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Editorial Note. Experientia is glad to be able to publish the following article of the well-known neuroembryologist, Professor VIKTOR HAMBURGER: In Memoriam HANS SPEMANN. It contains a survey of SPEMANN's work, together with a critical appraisal of general interest. As a contribution from one of those most familiar with the work of SPEMANN, it has its place in the series of papers given at the Symposium on the History of the Mechanism of Development last May in St. Louis (Missouri) in honour of the 100th anniversary of H. SPEMANN. Thus St. Louis and the Zoological Institute of Washington University, whose Director Professor HAMBURGER has been since 1942, became the meeting place of three of the most important of SPEMANN's scholars: V. HAMBURGER, J. HOLTFRETER and O. E. SCHOTTÉ, who all three turned their backs on Hitler's Germany in 1932 to go into emigration in America to carry on the SPEMANN ideas and experiments in fundamental research in neuroembryology, embryological transplantations and regeneration. None of them was invited to the Spemann Centenary in Freiburg i. Br. Therefore, we welcome these three well-remembered peace-makers in developmental physiology. H. M.

Hans Spemann and the Organizer Concept

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In his autobiography[2] (p. 171), SPEMANN says: 'My strongest inclination and talents are a combination of inquiry into general problems (allgemeine Fragestellung) and technical invention.' He achieved what he did by bringing these inclinations and talents to their fullest development. Those who are not familiar with the 'métier' of the experimental scientist can hardly realize how much attention to minute details and mere drudgery go into experimental work. SPEMANN had his full share, but no matter how painstaking the labors, the findings were never more than a few steps away from the problem. And it is true that he derived an extraordinary enjoyment and gratification from his very considerable manual skill. He could spend hours playing with glass tubing and rods over the Bunsen – or microburner, preparing instruments for his microsurgery. After his retirement, he writes in a letter to me (8 July 1937): 'At the moment my passion for playing (with instruments) celebrates orgies, and I feel transferred back to the times when I invented the glass needle technique; the same oblivion of time; the same curiosity and tension and "herzklopfende Seligkeit".' (He worked at that time on a technique of dissecting and mounting small insects.) This was certainly not a technological mind in the modern sense; it was more the spirit of the skilful craftsman of earlier times to whom the pride in the perfection of what he accomplished with his own hands was the better part of his reward. And with SPEMANN, the aesthetic and artistic pleasure in the design of the tools as well as of the experiments were an important element. When I prepared my first glass needles and hair loops, he looked over my shoulder and told me that the shape of the handle was not acceptable. This was not mere whimsey. His experimental success depended as much on his self-invented tools, as on his analytical acuity. This is more true in his case than in that of many other experimental embryologists, such as ROUX, DRIESCH and HERBST. Perhaps HARRISON and HOERSTADIUS had similar sensitivity for their tools.

There is a third motive underlying his chosen vocation, the experimentation with the living embryo. He recognized it quite clearly. He says in his autobiography[2] (p. 203): 'I wish to influence the living [the German word 'einwirken' has an ingredient of controlling, governing] in order to participate in other life. My passion for experimentation with the developing organism is innermost related to my pedagogic inclinations; with my enjoyment in knowing people, in teaching and education.' The psycho-analytically minded may detect a faint echo of the power-over-nature motive. Maybe so. But, of course, the embryo had to be handled gently! I detect a pedagogic streak also in the style of his writings: in the great precision in expressing what he wanted to convey, never omitting a single step in the argumentation. Actually, he invested a considerable amount of energy and time in pedagogic pursuits outside the university. He was the founder and director of the Adult Education Program ('Volkshochschule') in Freiburg from 1920 to 1933, the type of cultural innovations which flourished in the Weimar Republic, until Hitler terminated them. And his close friendship and association with one of the pioneers in progressive education, HERMANN LIETZ,

[1] Address, given at a Symposium on the 'History of Experimental Embryology' held at Washington University, St. Louis (Mo., USA), on 29 May 1969, in commemoration of the hundredth anniversary of H. SPEMANN (27.6.1869–12.9.1941).

[2] H. SPEMANN, *Forschung und Leben* (Ed. F. W. SPEMANN; Engelhorn Verlag, Stuttgart 1943). All translations are performed by the present author.

the founder of one of the private progressive schools, brought him close to this movement. As an overseer of this school he attended their meetings regularly; and he derived much satisfaction from the contact with young people. All this is significant, because he did not have a strong constitution, and he had to husband his strength carefully.

Scientific work and its motives

During the 20s and 30s the Freiburg laboratory under SPEMANN, and the Osborn laboratory at Yale under HARRISON, were the hub of the experimental embryological universe.

I do not intend to retrace SPEMANN's extraordinary scientific achievements on this occasion. But as an eye-witness of the 'classical Freiburg period', first as a candidate for the Ph.D., 1920–1924, and then as an assistant and instructor, 1927–1932, I shall try to convey some of the spirit of these times. When I began to contemplate what to say on this occasion of his 100th anniversary, I re-read his publications and his autobiography; and I became interested in the inner relations between his work and his personality, and how his personal philosophy is reflected in his work – in a word: his personal style. This will be the topic of my remarks.

The strength of both SPEMANN and HARRISON was in the self-imposed concentration on a few basic themes and problems, and on a single object, the amphibian embryo. SPEMANN complained occasionally that he missed out on so much in life and science by limiting himself so severely. He enjoyed playing with other forms, particularly invertebrates, and he indulged occasionally in this pleasant pursuit at Naples and in Woods Hole. But he never permitted himself to stray far away from his chosen path.

He entered the scientific scene around the turn of the century rather inauspiciously, with a series of constriction experiments on salamander eggs which were not particularly original in the problem nor in the experimental design. The basic problem, that is, the relation of the egg structure to the organization of the fully formed organism, the century-old problem of preformation versus epigenesis, had been restated by ROUX and DRIESCH in a new conceptual frame of reference that made it accessible to an experimental approach. The preformistic concept had been dealt its death blow by DRIESCH (1889) when he showed that half of an egg of a sea-urchin could give rise to a whole larva; and the isolation of blastomeres had become fashionable in the 90s. Constriction of salamander eggs had been done more or less successfully by others. And the tremendous regulative capacity of embryonic parts had been placed in the center of the stage by DRIESCH to stay with us and haunt us to this day. What was novel in SPEMANN's experiments was their greater thoroughness, their more extensive range and the astute exploitation of some unexpected results. He found that a number of eggs which were constricted in the 2-cell stage did not give identical twins but one embryo and a relatively unorganized spherical body which though remaining alive failed to develop axial organs. He related these differences to differences in the plane of constriction; if the latter corresponded to the median plane of the future embryo, then identical twins were obtained; but if it separated the dorsal part from the ventral part, then only the dorsal part gave an embryo, and the ventral part gave the spherical 'belly piece'. And he asked immediately: Why no axial organs in the belly piece, if the egg is as fully regulative as it was supposed to be? In the typical SPEMANN fashion, he considered the alternative explanations: either the building material is lacking or a stimulus for differentiation which, of course, would have to emanate from the dorsal half. He even thought of a chemical stimulus. In 1901[3] he says: 'The experiments give no information about the differentiation substance which is lacking in the ventral cell' (p. 256).

Upon further analysis, in 1903[4], he got the first inkling of the existence of an organizing center in the dorsal part. 'It is conceivable that at the beginning of gastrulation only certain cells in the middle of the upper blastoporal lip can be designated as an 'anlage', whereas cells lateral to them are not capable of self-differentiation and are only later incorporated in the

[3] H. SPEMANN, Wilhelm Roux Arch. EntwMech. Org. *12*, 223 (1901).
[4] H. SPEMANN, Wilhelm Roux Arch. EntwMech. Org. *16*, 606; *16*, 616 (1903).

'anlage'. And furthermore, in the same paper: 'It is not excluded that the differentiation of the medullary plate is induced by the archenteron' (p. 616). This is an almost uncanny premonition based on scanty data. But the essential point is that through these experiments, he had discovered the central theme of his life's work: to understand and analyze the factors which create the unit – organization, the individuality, of the organism, in an egg which is capable of producing more than one individual. And, perhaps more importantly, it was apparent that there is an experimental approach to this problem: namely, the analysis of the *determination of the axial organs* which identify the invidivual. The general problem was caught in the net of the experimenter.

But the problem had also its mystical undertones. Referring to his discovery that partial constriction results in double monsters with 2 heads, he states: 'It was probably the fascination with that mystery which surrounds the partially split individuality[5] – and then the enjoyment of the elegant technique . . . that forced me to lock myself up spring after spring, instead of roaming in the beautiful world, and to tie hair loops around slippery newt's eggs, until I had constricted a thousand and a half' (autobiography[2], p. 181).

I shall skip the period from 1904–1912 during which he was preoccupied with *lens induction*, except to say that these experiments put embryonic induction on the map as an important mechanism of progressive differentiation. This was also the occasion for the invention of the glass needle technique, without which further progress was not thinkable. This technique enabled him to do the ingenious transplantation and combination experiments on the salamander gastrula[6] which paved the way for the organizer experiment. They were done at the Kaiser-Wilhelm-Institut für Biologie in Berlin-Dahlem during the First World War. In 1919, he moved to Freiburg to occupy the chair formerly held by AUGUST WEISMANN, who had inspired his early interest in experimental embryology.[7]

The discovery of the *organizer*, the crowning experimental success in the Freiburg period, seemed, for a moment, to fulfil his major goal; to localize and analyze the factors that are responsible for the determination of the axial organs, and thus the individual. By transplantation of a small piece of the upper blastoporal lip of a salamander gastrula into a relatively indifferent region of another embryo, a second individual embryo was created which arose partly by self-differentiation of the material of the transplant and partly by complex induction on the part of the transplant, whereby host tissue was assimilated in an organized fashion. Exchange between embryos of different pigmentation, belonging to different species, made the distinction between donor and host embryo possible. In his own words, 'At the beginning of gastrulation, the individuality of the embryo is so-to-speak represented by the cells of the upper blastoporal lip which represents an organization center from which the other most important parts of the body are formed'[8]. (Notice that the concept of 'organization center' preceded that of 'organizer' by several years.) The experiments were done by HILDE PROESCHOLDT for her Ph.D. thesis. The first results were communicated in 1921[9] in a postscript to another paper, and the full publication appeared in 1924[10]. A few months later, HILDE PROESCHOLDT, who in the meantime had become MRS. MANGOLD, died in a tragic accident at the age of 26. SPEMANN was awarded the Nobel Prize in 1935.

If later experiments did not sustain the high hopes and the enthusiasm which inspired the choice of this magic word, 'organizer', the experiment was certainly of signal importance. To the extent that the upper lip material created an integrated axial system, and in the best cases, a rather complete secondary embryo, the name 'organizer' seemed to be justified. But soon it became clear that its radius of action in *normal development* was more limited than had been assumed. When 10 years later, HOLTFRETER made the momentous discovery that dead tissues could induce highly organized axial systems, the term would seem to have been ready for retirement, since as SPEMANN himself put it 'a dead organizer is a contradiction in itself'[11]. Yet, it lived on. One of the most important conclusions from the inductions by dead tissue was the shift of emphasis from the inducing stimulus to the responding system which in these instances seemed to bear the major responsibility for the formation of the secondary embryos. What seemed imposition of organization by an outside agency was really to a major part *self-organization* within the reacting system.

In all fairness, it should be stated that SPEMANN himself recognized early the provisional nature of the organizer concept; and in most of his writings and discussions the question of the relative share of inductor and responding system was clearly on his mind.

We may then ask the heretical question: What motivated SPEMANN to coin this term with the strange holistic and psychological undertones – a term which even at that time would seem strangely out of place in a rigorous scientific vocabulary? If SPEMANN had misgiv-

[5] He might have said 'personality'; when in a whimsical mood, he would contemplate the compassions and competitions between the two alter egos.

[6] H. SPEMANN, Wilhelm Roux Arch. EntwMech. Org. *43*, 447 (1918).

[7] He spent the winter of 1896/97 in Arosa (Switzerland) for reasons of health. As his only scientific reading matter, he took along AUGUST WEISMANN's book on *The Germ-Plasm* (1892), through which he became acquainted with the experimental work of W. ROUX and H. DRIESCH. They inspired directly his own constriction experiments (see autobiography[2], p. 178). He attested on several occasions to his intellectual debt to A. WEISMANN.

[8] H. SPEMANN, Naturwissenschaften *7*, 591 (1919).

[9] H. SPEMANN, Wilhelm Roux Arch. EntwMech. Org. *48*, 568 (1921).

[10] H. SPEMANN and H. MANGOLD, Wilhelm Roux Arch. EntwMech. Org. *100*, 599 (1924).

ings in 1932, why did he carry it over into his scientific testament, the book on 'Theory of Development'?[11] What are the roots of this strange ambiguity?

Let me get at the answer to this question in a roundabout way. The organizer experiments, and in fact all his experiments, were planned very carefully and methodically, as a sequence of steps with their inner logic, leaving very little to improvisation. The strategy of his research was well expressed in a letter to me: '. . . to tackle the most immediately solvable question, until, piece by piece, the whole is achieved.' Yet, progression in scientific research is not quite that simple. When one is on the road, the goal can be perceived only dimly. At the end of each breeding season, when the harvest was in, and the plans were laid for the next, there were usually more interesting possibilities than one, and choices had to be made. Nothing is more revealing than to track down the lines which the master found worthwhile pursuing, and, on the other hand, the experimental ideas which were put on ice. What intrigued him, for instance, was the regional structure of the living organizer: experiments which led to the discovery of the head- and trunk-tail organizer[12]. He placed much emphasis on the experiments which showed the awakening of inductive powers in a tissue which did not have inductive capacity before, because they led to the general concept that progressive differentiation is a chain of inductive processes: one part gets an instruction for organ formation by induction, and at the same time acquires the capacity to induce another still indifferent part to proceed along another line of differentiation[13]. He was particularly gratified when an old experimental dream of his was realized. The bold idea was to exchange embryonic tissue between frog and salamander which differ widely in many structures, as for example in mouth implements. Would the inductors of the urodele accept the challenge to produce inductions in the anuran (and vice versa), and, if so, what would the induced structures be like? In the early 30s OSCAR SCHOTTÉ performed this difficult technical feat successfully[14], and, as expected, profound new insight in the inductive mechanism was obtained. Briefly, the experiment showed that the prospective head ectoderm of the frog embryo when transplanted to the head of a salamander can respond to the inductors of the salamanders, but it does so according to its own genetic repertory: it forms frog-type mouth implements, that is, horny jaws and suckers, which are foreign to the salamander. The inductor gives the general instruction to form mouth parts to which the reacting system answers in its own specific way. These were some of the experimental ideas that were materialized. But how about those which were not?

As early as 1924[15], SPEMANN contemplated an experiment which nowadays would appear to be as exciting as any. 'By implantation in the blastocoel it will be possible to test whether only the living cells are capable of induction or also a structureless "Brei" or extract.' Significantly, the matter was not taken up until 1931, when SPEMANN[16] found that minced and squashed organizer retains its inductive capacity; however, his experiments with dried and frozen organizers were unsuccessful. The breakthrough came with HOLTFRETER's spectacular success of obtaining complex inductions not only from killed organizer but from a variety of dead animal tissues[17]. These experiments established the chemical nature of inductions, and paved the way for the chemical analysis of inductive agents.

Another idea of SPEMANN that had great potential was not followed up either. In 1918[18] he suggested the tissue culture method as one way of testing the state of determination of early gastrula parts. Again, it was HOLTFRETER[19] who many years later devised the culture medium which became a powerful tool in the analysis of amphibian development.

Clearly, the living organizer always took precedence; the commitment was to the embryo as a whole. As JANE OPPENHEIMER[20] put it in one of her essays: 'The integrative powers of the embryo at all of its levels are so pervasive that they never permit themselves to be overlooked by those who avail themselves of the privilege of looking at the embryo as a whole. . . . SPEMANN, for instance, who analyzed the relations between layers in terms of cellular interactions, never lost sight of the whole embryo.' And I may add: neither did HARRISON. But the theoretical and philosophical paths which the two men chose to follow from there led in opposite directions.

[11] H. SPEMANN, *Experimentelle Beiträge zu einer Theorie der Entwicklung* (J. Springer Verlag, Berlin 1936), p. 276. The English translation appeared under the title *Embryonic Development and Induction* (Yale University Press, New Haven 1938). All quotations are translations by the present author from the German edition.

[12] H. SPEMANN, Wilhelm Roux Arch. EntwMech. Org. *123*, 389 (1931).

[13] H. SPEMANN and B. GEINITZ, Wilhelm Roux Arch. EntwMech. Org. *109*, 129 (1927).

[14] H. SPEMANN and O. SCHOTTÉ, Naturwissenschaften *20*, 463 (1932).

[15] H. SPEMANN, Naturwissenschaften *12*, 1093 (1924).

[16] H. SPEMANN, Verh. dt. zool. Ges. *129* (1931).

[17] J. HOLTFRETER, Naturwissenschaften *20*, 973 (1932); Wilhelm Roux Arch. EntwMech. Org. *128*, 585 (1933). The preliminary report of HOLTFRETER's experiments was published jointly with H. BAUTZMANN, H. SPEMANN and O. MANGOLD (Naturwissenschaften *20*, 971, 1932). Full credit should go to HOLTFRETER who at that time (spring 1932) had obtained a considerable number of complex inductions not only from killed organizer but also from dead embryonic tissues which do not induce when alive. While the other contributors reported only few cases of neural inductions, not all of them convincing, HOLTFRETER's embryos were reared to advanced stages and showed fully differentiated induced structures such as brain and eyes, thus establishing the inductivity of dead tissues beyond doubt.

[18] H. SPEMANN, Wilhelm Roux Arch. EntwMech. Org. *43*, 526 (1918).

[19] J. HOLTFRETER, Wilhelm Roux Arch. EntwMech. Org. *124*, 404 (1931).

[20] J. OPPENHEIMER, *Essays in the History of Embryology and Biology* (M.I.T. Press, Cambridge, Mass. 1967), p. 9.

The philosophical foundations

The organizer concept symbolizes, perhaps subconsciously, SPEMANN's deep and strange conviction that all vital phenomena, including, of course, the doings of the embryo, are the emanation of a psychic force akin to, or identical with, the workings of our mind. He has expressed this idea most succinctly in the closing paragraph of his book[21]: 'Over and again, expressions have been used which denote psychological rather than physical analogies. This is meant to signify more than a poetical metaphor. What I mean to say is that the neighborwise ["ortsgemässe"] reaction of a pluripotential embryonic part in an embryonic field, its behavior in a particular situation is not an ordinary simple or complex chemical reaction. I imply that these developmental processes, like all vital phenomena, irrespective of whether or not they may once be resolved into chemical and physical processes, resemble in the way they are connected nothing more closely than those vital phenomena of which we have the most intimate knowledge, viz. the psychic phenomena.'

The sober voice of HARRISON, the wisest of all experimental embryologists, whose life-long preoccupation with the *Amblystoma* embryo brought him face to face with the same phenomena of regulation and determination, has a more modern ring. In the Harvard Tercentenary Lecture of 1936[22], the same year in which SPEMANN's book appeared, he says: 'In the amphibia, not only are early segmentation and gastrulation stages capable of regulation but also later embryos. This quality of "wholeness" in the parts of the organism, particularly the embryo, had led to much speculation and even to a system of philosophy. It is the capital problem of embryology [here SPEMANN would have ended the sentence; but HARRISON continues] to find the physico-chemical basis for it.' And further: 'In endeavoring to reach a physico-chemical description of life, one is baffled rather by the bewildering array of possibilities than by such dearth of material as would warrant recourse to so-called vitalistic forces. At least I am unwilling to accept the defeatism of the vitalist, so long as means of investigation by experiment are available.' I would disagree with HARRISON in only one point: If DRIESCH's vitalism may have sprung from defeatism, that of SPEMANN had entirely different roots; it was in the line of Goethe and the German natural philosophy.

The origin of SPEMANN's particular type of psychological vitalism can be traced back readily to his friend and mentor AUGUST PAULY, a Munich zoologist and theorist, a bearded sage, with a fiery spirit. His neo-Lamarckistic ideas on cell psyche had a lasting influence on SPEMANN, from his impressionable student days on. The central issue in PAULY's doctrine was the pervasive phenomenon of adaptation in organisms. He rejected violently selectionism as its explanation. Incidentally, he shared this view with many leading biologists of the turn of the century, as is well told in an illuminating article by GARLAND ALLEN on T. H. MORGAN[23], who himself was not converted until 1910. Here, then is actually an element of defeatism. But PAULY built up from there a special brand of neo-Lamarckism which endowed all cells with psychic powers of inventiveness, enabling them to meet new challenges with innovations the way we invent new tools to deal with new demands. The idea was elaborated in great detail in his book[24]. Although SPEMANN admitted the great shortcomings of PAULY's arguments and was profoundly critical of his dogmatism, it remained his innermost conviction that psychic properties are all-pervasive and not limited to the mind of man and higher animals[25].

If SPEMANN's natural philosophy sounds anachronistic today, we realize how deeply the advances of biology in recent decades have influenced our theoretical thoughts about vital phenomena. I think that, indeed, some of them are now less enigmatic than they were 30 or 40 years ago. But there is little cause for a particular pride or complacency. The holistic view is still with us and, I think, rightly so, though stripped of its metaphysical undertones. And do we really have a better understanding today of the regulative capacities of the embryo, of morphogenetic fields and self-organization? Or, for that matter, of the plasticity of our brain and our mind? Do we really believe that our efforts to reduce the biological phenomena to physical and chemical processes will answer all questions?

And we had better realize that the scientific approach altogether opens only a small window to the universe. We cannot expect our intellect to fathom all depths. In SPEMANN's words: 'All really fundamental questions are of an elementary, simple kind, and they do not come from pure reason but from the totality of the human personality'[26]. SPEMANN's was a very complex personality. The sharp analytical mind lived together with the artist's approach to life and work, and with the pedagogue's inclination to mould human beings – and to influence embryos. If his personal creed was the mainspring of his inner strength and achievements, that much the better for experimental embryology.

[21] H. SPEMANN, *Experimentelle Beiträge zu einer Theorie der Entwicklung* (J. Springer Verlag, Berlin 1936), p. 278.
[22] R. G. HARRISON, Trans. Conn. Acad. Arts Sci. *36*, 281 (1945).
[23] G. E. ALLEN, J. Hist. Biol. *1*, 103 (1968).
[24] A. PAULY, *Darwinismus und Lamarckismus* (E. Reinhardt Verlag, München 1905).
[25] See [2], p. 161. It is of great interest that the great cell biologist TH. BOVERI, SPEMANN's teacher and himself a friend of A. PAULY, shared the scepticism of the latter concerning the all-powerful role of natural selection in evolution and accepted the essential elements of PAULY's psycho-lamarckistic doctrine of cell psyche. See his 'Rektoratsrede', *Die Organismen als Historische Wesen* (Würzburg, Universitäts-Druckerei 1906) and F. BALTZER's biography *Theodor Boveri* (Wiss. Verlagsanstalt, Stuttgart 1962), p. 166.
[26] See [2], p. 151.