But they were technological, clinically useful developments – not primarily academic nor stimulating to the mind that probes for fundamentals.

However in 1949–50 Dr Weidmann introduced transmembrane, 'intracellular', recording from heart cells and initiated a new era of intellectual interest in the heart and its mechanisms of function. He effected a 'marriage' of the Purkinje fiber and the giant axon of the squid. He established a chain of thought in cardiology unified with the tradition of thought of Helmholtz, Du Bois Reymond, Mateucci, Bernstein and its modern aspects – the ion flux theories of Hodgkin and Huxley. Dr Weidmann would be the first to insist that others, several of whom are here, made magnificent contributions to this development of 'intellectual' cardiology but Silvio has been the leader. It has already been stated that many, many papers written relative to the heart and its components have begun thus: «Dr Weidmann has shown» –. He opened many doors for many people and provided new techniques which many of you came here to learn.

My second observation is this. It is a delight to be in a cultural environment that Dr Weidmann has done much to create. This is the age of 'rights' – in which individual rights are assumed to predominate over all others. Here, however, we feel a mutual concern, an interest in the welfare and the attainments of others. Your friendliness toward each other here in Bern, the friendship of the individuals here assembled – Silvio's students and associates – is very apparent. Here we see a predominance of Prince Kroptokin's concept of mutual aid for survival and accomplishment – it is much more pleasant and much more successful in the academic world than 'me first' and the attitude of survival of the fittest.

I would not like to embarrass Dr Weidmann by suggesting he is the one man here devoid of human frailty but I do say his influence is and has been strong in developing an ideal academic atmosphere wherever he has been. I know this from personal experience. When I invited him and his family to spend a year in Brooklyn as a Visiting Professor I felt considerable uneasiness concerning what might happen to them. It would be inappropriate to recount all the humorous occurrences and pleasant events of this association. They adapted nicely and demonstrated competence in dealing with life in New York. We did not have much to offer Silvio but he quickly assembled what he needed and quietly conducted experiments of significance. I remember these accomplishments and admire them but the point I would like to make is that while with us in Brooklyn Silvio exerted the same influence he has imprinted here in Bern. Both he and Ruth create a spirit of goodwill among men and provide an example and ideal that by contiguity improves the quality of life and of scientific accomplishment.

The third component of the perspective I present relates to the future. Dr Weidmann was primary among the leaders in the use of the type of thought and methodology which led to the formulation of this organization interested in 'cardiac cellular electrophysiology'. The group has prospered, developed a vocabulary and a focus of attention peculiarly its own. But what of the future – what is the future potential and destiny of the present interests? In my opinion something new will soon be needed. What will be the leadership that will open new areas for exploration – will you all have to become protein or lipid chemists, molecular biologists –? Perhaps it will be the old leadership that again generates the new. Silvio still possesses that power; he has told me that he does not like to do the usual things, to follow along the common way. He likes to try new ideas that often do not work out well but this probing of the barriers, this search leads to progress. Continual success in discovery is too much to expect of any man but there is the obligation to try and Silvio will do that and will succeed if not in discovering the new himself, at least in helping others to do so.

If I may presume to suggest a continuation I will say that there needs to be another unification, a marriage of those who study membrane potentials, the reactions of the heart cell, the integration of excitation and response with those who deal with humors, receptors and the cell's metabolic processes. The heart is not only a contractile organ, a pump, but also an emitter of humors that affect not only its own action but also distant organs such as the kidney and function of its tubules. Interest here has focused on the unification of action of demonstrable physical subdivisions of cardiac fibers that permits uninterrupted conduction. A related concern is how the heart contributes to the integration that unites all body parts and their components in the service of the totality. The heart directed by the autonomic nervous system has been assigned the responsibility of signalling to us the significance of events and situations. Aristotle suggested that the brain creates the 'cold humors' (reason) that control the 'firey humors' of the heart (emotions). The heart, as those who study conditional reflexes know, signals to us the need for alarm, the need for anger or resolve to oppose those things men should oppose. The heart signals the need for sympathy as Galen suggested long ago. Sympathy is the power that unites us and will be the salvation of man if that is possible. As scientists and humanists this integrative directive power of the heart should not be ignored.

It is appropriate that I link this third theme with the first and second. Dr Weidmann has opposed the wrongs men inflict on others. He has demonstrated and inspired the sympathy which we all hold for each other. Our hope and intent is to move with Silvio Weidmann, whom we honor because of the past, into an even brighter future dominated by the types of virtue Silvio has shown us.

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The conduction of the cardiac impulse 1951–1986

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Summary. The study of the propagation of the cardiac impulse during the last 35 years is reviewed with special attention to the contributions of Silvio Weidmann and his colleagues. Special emphasis is placed on the need to prove that the cardiac impulse is transmitted electrically, even when it is conducted under very abnormal conditions.

Key words. Cardiac electrophysiology; cardiac action potential; history of cardiac electrophysiology.

When our hosts invited me to take part in this event they suggested that I give a talk entitled 'Development of Cardiac Electrophysiology Over the Last Three Decades'. I demurred, partly on the ground that the topic was unmanageably large. The title I have chosen may, however, require a bit of explanation. Had I used as a title 'The Propagation of the

Cardiac Action Potential' most of my audience would have felt at home with its implications and concluded that I intended to talk about the conducted action potential rather than about the generation of activity, or membrane action potentials, or voltage clamps, or patch clamps or other aspects of cardiac electrophysiology. And so I do. But why 'impulse' rather than 'action potential?' The title itself has a history, having been used in 1917, whether by Keith Lucas himself, or by Adrian, who saw Lucas's book to completion after Lucas had been killed, for the famous monograph *The Conduction of the Nervous Impulse*[23]. Many of you will remember that Hodgkin used the same title for his Sherrington Lectures of 1961, published in 1964[16].

But what is this mysterious 'impulse' and why do I not behave sensibly and simply speak of the action potential? A quotation dating from 1886, gleaned from *The Oxford English Dictionary* (Series III, part III, July 1900, 4b, p. 122) may be helpful: 'Impulse, the wave of change which travels through nerve and muscle in passing from rest into action.' Another great dictionary of the English language, *The Century Dictionary*, gives us, around 1890, 'Nervous impulse, the molecular disturbance which travels along a nerve from the point of stimulation.'

Nothing about action potentials there, because it required the work of another half-century to convince most people that this 'wave of change' or 'molecular disturbance' is, in fact, the action potential. It was, after all, perfectly possible to regard the action potential as a trivial by-product of the 'molecular disturbance' and it is worth remembering that, as late as 1937, Hodgkin entitled his definitive studies 'Evidence for Electrical Transmission in Nerve'[15]. The second and third sentences of the first of Hodgkin's articles read: 'The most widely accepted theory is that transmission depends upon excitation by the action current. The theory is a plausible one, since the nervous impulse and electrical change travel at the same speed and have many similar properties ...' and later, '... it is difficult to accept the theory until more is known about the nature of the local circuits on which transmission is supposed to depend. The fundamental question is to decide whether the local circuits set up by an active region of a nerve fiber are able to excite an adjacent part.' At the end of his second article, Hodgkin remarked that 'The main conclusion from this research is that it is possible for nervous impulses to be transmitted by the electrotonic currents produced during activity.'

On the other hand, those of you who have read Lucas's monograph[23] know that he wrote it not to analyze the relatively uncomplicated conduction of the all-or-nothing nerve impulse but to argue that 'the same laws govern the conduction of an impulse in the central nervous system and in a peripheral nerve' and to express his belief that the properties of conduction in nerve under *abnormal* conditions could serve to explain 'the central nervous system as a network of conductors having different refractory periods, communicating through regions of decrement, easily fatigued, and capable of setting up a train of impulses in response to a single stimulus.'

When we speak of the conduction of the action potential we tend to think about conduction in a normal fiber. In that situation we know, as Hodgkin has said, that 'The nervous impulse in one fiber is of constant amplitude and shape and that its characteristics cannot be altered by changing the strength or quality of the stimulus.'[16] Such conduction exists in the heart, as we all know, but we also know that in some parts of the heart under normal conditions and in many parts of the heart under a wide variety of abnormal conditions, we find what Lucas found in the central nervous system, a 'network of conductors having different refractory periods, communicating through regions of decrement, easily fatigued, and capable of setting up a train of impulses in response to a single stimulus.' And although those events may all be *electrical* in nature, they are not what one expects from an all-or-nothing action potential conducting through a single fiber of uniform characteristics. Nor is it self-evident that such phenomena are necessarily even 'electrical' in nature. And, if you will permit a personal aside, that is why, after Hoffman and I had found that mere exposure of a segment of cardiac Purkinje fibers to high $[K^+]_0$ and epinephrine could induce slow conduction, one-way block, summation and inhibition, I used the term 'cardiac impulse' in the titles of three articles and a monograph[4,7-9]. I used it because it was not clear what relationship those findings bore to the propagation of the all-or-nothing action potential, and I use it again today to emphasize that a major task of the last 35 years has been to study the conduction of the cardiac impulse under both normal and abnormal conditions and to attempt to determine whether that conduction is, in fact, based on the electrical characteristics of cardiac fibers under normal and abnormal conditions or whether we must adduce other causes of the kind now known to exist in the central nervous system. Keith Lucas was wrong in believing that excitation and conduction in the central nervous system can be explained solely by the characteristics of excitation and conduction in normal and abnormal peripheral nerves, but we believe that we are right in relying on similar properties to explain the conduction of the cardiac impulse.

When I say that the conduction of the cardiac impulse under normal and abnormal conditions is an electrical event, what do I mean? I mean that the passive electrical properties or 'cable properties' of the cardiac syncytium, taken together with the active characteristics of currents flowing across the membrane and along the cable are 'electrical events' and that they suffice to explain everything that we know about the conduction of the cardiac impulse.

Now let me turn to some of the building blocks upon which we base that conclusion. An obvious starting point is the article that Draper and Weidmann published in 1951[11], from which we learned: 1) that the resting potential of canine 'false tendons' is about −90 mV and that it varies with $[K^+]_0$ approximately as required by the Nernst equation; 2) that the conduction velocity at 37 °C is about 2 m/s; 3) that the shape of the action potential is that already expected from studies of the 'monophasic action potential'; 4) that the fibers, if exposed to 2.7 mM $[K^+]_0$ are rhythmically active because of the presence of diastolic depolarization; 5) that cut ends of false tendons 'heal over'; 6) that the amplitude, reversal and upstroke velocity of the action potential vary with $[Na^+]_0$ in the manner described by Hodgkin and Katz[17] for the giant axon and may therefore plausibly be attributed to an increase in the permeability of the membrane to Na^+. These findings certainly allowed us to suspect that the cardiac impulse and the cardiac action potential may indeed be closely connected! Also in 1951, we learned from Weidmann[27] that if current pulses are applied across the membrane of a single Purkinje fiber of the kid heart, it can be shown that there is a profound fall in membrane resistance during the upstroke of the action potential, that phase 4 depolarization can be 'reset', that the membrane resistance is high during the plateau, that subthreshold cathodal pulses can cause graded local responses that are non-propagated but regenerative, and that an anodal pulse applied during the plateau can evoke all-or-nothing repolarization.

The Hodgkin-Huxley theory[16] not only predicts a dependence of the upstroke velocity and the amplitude of the action potential on $[Na^+]_0$, it also predicts that changes in the resting potential will change the amplitude and upstroke velocity by way of depolarization-induced inactivation. In 1954 Weidmann[29] determined the effects of resting potential and $[K^+]_0$ on the upstroke velocity and overshoot, and showed that they were entirely consistent with the predic-

tions of HH theory, thereby rounding off the argument, begun by Draper and Weidmann[11] three years earlier, that the upstroke of the action potential of cardiac Purkinje fibers is fundamentally the same as that of the giant axon.

In 1952, Weidmann[28] reported his measurements of the electrical constants of Purkinje fibers, remarking that 'A knowledge of these characteristics is important in any discussion of cardiac excitation and conduction, and may also be of interest to those concerned with the movement of ions through cell membranes.' In that study Weidmann again emphasized the importance of healing over, drew the significant conclusion that Purkinje fibers are not subdivided by high-resistance transverse membranes, and reported values for membrane resistance, myoplasmic resistance and the space constant, as well as an unexpectedly large value (12 $\mu F/cm^2$) for membrane capacity.

I digress here to comment on the fact that results published from Weidmann's laboratory have never had to be withdrawn and only rarely have had to be reinterpreted (for a few reinterpretations and cautionary remarks the reader may consult a recent article[36] by Weidmann himself). This is gratifying but not, for those who know Silvio, surprising, since the scientific style of his laboratory has left little or no room for the publication of hastily obtained results or merely speculative conclusions.

The membrane capacity measurement did, in fact, require reinterpretation and an important step towards clearing up the discrepancy between the apparent membrane capacity of Purkinje fibers and that of other excitable tissues was soon taken by Fozzard[12], working, of course, in Weidmann's laboratory. A more complete resolution of that problem had to await new morphometric information[34].

Let me now remind you of other important studies of electrical constants that we owe to Weidmann or to his colleagues. The passive electrical properties of trabecular muscles of sheep and calf hearts were determined by Weidmann in 1970[32]. The passive electrical properties of atrial fibers of the rabbit heart and the passive electrical properties of the sinoatrial node of the rabbit heart were determined by Bonke[1,2] in Weidmann's laboratory and were published in 1973. The effects of sucrose on the longitudinal resistance of trabeculae of sheep and calf hearts were ascertained by Kléber[21] in 1973; he too conducted his work in Weidmann's laboratory. And as recently as 1984 Pressler[25], also working in Weidmann's laboratory, determined the cable properties of sheep Purkinje fibers both when they are quiescent and when they are active. Thus it seems that Silvio adhered to his belief that 'a knowledge of these characteristics is important in any discussion of cardiac excitation and conduction.'

A major challenge to regarding the conduction of the cardiac impulse as being essentially the propagation of a 'Hodgkin-Huxley' upstroke in a fiber with cable properties of the sort described by Hermann[14] in the late 19th and early 20th centuries, arose with the assertion that the intercalated disk is virtually impermeable to small ions so that conduction of the impulse from one 'cell' to the next must be mediated chemically rather than by local circuit currents[31]. A remarkable series of studies grew out of addressing this challenge, studies carried out in Weidmann's institute, the Physiological Institute of the University of Berne. In the first major study of that series, Weidmann[30] showed that K ions diffuse freely across the intercalated disk, that the electrical resistance of the disk is low and that one may conclude both that 'the propagation of the cardiac action potential is possible by local circuit currents' and that 'there is no need to postulate special modes of cell-to-cell conduction.' I will say no more of this study, apart from pointing out that its conduct required horrendously difficult and painstaking techniques and meticulous attention to detail.

In 1974, Weingart[37] was able to show that TEA^+ diffuses across the intercalated disk almost as freely as K^+. In the same year, Imanaga[19] studied the diffusion of Procion Yellow in the cytoplasm of sheep and calf Purkinje fibers. Imanaga showed that even this large molecule can diffuse across the intercalated disk, although not freely. Since Procion Yellow can barely, if at all, enter across the membrane of resting fibers, it must have diffused across the disks. This provided a further important piece of evidence that the disks are permeable even to molecules that are much larger than the K ion.

In 1977, Weingart[38] published a study of the effects of ouabain on intercellular coupling that I will discuss in more detail below. Here I note only that it seems fair to assume that Weingart's interest in this problem owed much to Weidmann's concern with it, as did the much later and very elegant studies by Weingart[39] and by Metzger and Weingart[24] of the flow of current between cell pairs and of the electrical properties of the nexal membrane.

In fact, if we take into account this series of studies, conducted from 1966 through 1986, we can say that they have proven beyond any reasonable doubt that, *under normal conditions,* the intercalated disk has a low resistance and offers no significant impediment to the flow of longitudinal current. For that reason we can confidently assert that, *under normal conditions,* the propagation of the cardiac action potential is mediated by local circuit currents.

But this brings us to the second area that we must consider. For even if the 'conduction of the cardiac impulse' and the 'propagation of the cardiac action potential' are one and the same thing under normal conditions, and are not fundamentally different from the conduction of the action potential in the giant axon, we must still deal with nonuniform conduction and with the conduction of the cardiac impulse under abnormal conditions, conditions in which, to use Lucas's words[23] for a third time, we see 'a network of conductors having different refractory periods, communicating through regions of decrement, easily fatigued, and capable of setting up a train of impulses in answer to a single stimulus.' Here we must deal with abnormal excitatory currents or with inward currents other than those that cause the fast upstroke, with abnormally leaky membranes that cause abnormal cable properties, and with the possible effects of an internal longitudinal resistance that is not low but, because of uncoupling at the intercalated disks, may be very high.

When Dodge and I became interested in this question[5,10] we soon realized what we should have known, that Weidmann and his colleagues had been there before us, and well before. In 1977, Weingart[38] published his study of the effects of ouabain on coupling and conduction velocity, using the silicon oil chamber developed by Weidmann[32] for his study of the electrical constants of ventricular trabeculae. Weingart showed, among other things, that exposure to ouabain does lead to an increase in R_i, an increase that is presumably attributable to a decrease in coupling and he showed that conduction velocity fell from about 50 cm/s to about 30 cm/s, a decrease that could be explained partly by the change in R_i and partly by the change in the characteristics of the action potential. He also showed that a terminal, massive and irreversible increase in R_i occurred only after exposure to severely toxic levels of ouabain. Soon thereafter, again using Weidmann's silicon oil chamber, Wojtczak[41] showed that exposure to hypoxic solutions also produces an increase in R_i and a fall in conduction velocity. Once again, however, a massive rise in R_i was a terminal and irreversible event. These findings prove that uncoupling can occur and can affect conduction velocity but they also suggest that profound lowering of conduction velocity is a terminal and irreversible event. As Weidmann[35] said in the 1980 Rio symposium, 'It is only when internal resistivity has risen by a factor of the order of 20 that it becomes impossible to set up a conducted

action potential. With reference to a border zone between an ischemic and a well-perfused region, this is precisely the situation we dislike: cells that will never have a chance to recover, yet refuse to uncouple.'

Time permits me only to mention later very important studies on hypoxia, those by Janse and Kléber[20], by Kléber[22], by Hofmann[18], and by Wilde and Kléber[40] which are gradually helping us to understand the very complex interactions between the abnormalities of the excitatory inward currents and the abnormalities of the cable properties that occur during local or global ischemia or hypoxia. Nor can I do more than remind you that our present awareness of the possible importance of 'anisotropy', i.e. of the differences in longitudinal resistance along the length of the fiber and transversely to it began in this institute with the work of Clerc[3], once again using the silicon oil chamber perfected by Weidmann.

I must confess that there is one development that I regard as quite important that occurred largely outside Weidmann's laboratory, and that is the study of the slow inward current and the demonstration that an impulse can be conducted even if its upstroke depends exclusively on the slow inward current. I have reviewed the history of that subject at some length elsewhere[4] and I still regard the single key article to be that in which Hagiwara and Nakajima[13] showed that TTX affects the upstroke whereas Mn^{++} affects the plateau. But we should not forget, and certainly not on this occasion, that it was Coraboeuf and Weidmann who obtained, however inadvertently, the first record of a 'slow response' action potential in a Purkinje fiber (see ref. 33) and we should certainly note that Reuter's 1966 article[26] was a report of work done in this institute. We might also note that in 1974, when it was being confidently asserted that slow conduction is to be explained almost entirely by a large increase of inside longitudinal resistance, Weidmann[34] commented, 'In my opinion there is yet another possibility. Two factors may be important: maximal g_{Ca} is small when compared to maximal g_{Na}, and g_{Ca} rises much more slowly than g_{Na}.'

It is not easy to give a summary of a summary, but I will try. As far as the conduction of the cardiac impulse is concerned, 35 years ago we were much concerned with establishing the characteristics of the conduction of the normal, all-or-nothing, fast-upstroke action potential. During the past 15 years we have been increasingly concerned with the study of nonuniform propagation under abnormal conditions. This has led to a concern with inward currents other than those carried by the fully normal fast channel, with stimulus-dependent responses, graded and local responses, conduction with long delays, one-way block, rate-dependent block, uncoupling, anisotropy, highly nonuniform cables that connect abnormal sources of excitatory current with regions of diminished excitability and abnormal responsiveness, and with the role in creating these things of anoxia, elevated $[K^+]_o$, ischemia, inhibition of Na/K exchange, abnormalities of $[Ca^+]_i$ and a host of other noxious influences.

Under many of these conditions it really does seem prudent to speak of the cardiac impulse rather than the cardiac action potential. Nevertheless, I believe, as I am sure do the members of the audience, that the conduction of the cardiac impulse is, under both normal and highly abnormal conditions, an electrical event. I also hope that you will agree that narrowing my assigned topic from 'cardiac electrophysiology' to 'the conduction of the cardiac impulse' and then further narrowing it to an examination of the work of this institute was justified by the fact that the study of the conduction of the cardiac impulse has, in fact, been Silvio's main objective during the past 35 years.

Even so, I have not been able to mention all of Silvio's contributions nor to even allude to a great deal of other work influenced by him to a greater or lesser degree. My apologies, therefore, to Carmeliet, Délèze, DeMello, Giebisch, Haldimann, Hauswirth, Irisawa, Kavaler, McGuigan, Maughan, Mendez, Müller, Niggli, Otsuka, Pillat, Streit, Sumbera, Surawicz, Vassalle and Wood (in alphabetical order!).

That accomplished, I will close with an anecdote. In 1958, Brian Hoffman and I[6] reported our finding of propagated repolarization in ventricular muscle. Some time later I asked Silvio what he thought of our article. He replied that it was a very nice study and that he particularly liked the way the article began. When I confessed that I did not remember how the article began, Silvio reminded me that it begins 'Weidmann has shown ...'.

I am sure that you will agree that any review of the advances in our understanding of the conduction of the cardiac impulse that have been made during the past 35 years might well begin with the words:

'Weidmann and his colleagues have shown ...'

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Impulse propagation from the SA-node to the ventricles

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Summary. Normally the pacemaker of the mammalian heart is located in the sinus node. In the rabbit the sinus node can be subdivided into two regions, the center of the node where the impulse originates and the border zone through which the impulse is conducted towards the atrium. Conduction properties of both regions were investigated. It appeared that conduction velocity increases and refractoriness decreases when one goes from the nodal center towards the atrium. The tissue mass of the atrium is large in comparison to the sinus node and normally the resting membrane potential of atrial fibers is more negative than that of nodal fibers; consequently, a potential difference exists causing a current flow between both areas. Evidently this hyperpolarizing current flow depresses impulse formation in the border zone fibers which have better intrinsic pacemaker properties than fibers in the nodal center. If the impulse has reached the atrium it is conducted with a relatively high safety factor and will reach the AV node in principle without difficulty. The AV node, if deprived of sinus nodal dominance, develops spontaneous activity originating from the lower nodal fibers. Also in this structure, electrotonic depression by surrounding tissue causes deceleration of the pacemaker.
Key words. Sinus node; nodal impulse conduction; AV node; impulse formation; electrotonic influence.

Introduction

The electrical impulse which initiates every beat of the mammalian heart normally originates from the sinus node. Although impulse formation represents only a small part of the electrical events in the heart, different electrophysiological disturbances can occur which influence sinus nodal functioning[6, 11].

The isolated rabbit sinus node has been investigated widely and has yielded a lot of knowledge about this structure. Within the rabbit sinus node two distinct regions can be distinguished: the compact zone or nodal center and the periphery or nodal border zone[3, 16]. Normally the site of impulse origin is found in the center of the isolated sinus node[3]. The action potentials recorded from these fibers have typical characteristics of automaticity. The fibers which generate the earliest action potential within a heart cycle are indicated as the pacemaker of the sinus node and thus of the heart. It is probable that the impulse does not originate in one particular fiber but in a group of fibers depolarizing simultaneously and located somewhere in the nodal center. However, since this impulse should activate the atrial myocardium and the rest of the heart, it has to be conducted from its site of origin through the nodal center and border zone towards the atrium (crista terminalis).

Impulse conduction in the rabbit sinus node

From earlier studies it is known that intra-nodal impulse conduction is slow and deterioration can lead to sinus nodal dysfunction[9, 17]. We investigated conduction properties in the border zone as well as in the center of the isolated rabbit sinus node.

The preparation used included the roof of the right atrium, the crista terminalis and the intercaval tissue in which the sinus node is embedded. An incision was made, perpendicu-