

Chapter 2

Becoming Hopkins' Associate

Stephenson started her new career in the favourable post-World War I climate of social liberation, typified by such progressive legislation as the granting of the vote to women and the Sexual Disqualification [Removal] Act, which regulated academic degrees for women [1, p. 239]. But association with F.G. Hopkins (Fig. 2.1), his laboratory and his school represented a decisive step in her life and work also for many other reasons. She became part of a community of scientists pursuing a young scientific discipline that was to accomplish in the upcoming decade's substantial progress in exploring biological phenomena in terms of chemical processes in organisms.

Biochemistry in Britain did not have a long tradition compared to the subject in Germany. The first biochemistry chair in Britain at the University of Liverpool was held by the physiologist Benjamin Moore who founded the *Biochemical Journal* in 1906.¹ From the same roots, that is physiology, also emerged Hopkins' biochemistry. Hopkins [3–16] who qualified in sciences and medicine, started his scientific career in 1894 as a demonstrator in practical physiology at Guy's hospital. He was unexpectedly invited to Cambridge by the professor of physiology Michael Foster² in 1898 to become lecturer in physiology and introduce there the physiological chemistry subject, as biochemistry was mostly called then. Hopkins had never had any formal training in biochemistry and unlike most of his contemporaries “never paid the then orthodox visit to a German laboratory and, indeed had had no contact with any master of the subject” [8, p. 21]. But perhaps this

¹Benjamin Moore (1867–1922), trained as a physiologist, according to Fruton “proved to be a rather undistinguished scientist, despite his later designation as Whitley Professor of Biochemistry at Oxford.” [2, p. 267].

²Sir Michael Foster (1836–1907), British physiologist. On his role in the development of British biochemistry, see e.g. [17, pp. 42–59].



Fig. 2.1 Hopkins' caricature in *Brighter Biochemistry* laboratory journal (1926–27, p. 17)

“innocence” enabled him to think of biochemical phenomena in living bodies in an innovative way. His independent vision of the chemical aspect of life processes led him stepwise away from the established German model of physiological chemistry,³ and enabled him to articulate a few years later his programme of

³In most German universities physiological chemistry was considered part of physiology. This model was characterized in detail in [17], pp. 9–39. “The history of physiological chemistry in Germany was one of repeated and generally unsuccessful efforts to establish chairs independent of physiology” [17, p. 32]. See also [18–21].

biochemistry as a self-governing discipline.⁴ His appointment in 1902 to the position of Reader in Chemical Physiology “at any rate implied that in his four years in Cambridge, Hopkins had convinced some authorities that the subject [biochemistry] existed and was worthy of support”, remarks Stephenson in her obituary notice [4].

Among the findings that brought Hopkins international reputation was the discovery of a new amino acid tryptophan in 1901 with Cole [23] and the proof (with Fletcher) that the working muscles accumulate lactic acid during anaerobic contraction in 1907 [24]. These experiments started the study of muscle metabolism and its relation to muscular contraction in many laboratories all over the world. The years 1912–1914 turned out to be essential in his scholarly life. His research into tryptophan, made Hopkins interested in nutrients. In the years 1906–1912, he performed series of experiments in rats that showed how rats fed with ‘pure’ food-stuffs failed to thrive and how the addition of just very small quantities of milk restored their growth and health. This way he entered the new only barely explored field of dietary essentials. Hopkins published his results in 1912 [25] and asserted that animals need for their growth and survival not only carbohydrates, proteins and lipids, but also tiny quantities of what he called “accessory food substances” which we know today under the name of vitamins. His paper, which made him publicly known and extremely famous,⁵ was followed by a great upsurge of research into vitamins, and finally brought him the Nobel Prize in 1929.⁶

The first two decades of the 20th century witnessed the gradual formation of biochemistry as an independent academic discipline [17, 19–21] with all its necessary attributes: an institutional base for research and teaching, a communication base with specialized journals and international scientific community associated in national scientific societies, an independent subject taught at universities, a specific social mission and social acknowledgement, and existence of strategic

⁴Freedman [16] notes that for Hopkins this separation from physiology was not a straight route. Between 1896 and 1912 Hopkins published most of his papers in the *Journal of Physiology* [for instance 23, 24] and only started to publish in the *Biochemical Journal* in 1913 when it formally became the house journal of the Biochemical Society. He also did not participate in creation of the Biochemical Club and became the member of its Committee only for the session 1911–12 [22, p. 15]. Weatherall and Kamminga state that Hopkins “is thought to have disliked the name ‘biochemistry’, possibly through a vague feeling that the name implied some vitalistic bent.” [14, p. 19].

⁵Weatherall and Kamminga [14, p. 19] pointed out that “Hopkins established his precedence in the field of vitamin research over other workers such as Casimir Funk [...] McCollum and Davis [...] or Osborne and Mendel [...], despite the fact that others found his results difficult, if not impossible, to duplicate. Of course it can only have helped that Hopkins was the chairman of the Accessory Food Factors Committee, established in 1918 [...] which produced the first monograph on the subject to contain a historical sketch of its development”.

⁶Hopkins received the Nobel Prize for Physiology or Medicine “for his discovery of the growth-stimulating vitamins jointly with the Dutch biochemist Christiaan Eijkmann though “one might speculate that the award was given as much for what Hopkins, by that stage, had done for biochemistry as a whole, as for any particular piece of research.” [14, p. 19].

concepts outlining its programme. No doubt, Hopkins was one of the actors and architects of this process not only in Great Britain, but also on the world scale especially thanks to his ground-breaking concept of “dynamic biochemistry” that he outlined and explained in detail in 1913. He presented it first in his presidential address to the Physiological Section of the 1913 Birmingham meeting of the *British Association for the Advancement of Science*, and then published it in *Nature*, *Lancet* and the *British Medical Journal* under the title *The Dynamic Side of Biochemistry* [26, 27].⁷

Let us note, first of all, that the attributes of “static” and “dynamic” biochemistry were not Hopkins' invention; they had appeared quite frequently in various treatises and textbooks even prior to 1913,⁸ but Hopkins gave the term “dynamic biochemistry” new comprehensive content and meaning in terms of a strategic concept of a scientific discipline. He was concerned above all by cellular metabolic pathways and energy formation as a key to understanding chemical processes in organisms, their generality in living nature and relations to physiological function. His concept thus focused on the cell as an organised polyphasic system maintaining its dynamic equilibrium and its relation to life phenomena [27, p. 220]:

...We can scarcely speak at all of living matter in the cell; at any rate we cannot speak of the cell life as being associated with any one particular type of molecule. Its life is the expression of a particular dynamic equilibrium which obtains in a polyphasic system... Life, as we instinctively define it, is the property of the cell as a whole, because it depends upon the organisation of processes, upon the equilibrium displayed by the totality of the coexisting phases.

As regards the cellular organisation [27, p. 221], Hopkins remarks: “It is clear that a special feature of the living cell is the organisation of chemical events within it.”

In order to assess the importance of Hopkins' concept for the evolvement of biochemistry, and particularly for Stephenson's future specialisation, it is necessary to point out that Hopkins imposed his teaching especially against the organicist doctrines of the field called “chemical physiology” which implied that the cellular chemical processes are incognizable because life is connected with too complicated chemical phenomena. In contrast with such allegations, Hopkins accentuated the simplicity of substances, taking part in the intermediate processes of cell metabolism and the comprehensibility of the cellular chemical reactions,

⁷The issue of Hopkins' concept of “dynamic biochemistry” has been tackled in the literature on Hopkins life and work and analyzed e.g. in [19–21] with regard to other strategic biochemical concepts of the 19th and 20th century. Recently Weatherall and Kamminga have presented a new perspective on Hopkins' concepts and activities [28, 29]. Both papers offer a realistic picture of Hopkins based on detailed analysis of his personality and experimental and theoretical work. The authors attempted to deprive Hopkins' image of various constructions and present a “novel interpretation of Hopkins, which teases out his own intentions from those of his colleagues and pupils.” [29, p. 436].

⁸“Static” biochemistry/physiological chemistry was understood in the textbooks or monographs as the study of the chemical components of the organisms, while its “dynamic” part concerned the chemical and physical side of physiological reactions. See e.g. [30, 31].

which allow customary chemical approach to their study. Contrary to the obsolete “static” biochemistry he introduced “dynamic” biochemistry—investigation of chemical processes taking place in organisms—the dynamic side of biochemical phenomena [27, p. 214]:

My main thesis will be that in the study of the intermediate processes of metabolism we have to deal, not with complex substances, which elude ordinary chemical methods, but with simple substances undergoing comprehensible reactions... I intend also to emphasise the fact that it is not alone with the separation and identification of products from the animal... but with their reactions in the body; with dynamic side of biochemical phenomena.

Despite the fact that Hopkins underlined so strongly the necessity of identifying chemical processes underlying vital functions, we cannot call Hopkins a reductionist or a mechanical materialist [11, p. 161]: “In his lectures he always dissociated himself from the idea that life was nothing more than a set of chemical reactions”.

Hopkins' concept of dynamic biochemistry became a unifying agent of the various biochemical programmes presented earlier and also a particular agenda of biochemistry development for the years to come. He invited chemists and biologists to participate in this agenda with a special appeal on organic and physical chemists who in the 19th century had kept aloof from biological problems. His call evoked a huge response not only in Britain, but also among other European scientists, and in due course, it took up the role of directive along which biochemistry developed up to the 1950s. But before his strategic concepts were widely disseminated and appropriated by the chemical community, Hopkins had endeavoured to realize them with his collaborators. In 1914, the Cambridge University created for him a chair of biochemistry and elected him professor and this prominent position offered Hopkins the chance to accomplish his vision at his own Department. In reality, he was able to put it into practice only ten years later as he had to live for a long time without a decent well-equipped laboratory fighting for adequate financial resources. The constrained conditions became critical after World War I, when the staff in the Department began to swell and in 1922–23 it already listed 47 people at work. Therefore, Hopkins only could implement his ideas to the fullest extent at his new Institute—the Cambridge Dunn Institute of Biochemistry (Fig. 2.2), which opened in Tennis Court Road in 1924.⁹ The financial support for building the new institute came from the Sir William Dunn¹⁰ Trustees who on the advice of Walter Fletcher¹¹ dedicated more than £ 210,000 to the development of the subject in Cambridge.

⁹On the creation of the Dunn Institute of Biochemistry, see [12]. The official name of the institute was Sir William Dunn Institute of Biochemistry, but we may find in the literature several other synonyms for the Institute, like Dunn Biochemistry Laboratory, Department of Biochemistry, Biochemistry Department, School of Biochemistry or Cambridge Biochemical Laboratory. These synonyms also appear in this book.

¹⁰Sir William Dunn (1833–1912) was a banker and philanthropist who left his fortune to charity.

¹¹Sir Walter Fletcher (1873–1933), British physiologist, Secretary of the MRC and Administrator of the MRC between the wars, influential organizer of science. On his important role in the establishment of the Dunn Institute of Biochemistry, see [12].



Fig. 2.2 Sir William Dunn Institute of Biochemistry at the Tennis Court Road in Cambridge—historical photograph (Archive of the Department of Biochemistry, University of Cambridge. Picture reproduced with the permission of the Archive)

The new institute became a model for other departments of biochemistry in universities and hospitals which were regularly staffed by Hopkins's students. In the new well equipped Institute Hopkins [14, p. 21]:

offered young scientists a part in shaping and extending his view of the world, an almost philosophical context in which the problems set by the study of biological systems could be tackled. In these words, he did not just outline a way of looking at the processes of life, but also a way of doing science. By these criteria, science too would be a series of dynamic processes in equilibrium, each researcher an integral, but mutually interdependent part of an organised whole.

To realize such working programme, Hopkins motivated ambitious talented young scientists with the prospect of solving big biological problems in their specific areas. This way he attracted many outstanding individuals with a wide scope of interests who were ready to develop the grand scheme of “dynamic biochemistry” in various biological systems. For instance J.B.S. Haldane¹² worked on enzyme kinetics and made influential contributions to genetics and evolutionary theory. In the laboratory worked the Needhams, the famous married couple: Joseph Needham¹³ was pioneer of a new field called chemical embryology and introduced another new field—comparative biochemistry which was further developed by

¹²John Burdon Sanderson Haldane (1892–1964) was an ingenious polyhistor, who made his name in several scientific disciplines. In 1933, he became professor of genetics at the University College London.

¹³Noel Joseph Terence Montgomery Needham (1900–1995) pioneered especially chemical embryology and comparative biochemistry. He also was a notable sinologist, historian and historian of Chinese science.

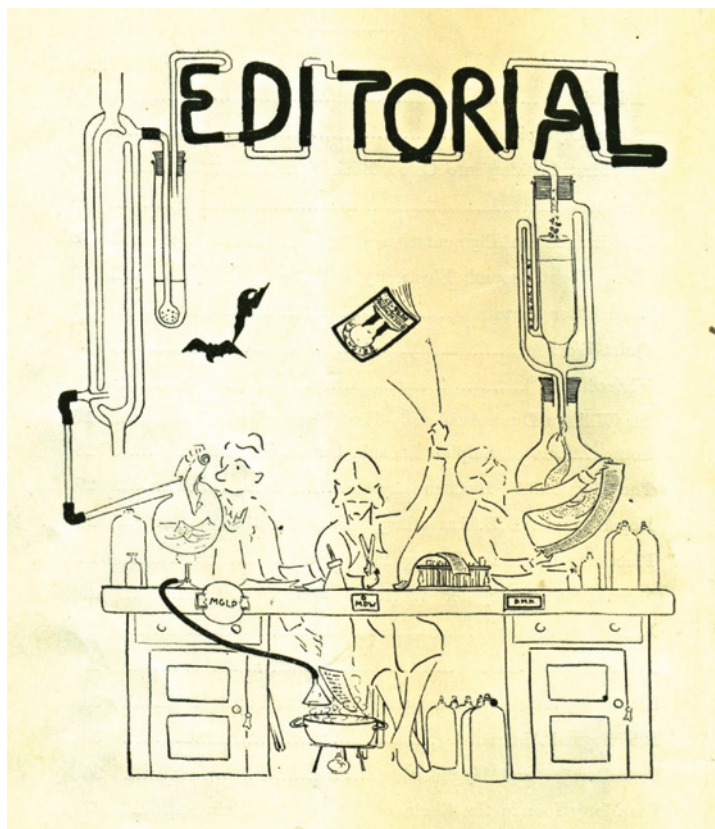


Fig. 2.3 M.G.L. Perkins, M. Whetham and D. Needham depicted as editors of the *Brighter Biochemistry* journal (*Brighter Biochemistry*, 1926–27, p. 4.)

Ernest Baldwin¹⁴; his wife Dorothy Moyle Needham¹⁵ (Fig. 2.3) pursued muscle biochemistry. Other subjects were opened up by Rudolph Peters¹⁶ and Juda Quastel¹⁷ who investigated the biochemistry of cellular microstructures, while Muriel Wheldale Onslow and later Rose Scott-Moncrieff¹⁸ with Haldane were

¹⁴Ernest Hubert Francis Baldwin (1909–1969); his *Introduction to Comparative Biochemistry* (1937; total four editions until 1964) and *Dynamic Aspects of Biochemistry* (1949) became classics.

¹⁵Dorothy Moyle Needham (1896–1987). In 1924 Needham married Dorothy Moyle who had been recruited by Hopkins in 1919 to work on muscle biochemistry and substrate-level phosphorylation. When she was elected an FRS in 1948, they became the first husband and wife to be so honoured, Needham having been elected in 1941.

¹⁶Sir Rudolph Albert Peters (1889–1982) was until 1924 University Lecturer in biochemistry Cambridge. 1924–1954 he held the Whitley Chair of Biochemistry at Oxford.

¹⁷Juda Hirsch Quastel (1899–1987) became in 1947 professor of biochemistry at McGill University in Canadian Montreal where he pioneered research in neurochemistry.

¹⁸Rose Scott-Moncrieff (Mrs. Meares).

inventing biochemical genetics through the study of flower pigments and Scott-Moncrieff's successor in plant biochemistry Robert Hill¹⁹ developed biophysical chemistry of plant proteins and photosynthesis. Norman Pirie²⁰ investigated the physical properties of proteins and viruses; Synge,²¹ Bailey²² and Sanger²³ learned protein chemistry from Pirie, Malcolm Dixon²⁴ investigated biological oxidations. Among the foreign guest researchers became renowned the Hungarian Albert Szent-Györgyi²⁵ who worked on his discovery of hexuronic acid—a strong reducing agent from the adrenal cortex. Hopkins usually left his co-workers full freedom to decide about the topic of their research. “Some considered that Hopkins did not organize research at all”, but in spite of that about 600 excellent papers were published from Hopkins' laboratory by 1938 [9, p. 200]. Through the 1920s and 1930s the laboratory trained many subsequent leaders in the field, including future Nobel Laureates like Hans Krebs,²⁶ Ernst Chain,²⁷ Fred Sanger, Richard Synge, Albert Szent-Györgyi, Rodney Porter²⁸ and Peter Mitchell.²⁹ Thus Stephenson got a blank ticket to this distinguished “club” with the greatest concentration of biochemical brains she could imagine; but this is yet to come in the future.

¹⁹Robert Hill (1899–1991), plant biochemist.

²⁰Norman Wingate Pirie (1907–1997) was known especially for his work on plant viruses. In 1936 he crystallized the tobacco mosaic virus.

²¹Richard Laurence Millington Synge (1914–1994) worked with Hopkins 1936–1939. He got the Nobel Prize in chemistry jointly with A. Martin in 1952 for the invention of partition chromatography.

²²Kenneth Bailey (1909–1963); his main research topic was the biochemistry of muscle contraction.

²³Frederick Sanger (1918–2013) won the 1958 Nobel Prize in Chemistry for “his work on the structure of proteins, especially that of insulin” and shared the 1980 Nobel Prize in Chemistry with Walter Gilbert for nucleic acid sequencing.

²⁴Malcolm Dixon (1899–1985) specialized in physical biochemistry, namely kinetics of enzyme reactions.

²⁵Albert Szent-Györgyi de Nagrapolt (1893–1986), Hungarian biochemist, got his Ph.D. with Hopkins at the Cambridge Department of Biochemistry in 1927 and stayed at Hopkins's laboratory until 1930 when he accepted a position at the University of Szeged in Hungary. He was awarded the Nobel Prize in 1937 “for his discoveries in connection with the biological combustion process, with special reference to vitamin C and the catalysis of fumaric acid”.

²⁶Sir Hans Adolf Krebs (1900–1981), British biochemist who came from Germany as refugee in 1933, known for identification of several cellular metabolic pathways. He was awarded Nobel Prize for his discovery of the citric acid cycle in 1953.

²⁷Sir Ernst Boris Chain (1906–1979), German born British biochemist who escaped Nazi Germany in 1933. He was awarded Nobel Prize 1945 jointly with Sir Alexander Fleming for his penicillin research.

²⁸Rodney Robert Porter (1917–1985) shared in 1972 the Nobel Prize with G.M. Edelman “for discoveries concerning the chemical structure of antibodies”. As Fred Sanger's first Ph.D. student he got his degree in Cambridge in 1948.

²⁹Peter Dennis Mitchell (1920–1992) was awarded Nobel Prize in chemistry in 1978 “for his contribution to the understanding of biological energy transfer through the formulation of the chemiosmotic theory”.

Stephenson, still on the Beit Memorial Fellowship, came to Hopkins in 1919 to work on fat-soluble vitamins. A year later she even succeeded to publish two papers on vitamin A in rats [32, 33]³⁰ but she soon came to realize that Hopkins was no longer interested in the field which had brought him recognition and which she considered so motivating. The disappointed young biochemist was certainly not aware how lucky she was when Hopkins proposed her to explore a new field—bacterial biochemistry.

Microbes had captured Hopkins' imagination long before the war when he worked on the amino acid tryptophan in the early 1900s [34]. Their chemistry also played a central part in his post-war plans, as Hopkins understood very well that bacteria represent an ideal example of cell for clarification of the cellular biochemical processes and their organisation. Therefore, during the war, he had employed a young chemist, Harold Raistrick³¹ whose task was to work on chemistry of micro-organisms, but Raistrick left in 1921 and Hopkins needed a successor. And so it happened that the new field which Hopkins pegged out for Stephenson, became exploration of enzymes, their activities and organisation in bacteria. Bacteria were not to be studied from the perspective of medical application, but as models of biochemical systems responding to their environment. Eventually, convinced by Hopkins,³² Stephenson (perhaps not very contentedly at the beginning) switched her research programme to microbial biochemistry and stayed in the new field for the rest of her life. One year later another momentous change in Stephenson's life occurred; her Beit Fellowship expired, but Hopkins wrote a begging letter to Walter Fletcher at the Medical Research Council (MRC)³³ in which he described Stephenson as a "sound bacteriologist and from the stand-point of metabolic studies of micro-organisms (...) a real expert." Thanks to Hopkins' intercession, MRC offered Stephenson an MRC grant of £400 pa renewed annually, and this was the beginning of her lifelong cohabitation with the MRC affirmed in 1929, when the MRC made her a full-time "external" member of its staff [34].³⁴

Although it was Hopkins who found for Stephenson the appropriate niche of a yet undefined field, she was developing bacterial chemistry from the very first moment according to her own vision. Bacteria were for her tools for her biochemical research

³⁰One of the papers [33] Stephenson published with Anne Barbara Clark (Mrs. Callow) who became a successful author of books about nutrition.

³¹Harold Raistrick (1890–1971), biochemist and microbiologist known for his biochemical studies on moulds, worked with Hopkins 1914–1921 [35].

³²As Stephenson remarks in Hopkins' obituary: "Hopkins's own character contributed greatly to his success in persuading scientists to consider and ultimately to accept his views." [4, p. 168].

³³"The Medical Research Council (MRC), founded in 1913 is a publicly funded British government agency responsible for co-ordinating and funding medical research in the United Kingdom. It is one of seven research councils in the UK and is answerable to, although politically independent from, the Department for Business, Innovation and Skills" (see Wikipedia [https://en.wikipedia.org/wiki/Medical_Research_Council_\(United_Kingdom\)](https://en.wikipedia.org/wiki/Medical_Research_Council_(United_Kingdom))), accessed November 3, 2015). The MRC was originally called the Medical Research Committee and Advisory Council. The present name was introduced in 1920. The MRC and Stephenson's role in it will be treated in detail in Chap. 5.

³⁴The quotation is copied from Cope's article [34].

and what made her curious was their cellular essence, their metabolism, actions happening inside them. Her first papers in this new field she published in 1922 and 1923 jointly with Margaret Whetham [36, 37], then still a student.³⁵ Actually, cooperation with young people became also typical for her working style, and probably not by chance, often many of those whose names appeared on publications next to Stephenson, later became leading scientific personalities. And how did Stephenson manage to bridge the wide gap between her vitamin research and the entirely new problem matter of bacterial metabolism? Apparently her previous interest in fat-soluble vitamins led on to explore the effect of different media on the fat formation by the Timothy grass bacillus (*Mycobacterium phlei*). In this early research into the metabolism of bacteria, Stephenson and Whetham paid attention especially to the relation of the sugar and fat metabolism using original methods both for determination of the respiratory quotient and the carbon balance-sheet which were then successfully applied in the future. They grew the bacteria in a synthetic medium where the carbonaceous food was supplied as lactic acid or glucose, and they observed that when the supply of carbon was exhausted, the bacteria utilized and burnt the cellular lipids, while the protein contents remained untouched. The continuing paper of Stephenson with Whetham [40] used another bacterium, *Escherichia coli*. They observed a remarkable phenomenon, namely when glucose was added to the growth medium as carbon source, the bacteria considered to be an aerobic organism, suddenly behaved like anaerobic organism: for the first 24 h they did not take up oxygen although they grew happily and were consuming glucose with great taste. This finding focused Stephenson attention on the anaerobic way of life in microorganisms and to *E. coli*, which was to become the repeatedly explored “experimental animal” in her laboratory. Its easy and inexpensive handling in the laboratory predetermined it to become the most popular model organism in the field of molecular biology until today. Stephenson landed on the unexplored territory of bacterial metabolism and shortly research in her laboratory yielded results of great general importance.

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³⁵Margaret Dampier Whetham (1900–1997), Newnham graduate, biochemist, worked with Stephenson 1920–1927. She married in 1927 A.B. Anderson a clinical pathologist, gave up science, had five children and started to work only in 1948 as an abstractor for Chemical Abstracts. Later she became a sought after indexer and writer of articles [38, pp. 507–508; 39, p. 38].

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Holding Hands with Bacteria

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