]. This work was followed by further studies on this subject in Basel and Mainz. It was shown that the isolated vein, perfused by physiological solutions in vitro, also demonstrated a spontaneous rhythmical activity, whose frequency and amplitude could be modulated by temperature and hydrostatic pressure changes following the van t'Hoff Q_{10} law and Starling's law[5]. Mislin spoke of an 'authochthonous automatism' that is inherent in the highly developed smooth muscle cells of the T. media, and saw small 'vein hearts' in the single vessel segments between two valves[5,29]. The myogenic character and the relative physiological independence of the 'vein hearts' were demonstrated by the recording of the biphasic electrovenogram (EVG) of 80–120 μM by means of a sophisticated micro-method using glass cannula suction Ag or Pt electrodes. It was the first precise registration of the EVG of an autonomous pulsing vein (fig. 1)[6,7,11]. Electrostimulations by 0.1–3 V revealed that the vessel does not follow the 'all-or-none law' and that because of a very short refractory period tetanic contractions could be induced[29].

Mislin's further physio-pharmacological and electrophysiological research on this preparation clarified some important aspects of the neurohumoral regulation of the venous pulse and gave initial fundamental data about the rate of excitation conductance within the vessel wall during phases of anterograde and reverse peristalsis (fig. 2, table)[9-11,20]. There, Mislin's ingenious 'three-veins-preparations', with synchronous recording of the EVG at 3 different points of an isolated vein-

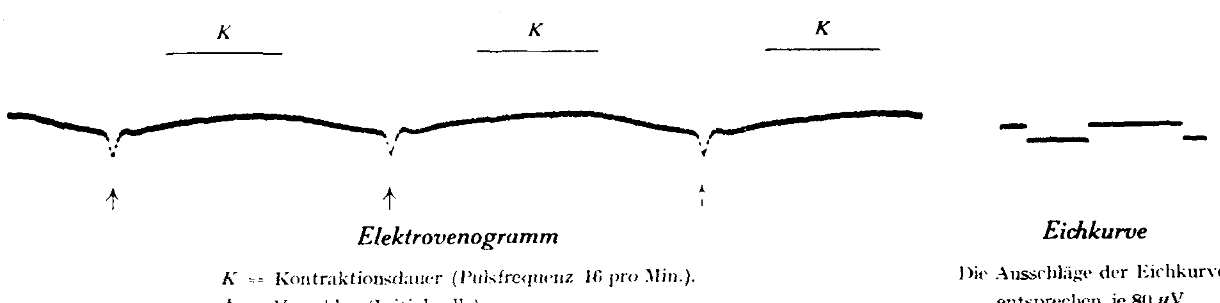


Figure 1. Electrovenogram (EVG) of the isolated vein from the wing membrane of *Myotis* (Chiroptera) (from Mislin[6]). K = duration of contraction (pulse frequency 16/min.); ↑ = initial wave.

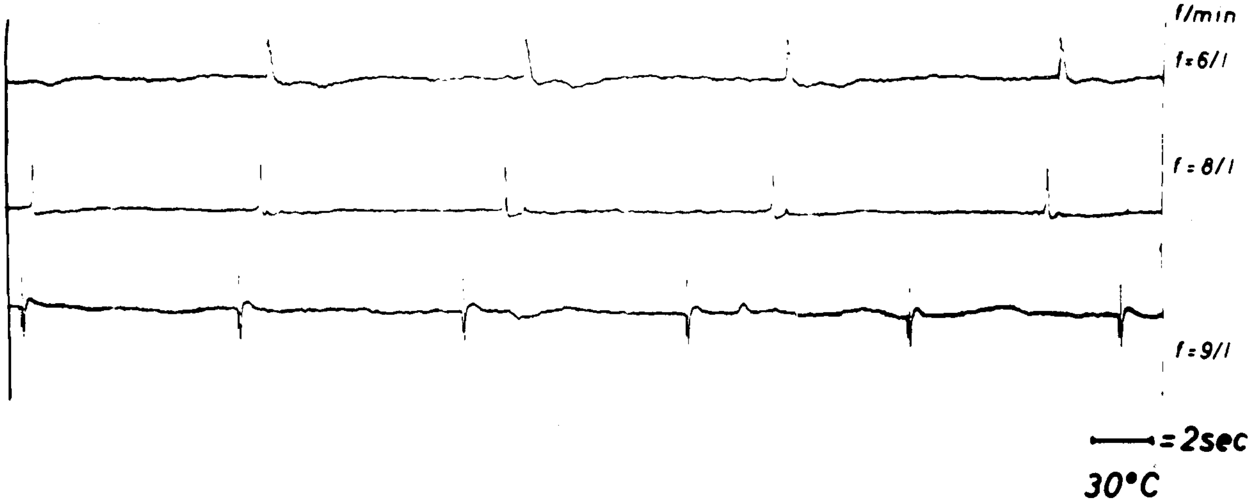


Figure 2. Electrovenograms (EVG) synchronously recorded from 3 sites of an isolated vein segment from the wing membrane of *Pteropus vampyrus* (Chiroptera) show a discontinuous spreading out of the pulse waves (from Mislin[20], reprinted with permission).

Rates of the excitation conductance in 7 different isolated vein preparations from the patagium of *Myotis myotis* (Chiroptera) (from Mislin[21], reprinted with permission). Pulsrichtung = direction of pulsation; per. = periphery; zentr. = centre.

Distanz der Elektroden (mm)	ERL-Werte (mm/sec)	Frequenz (f/min)	Pulsrichtung
0,24	16,4	28	per. → zentr.
0,38	17,3	30	dto
0,40	40,0	Puls periodisch	dto
0,46	11,7	per = 32, z = 40	dto
0,50	27,2	per = 35, z = 18	zentr. → per.
0,58	45,5	23	per. → zentr.
0,64	13,4	27	dto
0,74	10,7	per = 44, z = 20	dto
0,76	28,0	per = 25, z = 19	dto
0,80	16,0	Puls periodisch	dto
0,80	12,9	per = 24, z = 48	zentr. → per.
0,90	18,8	18	per. → zentr.
1,66	12,2	per = 32, z = 40	dto
2,10	17,8	27	zentr. → per.
2,18	43,0	21	per. → zentr.
3,34	28,3	23	zentr. → per.
3,90	14,4	18	per. → zentr.
4,86	19,2	Puls periodisch	dto
6,48	11,6	30	dto
8,18	26,4	14	dto

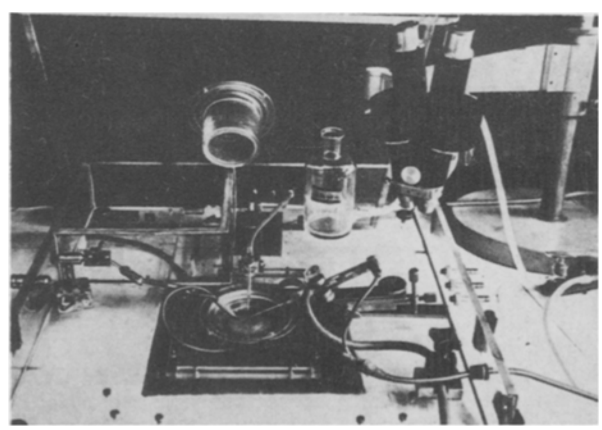


Figure 3. Gas perfusion chamber for the recording of the EVG from the isolated V. portae of *Mus musculus* under the influence of different atmospheric gases (from Mislin[22], reprinted with permission).

bifurcation from the patagium of *Myotis* or *Pteropus* were of particular help[27]. The results showed vessel-typical differences in the excitation conductance, and Mislin thereupon formed the hypothesis that there is syncytial contact between the smooth muscle cells – a hypothesis that was verified later by the detection of gap junctions by means of electron microscopy[21,37].

In the 1960s, with the increased perfection of the method for synchronous recording of the EVG and the acto-myogram, Hans Mislin extended his studies in comparative angiophysiology, devoting a great deal of attention to the V. portae of the mouse and the V. cava system of *Rana*, which also pulsate autonomously. The results in the V. portae produced data concerning the influence of CO_2, O_2 and N_2 on vessel activity, as well as on the action of different putative neurotransmitters and mimetics on the EVG and the actomyogram (fig. 3)[15,23]. His work on the vena cava system of *Rana* revealed the surprising finding that the pulsating venae cavae seem to be involved in the pace-maker function of the sinus venosus[23].

Dealing with the function of contractile blood vessels from the point of view of comparative physiology, one is bound to be confronted with the highly evolved and complex circulatory system of the cephalopods. In coleoids it is an enclosed system, and apart from the systemic heart and two additional branchial hearts there are peristaltic pulsating central and peripheric veins which drive the blood[35,36,42]. By means of the EVG and the actomyogram of the isolated arm-membrane veins in octopods, Mislin and Kauffmann[12,28] first demonstrated the autonomous myogenic character of this vessel pulse. Furthermore his in situ preparations showed correlated reflectory mechanisms between vein pulse and respiratory movements[8,12]. New, and of a similar fundamental significance, were Mislin's synchronous

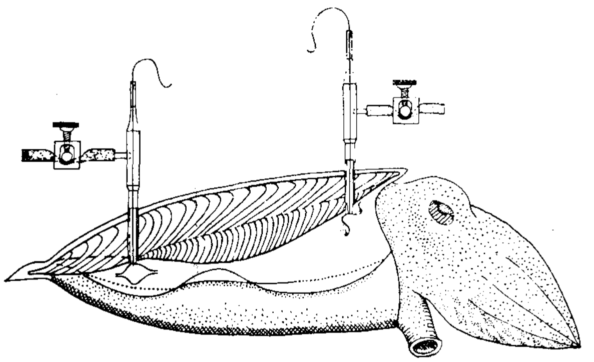


Figure 4. Position of electrodes for a synchronous recording of ECG and electromyogram of the respiratory movements of free-moving *Sepia officinalis* L. (from Mislin[19], reprinted with permission).

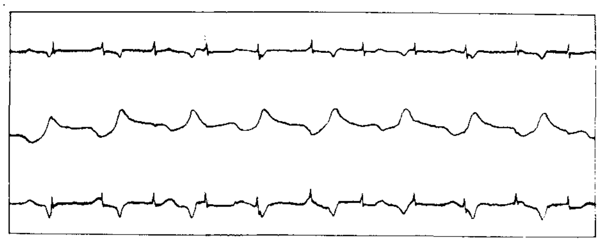


Figure 5. Synchronously recorded ECG (upper and lower curve) and electromyogram of the mantle muscle of free-moving *Sepia officinalis* L. (from Mislin[19], reprinted with permission).

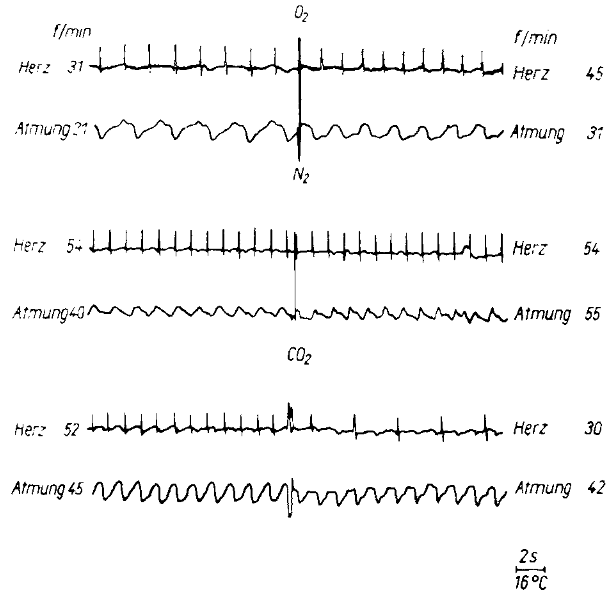
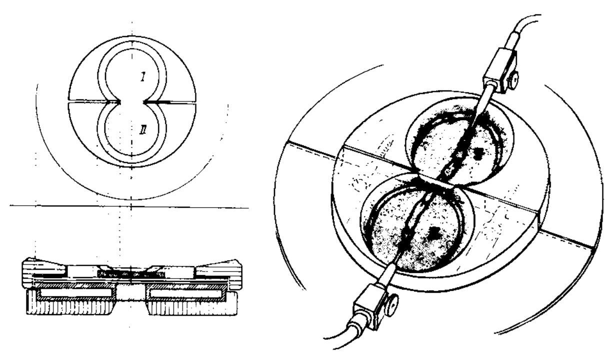


Figure 6. The action of O_2, N_2 and CO_2 on the ECG and the respiratory ventilation of a free moving *Sepia officinalis* L. Herz = heartbeat; Atmung = respiration; (from Mislin[19], reprinted with permission).

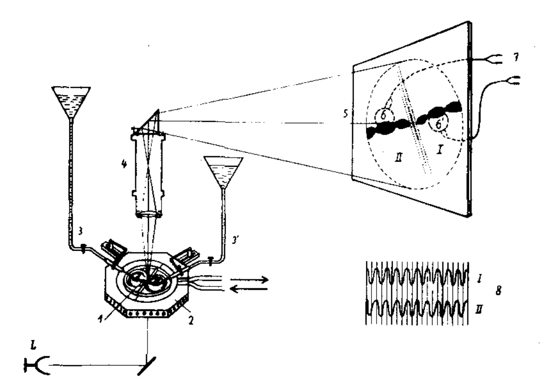
recordings of the electrocardiogram (ECG) and the respiratory movements of the mantle muscle in free swimming *Sepia officinalis*, that also demonstrated a relative coordination in heart activity and respiration, as well as providing the first valid cardiophysiological parameters of anaesthetized free moving animals (figs. 4, 5 and 6)[19,42].

Animated by the structural studies and cinematographic in vivo observations on the rhythmically contracting lymph vessels by Horstmann[2,3], Mislin was also deeply involved in analysing the functional peculiarities of this vessel type in the 1960s. He was the first who managed to isolate small parts, in fact single valve segments of the chylus-transporting lacteals from the mesenterium of juvenile guinea pigs (*Cavia porcellus*) and to perfuse them in vitro by means of small glass cannulae. By recording the electro-lymph-angiogram (ELG) using Pt micro-suction-electrodes, he could demonstrate that even the single segment between two valves showed an autonomous, myogenic rhythmical contractility. Mislin called these valve segments lymphangions; they represent something like mini hearts – with a distal muscle-free 'atrial' area and a central muscle band (muscle sleeve)[13,14].

In further in vitro experiments he perfused lymph vessel segments of 3–4 lymphangions in a sophisticatedly constructed 'two-bath chamber system' (figs. 7a and b). By simultaneous recordings with two electrodes, applying



(a)



(b)

Figure 7a and b. Two-baths-chamber system (I/II in a) for the recording of the intramural excitatory conductance in the isolated mesenteric lymph vessel (*Cavia porcellus* L.) by the registration at 2 sites of the electrolymphangiogram (ELG-electrodes 6/6' in b) (from Mislin and Rathenow[30], reprinted with permission).

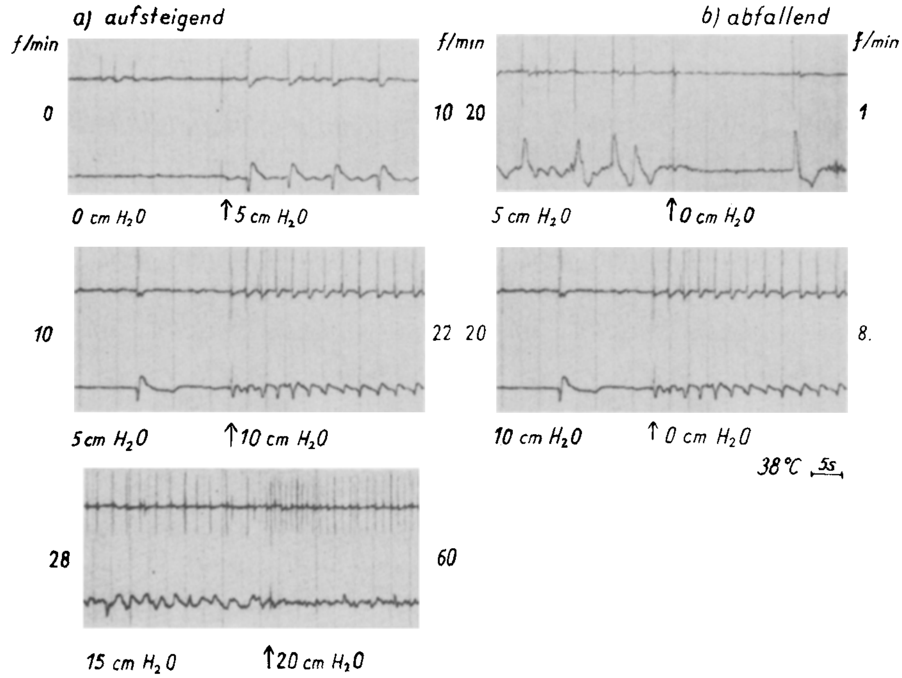


Figure 8. The action of increasing hydrostatic pressure on the electrolymphangiogram (ECG) (upper curves) and the lymphangiomyogram (lower curves) of the mesenteric lymph vessel of *Cavia porcellus* L.
aufsteigend = ascending; abfallend = descending; (from Mislin[16], reprinted with permission).

changing hydrostatic pressures and temperature stimuli in distal or proximal lymphangions, he analysed their metachronic pulses and their transporting capacity and frequency modulating factors, as well as their co-ordinating regulatory mechanisms (fig. 8). Experimentally eliminating Starling mechanisms in these preparations he suggested that there also exists an intramural conductance which is probably generated by the adventitial nerve plexus or endothelial cells, because muscle fibres are absent from the valve area, i.e. there are no muscle structures linking the lymphangions[30,32–34]. Further results gave the first pharmacological data concerning the effects of putative neurotransmitters on the actomyogram and ELG, and stretching experiments already anticipated the existence of stretching receptors in the sarcolemma of the smooth muscle cells of the vessel[16,25,26,30].

No survey would be complete without an adequate appreciation of Mislin's fundamental work on the automatism and the reversal shown by the peristaltic activity of the ascidian heart. Once more, the successful method of in vitro perfusion, combined with synchronous multiple recordings of the ECG and the actomyogram, yielded a better understanding of phenomena already described long before[24,39,40].
His studies on the myoepithelial heart tube of *Ciona intestinalis* gave evidence that the spontaneous rhythmic activity is derived from an intrinsic myogenic pacemaker system, because of the absence of any innervation. Especially his ECG recordings from segments, i.e.

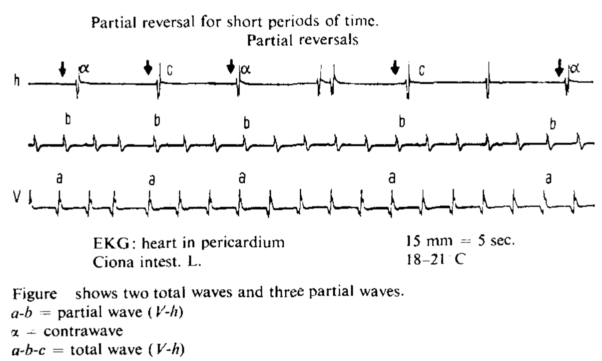


Figure 9. Synchronous ECG-recordings from hypobranchial (h) and visceral (v) end as well as middle area (middle curve) of the heart of *Ciona intestinalis* show the reversal phenomenon (from Mislin[24]).

1/2 or 1/3 of the heart tube, showed that there are not two structurally and functionally localized pace makers A and B at the visceral and hypobranchial ends of the heart tube, as was presumed by von Skramlik[39,40], but a diffuse, ubiquitary system whereby single groups of cells, probably also single myoepithelial cells, can represent actual pace makers from which excitation spreads out (fig. 9)[17,18,24,31,38].
Furthermore, Mislin also observed that the phenomenon of the reversal of heart pulse already occurred in small heart segments; he explained it as an interaction among changing groups of myoepithelium cells which were in excitatory or refractory phases. This concept was confirmed later by intracellular recording by other authors[1,24].

Here, we have concentrated on some aspects of Hans Mislin's physiological work – with the inevitable result that other fields have been neglected. Mislin was a man of universal intellect. However, he definitely contributed numerous and especially colourful stones to the constantly evolving large-scale mosaic of the comparative physiology of the circulatory system.

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