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OPTIMISTIC ANALYSIS—CHEMICAL EMBRYOLOGY IN CAMBRIDGE 1920–42

by

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INTRODUCTION

Chemical embryology in Cambridge was centred around the experimental work, and scientific and philosophical outlook of Joseph Needham and a group of close colleagues that included Dorothy Needham and C. H. Waddington, and extended to members of the Theoretical Biology Club such as Joseph Woodger, J. D. Bernal, and Dorothy Wrinch.[1] It arose from the successful attempt to bring together two fields of endeavour—the experimental study of the developing embryo and the biochemical analysis of living systems. It was thought by many at that time that these fields were irreconcilable, and the purpose of this paper is to describe how Cambridge came to be the place where the reconciliation was attempted.

Beginning about 1920, Needham embarked on a concerted effort to understand the biochemical basis of embryonic development, for, as he put it, "For the biochemist the problem of organic form is ultimately unavoidable".[2] Initially concerned with charting the biochemical changes going on during the development, he came to believe that what was needed was a deeper understanding of the relationship between "the gross morphological forms manifested by living things and the specific molecular constitutions which they possess".[3] Needham's campaign to achieve this understanding came to an end in 1942 when he set out for China.

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[1] H. Holorenshaw, 'The making of an honorary Taoist', in M. Teich and R. Young (editors), *Changing perspectives in the history of science*, London, Heinemann, 1974. "Henry Holorenshaw" was a pseudonym first used by Needham for his book on the English Civil War, published in 1939 (*The Levellers and the English Revolution*, London, Gollanz); G. Werskey, *The visible college*, London, Allen Lane, 1978, concentrates on Needham's political and social development, particularly in relation to the group of socialist scientists that included J. B. S. Haldane, Hyman Levy, J. D. Bernal, and Lancelot Hogben; D. Haraway, *Crystals, fabrics and fields*, New Haven, Conn., Yale University Press, 1976, discusses the work of Ross Harrison, Needham, and Paul Weiss in terms of organicism and deals in detail with Needham's philosophical outlook.

[2] J. Needham, 'Chemical aspects of morphogenetic fields', in J. Needham and David E. Green (editors), *Perspectives in biochemistry*, Cambridge University Press, 1937.

[3] J. Needham, 'Biochemical aspects of form and growth', in L. L. Whyte (editor), *Aspects of form*, Bloomington, Indiana University Press, 1951, pp. 76–86, p. 78.

Needham's study of biochemical embryology was possible because of the unique nature of biochemical research in Cambridge at that time. Cambridge was the pre-eminent centre for biochemistry in Britain, due largely to the efforts of Frederick Gowland Hopkins.[4] The phrase "optimistic analysis" was used by Needham to describe Hopkins' attitude to biochemistry: "I think that he [Hopkins] was one of the great victors in the perennial contest between optimistic analysis and obscurantist organicism".[5] The same phrase also describes the spirit in which the Needhams, C. H. Waddington, and their colleagues embarked upon their biochemical investigations of the embryo.

An alternative title for this paper might have been 'From *Chemical embryology* to *Biochemistry and morphogenesis*', taken from the titles of the books published by Needham in 1931[6] and 1942.[7] The contents and style of these books exemplify the nature and the style of research at the beginning and at the end of the period I want to cover, and show a transition from a concern with *chemical analysis* of the embryo to an interest in the *dynamic biochemistry* of developmental processes. *Chemical embryology* was a massive compilation of what was known of the chemical composition of embryos at various stages of their development. By the time *Biochemistry and morphogenesis* was written, experimental embryology[8] had revealed something of the morphogenetic mechanisms that needed to be described or perhaps even explained by biochemistry. At the time that Needham began writing *Chemical embryology*, it was by no means generally accepted that chemistry had anything interesting to say about embryology. Embryology was one of the last bastions of vitalism,[9] and I shall refer to Needham's trenchant justification of a physico-chemical approach to embryology.

The Cambridge group undertook a wide-ranging study of the developing embryo, but a single episode will show how an attempt was made to apply biochemical analysis to a dynamic, complicated developmental system. Between 1933 and 1938, Needham and his colleagues attempted to determine the biochemical basis of one of the most significant and spectacular events in early development, that is, the laying down of the primary axis of the vertebrate body in early gastrulation. The embryological experiments that revealed this phenomenon were performed initially by Hans

[4] H. H. Dale, 'Frederick Gowland Hopkins', *Obit. Not. Fellows Roy. Soc.*, 1948, **17:** 115–145; N. W. Pirie, 'Sir Frederick Gowland Hopkins (1861–1947)', in G. Semenza (editor). *Selected topics in the history of biochemistry: personal recollections*, Amsterdam, Elsevier Science Publishers, 1983, pp. 103–128; J. Needham, 'Frederick Gowland Hopkins', *Pers. Biol. Med., 1962,* **6:** 1–46. This article, as well as being a fascinating account of Hopkins and having some delightful illustrations, demonstrates the affection that Hopkins inspired in his pupils and colleagues.

[5] Needham, op. cit., note 4 above, p. 4.

[6] J. Needham, *Chemical embryology*, Cambridge University Press, 1931.

[7] J. Needham, *Biochemistry and morphogenesis*, Cambridge University Press, 1942. This was published under conditions of great difficulty during the Second World War, with proofs being sent to E. J. Boell at Yale, who had undertaken to see the book published should Needham have been prevented from doing so. Boell was Needham's colleague for a good deal of the work on the respiratory activity of embryos, and he published a comprehensive review of their work. E. J. Boell, 'Biochemical differentiation during amphibian development', *Ann. N. Y. Acad. Sci.* 1948, **49:** 773–800.

[8] J. Huxley and G. de Beer, *The elements of experimental embryology*, Cambridge University Press, 1934.

[9] L. von Bertalanffy, trans. J. H. Woodger, *Modern theories of development*, London, Oxford University Press, 1933; J. H. Woodger, *Biological principles*, London, Kegan Paul, Trench, Tubner, 1929. See especially Part II. Woodger is best remembered for his role in the Theoretical Biology Club, which included, among others, the Needhams, C. H. Waddington, J. D. Bernal, and Dorothy Wrinch. Woodger attempted to show

Spemann and Hilde Mangold[10] in 1924, and its importance was immediately recognized, Waddington going so far as to claim that "the causal analysis of development may be said to have first started with this discovery".[11] It was quickly apparent that what Spemann called the organizer centre cried out for biochemical analysis, and in 1935, Needham wrote that "the nature of the organiser influence was from the first recognised to set a problem the solution of which would profoundly affect our picture of the process of development".[12]

I have chosen this topic rather than other biochemical researches on the embryo pursued in Cambridge because the problem was then recognized as a fundamental challenge to the physico-chemical approach to the living organism. It is also a problem that continues to resist solution, so much so that fifty years after Spemann and Mangold's paper it was possible to claim that the study of induction phenomena was ". . . still in its infancy".[13]

I shall describe the biochemical hunt for the organizer that went on in Cambridge in the 1930s in relation to contemporary biochemistry and embryology, and the peculiar features of biochemistry in Cambridge that provided the environment in which esoteric subjects like chemical embryology could flourish. I shall then discuss Needham's initial foray into chemical embryology, before looking at the work of Hans Spemann that inspired embryologists throughout the world to take up the study of induction. These topics come together in the biochemical work of the Cambridge group on the organizer.

Biochemistry in Cambridge–I. Foster, Lea, and Physiological Chemistry

I have already referred briefly to Hopkins, who has been described as the Father of British Biochemistry, but the development of biochemistry at Cambridge begins with the man who brought Hopkins to Cambridge, the physiologist, Sir Michael Foster.[14] There are striking parallels in the careers of Foster and Hopkins.

Foster had always had an interest in chemistry, and as a medical student at University College London he won a gold medal for chemistry in 1856. This interest continued after graduation, and in 1865, he published a paper reporting the presence of

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that a logical analysis of biological phenomena was possible, culminating in his axiomatization of genetics in *Biology and language*, Cambridge University Press, 1952. A brief biography of Woodger will be found in the volume published to celebrate his seventieth birthday; W. F. Floyd and F. T. C. Harris, 'Joseph Henry Woodger, curriculum vitae', in J. R. Gregg and F. T. C. Harris (editors), *Form and structure in science*, Dordrecht, Reidel, 1964, pp. 1–6. For a recent assessment of Woodger see N. W. Tennant, 'Reductionism and holism in biology', in T. J. Horder, J. A. Witkowski, and C. C. Wylie (editors), *A history of embryology*, Cambridge University Press, 1986, pp. 407–433, p. 409.

[10] H. Spemann and H. Mangold, 'Ueber Induktion von Embryonalanlagen durch Implantation artfremder Organisatoren', *Arch. Entwick. Mechanik*, 1924, **100:** 599–638. An English translation is given in B. H. Willier and J. M. Oppenheimer, *Foundations of experimental embryology*, Englewood-Cliffs, NJ, Prentice-Hall, 1964, pp. 146–184. Spemann reviewed his long research career in H. Spemann, *Embryonic development and induction*, New Haven, Conn., Yale University Press, 1938.

[11] C. H. Waddington, *Organisers and genes*, Cambridge University Press, 1947.

[12] J. Needham, *Order and life*, New Haven, Conn., Yale University Press, 1936.

[13] O. Nakamura and S. Toivonen, *Organizer—a milestone of a half-century from Spemann*, Amsterdam, Elsevier, 1978.

[14] G. L. Geison, *Michael Foster and the Cambridge School of Physiology*, Princeton University Press, 1978.

large amounts of glycogen in the nematode worm *Ascaris*, and in 1867, a paper on enzymes responsible for converting starch to sugar. In January of 1867, Foster was appointed instructor in practical physiology and histology at University College. The originality of his approach to physiology was evident in his first course. This was composed of three parts—histology, and chemical and experimental physiology. The chemical part included studies of "the constituents of blood and serum, spectroscopic appearances of haemoglobin and its derivatives, the components of bile and urine, the phenomena of gastric and pancreatric digestion, the general properties of albumins, carbohydrates and fats".[15] Geison has remarked that physiological chemistry was absent from the course previously taught by Sharpey and that this part of Foster's course must have been a "revelation" to many of his students.[16]

Foster's great opportunity came in 1870, when he accepted a praelectorship in physiology at Trinity College, Cambridge. Foster received little financial support from the University authorities, and he was fortunate that Trinity was a progressive college that supported science teaching and research. Trinity gave Foster a grant of £400 to establish his course, as well as funding for assistants. In 1873, Foster began his "practical course of elementary biology" that Geison describes as "marking the beginning of a new epoch in the teaching of biology in the English universities".[17] The course was based on that of Foster's mentor, T. H. Huxley, at the School of Mines in South Kensington, and ranged over such diverse organisms as yeast, hydra, amoeba, frog, and rabbit, and dealt with anatomy, histology, and physiology. This broad range of interests was also evident in the research pursued in Foster's department. Gaskell and Sharpey-Schafer recalled that Foster took care to encourage his students to pursue whatever line of research most interested them.[18] Indeed, by 1877, Foster wondered whether his report *Studies from the Physiological Laboratory* . . . should be re-titled *Studies from the Biological Institute* . . ..[19] An example of Foster's guidance of his students was his suggestion to Francis Balfour that he should take up embryology: "Balfour . . . asked Foster to advise him as to his future career. Gnawing on his moustache for a moment, Foster's eye fell upon an egg lying on a bench, which he cracked showing the embryo inside, with the suggestion 'What do you think of working on that?' "[20] This anecdote, probably apocryphal, will reappear later. (Balfour went on to become one of Britain's greatest embryologists.[21])

At this time, physiological chemistry was taught in Cambridge by Sheridan Lea,[22] who had studied with Kühne in Heidelberg. Lea was appointed university lecturer in

[15] E. A. Sharpey-Schafer, *History of the Physiological Society during its first fifty years, 1876–1926*, Cambridge Unversity Press, 1927, p. 2.

[16] Geison, op. cit., note 14 above, p. 72.

[17] Ibid., p. 117.

[18] W. H. Gaskell, 'Sir Michael Foster, 1836–1907', *Proc. Roy. Soc. Lond.*, Ser. B., 1908, **80:** lxxi-lxxxi, p. lxxiv; Sharpey-Schafer, op. cit., note 15 above, pp. 24–25.

[19] Quoted in Geison, op. cit., note 14 above, p. 116.

[20] Ibid., p. 125. The story is taken from F. H. Garrison, 'Sir Michael Foster and the Cambridge School of Physiologists', *Maryland med. J.*, 1915, **58:** 106–118.

[21] M. Ridley, 'Embryology and classical zoology in Great Britain', in Horder *et al.*, op. cit., note 9 above, pp. 35–67. Ridley gives an informative and entertaining account of embryology in Great Britain between about 1860 and 1930. His discussion of Balfour's contribution will be found on pp. 41–50. See also Geison, op. cit., note 14 above, pp. 124–130.

[22] Ibid., pp. 182–184; R. E. Kohler, *From chemistry to biochemistry*, Cambridge University Press, 1982, pp. 48–49.

physiology in 1883, although he had probably taught physiological chemistry on an informal basis since his return from Heidelberg. Lea's main contribution to promoting the advancement of chemical studies in biology was his *Chemical basis of the animal body*.[23] Originally an appendix to Michael Foster's classic *Textbook of physiology*, by the fifth edition in 1892, it was published as a separate volume. Lea distinguished, on the one hand, between the "actual 'living substance', sometimes spoken of as protoplasm in its various modifications, and, on the other hand, numerous lifeless products of metabolic activity".[24] Nothing definite was known about "the molecular composition of the active living substance"; all that could be said was that the living substance when killed yielded proteins, carbohydrates, and fats. Quite clearly, Lea did not deal with *bio*chemistry but rather with the *organic* chemistry of the various substances that could be isolated in more or less pure form from the animal body.

However, Lea was aware of the primary importance of metabolism; at one point, he remarked that there were substances such as urea that "are important not so much from the quantity in which they occur in the animal body at any one time as from their throwing light on the nature of animal metabolism".[25] In some ways Lea's book stands in the same relation to the coming biochemistry as Needham's *Chemical embryology* was to stand to biochemical embryology. Lea considered the chemical features of substances that "possess or promise to possess physiological interest. The physiological function of any substance must depend ultimately on its molecular (including its chemical nature); . . . [while] at present our chemical knowledge of the constituents of an animal body gives us but little insight into their physiological properties, it cannot be doubted that such chemical information as is attainable is a necessary preliminary to all physiological study."[26]

Chronic illness forced Lea to resign in 1895, and there is no way of knowing whether he would have gone on to make the transition from the chemical analysis of bodily substances to an analysis of their metabolic relationships. It was left to his successor, Gowland Hopkins, to achieve this and to create a department of biochemistry rather than one of physiological chemistry.

Biochemistry in Cambridge–II. Gowland Hopkins and dynamic biochemistry

Gowland Hopkins (plate 1) was born in 1861 and followed a rather unusual path to Cambridge.[27] Initially set to work as a clerk in the City, Hopkins lasted only six weeks there before becoming an articled pupil in an analytical laboratory. He spent three years in what he described as "the rough and tumble of a very busy analytical practice", years that he said taught him how to obtain results in the shortest possible time but that were intellectually sterile. Hopkins took a course in chemistry at the Royal School of Mines, and then went on to take the examination for the Associateship of the Institute

[23] A. S. Lea, *The chemical basis of the animal body*, London, Macmillan, 1892.
[24] Ibid., p. 3.
[25] Ibid., p. 4.
[26] Ibid., p. 5.
[27] F. G. Hopkins, 'Autobiography of Sir Frederick Gowland Hopkins', in J. Needham and E. Baldwin (editors), *Hopkins and biochemistry*, Cambridge, Heffer, 1949. This was a commemorative volume published to celebrate the holding of the First International Congress of Biochemistry in Cambridge in 1949. It contains essays by pupils and colleagues of Hopkins, a selection of his writings, and a bibliography of his publications.

of Chemistry. His success in this examination brought him to the notice of Sir Thomas Stevenson, and he became an assistant in Stevenson's forensic laboratory. He spent five happy, interesting years there before acquiring an external University of London BSc. degree in 1887. At the age of twenty-seven, he entered Guy's Hospital as a medical student, and in 1894, at the mature age of thirty-three, qualified with a London MB. He managed some research during his student days, and in 1895–96, he carried out collaborative research with Archibald Garrod. At the same time, he operated a small commercial laboratory—the Clinical Research Association—that was a great success. However, Hopkins was still expecting to follow a clinical rather than a laboratory career.

This was changed at a meeting of the Physiological Society in Cambridge in 1898; "As, after dinner, I was emerging from the Great Gate [of Christ's College], Michael Foster caught me up, took my arm and proposed then and there that I should come to Cambridge and develop their teaching and research in the chemical side of physiology".[28] Hopkins accepted, but his early years at Cambridge were far from easy. Sheridan Lea's lectureship had lapsed with his resignation, and to supplement his income of £200 from Foster's department, Hopkins undertook to supervise the medical students of Emmanuel College. This involved the teaching of anatomy as well as physiology, and as the minutiae of anatomy had completely slipped his memory, it was a tremendous strain to prepare for the anatomy classes. In 1902, the financial burden was alleviated when Hopkins was elected to a university readership, and in 1910, he was elected to a praelectorship in biochemistry by Trinity College. This, he later recalled, was "salvation" and played a large part in his recovery from a mental breakdown that he suffered earlier in that year. In 1914, Hopkins became Professor of Biochemistry, but it was not until after the war, at the grand age of fifty-seven, that he developed the research programme in general biochemistry that made Cambridge the pre-eminent British centre for biochemistry.[29]

As early as 1913, Hopkins had staked out what he believed were biochemistry's legitimate claims to its intellectual territory. He began his address to the Physiology section of the British Association meeting in Birmingham by referring to Liebig, who had addressed the British Association in 1837. Liebig had been enthusiastic about the advances to be made by the application of the new science of organic chemistry to biology. But, Hopkins remarked, that combination of biology and organic chemistry "never happened in any country within the limits of his [Liebig's] own century, while in this country, up to the end of that century, it can hardly be said to have happened at all".[30] Hopkins went on to say that it was a rare thing to meet a biologist with a knowledge of organic chemistry, and there were few present leaders of chemical thought who had set out to learn "with sympathy the drift of biological processes or the nature of the problems that biologists have before them".[31] As an example of what might be achieved, Hopkins turned to the work of Folin, Slyke, and Abel on the

[28] Ibid., p. 20.
[29] Kohler, op. cit., note 22 above, pp. 47–55, 73–92.
[30] F. G. Hopkins, 'The dynamic side of biochemistry', *Rep. Br. Ass.*, 1913, p. 652. Reprinted in Needham and Baldwin, op. cit., note 27 above, pp. 136–159, p. 136.
[31] Ibid., pp. 136–137.

metabolism of proteins and amino acids:". . . the progress made in these matters could only have come through the work and thought of those who combined with chemical knowledge the trained interest and feeling for biological possibilities".[32] It was not sufficient for the young chemist to analyse the constituents of the body or to study their reaction *in vitro*: "We want to learn how reactions run in the organism, and there is abundant evidence to show how little a mere knowledge of the constitution of substances, and a consideration of laboratory possibilities, can help such knowledge. The animal body usually does the unexpected."[33]

It was many years before he had the money or facilities to realize his vision of a general biochemistry. Indeed, Robert Kohler[34] has argued that Hopkins' research programme arose in part from Hopkins' desire and need to institutionalize biochemistry as a discipline distinct from that of physiological chemistry. In 1926, Hopkins wrote: "I am among those who believe that independent Institutes of Biochemistry with specialized staffs for teaching and research should in every university stand by the side of the existing Institutes of Physiology."[35] Biochemistry would then study under one roof all living material, "of course, from its own special standpoint alone". Liberating biochemistry from its connexions with medicine, and the demands of teaching medical students and of performing routine analytical work, enabled more esoteric research to be undertaken, in turn reinforcing the identity of biochemistry as a subject worthy of study and support in its own right.

But removing biochemistry from medicine removed the support that physiological chemistry had enjoyed, and there were difficulties in getting funding for Hopkins' general biochemistry programme. Although appointed to the Chair of Biochemistry in 1914, he had few research funds, cramped and inadequate laboratory accommodation, and little modern equipment. However, Hopkins had friends in high places, for Walter Morley Fletcher,[36] with whom he had carried out classic research on the biochemistry of muscle contraction,[37] was now secretary of the Medical Research Committee. The Medical Research Committee had been founded in 1913 and, although the First World War frustrated planned development of medical research in Britain, the MRC's performance in organizing the war effort of the medical sciences established its importance. By the end of the First World War, Fletcher exercised considerable power and patronage. He was keen to promote the new biochemistry. The Dunn Trustees had decided to encourage medical research by making several very large donations, and by late 1919, W. B. Hardy and Fletcher were urging the Dunn Trustees to endow an institute of biochemistry at Cambridge. In the event, they gave a total of £210,000, and in 1924, the Dunn Institute was formally opened.

There was an immediate impact on Hopkins' research efforts as shown by the increased number of his research workers (fig. 1) and by the diverse interests that these

[32] Ibid., p. 145.
[33] Ibid., pp. 158–159.
[34] Kohler, op. cit., note 22 above, p. 74.
[35] F. G. Hopkins, 'On current views concerning the mechanism of biological oxidation (with a foreword on the institutional needs of biochemistry)', *Skand. Arch. Physiol.*, 1926, **49:** 33. Quoted in L. J. Harris, 'A catena of excerpts from the scientific papers of Sir Frederick Gowland Hopkins', in Needham and Baldwin, op. cit., note 27 above, pp. 39–110, p. 83.
[36] T. R. Elliott, 'Walter Morley Fletcher, 1873–1933', *Obit. Not. Fellows Roy. Soc.*, 1934, **1:** 153–163.
[37] W. M. Fletcher and F. G. Hopkins, 'Lactic acid in amphibian muscle', *J. Physiol.*, 1907, **35:** 247–309.

workers were able to pursue. A striking feature of the research in Hopkins' department was its strong base in biology, and as Marjory Stephenson remarked, "Hopkins delighted to foster in his department lines of work far removed from his own personal studies".[38] These lines of work included bacterial chemistry, invertebrate and comparative biochemistry, the chemistry of muscle contraction, plant biochemistry, studies of biological oxidations and enzymes, and, of course, chemical embryology. And, given this broad range of interests, the sources of tissues and the types of organism studied were even more diverse.

Hopkins' presidential address to the British Association meeting in 1933 makes an interesting contrast to his address given twenty years earlier. The biochemist should not overrate the value of his contributions to biology, but, Hopkins said, "it is surely right, however, to claim that in passing from its earlier concern with dead biological products to its present concern with active processes within living organisms, biochemistry has become a true branch of progressive biology".[39] He went on to make even stronger claims: "It has opened up modes of thought about the physical basis of life which could scarcely be employed at all a generation ago. Such data and such modes of thought as it is now providing are pervasive, and must appear as aspects in all biological thought."[40] It was now possible to define biochemistry's "essential or ultimate aim" as no less than "an adequate and acceptable description of molecular

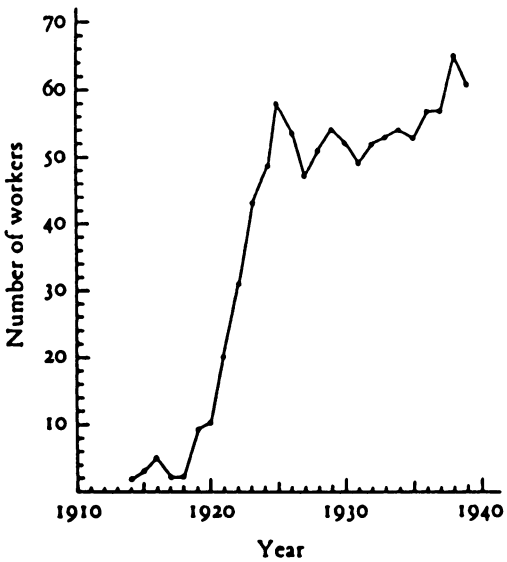

Figure 1 A graph showing the numbers of research workers by year associated with Gowland Hopkins. The award by the Trustees of the Dunn Estate was announced in 1923 and the Institute of Biochemistry opened officially in 1924. (From Kohler, op. cit., footnote 22, fig. 4.1. By courtesy of Cambridge University Press.)

[38] M. Stephenson, 'Sir F. G. Hopkins' teaching and scientific influence', in Needham and Baldwin, op. cit., note 27 above, pp. 27–38, p. 36.

[39] F. G. Hopkins, 'Some chemical aspects of life', Presidential Address, Brit. Assoc., Leicester Meeting, 1933. Reprinted in Needham and Baldwin, op. cit., note 27 above, pp. 242–263, p. 257.

[40] Ibid.

dynamics in living cells and tissues".[41] "Molecules display in such [living] systems the properties inherent in their structure even as they do in the laboratory of the organic chemist."[42] It was this change in attitude that Hopkins felt illustrated best the progress that had been achieved in biochemistry. This was the intellectual environment in Cambridge biochemistry that prevailed when Joseph Needham went there as a student in 1920.

Chemical Embryology

How did chemical embryology come to be a part of the eclectic research going on in Hopkins' department? Needham has described how he came across a dissertation by a young German scientist called Klein. In this thesis, Klein reported that while the hen's egg at laying contained no inositol, large amounts appeared by the time of hatching. Needham was inspired with "a vision of the developing egg as a most wonderful factory of changes and syntheses", and he went with "much excitement" to tell Hopkins. Hopkins responded enthusiastically, and in turn told Needham a version of the anecdote of Michael Foster and the egg referred to earlier.[43]

Needham set out to explore this "most wonderful factory", and his first biochemical publications dealt with an improved method for measuring inositol, and a study of its metabolic behaviour in the developing avian embryo. He and Dorothy Needham (plate 2) embarked on a series of experiments measuring hydrogen ion concentration and oxidation-reduction potentials in marine eggs, energy metabolism and respiration in the avian embryo, phosphorous metabolism in invertebrate eggs, and, in a sideways step into biophysics, the osmotic properties of the isolated vitelline membrane. The Needhams' research interests in chemical embryology between 1923 and 1933 were nothing if not catholic in their range!

At the same time that Needham was working industriously at the laboratory bench, he was no less industrious in the library, for between 1928 and 1930, he prepared his first great book, *Chemical embryology*. A quite extraordinary work of three volumes, totalling over 2000 pages, *Chemical embryology* was Needham's attempt to act as midwife for the new science of physico-chemical embryology. He set out "to collect together out of all the original papers on the subject the facts which are known about the physico-chemical basis of embryonic development".[44] But, at the same time, he attempted to relate these facts to each other and to the results of experimental embryology, and to draw general conclusions about them. "Classification," he wrote in the Prolegomena, "indexing and maturer considerations about the facts we actually possess are at least as great a need at the present moment as the invention of new facts."[45]

[41] Ibid., p. 244.
[42] Ibid., p. 247.
[43] 'Holorenshaw', op. cit., note 1 above, p. 7. The first version of the egg anecdote was given by Garrison in 1915 and concerned Foster and Balfour (see p. 6 and note 22 above). The version that Needham recalls Hopkins telling him concerned Foster and Hopkins. In 1898, Hopkins was breakfasting with Sir Michael Foster and, as he opened his breakfast egg, Foster said to him, "Now here's a fascinating problem, Hopkins. Why don't you have a look at the question of how the wonderful red pigment of the blood is synthesised from the raw materials, the white albumen and the yellow yolk?" Needham, op. cit., note 8 above, p. 34.
[44] Needham, op. cit., note 6 above, p. 1.
[45] Ibid., p. 2.

He certainly succeeded in classifying and indexing the facts, but a striking feature of *Chemical embryology* is the space that Needham devoted to a critical analysis of the philosophical principles underlying the study of embryological phenomena. Needham had always had strong interest in the philosophy of science and biology in particular, an interest that was heightened by his Christian and socialist outlook. His views on the general principles of embryology developed in discussions with other members of the Theoretical Biology Club, especially J. H. Woodger, and his mature statement on them is given in his second great book *Order and life*,[46] the record of his Terry lectures of 1935.

He remarked at the beginning of *Chemical embryology* that "The penetration of physico-chemical concepts into embryology has not been entirely peaceful".[47] The development of the embryo from an apparently formless egg is a wonderful and extraordinary event, and embryology had been for "so many years the happy hunting ground of vitalistic and neo-vitalistic theory that the first treatise on the physico-chemical aspect of it could hardly go without some form of theoretical introduction".[48] (It is worth pointing out that Needham had written in similar vein about biochemistry in an essay published in 1925. He wrote that "the biochemist especially should be careful to consider how his results fit in with those of philosophy. His central problem, the Nature of Life, is itself partly a philosophical one.... In physiology and biochemistry... we approach life in its most intimate aspect; as we pass from distribution to form, and from form to function, we become progressively less able to neglect philosophical considerations."[49])

Needham characterized his position as "neo-mechanistic", that is, he accepted strict mechanism in science but rejected a metaphysical materialism. "The physico-chemical embryologist is not committed to any opinion on what his material really is, but he is committed to the opinion that the scientific method is one way of describing it, and that it is best to apply that method in its full vigour if it is to be applied at all."[50] He had no time for any views of embryology that included such notions as entelechy, vitalism, or psychic factors, and he was particularly scathing of J. S. Haldane's organicism. Haldane believed that the components of a living organism were so interdependent that when they were isolated for study, they lost the characteristic properties that they possessed by virtue of being part of the organism. For example, he made the extraordinary statement that "... apart from their co-ordination and

[46] Needham, op. cit., note 12 above.

[47] Needham, op. cit., note 6 above, p. 7. Needham published in a wide variety of learned journals. Some of the philosophical parts of *Chemical embryology* originally appeared as an essay in *Monist:* 'Philosophy and embryology: prolegomena to a quantitive science of development', *Monist,* 1930, **40:** 193–210.

[48] Needham, op. cit., note 6 above, p. 37.

[49] J. Needham, 'The philosophical basis of biochemistry', *Monist*, 1925, **35:** 27–46. This essay, published when Needham was twenty-five, had some nice touches. Against the argument that the entelechy or vitalism is not to be found in the laboratory "... has been urged one of the most futile of all arguments to be met in this subject. 'If you ask the organism physico-chemical questions', it says, 'what can you expect to get except physico-chemical answers?'. The only reply to this is to point out that if you ask the organism other sorts of questions it refuses to answer at all, and you have to supply your answer yourself. What happens if you ask the organism theological questions is sufficiently illustrated by the melancholy history of the Bridgewater Treatise and Paley...".

[50] Needham, op. cit., note 6 above, p. 14; Haraway, op. cit., note 1 above, p. 127–128.

maintenance biophysical and biochemical phenomena are devoid of interest to biologists".[51] Such a view boded ill for all experimental biology that involved intervention with the organism, and Needham quoted the following verse with approval:

> You cannot demonstrate the soul
> Except upon the animal as a whole;
> Spiritual autolytic changes begin
> As soon as you push a needle through the skin.[52]

But, during the two years it took to write *Chemical embryology*, Needham's views had changed, and the problem of organization, of the inter-relationship of the developing parts of the embryo, assumed a new importance. "Chemical embryology", Needham wrote, "will never allow itself to be restricted to the description of relatively superficial events in the life of the embryo, such as the appearance of enzymes in the digestive tract. It will insist on expanding physics and chemistry, if necessary, to cover the animal level of organisation."[53]

Chemical analysis at this level had become an exciting prospect as a result of the embryological studies of Spemann and his colleagues on the organizer. It seemed to Needham that if the organizer turned out to be hormone-like, ". . . an extremely significant bridge will have been thrown across the ancient gulf between physico-chemical processes and their morphological manifestations".[54] Here, it seemed, was a situation where chemical embryology could turn away from cataloguing those superficial events of an embryo's life, and contribute to the deeper understanding of a real morphogenetic event. The organizer organized Needham's research, and he embarked on a research programme intended to build that bridge between embryology and biochemistry.

The Embryological Problem

In 1892, Weismann set out to explain the central problem of embryology, how the single cell that is the fertilized egg gives rise to an increasing number of cell types during development. In his *The germ plasm: a theory of heredity*, Weismann suggested that the characteristics of each cell type are specified by a nuclear factor that he called a "determinant".[55] The fertilized egg possesses a complete set of determinants and during subsequent cell divisions, the determinants are shared out amongst the daughter cells until each cell possesses only one determinant.

[51] J. S. Haldane, *The philosophy of a biologist*, Oxford, Clarendon Press, 1935, see pp. 69–70. Hopkins also took up the pen against Haldane's neo-vitalism, especially in a lecture given in 1927 (F. G. Hopkins, 'A lecture on organicism', in Needham and Baldwin, op. cit., note 27 above, pp. 179–190). He took particular exception to the remark by Haldane that "The attempt to analyse living organisms into physical and chemical mechanisms is probably the most colossal failure in the whole history of modern science" (ibid., p. 181). Hopkins' rejoinder was that "If there be any lack of reality about the knowledge won by such [analytical] efforts, it only emerges, I think, in those subtle workings of the philosophic mind which see reality disappear during every process of analysis." (Ibid, p. 190.)

[52] Needham, op. cit., note 6 above, p. 28.

[53] Ibid., p. 558.

[54] Ibid., p. 1626.

[55] A. Weismann, *The germ plasm: a theory of heredity*, London, Walter Scott, 1893.

Wilhelm Roux proposed a similar theory and set out to test it experimentally. If cell division results in different sets of determinants passing to different daughter cells, then even the two cells resulting from the first cleavage of the egg will be qualitatively different, each cell possessing one-half of the determinants necessary for proper development of the embryo. In his classical experiments described in 1888, Roux killed one of the blastomeres of a frog embryo at the two cell stage and found that abnormal, half-embryos resulted.[56]

Three years later, a quite different result was obtained by Hans Driesch, who separated the blastomeres of sea urchin eggs by shaking them vigorously in seawater.[57] As he wrote many years later, he was expecting to find half-embryos as had Roux, "but things turned out as they are bound to do and not as I had expected; there was a typically whole gastrula on my dish the next morning, differing only by its small size from a normal one".[58] Driesch was never able to reconcile the results of this experiment with any mechanistic explanation, and he took refuge in a non-material, vitalistic agency, the entelechy, which was responsible for maintaining the "wholeness" of embryonic development.[59] With the exception of die-hard vitalists like W. E. MacBride, the entelechy did not enjoy a great success. Needham, in particular, made a number of scathing attacks on it: "When we read that the entelechy is neither mind nor body, neither spirit nor matter, we are driven to ask ourseleves whether it is really anything at all".[60]

In the years at the turn of the century, many similar experiments were performed, variously compressing, constricting, and centrifuging eggs, and killing or separating the cells of early embryos, all directed to finding out at what stage cells become committed to specific pathways of differentiation. It was here that Hans Spemann made his first contributions to experimental embryology.

Hans Spemann (plate 3) was one of the greatest of experimental embryologists,[61] whose career culminated in the award of a Nobel Prize in 1935. He summarized his life's work in *Embryonic development and induction*,[62] the record of his Silliman Lectures given in 1934. Spemann was concerned with the process by which cells became committed to particular developmental fates. He performed his experiments ". . . in order to answer the general question whether and in what manner the larger partial processes of development are connected among themselves, whether one causes and

[56] W. Roux, 'Beiträge zur Entwickelungsmechanik des Embryo. Ueber die künstliche Hervorbringung halber Embryonen durch Zerstörung einer der beiden ersten Furchungskugeln, sowie über die Nachentwickelung der fehlenden Körperhälfte', *Virchows Arch. path. Anat. Physiol. kl. Med.*, 1888, **114:** 113–153. An English translation of part of the article is given in Willier and Oppenheimer, op. cit., note 10 above, pp. 4–37.

[57] H. Driesch, 'Entwicklungsmechanische Studien. I. Der Werth der beiden ersten Furchungszellen in der Echinodermentwicklung. Experimentelle Erzeugen von Theil-und Doppelbildung', *Zt. wiss. Zool.*, 1892, **53:** 160–178. An English translation is given in Willier and Oppenheimer, op. cit., note 10 above, pp. 40–50.

[58] H. Driesch, *The science and philosophy of the organism*, London, Adam & Charles Black, 1908.

[59] Ibid.

[60] Needham, op. cit., note 49 above, p. 32. See also Needham, op. cit., note 7 above, pp. 119–124.

[61] T. J. Horder and P. J. Weindling, 'Hans Spemann and the organiser', in Horder *et al.*, op. cit., note 9 above, pp. 183–242; V. Hamburger, 'Hans Spemann and the organizer concept', *Experientia*, 1969, **25:** 1121–1125.

[62] Spemann, op. cit., note 10 above.

conditions the other, or whether they proceed side by side independent of each other."[63]

Spemann, like Roux and Driesch, began by examining the Weismann-Roux theory. Instead of killing blastomeres, he used loops made of hair to separate the blastomeres of *Triton* embryos. This operation sometimes resulted in the production of two normal embryos (fig. 2a). If the same experiment was performed on the fertilized egg so that the nucleus was confined to one part of the egg cytoplasm, that part continued to divide. At some later stage, a single nucleus was allowed to move from the part that was now at the blastula stage, to the enucleated part. Despite the fact that this nucleus should now contain only a fraction of the determinants originally present in the egg nucleus, it was able to give rise to a normal embryo. Quite different results could be obtained depending on the orientation of the constrictions. If the constriction was in the median plane, dividing the embryo into left and right halves, normal embryos resulted. If the constriction divided the embryo into dorsal and ventral halves, only the dorsal half developed normally (fig. 2b).

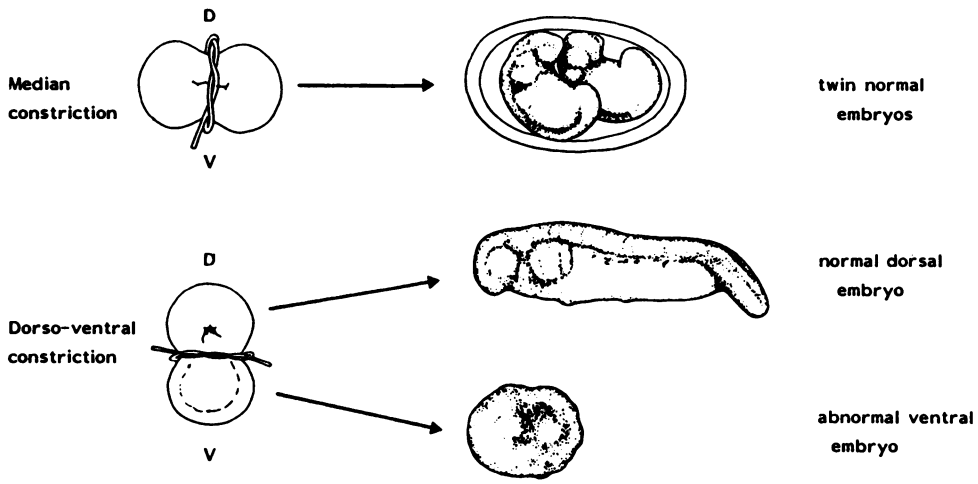

Figure 2 Constriction experiments performed by Hans Spemann using *Triturus* eggs and loops of fine hair. A. Constriction along the dorso-ventral line so that both halves contain part of the dorsal lip of the blastopore results in two small but normal embryos. B. A constriction that confines the dorsal lip of the blastopore to part of the egg results in only the latter part forming a normal embryo. (Adapted from Spemann, op. cit., footnote 10.)

Spemann went on to carry out an analysis on a finer scale by transplanting fragments of tissue between gastrulae or between embryos at different stages of development. He began by transplanting tissue between *Triton taeniatus* embryos, but to distinguish between host and graft, he was obliged to use embryos that were at different stages of development and differed in their pigmentation. Later, Spemann used grafts between the heavily pigmented *taeniatus* and light coloured *cristatus* newts so that transplants

[63] Ibid., p. 3.

could be distinguished from the host embryo. Reciprocal transplants of presumptive epidermis and brain between early gastrulae showed that these were not determined at this stage; presumptive epidermis was incorporated into the neural tube and presumptive brain became skin in conformity with their new surroundings.[64]

The behaviour of tissue taken from the upper lip of the blastopore was quite different. It invaginated as it would have done in the donor embryo, and a small secondary embryo was formed. Spemann first obtained this result in 1918 using *taeniatus* embryos in which it was difficult to distinguish transplant and host tissue.[65]

At the time these experiments were performed, it was not known that the tissue of the upper lip of the blastopore was presumptive mesoderm. This finding came from Vogt's vital staining experiments published in 1925.[66] Spemann believed that the transplants contained both ectoderm (giving rise to the secondary neural plate) *and* mesoderm (forming the secondary notochord and somites). Warren Lewis had obtained similar results in *Rana* as long ago as 1907 and had interpreted them in the same way.[67] It was Hans Petersen in Heidelberg who apparently drew Spemann's attention to the possibility that the seondary embryo developed as a consequence of the invagination of the graft[68] and that it was composed of host cells. In 1921, Hilde Proscholdt,[69] Spemann's student, repeated these experiments, transplanting the dorsal lip of the blastopore from a pale *cristatus* embryo to an early *taeniatus* gastrula, and in May 1921, she obtained her first successful transplant (fig. 3). She and Spemann found that the majority of the secondary embryo was derived from the *host* tissue.[70]

This was a most remarkable and important result. As Spemann wrote many years later: ". . . it appeared as if an organizing force which was introduced by the implant had been at work within the region of its domination regardless of any limits as to material".[71] The dorsal lip of the blastopore was called an "organization centre" and its cells, when invaginated and in contact with the overlying ectoderm *induced* the formation of the secondary embryo. Spemann was familiar with the process of induction from his earlier work on the relationship between the optic cup and the development of the lens.[72] He had recognized the possibility that parts of the embryo already determined might determine the fate of the still indifferent parts. Because the dorsal lip of the blastopore appeared to be the first such induction in embryonic development, it became known as the *primary organizer*, and inductions such as that of

[64] H. Spemann, 'Die Erzeugung tierischer Chimaeren durch heteroplastiche embryonale Transplantation zwischen Triton cristatus u. taeniatus', *Arch. Entwkl. Mech.*, 1921, **48:** 533–570.

[65] H. Spemann, 'Über die Determination des ersten Organanlagen des Amphibien-embryo I-VI', ibid., 1918, **43:** 448–555.

[66] W. Vogt, 'Gestaltungsanalyse am Amphibienkein mit örtlicher Vitalfärbung. Vorwort über Wege und Ziele. I. Methodik u. Wirkungsweise der örtlichen Vitalfärbung mit Agar als Farbträger', ibid., 1925, **106:** 542–610; *idem*, 'Gestaltungsanalyse am Amphibienkein mit örtlicher Vitalfärbung. II. Teil: Gastrulation und Mesodermbildung bei Urodelen und Anuren', ibid., 1929, **120:** 385–706.

[67] W. H. Lewis, 'Transplantation of the lips of the blastopore in *Rana palustris*', *Am. J. Anat.*, 1907, **7:** 137.

[68] Spemann, op. cit., note 10 above, p. 143.

[69] V. Hamburger, 'Hilde Mangold, co-discoverer of the organizer', *J. Hist. Biol.*, 1984, **17:** 1–11.

[70] Spemann and Mangold, op. cit., note 10 above.

[71] Spemann, op. cit., note 10 above, p. 145.

[72] Ibid., Chs. 3 and 4.

the lens by the optic cup were called *secondary* inductions. Eventually, a whole hierarchy of such inductions was recognized as illustrated in a figure adapted by Needham[73] from a paper by Holtfreter published in 1938 (fig. 4).

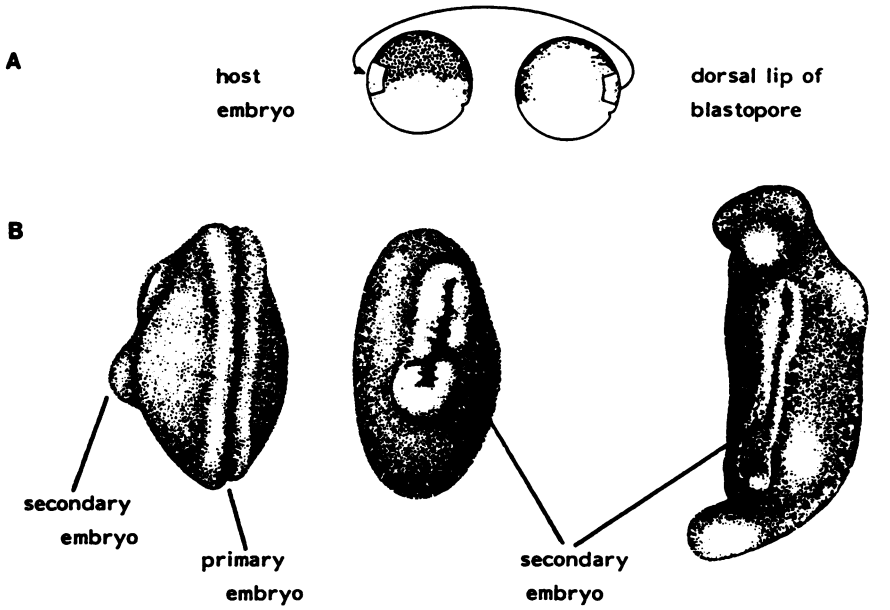

Figure 3 The organizer experiment. A. The dorsal lip of the blastopore was transferred from a lightly-pigmented *cristatus* gastrula to a darkly-pigmented host *taeniatus* gastrula. B. External views of an embryo showing the formation of a secondary body axis. (Adapted from Spemann, op. cit., footnote 10.)

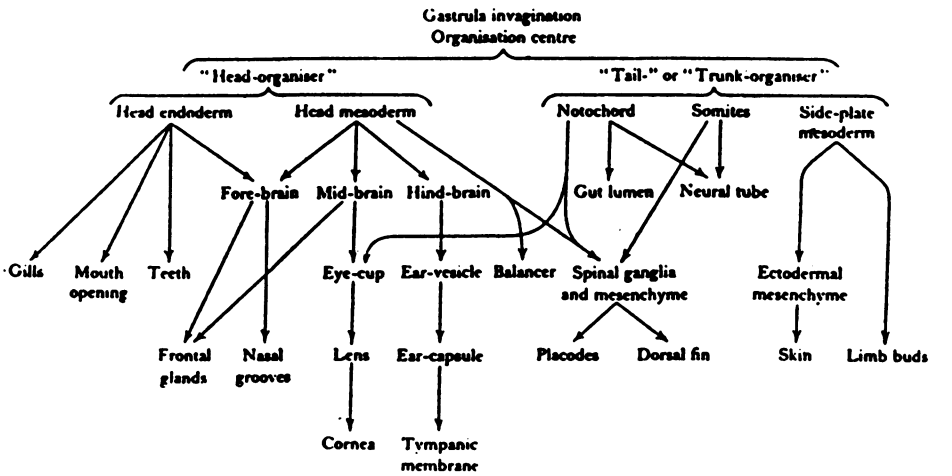

Figure 4 A diagram showing the complex interrelationships of inductive processes during embryonic development. (From Needham, op. cit., footnote 7, fig. 162. By courtesy of Cambridge University Press.)

[73] Needham, op. cit., note 7 above, p. 290.

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Hunting the Organizer

This, then, was the razor's edge of embryological research in the early 1930s, and it was inevitable that Needham would be drawn to the work on the organizer. At the same time that he was working away at *Chemical embryology*, he began research on the metabolic and biochemical processes of induction. Needham followed a number of lines of research, but I shall concentrate on only one, the hunt for the organizer itself. This was the most spectacular research on the organizer, and the research that was begun in the greatest excitement and with the greatest optimism. Other of Needham's researches, particularly those on respiratory changes in the embryo during induction,[74] were technically much more demanding, but they did not have the same impact as the attempt to isolate the organizer. The findings of the Cambridge Group were published in eight papers, seven of which formed a series entitled 'Studies on the nature of the amphibian organization centre', in the *Proceedings of the Royal Society* between 1935 and 1938.[75] I am going to refer in detail to four of these. Reviews of the early research period are given by Needham in *Biochemistry and morphogenesis* and by Jean Brachet in his *Chemical embryology*,[76] and both Needham and Brachet have written fascinating retrospectives of their work on the organizer.[77] Saxen and Toivonen, and Nakamura and Toivonen have reviewed more recent findings.[78]

The first steps in the chemical analysis of the organizer had been taken in 1931 by Marx, who had shown that dorsal lip of blastopore treated with alcohol was able to induce a second embryonic axis. Spemann found that crushing the tissue had no effect on its activity, and Bautzmann, Holtfreter, Spemann, and Mangold found that boiled organizer could still induce. Holtfreter performed the most extensive series of experiments with some remarkable results.[79] Organizer tissue denatured by prolonged

[74] Boell, op. cit., note 7 above.

[75] (a) J. Needham, C. H. Waddington, and D. M. Needham, 'Physico-chemical experiments on the amphibian organizer', *Proc. Roy. Soc. Lond.*, Ser. B., 1934, **114:** 393–422; (b) C. H. Waddington, J. Needham, W. W. Nowinski, and R. Lemberg, 'Studies on the nature of the amphibian organization centre. I. Chemical properties of the evocator', ibid., 1935, **117:** 289–310; (c) C. H. Waddington and D. M. Needham, 'Studies on the nature of the amphibian organization centre. II. Induction by synthetic polycyclic hydrocarbons', ibid., 1935, **117:** 310–317; (d) C. H. Waddington, J. Needham, and J. Brachet, 'Studies on the nature of the amphibian organization centre. III. The activation of the evocator', ibid., 1936, **120:** 173–198; (e) C. H. Waddington, J. Needham, W. W. Nowinski, R. Lemberg, and A. Cohen, 'Studies on the nature of the amphibian organization centre. IV. Further experiments on the chemistry of the evocator', ibid., 1936, **120:** 198–207; (f) N. G. Heatley and P. E. Lindahl, 'Studies on the nature of the amphibian organization centre. V. The distribution and nature of glycogen in the amphibian embryo', ibid., 1937, **122:** 395–402; (g) N. G. Heatley, C. H. Waddington, and J. Needham, 'Studies on the nature of the amphibian organization centre. VI. Inductions by the evocator-glycogen complex in intact embryos and in ectoderm removed from the individuation field', ibid., 1937, **122:** 403–412; (h) C. H. Waddington, 'Studies on the nature of the amphibian organization centre. VII. Evocation by some further chemical compounds', ibid., 1938, **125:** 365–372.

[76] Needham, op. cit., note 7 above; J. Brachet, *Embryologie chimique*, Paris, Masson, 1944. English translation, *Chemical embryology*, New York, Interscience Publishers, 1950.

[77] Needham, op. cit., note 7 above. The third impression of *Biochemistry and morphogenesis* published in 1968 contains a long foreword by Needham discussing his aims in writing the book. J. Brachet, 'Early interactions between embryology and biochemistry', in Horder *et al.*, op. cit., note 9 above, pp. 245–259. See also the article by Saxen and Toivonen, 'Primary embryonic induction in retrospect', ibid., pp. 261–274.

[78] L. Saxen and S. Toivonen, *Primary embryonic induction*, London, Logos Press, 1962; Nakamura and Toivonen, op. cit., note 13 above.

[79] Holtfreter's results were summarized by Needham in *Biochemistry and morphogenesis*, op. cit., note 7 above, pp. 156–162, 165–176. Holtfreter summed up his views of amphibian development in J. Holtfreter

boiling or by immersion in alcohol for many months was still active; treatment with xylol and embedding in wax was without effect; a variety of tissues from a variety of species was active (Waddington and Wolsky[80] later showed that *Hydra* was effective); and, extraordinarily, tissues that did not normally induce would do so if they were first boiled. This suggested that such tissues contained the organizer in a "masked form", and was the first hint of the complexities to come.

The Cambridge Group's first major publication[81] in this field was important not only for the results presented, but also for its introduction and discussion where many of the problems and pitfalls of the field were recognized and evaluated. Four suggestions had been made about the nature of the organizer centre: (i) that it was an example of a dominant physiological region that established an axial gradient of the kind proposed by Child; (ii) that it might have an electrical basis relating to differences in charge between cells and different parts of the embryo; (iii) that mitogenetic rays might be involved; (iv) that there was "a single definite chemical substance, working in an almost endocrinological manner on the competent ectoderm". Not surprisingly, Needham, Dorothy Needham, and Waddington decided to explore this last option. They first presented details of the cell-free extract experiments that had been reported briefly by them in 1933. Ten to fifty neurulae were crushed, taken up in a capillary tube and centrifuged. Three layers were obtained that were prepared for implantation into embryos by voiding them on to a hotplate where they coagulated. The upper layer of oil and fat and the middle watery layer were usually tested together and they induced secondary embryos (plate 4). The lower layer—described as "a muddy solid"—was also active. Ether (plate 5) and petrol ether extracts of neurulae were capable of inductions, and the unsaponifiable fraction of an ether extract of "several thousand" embryos was active. In addition, Needham *et al*, tested a number of pure substances including egg albumin, cholesterol, and calciferol. All were negative. Adult tissues and ether extracts of them gave positive inductions.

It must be said that these results were not particularly convincing. In the first place, it was difficult to determine what was a positive reaction by the host embryo, and it was suggested later that Needham and his collaborators had been rather optimistic in their assessments.[82] Furthermore, the ether extracts were not more active than the aqueous extracts and there was no evidence that the ether extracts produced inductions of better quality than might have been expected of even partially purified material.

So the results were rather inconclusive, despite the large number of embryos used (1196, of which 629 died before they could be examined), but an important point arose from their observations of these embryos. Needham distinguished two steps in the process of induction. The first, called evocation, is the determination that an embryonic axis will be formed and is always performed by the graft acting alone. The second step, called individuation, is the determination of the nature of that axis,

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and V. Hamburger, 'Embryogenesis: progressive differentiation—amphibians', in B. H. Willier, P. Weiss and V. Hamburger (editors), *Analysis of development*, Philadelphia, Saunders, 1955, pp. 230–296.

[80] C. H. Waddington and A. Wolsky, 'The occurrence of evocator in organisms which possess no nerve cord'. *J. exp. Biol.*, 1936, **13**: 92–94.

[81] Needham, *et al.*, op. cit., note 75 (a) above.

[82] Brachet, op. cit., note 76 above, p. 398.

whether it should be forebrain, or hindbrain, or spinal cord. Both host and grafted tissues take part in individuation. Needham suggested that individuation could not be performed by any dead organizer or extract. As to the nature of the organizer, Needham *et al.* could conclude only that it was ether-soluble.

The next two papers were published in 1935. The paper on the 'Chemical properties of the evocator'[83] opened with an attempt to reconcile the results of Fischer's group in Germany and of Barth in the USA, with those of the Cambridge Group. Waddington *et al.* concluded that the preparations of glycogen, muscle adenylic acid, and thymonucleic acid used by Fischer[84] were probably contaminated with the true organizer, and that the same might have been true for Barth's cephalin preparations.[85] Waddington *et al.* first prepared glycogen according to Fischer's method and then showed that ether extracts of this glycogen gave positive inductions. Subfractions of ether extracts of adult newt tissues were prepared by saponification with potassium hydroxide followed by digitonin precipitation. The unsaponifiable fraction and its digitonin precipitate were both positive (plate 6). The conclusion was that "the evocating substance, which is extracted by ether from adult tissues is unsaponifiable, precipitable with digitonin and separable with the cholesterol from the alcoholic solution of the crude unsaponifiable matter. These facts strongly suggest that the substance is a sterol."[86]

This conclusion was reinforced by the paper by Waddington and Dorothy Needham[87] that followed immediately. They were concerned with examining the connexion between the growth of tumour tissue and the normal processes of growth and development; could there be a relationship between the organizer (or evocator) and substances with similar chemical properties that have carcinogenic activities? Waddington and Needham tested seven such compounds and found three that gave inductions, one, dibenzanthracene producing 82 per cent inductions (plate 7). These results were considered especially significant in that these were pure, synthetic substances that could not be contaminated by the "natural" organizer. (Needham later attempted to produce a unified scheme linking a whole range of biological active substances (fig. 5).[88])

Other lines of research were being pursued concurrently with these on the chemical nature of the evocator. Julian Huxley[89] had suggested that the dorsal lip of the blastopore constituted a dominant region in an axial gradient of metabolic activity. C. M. Child had long been an enthusiastic advocate of metabolic gradients in

[83] Waddington *et al.*, op. cit., note 75 (b) above.

[84] F. G. Fischer and E. Wehmeier, 'Zur Kenntnis der Induktionsmittel in der Embryonalentwicklung'. *Naturwissenchaften*, 1933, **21:** 518; F. G. Fischer, E. Wehmeier, H. Lehmann, L. Jühling, and K. Hultzsch, 'Zur Kenntnis der Induktionsmittel in der Embryonalentwicklung', *Ber. chem. Ges.*, 1935, **68:** 1196–1199.

[85] L. G. Barth, 'The chemical nature of the amphibian organizer. I. The use of the cephalin-fraction of mammalian brain as an inducing agent', *Biol. Bull.*, 1934, **67:** 244–249.

[86] Waddington *et al.*, op. cit., note 75 (b) above, p. 306.

[87] Waddington and Needham, op. cit., note 75 (c) above.

[88] Needham, op. cit., note 7 above, fig. 138 and pp. 239–271. The relationship, if any, between organizer-like substances and cancer excited a great deal of attention. See, for example, C. H. Waddington, 'Cancer and the theory of organizers', *Nature*, 1935, **135:** 606–608.

[89] J. Huxley, 'Early embryonic differentiation', ibid., 1924, **113:** 276–278; Huxley and de Beer, op. cit., note 8 above.

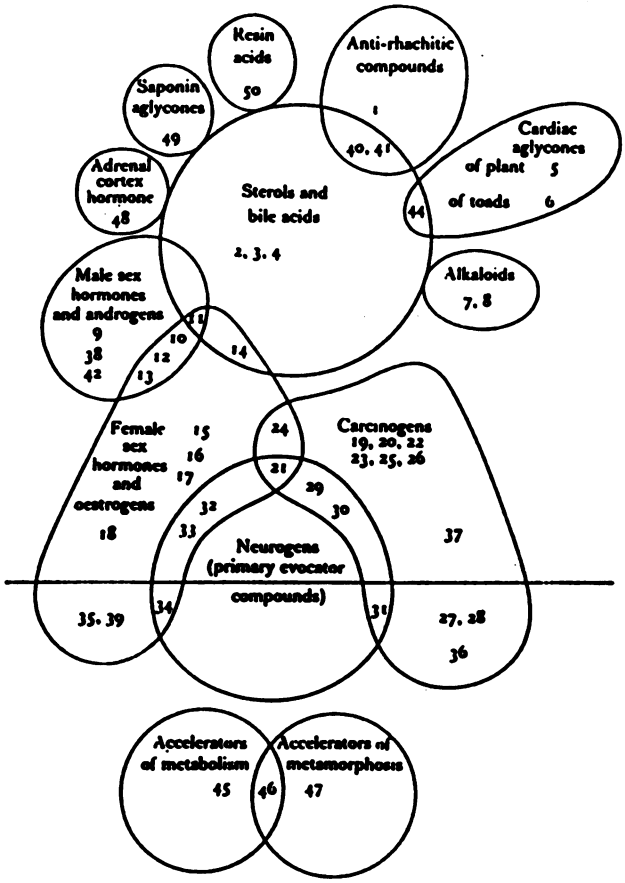

Figure 5 Needham drew up this figure to show the relationships of various classes of biologically-active substances. Each number refers to a specific substance, for example 3 is cholesterol, 16 is oestradiol, and 30 is methylcholanthrene. Compounds above the line are condensed polycyclic compounds, and those below are simple polycyclic and monocyclic compounds. (From Needham, op. cit., footnote 7, fig. 138.)

developmental processes, and a large number of investigations was undertaken to examine whether induction could be the consequence of the activity of such a gradient.[90] Child held that: ". . . the region of primary activation is an organizer only indirectly, by initiating and determining a gradient pattern; conditions at different levels of this pattern determine the orderly localization of parts along an axis. In short . . . the gradients are the real organisers."[91] He concluded that induction resulted from ". . . an imposition on the ectoderm of the axiate pattern of the inductor, and this pattern is the organizer".[92] However, Spemann thought that experimental data were insufficient to decide conclusively between the various theories, and ". . . surely not in

[90] C. M. Child, *Patterns and problems of development*, Chicago, University of Chicago Press; L. Wolpert, 'Gradients, position and pattern: a history', in Horder *et al.*, op. cit., note 9 above, pp. 347–362.
[91] Child, op. cit., note 90 above, pp. 435–436.
[92] Ibid., p. 503.

favour of the gradient theory in the special formulation of Child".[93] Needham made a similar point. While acknowledging that susceptibility to agents such as metabolic poisons could be demonstrated, "no evidence whatsoever" had been brought forward to justify a belief in the existence of "respiratory" or "metabolic" gradients in embryos.[94] Nevertheless, the respiratory activity of the embryo was of considerable interest to the Cambridge Group and to Jean Brachet, the great Belgian embryologist. In 1934, Waddington, Needham, and Brachet[95] undertook a set of experiments designed to determine if the evocator might be released in specific parts of the embryo in response to a respiratory gradient. They argued that metabolic catalysts such as methylene blue might raise the metabolic activity of isolated pieces of ectoderm and release the evocator. Pieces of ectoderm were therefore treated *in vitro* with methylene blue and then transplanted into the blastocode of gastrulae. These treated fragments of ectoderm gave positive inductions.

How did Waddington and his colleagues interpret these results? They suggested that there was a set of *substances*, including those found by Fischer, Barth, and the Cambridge Group, that brought about induction. There was also a set of *processes* that when applied to gastrula ectoderm made it capable of inducing an embryonic axis. These included the events of normal embryonic induction, boiling, and treatment with organic solvents. Methylene blue occurred in both sets, and they considered how these two sets could be reconciled. There were two possibilities. First, methylene blue might act in a way similar to the natural evocator, that is, directly as a stimulus to neural differentiation. "But it would be ridiculous to suppose that methylene blue *is* the natural evocator"[96] and hence one should assume that there was more than one such substance. On the other hand, methylene blue might act on some "masked" form of the evocator leading to its release in active form. In this case, all the substances so far found to act as inducers, and all the processes involved, might act by releasing the evocator from an inactive complex. After discussing the various sorts of complexes of important biological materials that had been found, Waddington *et al.* concluded that: "it is permissible to make the tentative hypothesis that throughout the ectoderm and endoderm of the blastula, there exists an evocator-glycogen-protein complex, analogous to desmo-glycogen lecitho-vitellin, or astacin. This complex breaks down wholly or partially only in the dorsal lip of the blastopore, liberating the active evocator".[97]

This view had serious consequences, as Waddington stated explicitly in the last of the series of papers.[98] How can one distinguish between the action of the true evocator, and the action of some substance or process that merely liberates the evocator in the

[93] Spemann, op. cit., note 10 above, p. 332.

[94] Needham, op. cit., note 7 above, p. 605. See also Needham, op. cit., note 6 above, pp. 582–606. However, Needham did acknowledge that Child had made a "great" contribution to embryology in introducing the gradient concept that had been assimilated by the concept of the "field". Needham, op. cit., note 12 above, p. 72. Needham disagreed with Child's insistence that the differential susceptibility of different parts of the embryo to agents such as cyanide demonstrated that the gradients were respiratory in character.

[95] Waddington *et al.*, op. cit., note 75 (d) above.

[96] Ibid., p. 186.

[97] Ibid., pp. 190–191.

[98] Waddington, op. cit., note 75(h) above.

responding tissue? Waddington *et al.* initially appealed to dosage effects, arguing that the smaller the dose of substance required to produce an effect, the less likely was that dosage to produce cell damage releasing the evocator. So the more active a substance on a weight basis, the closer it was likely to be to the true evocator. However, this would presumably apply to highly toxic substances as well! In 1938, Waddington wrote ". . . the only test we have for evocating power is to apply a substance to the ectoderm, in which the evocator is already present. Until this difficulty can be surmounted, it appears impossible to discover the true nature of the natural evocator by implanting synthetic substances."[99]

Conclusion

This paper by Waddington signalled the end of the Cambridge Group's hunt for the organizer. The difficulty posed by the ubiquitous presence of the masked evocator seemed insurmountable, and the onset of the Second World War rendered the events of early amphibian development less significant.[100] The Cambridge team split up. In 1942, Joseph Needham went to China, followed by Dorothy in 1944, and it was also in 1942 that Needham published his third book, *Biochemistry and morphogenesis*, which became his valediction to the field. On their return to Cambridge in 1950, Joseph Needham began his epic study of the history of Chinese science. Waddington was in operational research during the war and after it, in 1945, he was offered the Chair of Genetics in Edinburgh. His research became diversified, with theoretical writings on genetics, education, and biology side-by-side with experimental work.[101]

Although the first phase of biochemical work on the organizer was over, the future was not entirely bleak, even in 1939. Needham attended the first Growth Symposium in that year, and in his review[102] he was able to discuss the recent results of Chuang, who had found that adult kidney contained a heat-labile factor that induced mesodermal structures and a heat-stable factor with neural inducing activity. More recently, building on these results and using modern preparative and analytical techniques, Yamada, Tiedemann, and Saxen and Toivonen[103] have prepared mesodermalizing and neuralizing factors that in combination can mimic the activity of the organizer. Yet it can still be claimed that the mechanisms of induction are "hardly better understood now than when they were first discovered at the beginning of this

[99] Ibid., p. 370.

[100] In the foreword to the 1968 impression of *Biochemistry and morphogenesis*, Needham drew attention to other difficulties the Cambridge Group faced in pursuing their research. Remarking that external social factors should not be overlooked in the history of scientific research, Needham wrote that the Cambridge Group were unable to obtain sufficient long-term funding for their research. In 1934, Needham and Waddington applied to the Rockefeller Foundation for funds to establish an Institute for Physico-Chemical Morphology in Cambridge, with Needham, Waddington, J. D. Bernal, Honor Fell, and D. M. Wrinch as its members. The Rockefeller Foundation turned down the proposal, apparently because of discouraging opinions from eminent scientists such as Sir Henry Dale and Sir Edward Mellanby, and because Cambridge University was unenthusiastic about the venture. Haraway, op. cit., note 1 above, p. 134; P. Abir-Am, 'The discourse of physical powers and biological knowledge in the 1930s: a re-appraisal of the Rockefeller Foundation's policy in molecular biology', *Soc. Stud. Sci.*, 1982, **12:** 341—382. But see E. Yoxen, 'Form and strategy in biology: reflections on the career of C. H. Waddington', in Horder *et al.*, op. cit., note 9 above, pp. 309–329, pp. 316–317 for a different interpretation of the Rockefeller Foundation's aims.

[101] Yoxen, op. cit., note 100 above.

[102] J. Needham, 'Biochemical aspects of organiser phenomena', *Growth (Suppl.)*, 1939, **3:** 45–52.

[103] See Saxen and Toivonen, op. cit., note 78 above, and Nakamura and Toivonen, op. cit., note 13 above.

century".[104] In his penetrating analysis of the problems of embryology, Jonathan Slack wrote that "No subject in embryology has been so misinterpreted and misunderstood as the properties of the organiser".[105] He suggests that this is because several interactions and not just one are involved, and that different assay procedures detect different processes. He distinguishes between the activity of the organizer proper, and the mesodermal and neural factors already referred to. As to the hunt for factors specifying regional developments, Slack writes: "A search for the key substances involved in regional specification resembles the search for a contact lens in a swimming pool, with the added uncertainty that the lens may have dissolved in the water."[106]

In *Chemical embryology*, Needham wrote that the future of embryology lay in the closest contact between biochemistry and experimental embryology, and "... the biologist who will deserve most the gratitude of posterity will be he who finds the way to fuse these studies into one".[107] Eight years later, in 1939, he suggested that "it may be more like fifty years before we can expect certain knowledge concerning the chemical nature of the naturally-occurring substances involved in embryonic induction".[108] That fifty years is almost up, but Needham's biologist has yet to put in an appearance, and the biochemical analysis of dynamic embryological events remains formidably difficult.

[104] J. M. W. Slack, *From egg to embryo*, Cambridge University Press, 1983, p. 26. See also J. C. Smith, 'Solving the organizer', *BioEssays*, 1985, **2**: 277–280.
[105] Slack, op. cit., note 104 above.
[106] Ibid., p. 171.
[107] Needham, op. cit., note 6 above, p. 1664.
[108] Needham, op. cit., note 102 above, p. 52.

Plate 1 Frederick Gowland Hopkins in 1908. (From Needham and Baldwin, op. cit., footnote 27. By courtesy of W. Heffer & Sons Ltd., Cambridge.)

Plate 2 Hans Spemann. (From Hamburger, op. cit., footnote 61, p. 1122.)

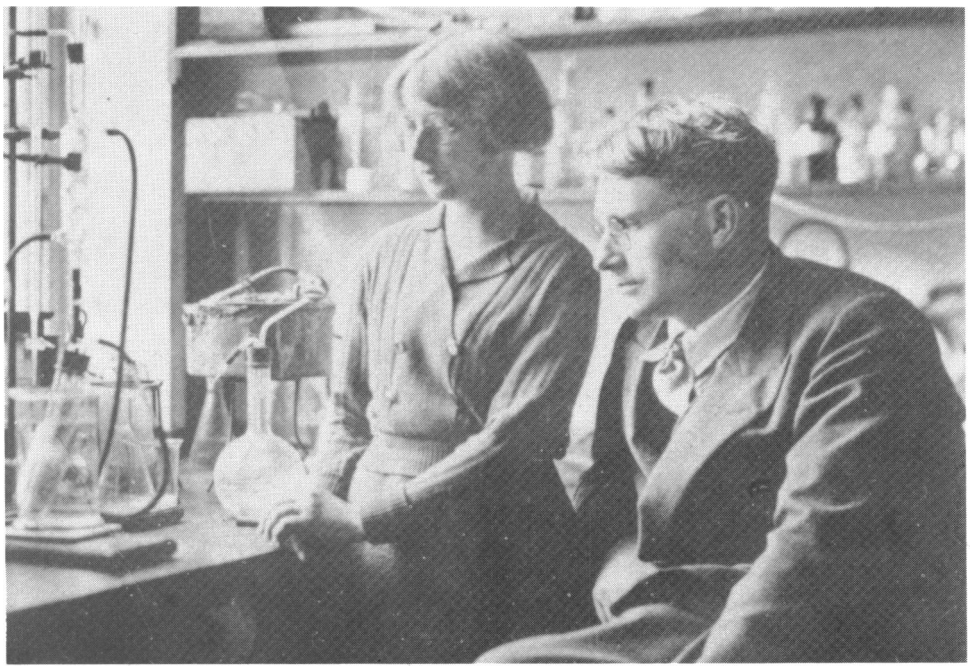

Plate 3 Dorothy and Joseph Needham in a laboratory in the Dunn Institute, 1927. (By courtesy of Dorothy and Joseph Needham.)

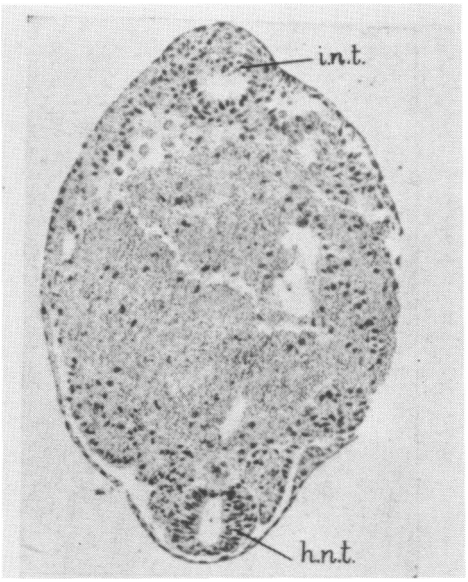

Plate 4

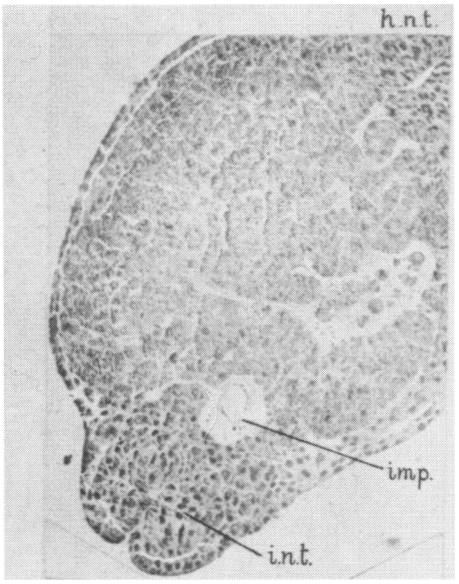

Plate 5

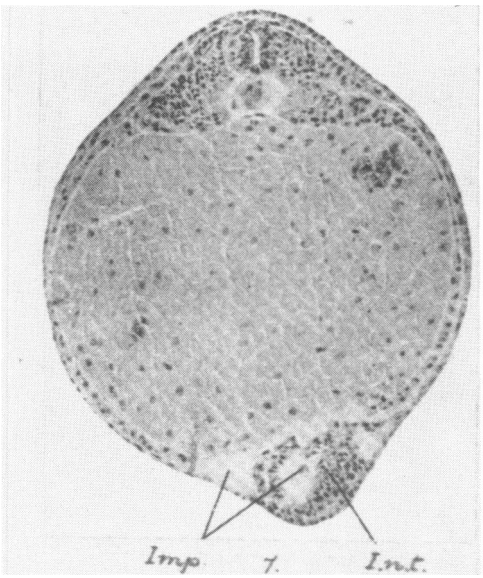

Plate 6

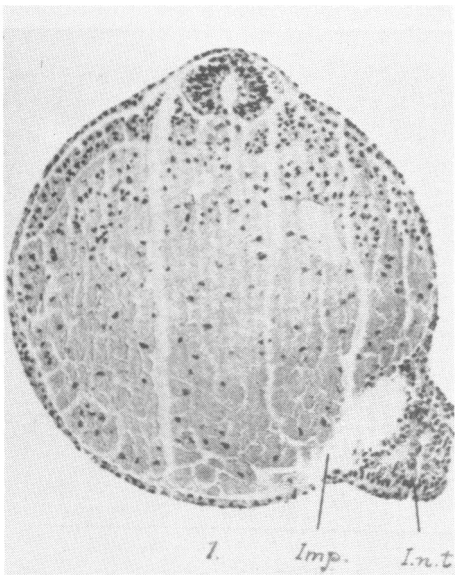

Plate 7

Plates 4–7 Transverse sections of neurulae showing development of secondary axis structures following implantation of experimental materials into young gastrulae. 4. Implantation of a cell-free extract of neurulae; 5. Implantation of an ether extract; 6. Implant of a digitonin precipitate of an ether extract; 7. Implant of dibenzanthracene. (Figs. 4 and 5 from Needham, Waddington, and Needham, op. cit., footnote 75 (a), plate 28 (1) and plate 29 (7). Fig. 6 from Waddington *et al.*, op. cit., footnote 75 (b), plate 18 (7). Fig. 7 from Waddington and Needham, op. cit., footnote 75 (c), plate 19 (1).)

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