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Holding Hands with Bacteria

The Life and Work of Marjory Stephenson

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Soňa Štrbáňová
Academy of Sciences of the Czech Republic
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Czech Republic

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Preface

This book is about Marjory Stephenson, almost forgotten but very significant British biochemist, exceptional woman and scientist, who in the 1930s opened new research fields—chemical and general microbiology—and stood at the cradle of the Society of General Microbiology. Books often have their own histories. The story of this one started in 1958 in the old building of the Faculty of Science in Prague, in the lecture theatre of the chemistry department. I was then a fourth year biochemistry student listening to the lecture of *dozent* Arnošt Kleinzeller, external member of the staff, whom we had not met before. Until this day, biochemistry consisted for us of its "static" and "dynamic" parts: we had learned about composition of living bodies, cellular enzymes and metabolic pathways, but this strangely looking man unlocked for us a new world of science. He spoke about Watson, Crick, Jacob and Monod, regulation processes going on in the cell we had never heard about and we hardly understood. The lecture had a flavour of a forbidden fruit since everything smacking of genetics used to be taboo in Communist Czechoslovakia of the 1950s. However, at that time barriers were slowly lifting and we were eagerly taking notes as no modern textbooks were available except rather outdated manuals. It was Dr. Kleinzeller's course where I heard first time in my life also about Marjory Stephenson whose *Bacterial Metabolism* Dr. Kleinzeller recommended us as one of the best contemporary books on biochemistry. I borrowed from the University Library the 1949 edition, which to my surprise was available, but admittedly I did not find it interesting at all, and so Stephenson's name was shelved for many years into the background of my mind. Only many years later I got to understand the high esteem Dr. Kleinzeller had for Stephenson. He succeeded to flee to England in 1939 from the Nazi occupied Czechoslovakia; Hans Krebs, Frederick Hopkins and Marjory Stephenson provided him refuge in their laboratories and introduced him to biochemical work with microbial model systems[1] which he brilliantly applied in his research after returning to his homeland [1].

[1]For details see Chap. 5.

All this, however, I only found out many years later. In 1963, I defended my Ph.D. thesis on lactose permease in *Escherichia coli* at the Prague Institute of Microbiology of the Czechoslovak Academy of Sciences and my research then concerned regulation of enzyme synthesis in some microorganisms. In 1964–65 thanks to the political thaw, I was allowed to accept the invitation of Luigi Gorini, Italian born microbiologist, to work as postdoc at the Department of Bacteriology and Immunology of the Harvard Medical School. Luigi had made some fundamental discoveries on regulation of bacterial enzyme synthesis and had a profound impact on thinking about regulation of gene expression [2, 3]. Three years later, in September 1968, I left under dramatic circumstances Prague occupied by the Warsaw Pact armies, to work for three months at Sussex University with the visionary biologist Brian C. Goodwin [4]. My stays in Luigi's and Brian's labs represented a fundamental change and inspiration for the rest of my life, but in the dark times of political "normalization" in Czechoslovakia I had to forget about all my aspiring plans.

After series of coincidences and fortuities I was converted in 1976 from biochemist to historian of science and, obviously, history of biochemistry became my main topic. Due to my previous research interests I wished especially for exploring history of research cellular regulation processes, however such ambitious project was unfeasible in Communist Czechoslovakia where travelling and research in the West almost equalled a dream. In 1992, after the "velvet revolution" a grant from the Wellcome Trust enabled me to work in the British archives for six weeks. The documents I found highlighted the ground-breaking role of Marjory Stephenson not only in the history of biochemical adaptation, but in the history of the 20th century biochemistry in general, and so she finally became my principal hero for the next twenty years. The more I have read about her, the more she has captivated me not only as a creative independent researcher who paved the way to molecular biology, but also as a personality who got such recognition as only very few women scientists of her time. Reading the documents was like peeling of onion.[2] Gradually I have got new insight into Stephenson's scientific achievements, leadership qualities and links to various people and institutions. Especially her correspondence containing a mix of matter-of-fact operational notes along with private passages offered some clue to the question which personal features and circumstances of her life had made her so exceptional.

My research on Stephenson, her collaborators and institutional background, has been progressing in the course of about twenty years when I have published several articles not only on Stephenson but also on other related matters linked to history of biochemistry, molecular biology and women in science. She has been "rediscovered" since the 1990s also by several other historians of science whose works, all quoted in this book, provided invaluable additional data. Two of them I owe special appreciation. Harmke Kamminga whom I met first in Cambridge in 1992, introduced me to the environment of the Hopkins laboratory and was the

[2]The expression was coined by the German novelist Günter Grass in the title of his autobiography Peeling the Onion (2006).

first who suggested me to write Stephenson's biography. She died untimely in 2013 and I lost in her a friend and also a brilliant colleague historian whose advice and criticism would have helped me a lot in preparing this book. Another treasured friend and expert on Stephenson and Cambridge women was Joan Mason, a distinguished British chemist, who founded after her retirement in 1994 the Association for Women in Science and Engineering (AWiSE) and devoted much of her time also to history of women in science and gender studies. We were in touch for many years, and when she attended the 21st International Congress of History of Science in 2001 in Mexico City in a wonderful shape and full of energy neither of us suspected that this was our last encounter. At that time she asked me to organize the symposium of the Women in Science Commission in Prague in 2003 and we also agreed to write jointly Stephenson's biography. Unfortunately, shortly before travelling to Prague Joan had an accident which did not allow her to participate in the meeting. She did not recover anymore and died in 2004 [5]. Joan remains irreplaceable and I am sure that the book would have been incomparably better with her collaboration

It took me a long time to write Stephenson's biography not only because I had to work on other projects, but also because "peeling the onion" has become a painstaking business of putting many bits and pieces together. Eventually, the narrative turned out to be not strictly chronological, although it preserves to a certain extent also the timeline. In the individual chapters I attempted to show various facets of Stephenson's life and work, both personal and professional, along with the historical background in which her story was unfolding. Some of the chapters, especially those describing Stephenson's experimental work might be too detailed to the lay reader; nevertheless certain particulars might be interesting to biochemists or microbiologists. I tried to understand in this book how does it happen that a woman scientist becomes an exceptional leader in an environment which tolerates women in science but does not expect them to play a role strictly reserved for men. Although in Stephenson's biography apparent dramatic events are missing, I became ever more fascinated by the intrinsic drama of her life and hope I was able to pass this captivation also on the reader.

Prague Soňa Štrbáňová
December 2015

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I must begin with particular thanks to a long line of archives, archivists and research institutions that provided me with essential material on which this book is based. The MRC Archives which I visited in London in 1992 were then unsorted and quite chaotic and therefore I must remember with admiration the archivist, the late Ms. M. Nicholas, who unearthed for me piles of documents which proved to be essential for my work.[3] Extremely useful was in 1992 also my stay at the Cambridge Wellcome Unit for the History of Medicine where I met with knowledgeable and helpful colleagues who introduced me to hitherto unknown materials related to the University of Cambridge and Hopkins' Biochemistry Department. I am indebted to Dr. Mark Weatherall, Prof. Soraya de Chadarevian and especially to my late friend Prof. Harmke Kamminga. Their hospitality and assistance encouraged me to start a project which proved to be more complicated than I would have ever expected. Among the other institutions, libraries, archives and especially librarians and archivists who supplied me with crucial documents let me mention especially[4]: Bodleian Libraries and Radcliffe Science Library, CARA Council for Assisting Refugee Academics (Ryan Mundy); Department of Special Collections (Colin Harris), University of Oxford; Cambridge University Library, Department of Manuscripts (Jacqueline Cox, Chelsea Carney); Churchill College Archives, Cambridge; Microbiology Society Archives (former Society for General Microbiology; Janet Hurst, Dariel Burdass, Chris Rowland, Marue Shrank, Peter Cotgreave); National Archives, Kew; Newnham College Register, Newnham College Roll Office (Dr. Van Houts) and Archives (Anne Thomson); The Royal Society Library (S. Edwards, Fiona Keates); University of Cambridge Department of Biochemistry Library; University of Reading (Zoe L. Watson); University of

[3]The MRC archives are now organized and placed at the National Archives in Kew.

[4]In alphabetical order.

Sheffield, The University Library Special Collections (Jacky Hodgson, Mary Sachett); University of Sussex Library, Special Collections (Karen Watson and Lisa Towner); Wellcome Institute for the History of Medicine and its Library; Archive of the Department of Biochemistry, University of Cambridge (Robin Hesketh).

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Much of the material used in the book had been presented at a variety of conferences. In this respect I would like to acknowledge especially the role of the Commission Women in Science of the IUHPS/DHST[6] (today Commission on Women and Gender in Science, Technology and Medicine IUHPS/DHST) which has stimulated research on women in science and gender and science since its creation in 1981. The Commission and its principal founder Prof. Margaret Rossiter have exceptional merit in the general acceptance of previously neglected studies on the role of women in history of science and technology and of better understanding science, technology and medicine through the gender perspective.

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[5]Fox Keller E (1983) A feeling for the organism. Freeman, New York.

[6]International Union of History and Philosophy of Science/Division of History of Science and Technology.

patience with the perpetually delayed and apologizing author and their continuing encouragement.

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Contents

About the Author

Soňa Štrbáňová is Associate Professor and Scientific Fellow Emeritus at the Centre for the History of Sciences and Humanities, Institute for Contemporary History of the Czech Academy of Sciences. She graduated in chemistry-biochemistry from the Faculty of Mathematics and Physics (today Faculty of Science) of the Charles University in Prague, received her Ph.D. in biology at the Institute of Microbiology, Czechoslovak Academy of Sciences (CSAS) in Prague and spent one year as a Postdoctoral Research Fellow at the Harvard Medical School in Boston, MA. Her biochemical research included regulation of cellular enzyme synthesis in micro-organisms, antibiotic resistance and bacterial pigments.

In 1976 she professionalized in history of science at the Institute for Czechoslovak and World History of the CSAS in Prague. Her historical research has focused since on the nineteenth- and twentieth-century history of chemistry, and biochemistry; science national style and genesis of the Czech scientific community; formation of interdisciplinary sciences; institutionalization and communication networks in modern science; science as part of the society's intellectual development and politics; women in science. She has been author and co-author of about 250 scientific studies and co-author and co-editor of about 15 monographs and edited volumes, among others: (with J. Janko) *Science in Purkinje's time* (1988); (with I. Stamhuis and K. Mojsejová) *Women Scholars and Institutions* (2004); (with B. Hoppe and N. Robin) *International Networks, Exchange and Circulation of Knowledge in Life Sciences 18th to 20th Centuries* (2006); (with A. Kildebæk Nielsen) *Creating Networks in Chemistry: The Founding and Early History of Chemical Societies in Europe* (2008); (with A. Kostlán) *One Hundred Czech Scholars in Exile* (2011); (with T. Hermann, A. Kostlán, D. Grygarová, T. Petráň and M. Šimůnek) *Homines Scientiarum* (2015). She was teaching history of biochemistry at the Faculty of Science, Charles University in Prague and medical ethics at the Palacký University Olomouc.

She is Effective Member of the International Academy of History of Science, Past President of the European Society for the History of Science, member of Commission on Women and Gender in Science, Technology and Medicine of the IUHPS/DHST, member of the Working Party on the History of Chemistry of the EuCheMS, and member of several professional societies and editorial boards.

Abbreviations

MRC	Medical Research Council
MRC Archives	Medical Research Council Archives[7]
MS	Marjory Stephenson; this abbreviation was often used by Stephenson's collaborators, friends and herself as nickname
SGM	Society for General Microbiology

[7]The references are related to the archives kept at the headquarters of the MRC studied in the 1990s. Currently the MRC Archives are kept at the National Archives and have different reference numbers.

Abstract

Marjory Stephenson (1885–1948), British biochemist, belonged among the first scientists who used microorganisms as models for research into cellular biochemical processes. Since 1919, she was institutionally linked to the Cambridge University Department of Biochemistry led by the guru of European biochemistry F.G. Hopkins. In 1922 she joined the Medical Research Council (MRC) and since 1929 she became the full-time member of the MRC's staff and the head of its Cambridge unit, but was never officially appointed. Thanks to her efforts, in 1944 the Society for General Microbiology (SGM) was founded with Alexander Fleming as its President. Stephenson was elected second President in 1947 and the same year appointed first Cambridge University Reader in Chemical Microbiology. In 1945, she was elected one of the first two women fellows of the Royal Society.

Stephenson's research concerned especially biochemistry of microorganisms, namely the organization and control of biochemical processes in their cells. In the 1930s, she began her investigations of cellular enzyme adaptation phenomena, which in their consequence profoundly influenced the rise of biochemical genetics and molecular biology. Her studies demonstrating that bacterial metabolism is governed by regularities analogous to those in higher organisms, contributed to the acceptance of the principle of unity in biochemistry in the 1930s. The strategic program of the new interdisciplinary field opened by Stephenson and coined as chemical microbiology was designed and communicated especially in her monograph and textbook Bacterial Metabolism (three revised editions, 1930, 1939 and 1949), which became reference work for several generations of biochemists and microbiologists all over the world. During World War 2 Stephenson participated in the British warfare programs: she investigated biotechnological production of organic compounds and organized the combat with infectious diseases in British hospitals. Before and during WW2 she belonged to the few women in science who pioneered a new field and managed a research team, nevertheless she had to cope during her whole life with practices of undeclared discrimination.

Keywords History of biochemistry · History of molecular biology · History of enzymology · Women in science · Bacterial metabolism · Cellular metabolism · Chemical microbiology

Chapter 1
Early Years

Marjory Stephenson was born on 24 January 1885 at Burwell, a village about ten miles from Cambridge in flat agricultural countryside that remained her homeland during most of her life [1–5, 6, pp. 320–323, 7–14]. Her mother Sarah[1] Stephenson née Rogers of Newmarket and her father Robert Stephenson had four children, one boy and three girls. Marjory was the youngest, fifteen years younger than her eldest sibling Alice May. The family she was born into encouraged her innate talent and opened before her the journey for education, each member in its own way. Her father must have been an extraordinary man who apparently much influenced her lifelong pursuit. We may find his brief and concise characteristics in Stephenson's personal records kept at the Royal Society Archives [14]:

> My father had no university education but a good secondary school education. He was a farmer in a large way of business and farmed a large Crown Estate in Burwell which with land of his own amounted to 5000 acres. He was enterprising and successful and extremely interested in scientific agriculture. He devoured such scientific books as were available to him. He was a believer in Darwin and possessed many of his books. Later he became interested in Mendelian genetics. He was….Chairman of the Camb.[ridge] County Council at the time when the Education Act of 1902 was put into operation. For his services in this connection the University gave him the honorary MA degree which he highly appreciated as it gave him the use of the University Library which he used to the full. He was active in getting local support for the Cambridge School of Agriculture at its commencement and for starting the Camb. [ridge] County Secondary School for boys (about 1903).

Robert Stephenson's lively intellect, his eager reception of scientific ideas which he applied to his farming, and his erudition, left an indelible mark on his

[1]Some sources, e.g. [7] state incorrectly that the first name of Stephenson's mother was Elizabeth. In Stephenson's Personal Records of Fellows of the Royal Society Stephenson writes her mother's name as "Sarah" in her own hand.

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young daughter's searching mind. Marjory easily absorbed even his explanation of symbiotic nitrogen fixation or in her own words [14]:

> Owing to position in my family almost an 'only child' + somewhat of a little prig I acquired a childish interest in science from my beloved governess and later from my Father. Also a sceptical attitude towards orthodox religion from the same sources. I recollect being told by my governess that the first Chapter of Genesis was not literally true (age about 7) + hearing the facts of symbiotic nitrogen fixation from my father as we owned a clover field (age about 10).

It must have been an unusually stimulating environment, which very early evoked in the young girl an interest in science. Obviously, the father did not oppose Marjory's further schooling. Nevertheless, mostly thanks to the women in the family—her mother and her governess—was Marjory ready to surpass that invisible fence between the future "hausfrau" and independent educated woman. Her governess "a woman of great character and considerable intellect" [14] endowed her with clear thinking and elementary knowledge. Speaking of her mother Marjory remembered [14]:

> From my mother I derived a taste for English literature and an interest in painting. especially the Dutch Flemish School. My sisters + I had our share of household duties about which my mother was somewhat of a martinet, + it is not her fault that I am not orderly. It is due to my mother rather than my father that my eldest sister + I went to Newnham College though he did not oppose it. On looking back I think my Mother felt that she had suffered from the lack of education available to girls of her day + determined that her daughters should not suffer in the same way.

The governess advised sending the bright girl to the Berkhamsted High School for Girls in Hertfordshire. In 1897, at the age of twelve, Marjory received an entrance scholarship to attend this school (Fig. 1.1), where "scientific education was very poor by modern standards. I was however taught elementary human physiology for one year quite well and I still think this is the best approach to biological studies" [14]. In turn, it was Sarah who insisted that Marjory obtains a university education, and that Newnham College in Cambridge was the appropriate place.

Newnham College[2] was founded in 1871 shortly after the Girton College Cambridge (1869) as the second residential women's college in England. Newnham began as a house for five students in 1871, and the first building Newnham Hall (Fig. 1.2) was constructed in 1875 on the site where Newnham still remains. In 1879 chemical laboratories were completed both at Girton and Newham. Cambridge had admitted women since 1869, but unlike Oxford, which granted women degrees in 1921, it refused to accept them as 'members of the University'. Nor were female students considered undergraduates, merely 'students of Girton and Newnham Colleges', even though they were admitted to the Previous and Tripos Examinations from 1881 [15, p. iii]. Women were not eligible

[2]For history of the Newnham College see the College web pages http://www.newn.cam.ac.uk/about-newnham/College-History/History/content/History-of-the-college. Accessed 2 May 2014.

Fig. 1.1 Berkhamsted school room. Valentine card from 1907

for degree status, instead they were awarded a certificate of proficiency.[3] Even so, as Maddox points out: "Newnham and Girton students considered themselves lucky to be among the 500 (the quota set for women so that their numbers would not exceed 10 per cent of the male undergraduate body)" [16, p. 44]. The Newnham students [16, pp. 44–45]:

> had men as supervisors and often as research partners. Most of the university societies, and all lectures, were open to women and marriage was no bar to teaching….Women were nonetheless anomalies in a medieval institution to which the monastic tradition still clung. Even those of high rank had no say in the affairs of the university. The mistress of Girton and the principal of Newnham were not allowed to participate in university ceremonies and functions but were required instead to sit, in hat and gloves, with the wives of the faculty at the ritual occasions when the men wore their scarlet academic robes and black velvet doctors' hats.

Only in 1921 a Grace was passed giving power to Cambridge University to confer Titles of Degrees on women. The new University Statutes issued in 1926 made women eligible as University Professors, Readers and Lecturers, but full membership of the University with all the rights and privileges was not granted to women until 1947 [15, p. iii].

Stephenson attended Newnham from 1903 until 1906, taking the Part I Natural Sciences Tripos in chemistry, physiology and zoology. "Of these physiology alone

[3]The 67 years' battle for formal degree status with all the rights and privileges lasted in Cambridge until 1947 as described in detail in [6, pp. 215–224].

Fig. 1.2 Newnham Hall (Photo and courtesy ©TimRawle)

was taught in the University laboratories as the others were not open to women at that date. Obtained a Class II in Part I 1906" [14]. At the time of Stephenson's studies, the Newnham chemistry courses were run by the Austrian born Ida Freund,[4] the first woman in the UK appointed as a full lecturer in chemistry. Freund's innovative approach to teaching was based on experiment and dialogue between the teacher and the pupil as favoured by Wilhelm Ostwald,[5] and brought

[4]Ida Freund (1863–1914) was born in Vienna, the capital of Austria-Hungary. After the death of her mother, she was brought up by her grandparents and since 1881 by her uncle and guardian, the violinist Ludwig Strauss who lived in England. She enrolled at Girton College, Cambridge, in 1886 where she gained first class honours in the Natural Sciences Tripos Course. In the years 1890–1913 Freund was lecturer in chemistry at Newnham College. She published only one scientific paper, but wrote two chemistry textbooks. Freund's classes ceased at Newnham upon Freund's retirement and women chemistry students had to undertake their education in the University Chemistry Laboratories. [6, pp. 225–229, 17].

[5]Wilhelm Ostwald. (1853–1932) German chemist, one of the founders of modern physical chemistry, awarded Nobel Prize in 1909.

remarkable results. Freund influenced her pupils, among them Stephenson, as not only a teacher, but also a conscious feminist and leader of women's battle for admission to the *Chemical Society*. Although we have no personal testimonial of Stephenson, we may imagine that the popular tutor might have left a deep impression on the young female student and promote her future career. Meeting Ida Freund was probably Stephenson's first encounter with someone from distant Central Europe. Thirty years later, many of those fleeing the Nazis from that part of the world, found safe shelter in her laboratory. At Newnham she also met the biochemist F.G. Hopkins[6] for the first time at his lecture which left a lasting impression on her [18, p. 34]:

> The writer well remembers an occasion in 1905 or 1906 when he substituted for the Professor of Physiology in an elementary lecture; he talked about lactic acid production and muscular contraction and, though much that he said was highly speculative (…) it opened a new world of thought which the didactic form of teaching previously handed out to us never hinted at.

It was Marjory's dream to study medicine, but she lacked financial resources, so after leaving Newnham, she had to stand on her own feet. She took teaching positions in domestic and household science at Gloucester School of Domestic Science[7] and from 1908 she was also as a Visiting Lecturer at Cheltenham Ladies' College [13]. In 1910 she started to teach at King's College for Women, in London (Kensington). Stephenson's arrival at King's College was welcomed in the *King's College Magazine, Women's Department*, where the combination of her Natural Science Tripos certificate and her "first class Diploma in Cookery" was accentuated as a "combination of certificates which seems at the present moment to have been achieved only by herself" [6, p. 321]. A clue to the contents of Stephenson's lessons is given by the programme of the Home Science and Economics Department at King's College whose aim was to give their graduates employment possibilities in hospitals, schools and other public organisations, and excellence in "scientific homemaking." The students were taught subjects like biology, chemistry, physics, hygiene, and so on, with the aim of linking women's practical work in the household with the "scientific principles on which they are based." In chemistry they performed "simple analyses to study hydrocarbons, alcohols, acids and so forth, so that in the final year they may deal effectively with water analysis, constituents and relative values of different foods, the chemical changes of ferments, preservation and deterioration of food, purity of milk, and so forth." [6, p. 103]. This description also suggests what sort of chemical knowledge the students of women colleges had access to, and how they had been expected to utilize it.

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[6]Frederick Gowland Hopkins (1861–1947), British biochemist, one of the founders of modern biochemistry as an independent discipline, leading representative of the British and world biochemistry in the first half of the 20th century, especially in the interwar period, Nobel Prize winner 1929. He is one of the main figures of this book. Details of his life and work and the related references will be given in Chap. 3.

[7]In the years 1928–1953 it became King's College of Household & Social Science, and afterwards until today Queen Elizabeth College.

Was chemistry in Stephenson's time a suitable and acceptable profession for women? The monograph on pioneer British women chemists [6] shows that British chemistry has traditionally been depicted as a solely male endeavour and that this statement is very far from the truth. Women studied academic chemistry from the 1880s onwards and made valuable contributions to their fields. Although many of the women chemists and biochemists have been lost to historical records, recent investigations unveil that despite the barriers placed in their path, a vibrant culture of female chemists did indeed exist in Britain in the first half of the 20th century and that they accomplished an enormous quantity of research. The favoured fields of women chemists were crystallography and biochemistry [6, p. 7]. Several hundred women have been identified as members of British chemical societies before 1945, especially after 1920 when the *Chemical Society* granted equal membership to women. The *Institute of Chemistry* admitted women from 1892 on and the *Society of Chemical Industry* appears never to have excluded them [19, p. 144]. The Founding Committee of the *Biochemical Club*, predecessor of the *Biochemical Society*, initially excluded women from membership in its first meeting on 18 January 1911. However the elimination of women "fortunately" did not last long, for as early as 5 February 1911 the first three women were elected as members [19, p. 14][8]: Harriette Chick,[9] Ida Smedley[10] and Muriel Wheldale.[11] Harriette Chick was the first woman to serve on The Committee in 1918.

Just at the time when women started to make their way among the men in the *Biochemical Club*, Stephenson launched her scientific career. Unpredictably, her earlier engagement in nutrition science happened to become a bridge between "scientific homemaking" and serious research in biochemistry. She must have been very content when in 1911, Robert H.A. Plimmer,[12] University Reader in physiological chemistry at University College London, invited her to teach advanced classes in the biochemistry of nutrition and join his research group. We may speculate that Stephenson's erudition in nutrition and dietetics could have been useful to the nutritionist Plimmer; on the other hand, Stephenson could not have obtained a better start in biochemistry. Plimmer got his scientific education with the most competent teachers; he learned organic chemistry with Carl

[8]"Fortunately" is the expression used in the official history of the Biochemical Society [20, p. 14].

[9]Harriette Chick (1875–1977). In the interwar period Chick worked at the Lister Institute in London, among other things on the relation of nutrition and disease and became one of the founding members of the Nutrition Society [6, pp. 61–62].

[10]Ida Smedley Maclean (1877–1944); in 1906 she was the first woman appointed to the Chemistry Department at the University of Manchester. Smedley became a prominent biochemist who researched the essential fatty acids and their importance in the human diet [6, pp. 58–61].

[11]Muriel Wheldale (Mrs. Onslow, 1880–1932). Onslow became an acknowledged plant biochemist in Hopkins' Biochemical Department in Cambridge, and as one of the first women at Cambridge was promoted to University Lecturer [6, pp. 316–320; 21].

[12]Robert Henry Aders Plimmer (1877–1955), British chemist with German roots, William Ramsay's (1852–1916) pupil [22].

Graebe[13] in Geneva and biochemistry with Emil Fischer[14] in Berlin. When Plimmer returned in 1904 to the University College and became an assistant to Starling and Bayliss[15] in the Department of Physiology, he was prepared to replace outdated physiological chemistry by modern chemically-oriented biochemistry, which was still at its beginnings in Britain. With this goal in mind, he created the Department's biochemical laboratory around 1912 (the first establishment of this kind in Britain),[16] became co-editor with F.G. Hopkins of the extremely valuable series of *Monographs in Biochemistry* (1908), and in 1911 he founded jointly with his friend J.A. Gardner[17] the *Biochemical Club* (later *Biochemical Society*). Plimmer's lines of research were concerned, among others, with enzymology and intestinal biochemistry, but his main subject, following his teacher Emil Fischer, was chemistry of proteins.

In 1912, Stephenson published her first experimental paper in the *Biochemical Journal* on the enzyme lactase in dog intestine [23], which followed up earlier papers of Plimmer [25, 26] on adaptation of enzyme production in animals to added substrate, in this case the effect of lactose on the production of the enzyme lactase. Stephenson examined an opposite effect: inhibition of lactase activity in dog's gut by the presence of glucose. Nothing in the style and contents of the paper indicates that its author was a beginner in the field of biochemistry. It is particularly noteworthy that already the theme of Stephenson's very first paper implies her future preoccupation with the problems of enzyme adaptation. She submitted the paper to the *Biochemical Journal* (Fig. 1.3) on May 15, yet somewhat earlier, on March 12, she presented the topic at the meeting of the *Biochemical Club* in a lecture entitled "The Effect of Glucose and of Galactose on Intestinal Lactase" [27].

From the time when Stephenson started to work with Plimmer, her path had been converging with that of F.G. Hopkins thanks to common professional interests. We have no evidence where Hopkins and the promising young biochemist met in person

[13]Carl James Peter Graebe (1841–1927), a German organic chemist, pioneer in benzene chemistry and chemistry of synthetic dyes.

[14]Hermann Emil Fischer (1852–1919), a leading German organic chemists, winner of the Nobel Prize in 1902, known especially for his essential contributions to the chemistry of carbohydrates and proteins.

[15]Ernest Henry Starling (1866–1927) and William Maddock Bayliss (1860–1924), British physiologists.

[16]Stephenson calls the laboratory in her paper of 1912 [23] "Bio-Chemical Laboratory, Institute of Physiology, University College, London", while the official title "Ludwig Mond Research Laboratory for Biological Chemistry, Institute of Physiology, University College London" appears in Stephenson's paper of 1913 [24]. In any case, we may assume that the biochemical laboratory must have been established around 1912–1913. It was named after Ludwig Mond (1839–1909) a British chemist and industrialist with German roots, benefactor of several British scientific institutions.

[17]John Addyman Gardner (1867–1946), British biochemist associated with the St. George's Hospital in London, known especially for his research on cholesterol.

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ON THE NATURE OF ANIMAL LACTASE

By MARJORY STEPHENSON.

From the Bio-Chemical Laboratory, Institute of Physiology, University College, London

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The rate of hydrolysis of disaccharides by enzymes has been found to be considerably influenced by the presence of the products of hydrolysis. The cases of invertase and emulsin by Tammann in 1892,[1] maltase by Croft Hill[2] in 1898, and lactase by Armstrong[3] in 1904. V. Henri,[4] in 1901, showed that the retarding effect on invertase was mainly due to the fructose, an observation which was confirmed in 1902 by Adrian Brown,[5] who proved that it was not due to the increased viscosity of the solution. E. F. Armstrong found that the lactase present in Kefir grains was retarded in its action by galactose, but that the lactase present in emulsin was retarded by glucose. He thus showed the existence of two kinds of lactase—a galacto-lactase, inhibited only by galactose and a gluco-lactase inhibited only by glucose. As no data as to the nature of animal lactase at present exist, it was of some interest to ascertain whether the lactase in the intestines of animals was of the type present in Kefir grains or of the type present in emulsin.

The procedure for examining for the existence of animal lactase which was adopted in these experiments was essentially the same as that of Plimmer.[6] The enzyme solution was prepared by extracting the ground-up mucous membrane of the intestine of the dog for forty-eight hours with water containing toluene as antiseptic, and then filtering through cambric.

A definite volume of this extract was mixed with an equal volume of (*a*) 5 per cent. lactose solution, (*b*) 5 per cent. lactose solution to which glucose or fructose, in varying concentrations were added, to both mixtures 5 per cent. toluene was then added as antiseptic.* Samples of 50 c.c. were withdrawn immediately after mixing; the remainder was kept at 37° C.; and at intervals of one to four days, so as to give ample time for the enzyme to act, further samples of 50 c.c. were withdrawn. Each sample was treated with 5 c.c. mercuric nitrate solution to

* In all the experiments the same volume of extract was added to 5 per cent. solutions of glucose and galactose, to ascertain if there were any disappearance of reducing carbohydrate. No disappearance was obtained in any of the experiments here recorded.

Fig. 1.3 The title page of Stephenson's first scientific paper published in 1912 in the *Biochemical Journal*

for the first time, but we can imagine that it could have happened somewhere at *Biochemical Club* meetings. In any case, Hopkins apparently followed Stephenson's career and was aware of her capacities as evidenced by the letter of Hopkins to Schäfer[18] dated April 25, 1913 [29]. In this letter, Hopkins complains about the

[18]Sir Edward Albert Sharpey-Schäfer (1850–1935), notable English physiologist [28].

grant policy of an undeclared institution, probably the *British Association for the Advancement of Science*, of which Schäfer had been President since 1912, and expresses his indignation over the chemists who "threw over Plimmer and his colleague Stephenson". The mere fact that Hopkins calls Stephenson a "colleague" of Plimmer shows his appreciation of Stephenson in spite of her age and gender. Positive reception of Stephenson's research can also be ascertained from Hopkins' review on the progress in physiological chemistry published in 1915 [30], where he comments in detail the "important paper" by Moorhouse, Patterson and Stephenson [31] on carbohydrate and fat metabolism in depancreatized dogs with experimental diabetes, where according to Hopkins "the research described was clearly very carefully planned and organised, whilst the technique used seems above criticism" [30, p. 198]. Since 1913, Stephenson could feel somewhat more secure and independent thanks to a grant from Newnham College and the Beit Memorial Research Fellowship for Medical Research that she obtained the same year. The promising start of her career was, however, suddenly interrupted when the Great War broke out.

The war paradoxically opened up new challenges for the women chemists whose professional skills came into demand when men went to war.[19] Women chemists got employment at university chemistry departments, where they participated in war-related research and production of chemicals serving wartime needs, such as synthetic drugs, explosives and poisonous gases. A number of women chemists got jobs in chemical industry as analytical chemists or just unskilled workers. Stephenson did not make use of any of these opportunities and volunteered instead for war service with the Red Cross. From October 1914 until May 1915 she worked as a cook in rest stations in France, following which she was appointed as 'Head Cook' and worked successively in two Red Cross hospitals in Normandy. (…) In May 1916 she was one of the first VAD[20] cooks to be sent to Salonika in Greek Macedonia where she (…) completed her service in 1918. She returned home in autumn 1918 and for her war services was decorated by the King on 12 December 1918 Member of the Order of the British Empire (M.B.E.)[21] and Associate of the Royal Red Cross (A.R.R.C.) 2nd Class awards [13].

After the war, Stephenson started to research again. She took up her Beit Fellowship and in 1919 she joined F.G. Hopkins in the Biochemical Laboratory in Cambridge. She also became an associate (later a fellow) of Newnham College.

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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 Foster[2] 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

[1]Benjamin 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].

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

S. Štrbáňová, *Holding Hands with Bacteria*, SpringerBriefs in History of Chemistry, DOI 10.1007/978-3-662-49736-4_2

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

[3]In 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' foodstuffs failed to strive 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

[4]Freedman [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].

[5]Weatherall 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".

[6]Hopkins 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,

[7]The 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 Dunn[10] Trustees who on the advice of Walter Fletcher[11] dedicated more than £ 210,000 to the development of the subject in Cambridge.

[9]On 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.

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

[11]Sir 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. Haldane[12] worked on enzyme kinetics and made influential contributions to genetics and evolutionary theory. In the laboratory worked the Needhams, the famous married couple: Joseph Needham[13] was pioneer of a new field called chemical embryology and introduced another new field—comparative biochemistry which was further developed by

[12]John 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.

[13]Noel 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.

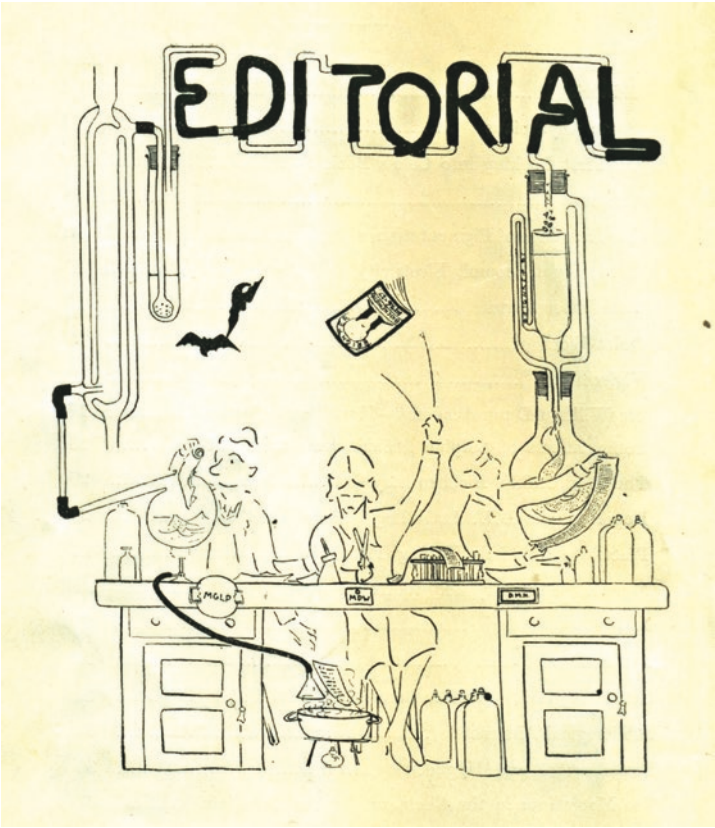

Fig. 2.3 M.G.L. Perkins, M. Whetham and D. Needham depicted as editors of the *Brighter Biochemistry* journal (Brighter Biochemistry, 1926–27, p. 4.)

Ernest Baldwin[14]; his wife Dorothy Moyle Needham[15] (Fig. 2.3) pursued muscle biochemistry. Other subjects were opened up by Rudolph Peters[16] and Juda Quastel[17] who investigated the biochemistry of cellular microstructures, while Muriel Wheldale Onslow and later Rose Scott-Moncrieff[18] with Haldane were

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

[15]Dorothy 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.

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

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

[18]Rose Scott-Moncrieff (Mrs. Meares).

inventing biochemical genetics through the study of flower pigments and Scott-Moncrieff˙s successor in plant biochemistry Robert Hill[19] developed biophysical chemistry of plant proteins and photosynthesis. Norman Pirie[20] investigated the physical properties of proteins and viruses; Synge,[21] Bailey[22] and Sanger[23] learned protein chemistry from Pirie, Malcolm Dixon[24] investigated biological oxidations. Among the foreign guest researchers became renowned the Hungarian Albert Szent-Györgyi[25] 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 Porter[28] 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.

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

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

[21]Richard 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.

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

[23]Frederick 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.

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

[25]Albert Szent-Györgyi de Nagyrapolt (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".

[26]Sir 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.

[27]Sir 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.

[28]Rodney 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.

[29]Peter 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 Raistrick[31] 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

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

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

[32]As 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), 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.

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

and what made her curios 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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Chapter 3
Fruitful Years. What Alice Found in the Microbes

Marjory Stephenson and Margaret Whetham were not the only workers in Hopkins' laboratory involved with microorganisms. In 1921, Hopkins accepted a young graduate student with a good knowledge of microbiology. As usually, he did not task him with any particular problem and encouraged him to go ahead with whatever he liked. This way started the scientific career of Juda Quastel [1–3] who has ultimately become known for his later research into neurochemistry. With Quastel's arrival a new parallel line of research in microbial biochemistry began to develop. He was interested in what we would call now the processes of intermediary metabolism and soon attracted attention with his experiments which showed for the first time that in *Bacillus pyocyaneus*[1] succinate or fumarate was the biological precursor of pyruvate.[2] Quastel's decision to work with a new model organism, *Escherichia coli*, and his effort to examine the bacteria in a non-proliferant condition had important consequences not only for his research, but also for the future development of biochemistry. *E. coli* turned out to be a very suitable organism, easy to grow, and its saline suspensions were simple to handle. He and Margaret Whetham jointly developed a technique of the so called "resting" cells originating in Pasteur's "washed suspension" method. The procedure consisted in working with washed bacterial suspensions under conditions that prevented their growth, for instance, when a source of nitrogen was missing from the medium. This way Quastel and Whetham observed that a reversible equilibrium existed between succinate and fumarate and that fumarate acted as hydrogen acceptor and even could replace oxygen as an oxidant [4]. These findings threw new light into the cellular oxidation-reduction reactions, as they have proven that not only oxygen but also other substances (e.g. nitrate, fumarate) can play the role of terminal hydrogen acceptor in cellular oxido-reduction systems.

[1]Today called mostly *Pseudomonas aeruginosa*.

[2]Quastel never mentioned in his personal recollections [2, 3] whether Stephenson influenced him in his choice of research themes, but we must consider (as will be shown later) that their farewell apparently was not harmonious.

S. Štrbáňová, *Holding Hands with Bacteria*, SpringerBriefs in History of Chemistry, DOI 10.1007/978-3-662-49736-4_3

The "resting" cell technique[3] brought together for a few years also the trajectories of Stephenson and Quastel.[4] Jointly with Margaret Whetham [7] they standardized the "resting" cell method which proved to be very useful for the study of bacterial metabolism isolated from the complexities of growth under controlled conditions. "Resting" bacteria were defined as bacteria that had been grown in nutrient broth, centrifuged, washed with saline and re-suspended in minimal medium where multiplication of the cells did not occur [7, p. 305].[5] Moreover, Quastel, Stephenson and Whetham started to use for the cultivation of bacteria synthetic media instead of the usual broth (probably for the first time) where variety of bacteria could grow under anaerobic conditions, namely when fumarate or aspartate were present [9]. These investigations enabled them to outline "the principles concerning oxido-reduction processes in bacteria that nowadays are referred to as electron-transport systems" [3, p. 142].

Not only strictly scientific work was going on in the Cambridge laboratory in those times "full of rich promise and achievements" [3, p. 144]. Whetham's and Quastel's collaboration bore a noteworthy fruit in 1923, when they founded the lab journal *Brighter Biochemistry* (Fig. 3.1) "illustrated annual outpouring of the Biochemical Laboratory in Cambridge." Articles, verses, cartoons, witticisms, tales and stories from the pens of the lab crew, including Stephenson, "reflected the expression of a laboratory in good heart and buoyant spirit, full of brightness and lively comradeship, due to the warmth and inspiration of its leader [F.G. Hopkins]" [3, p. 145]. The magazine issued irregularly until 1931 is still an enjoyable and even hilarious reading revealing the hidden layers of the laboratory life and testifying about the human qualities of its members and their tremendous sense of humour.

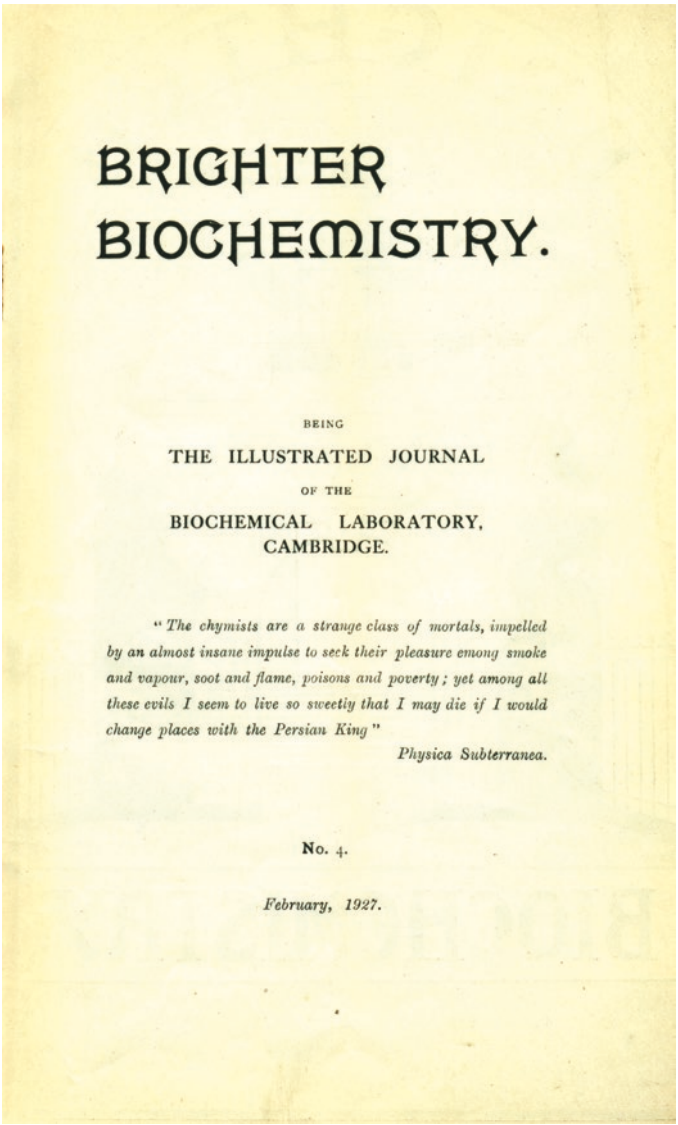
This is how the resting cell technique was acknowledged in the famous lab journal accompanied by a cartoon of Quastel surrounded by "protesting bugs" (Fig. 3.2) [10]:

> Attached hereto there is a pastel
> Portraying D. J. H. Quastel
> Surrounded by his bugs protesting
> Against the work they're given when resting.
> Woolridge and Woolf (who will not rhyme)
> Assisted in this sordid crime.
> Still harder were the problems set 'em
> By Misses Stephenson and Whetham.

[3]Synonym for "washed cell" technique.

[4]The relation of Stephenson and Quastel has been sometimes misinterpreted as if Quastel would be leading figure in their cooperation. For instance, Kohler mentions that "she was greatly influenced by Juda Quastel, a young organic chemist (sic!)…" [5]. Holmes even states [6, p. 45] that Stephenson was "introduced to the metabolism of bacteria in 1924 by Juda Quastel" before "she had become the international leader in that field".

[5]Cope brought up [8] that in 1926 Stephenson spent 3 months at the University of Manchester with the bacteriologist W.C. Topley (1886–1944); here she learned from Graham S. Wilson (1895–1987) to count viable cells. "With this method she was able to counter the criticism that her 'resting' cells were in fact dead".



BRIGHTER
BIOCHEMISTRY.

BEING
THE ILLUSTRATED JOURNAL
OF THE
BIOCHEMICAL LABORATORY,
CAMBRIDGE.

"The chymists are a strange class of mortals, impelled by an almost insane impulse to seek their pleasure emong smoke and vapour, soot and flame, poisons and poverty; yet among all these evils I seem to live so sweetly that I may die if I would change places with the Persian King"

Physica Subterranea.

No. 4.

February, 1927.

Fig. 3.1 Title page of *Brighter Biochemistry*, the journal of the Biochemistry Laboratory

Stephenson's contributions to *Brighter Biochemistry* offer us insight into the private corners of her personality: wittiness and affectionate relationship to her invisible friends—the microbes. In her *Down the Microscope* essay [11] Stephenson identifies with Alice in Wonderland and fulfils her wish to shake hands with the microbes (Fig. 3.3), in her case with the polite *Bacillus pyocyaneus*, as he says: "Pyo to real friends". Pyo introduces her to other bacteria, takes her to a

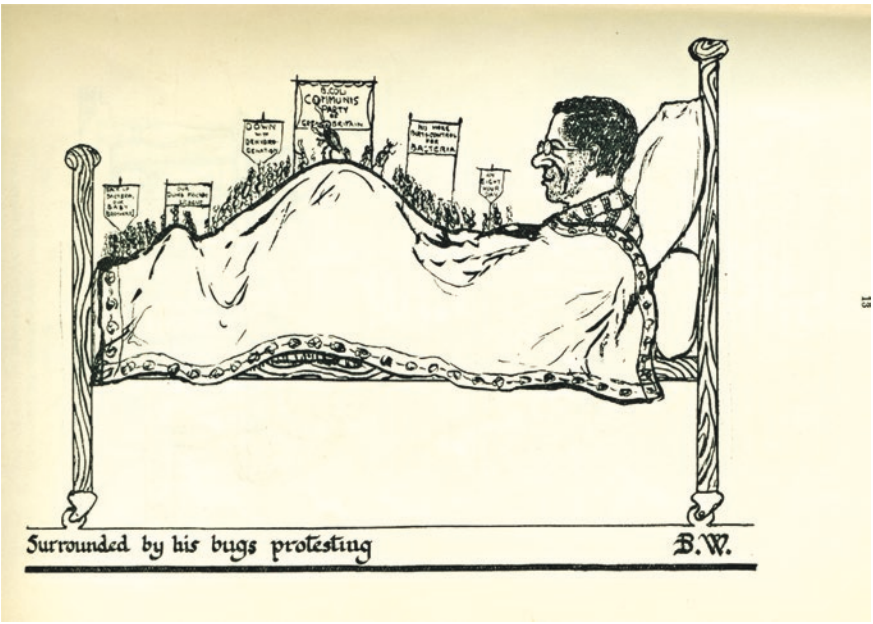


Fig. 3.2 Quastel surrounded by protesting bugs (From *Brighter Biochemistry* No. 3, December 1925, p. 13. The author was most probably Barnet Woolf who collaborated with Quastel)

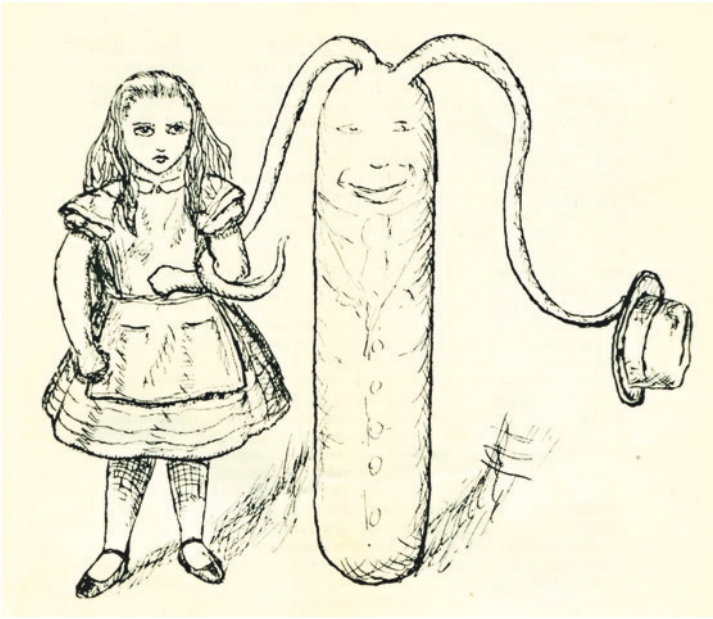


Fig. 3.3 Self-portrait of MS as Alice in Wonderland shaking hands with a polite bacterium. (From *Brighter Biochemistry* No. 5, December 1927, p. 37)

lecture of "an active little coccus on 'Housing Conditions in the Human Body'", and invites her to an amazing ball, where "Alice recognised at once the Bacterial Origin of the Charleston". Sadly enough, the excursion culminates in Alice's trial where the "alleged crime was no less than treason to the Bacterial State". Apparently Alice has to suffer for Marjory's sins like superficiality (bacteria "persistently described as mere aggregation of enzymes"), or pathogenicity; all humans are declared to be pathogenic, and so Alice is sentenced to autoclaving.[6]

Tensions can bubble under the surface of a happiest group. The progressing collaboration of Quastel with Stephenson was suddenly interrupted in 1926, after their last joint paper was published [13].[7] Quastel continued to work at the Biochemistry Department independently of Stephenson and in 1928 he observed with Woolridge [14] that malonate inhibited the oxidation of succinate catalysed by the enzyme succinic dehydrogenase. Generally speaking, this was a case when an enzymatic reaction was inhibited by a compound (malonate) which was chemically very similar to one in which the enzyme normally produced a change (in this case succinate). The phenomenon later called competitive inhibition has become one of the principal concepts of modern chemotherapeutic theory.[8] Quastel comprehended that he was on the track of an important discovery, but he became discouraged by the negative reactions of both Hopkins and Stephenson: "Hopkins was only mildly interested. Marjorie [sic!] Stephenson seemed to have no interest …at all—she was, if anything, hostile" [3, p. 150]. This short memory supports the conjecture that there might have been some discrepancy between Quastel and Stephenson, and Quastel's frustration could have been the reason why he left Cambridge in 1930 and shifted to an entirely different branch of biochemistry.

At the turn of the 1920s, the MRC was ever more motivated to promote research in bacterial chemistry by the "fundamental necessity for the better understanding and control of infectious diseases and of all morbid states involving sepsis," [15, pp. 144–145]. Nevertheless, the original plan to establish in Cambridge a permanent MRC research unit in bacterial chemistry consisting of a director and a small team of full-time researchers did not materialise. Initially, the Council's candidate for this job was the chemist Harold Raistrick, but he decided to take a university chair at the London School of Hygiene and Tropical Medicine. As a consequence of this situation no formal unit was created in Cambridge as the MRC did not consider Stephenson able to manage a laboratory. Walter Fletcher, the Secretary of the MRC "deeply respected Stephenson's ability and accomplishments at the bench, [but he] clearly did not think she had Raistrick's entrepreneurial talents. He expected less of her and expected her to manage on less" [16, p. 174]. No doubt, the main reason of this decision was that MRC was not inclined to employ women in leading positions. This distrust was also nurtured by

[6]Another article [12], where Stephenson and the Needhams jokingly report about their participation in the International Congress of Physiology in Stockholm in 1926 is mentioned in Chap. 4.

[7]Apparently, as the title of the paper suggests, they had planned a series of publications.

[8]More on this will be presented in the next chapter.

a certain divergence between Stephenson's wide-ranging approach to bacterial chemistry and the MRC's programme that mainly supported medically-oriented investigations. Finally, on 1 April 1929, Stephenson was appointed a permanent "external" member of MRC's staff, but without any formal authority.[9]

Stephenson's undefined, yet permanent, status between the Department and the MRC became a source of a long-time tension,[10] but at the same time her quasi-autonomous position proved to be a certain advantage with respect to her research. MRC's somewhat disparaging attitude did not discourage her and she made the best of the stimulating environment of Hopkins' institute and its multidisciplinary programme as she expressed in the Preface to the 2nd edition of her *Bacterial Metabolism* [17]:

> We have been singularly fortunate in being incorporated into the School of Biochemistry and so enabled to profit by contact with workers investigating many branches related in varying degrees to our own studies. As biochemistry advances, it enfolds a bewildering complexity yet at the same time displays a frequent repetition of pattern; only by co-operative working and thinking can progress be achieved.

Although the MRC had challenged her leadership abilities, she was never left single-handed. Her original working style and inspiring mentorship became magnets for young researchers who gathered around her; some of which got their salary or stipend from the MRC, some were attached to the Department of Biochemistry, and some simply came as visitors attracted by the fame of the laboratory.

3.1 New Experimental Techniques

To assess Stephenson's pioneering role in chemical microbiology, we must keep in mind that using microorganisms as primary models in biochemistry and molecular biology became quite customary in the 1950s, but in the times we are talking about here, only little was known about the metabolism of the bacterial cell or cell on the whole. To make their way into the enigma of the microbial cell, Stephenson with her collaborators had to first develop new experimental techniques. We have mentioned some of them earlier already. The "balance sheet" technique which Stephenson introduced with Whetham in the early 1920s, became widely applied in research into bacterial metabolism. The washed cell or resting cell technique of Quastel, Whetham and Stephenson, and use of synthetic growth media had far-reaching consequences for the programme of Stephenson's laboratory in the next twenty years. Suspensions of "resting" cells offered a rich field of investigation-not transformed directly and had a number of advantages: the substrate could be

[9]See Fletcher's letter offering Stephenson appointment to the scientific staff of the MRC, 18 March 1929, and Stephenson's answer to Fletcher, 19 March 1929; MRC Archives P.F. 216.

[10]More on this will be presented in the next chapter.

simplified to one or more substances; pH and salt content of the external environment could be strictly controlled; some metabolic reactions of the cell could be restricted, others stimulated; compounds or even poisons whose effect on the cellular processes were studied, could be added to the external medium in various concentrations to study the intermediate steps in cellular metabolic reactions. The synthetic chemically well-defined growth media allowed to handle the growth conditions of pure cultures of bacteria with great accuracy, enabled to gain insight into the cellular biochemical reactions and study the requirements for bacterial growth. The use of washed suspensions together with methylene blue, manometric and other contemporary techniques of biochemistry, opened new ways for study of enzyme kinetics and the growth conditions necessary for the optimal formation of enzymes.

In the years 1920–1950, intensive research into the nature and mode of action of enzymes, and the cellular metabolic pathways was going on in a number of European and overseas laboratories. Hopkins' Cambridge laboratory and Otto Warburg's Kaiser Wilhelm Institute for Cell Physiology in Berlin belonged among the leading ones. The experiments performed in Stephenson's laboratory since 1922 indicated that the bacterial cell apparently contains enzyme systems similar to those in the cells of higher organisms. Stephenson understood that she can investigate effectively these enzyme systems only if she finds her way to the inside of the cell. In 1928, she disrupted thick washed cell suspensions of *Escherichia coli* by autolysis in a phospate buffer and purified them by centrifugation and filtration through kieselguhr.[11] In the cell-free autolysate she detected the enzyme lactic dehydrogenase [18]. This enzyme had a very specific mode of action: in the presence of lactate it could bring about the transfer of hydrogen to methylene blue but not to oxygen.

It is necessary to mention beforehand that the washed suspension technique allowed investigating the properties of enzymes as they exist in the bacterial cell but such studies were necessarily restricted by the presence and action of other enzymes in the cell, by the permeability of the cell membrane towards the enzyme substrate, and other circumstances. The autolysis method enabled Stephenson to isolate for the first time in the history of microbiology an active cell-free enzyme from a bacterial cell, but it only had limited use because only sturdy enzymes could resist the drastic process of extraction. In 1938, V.H. Booth and D.E. Green, Stephenson's colleagues from Hopkins' department, constructed the wet-crushing mill that made possible the preparation of cell-free enzymes from bacteria [19]. With this new device Stephenson and several other collaborators from her laboratory, especially Gale and Still, prepared a number of enzymes from *E. coli*, like *l*-malic dehydrogenase, alcohol dehydrogenase [20], formic dehydrogenase [21], enzymes of amino acid metabolism [22], and others. The techniques which Stephenson's team put into practice became in the upcoming decades part of the

[11]Kieselguhr is a clay formed from the fossilized shells of microscopic unicellular aquatic plants and has been often used for filtration in laboratories and industry. Modern commercial sources are marketed under the name Celite.

methodical arsenal of biochemical and microbiological laboratories all over the world. The new methods served naturally also the Stephenson team to explore systematically the biochemical phenomena in the bacterial cell especially in the inter-war period.

3.2 Investigation of Bacterial Enzymes

In 1930, the Cambridgeshire river Ouse was polluted by waste from the local sugar-beet factory to such extent that active fermentation with evolution of gas could have been observed in the river itself. Stephenson with her collaborator Leonard H. Stickland[12] (Fig. 3.4) isolated from the water of the polluted river a mixed bacterial culture. The mud proved to be a source of several exciting micro-organisms which produced methane from formate, reduced sulphate to sulphite and made methane from formic acid as well as from carbon dioxide and hydrogen. From the mixture they were able to isolate the methane producer, a coliform organism, possibly *Escherichia formica* [23]. In washed suspension the bacteria reduced methylene blue in the presence of hydrogen; the yet unknown enzyme that was responsible for this reaction was named hydrogenase [24]; once discovered it proved to have wide distribution among bacteria. Also the sulphate reducer [25] morphologically similar to *Desulphovibrio desulphuricans* was soon detected and details of sulphate reduction were studied manometrically. The third bacteria[13]—the methane producer, turned out to be unique in its ability to reduce several compounds to methane; but only compounds containing one carbon atom, like carbon dioxide, methanol, formaldehyde and formate, yielded methane [27]. The organism grew well on synthetic medium where ammonium was the source of nitrogen and formate as carbon source. Experiments with washed suspensions showed that the energy yielding reaction was:

$$4\mathrm{HCOOH} = \mathrm{CH_4} + 3\mathrm{CO_2} + 2\mathrm{H_2O} + 39\,\mathrm{kcal}$$

Further experiments revealed that formate was not transformed directly to methane; it was first split to molecular hydrogen and carbon dioxide and part of the latter was then reduced by the molecular hydrogen to methane.

Research into formate metabolism turned out to be a milestone in the lab's research agenda (Fig. 3.5). In 1929, Stickland studied in washed suspensions of *E. coli* grown on agar the decomposition of formic acid [28] and found that the bacteria possessed a powerful enzyme—formic dehydrogenase. Stickland was able to make a very active enzyme preparation by tryptic digestion of the cell suspension and subsequent filtration. The enzyme catalysed the aerobic decomposition of formate

[12]Leonard Hubert Stickland (1905-?), worked with Stephenson 1928–1934.

[13]The isolation of the methane producing bacteria by the single-cell technique was quite tricky and Stephenson was not able to identify it as it was most probably contaminated by another sulphate reducing bacteria [26, p. 332].

Fig. 3.4 L.H. Stickland (*second from the left*) by the lab window with H. Mowl (on his *left*), Stephenson's dog Judith and J. Coard (later Lawrie) (Archive of the Department of Biochemistry, University of Cambridge. Picture reproduced with the permission of the Archive)

into water and carbon dioxide, but did not liberate from formate molecular hydrogen. When the cell suspension had been in contact with formate for several hours, the enzyme preparation started to liberate hydrogen from formate. In 1932, Stephenson and Stickland reinvestigated these three year old experiments and found out that there exist actually two modes of formate decomposition: into water and carbon dioxide or molecular hydrogen and carbon dioxide.[14]

$$(1)\ HCOOH + O \rightarrow H_2O + CO_2$$

$$(2)\ HCOOH \rightarrow H_2 + CO_2$$

It turned out that both reactions were catalyzed by different enzymes: the first one by formic dehydrogenase, while the second one by a so far unknown enzyme which appeared in the microbial cells after their incubation with formate. This way Stephenson and Stickland discovered a new group of enzymes which liberated from various substrates molecular hydrogen; they named these enzymes hydrogenlyases to distinguish them from the dehydrogenase type enzymes [30, 31][15];

[14]Stephenson's pupil Woods proved in 1936 that the enzymic reaction was reversible [29].

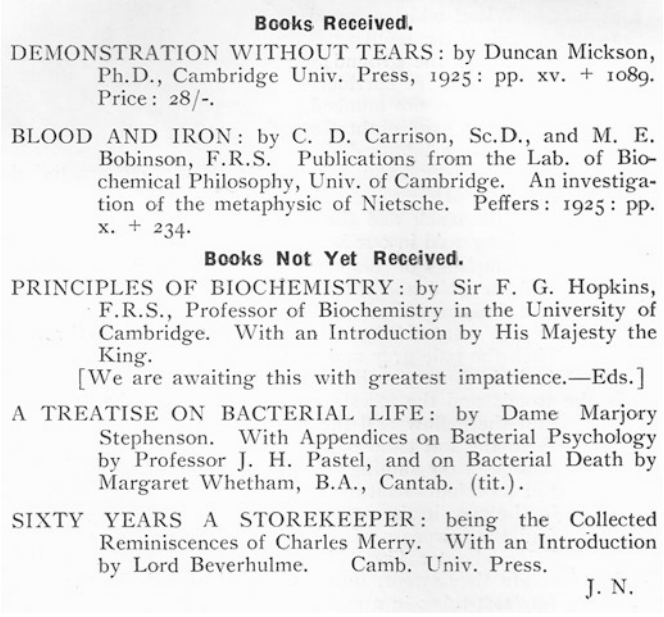
[15]Formic hydrogenlyase, catalysing the decomposition of formic acid into carbon dioxide and molecular hydrogen is made up of two enzymes: (a) formate dehydrogenase which catalyses formate + $NAD^+ \rightarrow CO_2$ + NADH; (b) hydrogen dehydrogenase which catalyses $H_2 + NAD^+ \rightarrow H^+ +$ NADH (according to [32], p. 710).

hence the enzyme which liberated molecular hydrogen from formate was called formic hydrogenlyase. The discovery of a new group of enzymes was a fundamental contribution to enzymology that helped to shed light to the nature of anaerobic existence of microorganisms, and also became the point of departure to new exciting investigations of the Stephenson team.

3.3 Adaptation Studies

Stephenson understood very well the significance of the discovery of a new group of enzymes. It prompted her and her collaborators to perform in the 1930s a series of investigations on formic hydrogenlyase in different microorganisms with a view to study the different factors involved in cellular enzyme formation. The observation that an enzyme (for instance formic hydrogenlyase) had been produced only if the bacterial cells were incubated in the presence of its substrate (formate) attracted Stephenson's attention especially to the phenomenon of chemical adaptation.

Adaptation was not a recent problem. The remarkable ability of organisms, especially microorganisms, to adjust their chemical activities to the variations in



Books Received.

DEMONSTRATION WITHOUT TEARS: by Duncan Mickson, Ph.D., Cambridge Univ. Press, 1925: pp. xv. + 1089. Price: 28/-.

BLOOD AND IRON: by C. D. Carrison, Sc.D., and M. E. Bobinson, F.R.S. Publications from the Lab. of Biochemical Philosophy, Univ. of Cambridge. An investigation of the metaphysic of Nietsche. Peffers: 1925: pp. x. + 234.

Books Not Yet Received.

PRINCIPLES OF BIOCHEMISTRY: by Sir F. G. Hopkins, F.R.S., Professor of Biochemistry in the University of Cambridge. With an Introduction by His Majesty the King.

[We are awaiting this with greatest impatience.—Eds.]

A TREATISE ON BACTERIAL LIFE: by Dame Marjory Stephenson. With Appendices on Bacterial Psychology by Professor J. H. Pastel, and on Bacterial Death by Margaret Whetham, B.A., Cantab. (tit.).

SIXTY YEARS A STOREKEEPER: being the Collected Reminiscences of Charles Merry. With an Introduction by Lord Beverhulme. Camb. Univ. Press.

J. N.

Fig. 3.5 The *Brighter Biochemistry* announced in 1925 (p. 62) under the heading "Books Not Yet Received" also the fictitious edition of A TREATISE ON BACTERIAL LIFE by "Dame Marjory Stephenson". The joke testifies the attention Stephenson's research had raised among her colleagues. Quastel is nicknamed here as "Pastel"

their environment had been observed since Pasteur's times by a number of investigators who mostly understood that adaptation to a new nutrient in the medium is connected with changes in the specific enzyme composition or enzyme activity.[16] Already in 1913, in his programme of dynamic biochemistry Hopkins accentuated the necessity of studying cellular regulation mechanisms visualized in terms of chemical processes which "may be brought de novo into play as the result of intrusion of a new molecule into reactions which were in dynamic equilibrium." [36, p. 217]. Enzyme adaptation Hopkins characterised quite appositely in terms of de novo enzyme synthesis as part of the cell organization: "Evidence continues to accumulate […] that the living cell can acquire de novo as the result of specific stimulation new catalytic agents previously foreign to its organisation." [36, p. 222]. Nevertheless, it took twenty years before this part of Hopkins' programme was ripe for realization. By 1930, research in several European laboratories provided extensive data indicating the wide occurrence of adaptation phenomena in the microbial world, but the nature of adaptation remained unclear. Was it enzyme activation or inhibition, de novo enzyme synthesis, cell mutation combined with selection, or some other entirely unknown phenomenon?

Confusion evoked by the ever increasing amount of experimental data, various interpretations and theories, often irrelevant or contradictory, was settled to a certain extent in 1930 by a young Finnish biochemist Henning Karström[17] (1899–1969) in his dissertation published under the title *Über die Enzymbildung in Bakterien* [37, 38]. Karström, in attempting to generalize the known experimental data, arrived at a unified classification of enzymes into constitutive and adaptive. According to Karström, "constitutive" enzymes were those always present in the cells of a given species irrespective of the composition of the environment, while the "adaptive" enzymes were produced as a response of the homologous substrate in the culture medium. This somewhat simplified view correlated adaptation with cell multiplication and did not consider the possibility that adaptive enzymes might be produced by non-growing cultures as shown earlier by other researchers.[18] Although Karström did not formulate any comprehensive hypothesis about the mode of action of the specific substrate nor about the way the adaptive enzymes arise in the cells, his dissertation received almost immediate attention of Stephenson because it clearly defined the subject of enzyme adaptation, demarcated the field of investigation and proposed its terminology. In terms of Karström's classification she reinvestigated with Stickland in 1931 their earlier work on formate decomposition and "concluded that the enzyme in question is an

[16]The problem matter of adaptation was discussed, for instance, in 1956 by Kluyver, and Van Niel [33], see especially. Chap. 4, pp. 93–129 entitled Life's Flexibility; Microbial Adaptation. For early history of adaptation studies in microorganisms see [34, 35], where the reader can find much additional literature.

[17]Henning Karström (1899–1969) belonged to the pioneers of the Finnish biochemistry. He was close collaborator of the Nobel Prize winner A. Virtanen (1895–1973).

[18]For instance Dienert found in 1900 already [39] that adaptive "galactozymase" may be produced in non-growing yeast.

adaptive one in the sense used by Karström, and occurs as the result of growing the cells in the presence of formate." [30, p. 715].

Since 1931, enzyme adaptation became the central topic in Stephenson's laboratory. In this year came to the Biochemistry Department John Yudkin[19] a biochemist who joined Stephenson's lab as her Ph.D. student. As the ambitious and hard-working young man did not have a scholarship, Stephenson paid for his grant out of her own pocket until he was able to get a Research Studentship in 1933 [42]. Yudkin postulated in 1932 two possibilities of adaptation; either natural selection or chemical adaptation, i.e. direct chemical action of the substrate on the cell [43]. Since 1933, Stephenson supervised her other graduate student Donald D. Woods[20] and since 1936 the biochemist Ernest Gale[21] who obtained a MRC grant to work as assistant to Stephenson. Yudkin, Stickland, Woods and later Gale, performed under Stephenson's guidance series of experiments investigating adaptive enzymes using as a model formic and glucose hydrogenlyases in *E. coli* and *Bacterium lactis aerogenes*[22] and also other enzyme systems, namely glucozymase and galactozymase[23] in *E. coli* and yeast [31, 35, 46–48]. This unique teamwork gathered in the years 1932–1938 a large amount of experimental data, which eventually enabled to draw some more general conclusions about the nature of enzyme adaptation in microorganisms. By 1936 there was enough evidence available to state that adaptation can occur in non-growing bacterial cultures and that individual cells are capable of fast adaptive formation of substrate-specific enzymes as a direct response to the chemical changes in the environment, namely if a new substrate appears in the medium. Stephenson and Yudkin in their joint paper (Fig. 3.6) definitely stated that "**Adaptation can occur without cell multiplication. […] not as a result of natural selection, but as a response of the cell to its chemical environment**" [46, p. 514].[24] This temporary change in enzyme activity due to

[19]John Yudkin (1910–1995), British physiologist and nutritionist. Since 1931, he worked on his Ph.D. thesis on adaptive enzymes under Stephenson's supervision. In 1945, shortly after the end of the war John Yudkin was elected to the Chair of Physiology at King's College of Household and Social Science in London. In 1954 the Department of Nutrition was officially opened at the University of London and Yudkin's Chair was converted into a Professorship of Nutrition [40, 41].

[20]Donald Deveraux Woods (1912–1964), British microbiologist. In 1939 Woods started to work with Paul Fildes at the MRC Unit for Medical Bacteriology in London, where he discovered the antagonistic action of *p*-aminobenzoic acid against the antibacterial action of sulphonamides. This accomplishment will be treated in the next chapter. In 1955 he became professor of chemical microbiology at the University of Oxford [44].

[21]Ernest Frederick Gale (1914–2005), British microbiologist. After Stephenson's death in 1948, he became Director of the MRC Unit for Chemical Microbiology in Cambridge. In 1960 he was appointed professor of chemical microbiology at Cambridge University [45].

[22]Today called *Aerobacter aerogenes*. Yudkin investigated these enzymes also in other bacterial species.

[23]Glucozymase and galactozymase are obsolete historical names of enzymes. Glucozymase represented a complex of glycolitic enzymes participating in the glycolytic pathway: hexokinase, glucose phosphate isomerase and phosphofructokinase; galactozymase was the historical name for galactokinase.

[24]Highlighted by SŠ.

LXXVI. GALACTOZYMASE CONSIDERED AS AN ADAPTIVE ENZYME.

By MARJORY STEPHENSON and JOHN YUDKIN.

From the Biochemical Laboratory, Cambridge.

(*Received January 29th, 1936.*)

Previous studies from this department on adaptive enzymes have been concerned with hydrogenlyases. It has been shown that the formation of these enzymes in the Bacteriaceae is controlled by the medium in which the cell is grown, one factor being the presence of the substrate, *e.g.* formate in the case of formic hydrogenlyase, another being some substance in broth which so stabilises the enzyme that it is active in washed suspensions [Stephenson and Stickland, 1932; 1933; Yudkin, 1932]. The mechanism by which the medium conditions the formation or stabilisation of enzymes was discussed by Yudkin [1932], who postulated two possibilities, either natural selection or chemical adaptation, *i.e.* direct chemical action of the substrate on the cell. He concluded, chiefly from theoretical considerations, that the production of formic hydrogenlyase by *Bact. coli* was of the nature of a chemical adaptation. This was later proved by Stephenson and Stickland [1933], who showed that natural selection was not operating, since the enzyme was formed in the absence of cell multiplication. In the present study we present some facts connected with the formation of galactozymase, the enzyme complex concerned with the fermentation of galactose by *S. cerevisiae.*

The literature already contains material on this subject. Dienert [1900] first recorded the adaptive nature of galactozymase by showing that certain strains of yeast, which at first are unable to grow in media where galactose is the sole carbohydrate, become able to do so if previously grown for a few weeks on a mixture of glucose and galactose. In such cases the same result is achieved by lactose or melibiose, doubtless because these sugars give galactose on hydrolysis. Yeast grown on glucose alone is unable to ferment added galactose, whilst yeast grown on galactose or on a mixture of glucose and galactose, when subsequently placed in contact with galactose, causes an immediate fermentation of that sugar, *i.e.* is adapted to galactose. Non-adapted yeast if left in contact with galactose for 24 hours or longer begins a slow fermentation; after this is complete, a further addition of galactose is fermented immediately, *i.e.* the yeast has become adapted. Moreover, adapted yeast, if allowed to ferment glucose, showed subsequently a diminished power to ferment galactose, that is, adaptation is partly reversible. This observation was confirmed by Euler and Johansson [1912] and Euler and Lövgren [1925] and by Söhngen and Coolhaas [1924], and contradicted by Abderhalden [1926, 2].

These experiments of Dienert, though highly suggestive, are difficult to interpret owing principally to their non-quantitative nature, rates of fermentation, quantity of yeast and change in cell numbers not being recorded.

Slator [1908] showed that only certain strains of yeast can be adapted to galactose. He was of opinion that the fermentation of galactose does not occur through glucose or through a form common to both sugars, since unadapted yeast when added to adapted yeast does not increase the rate of fermentation of galactose.

Fig. 3.6 Title page of the essential joint paper of Stephenson and Yudkin on enzymic adaptation published in *Biochemical Journal* in 1936 (pp. 506–516)

changes in the growth medium is characterised by Stephenson in the third edition of her *Bacterial Metabolism* in the following statement [49, p. 296]:

> This type of adaptation is a direct response of the enzymic composition of the cell to the constituents of the growth medium. **It is definitely temporary and does not affect the heredity mechanism of the cell,** which reverts to normal (if indeed a "normal" bacterial cell exists) when the organism is grown without the specific stimulus (see footnote 24).

In the memorial volume *Perspectives in Biochemistry* prepared by Hopkins' collaborators in honour of the 75th birthday of F.G. Hopkins (issued in 1937) Stephenson deliberates about the phenomenon of adaptation versus the economy of the bacterial cell and declaims against teleology—the adaptation of the means to the end. She concludes from the adaptation experiments that not all enzymes in bacteria must be of functional importance and states that the bacterial cells have three types of enzymes: those which are "organized to serve growth and division, whilst others are more loosely coordinated and others mere free lances" [50, p. 95]. The greater fluctuation in enzyme composition in bacterial cell compared to the cells of higher organisms is due to the fast reaction of the bacterial cell to the composition of the environment.

Such reasoning resulted from the many years lasting painstaking joint effort based on original methods developed in the laboratory which enabled to attack the problem of adaptive enzyme synthesis in non-growing cultures and thus to distinguish between selection of genetically altered cells occurring only during multiplication, and cultures capable of fast adaptive formation of substrate-specific enzymes. This way, the old dilemma of adaptation was resolved, however, the theoretical explanation of adaptive enzyme formation remained obscure. The theory was eventually published in 1938 by John Yudkin, two years after his joint paper with Stephenson, and three years after the first version of the theory was articulated.

John Yudkin (Fig. 3.7) got his PhD in 1935 [42] and after leaving Stephenson's laboratory he pursued clinical studies at the London Hospital, while continuing to teach part time in Cambridge. In 1938, Yudkin was appointed Director of Medical Studies at Christ's College and started research at the Dunn Nutritional Laboratory in Cambridge; nutrition science remained then his life-long engagement. It is unclear why only in this year (two years after the article had been received for publication), appeared in *Biological Reviews of the Cambridge Philosophical Society* the published version of his PhD thesis *Enzyme Variations in Micro-Organisms* where Yudkin made public **the first general theory of enzyme adaptation** [51].

In this paper, Yudkin principally distinguishes enzyme adaptation from "training"—the genetically permanent adaptation involving selection of mutant cells, which synthesize a constitutive enzyme. Enzyme adaptation is characterized here as a "specific response to a change in the environment […] of the nature of a non-inheritable acquired character" [51, p. 94]; adaptive enzyme production is according to Yudkin a result of a direct interaction between the cell and the substrate. Careful analysis of experimental results on adaptive enzyme production in micro-organisms permits him to postulate his **mass action theory of adaptive enzyme formation.** In the statement of his theory, Yudkin anticipates that even in the

Fig. 3.7 J. Yudkin, as a graduate student working with the micromanipulator for isolating single bacteria (Archive of the Department of Biochemistry, University of Cambridge. Picture reproduced with the permission of the Archive)

absence of substrate the cells contain a small, sometimes immeasurable amount of the adaptive enzyme which normally is in equilibrium with its precursor. In the presence of the substrate, the pre-existing enzyme combines with it and upsets the equilibrium. In consequence, the cell produces more enzyme from its precursor until the equilibrium is restored.

Yudkin's mass action theory signified a culmination of about ten years of systematic studies of enzyme adaptation in Stephenson's laboratory. For Stephenson enzyme adaptation represents an essential process which helps the cell to maintain itself in equilibrium with its environment. In her own words [49, p. 311]:

> It is impossible to exaggerate the importance of the variability of the bacterial cell or the desirability of studying the laws regulating it. The bacterial cell, by reason of its small size and consequent relatively large surface, cannot develop by maintaining a constant chemical environment, but reacts by adapting its enzyme systems so as to survive and grow in changing conditions.

Comprehensive chapters on adaptation in the second (1939) and third (1949) editions of *Bacterial Metabolism* [17, pp. 301–315; 49, pp. 287–312] declare this importance.

Stephenson and her group laid the foundation for the later work of Jacques Monod[25] who took up enzymatic adaptation (later known as enzyme induction) in 1940 as basis for developing his theories of cellular regulatory mechanisms and protein synthesis in the 1950s and 1960s. By Monod's own testimony [52] and Lwoff's memories [53] Monod got acquainted with Stephenson's and Yudkin's studies in December 1940 when he investigated the growth of *E. coli* in a mixture of two sugars and observed a strange growth curve with two distinct exponential growth phases separated by a lag phase.

> This he called diauxy. Jacques Monod […] came and showed me the diauxic curve and asked: 'What could that mean?' I said it could have something to do with enzymatic adaptation. The answer was: 'Enzymatic adaptation, what is that?' I told Monod what was known […] and he objected that the diauxic curve showed an inhibition of growth rather than an 'adaptation'. […] I simply repeated that diauxy should be related to adaptation [53, p. 388].

And this is how Monod recalled the story [52]:

> Lwoff's only reply was to give me a copy of the then recent work of Marjorie [sic!] Stephenson, in which a chapter summarized with great insight the still few studies concerning this phenomenon, which had been discovered by Duclaux at the end of the last century. […] it was more or less rediscovered by Karström, who should be credited with giving it a name and attracting attention to its existence. Marjorie Stephenson and her students Yudkin and Gale had published several papers on this subject before 1940. […] Lwoff's intuition was correct. The phenomenon of 'diauxy' that I had discovered was indeed closely related to enzyme adaptation, as my experiments, included in the second part of my doctoral dissertation, soon convinced me. […] The die was cast. Since that day in December 1940, all my scientific activity has been devoted to the study of this phenomenon.

Adaptive enzymes became in Monod's terminology **inductive enzymes**, and **induction** and **repression** main complementary elements in the control of cellular enzyme synthesis. We should keep in mind, however, that the term "induction" was already coined by Yudkin in 1938 who used it in the following sense: "We have here then a simple conception of the process by which enzyme production may be **induced** by the presence of the substrate of the enzyme." [51, p. 101] (see footnote 24).

3.4 Cell Metabolism

In the 1920s still relatively little was known of the intermediary metabolism of higher organisms and microorganisms, and nothing of the mechanisms of biosynthesis of amino acids or nucleotides, let alone proteins or nucleic acids. This was

[25]Jacques Lucien Monod (1910–1976), French biologist, who jointly with François Jacob (1920–2013) postulated the repressor model of regulation of gene activity, which exerted a tremendous impact on the further development of molecular biology. In 1965, they were awarded the Nobel Prize together with André Lwoff "for their discoveries concerning genetic control of enzyme and virus synthesis".

soon going to change. The 1930s were the golden age of "dynamic biochemistry" with its flourishing examination of intracellular biochemical processes and their relation to fundamental life processes. Detection of new enzymes, cellular enzyme synthesis and kinetics and metabolic pathways became central components of biochemical research. The Cambridge Department of Biochemistry with its multifaceted research programme focused mainly on these areas, occupied a prominent place among the European and overseas laboratories. Stephenson, although independent, perceived herself as part of this extraordinary squad. Hence, even if she considered work on adaptive enzymes of utmost importance, seeing it as part of the cellular organization, she did not drop other biochemical topics in her laboratory.

During the thirties, two members of the Stephenson group, L.H. Stickland and later D.D. Woods carried out under Stephenson's guidance investigation on the amino acid metabolism in *Clostridium sporogenes*. Ernest Gale (Fig. 3.8), who started in 1936 his PhD studies with Stephenson, followed up on these papers, and besides adaptation he also explored with Stephenson in the years 1936–1938 deamination of several amino acids and the various paths that can lead to their deamination, including oxidative, dehydration and desaturation reactions [47, 54, 55]. In 1938, Gale discovered that *E. coli* contained two distinct enzymes capable of deaminating aspartic acid, which he called aspartase I and aspartase II.

Fig. 3.8 F.G. Hopkins with E.F. Gale, Helen Epps and an unidentified person around 1941. (Archive of the Department of Biochemistry, University of Cambridge. Picture reproduced with the permission of the Archive)

His observation that adenosine could play the role of coenzyme for aspartase II [54] awakened Stephenson's interest in nucleic acids and their derivatives in cell metabolism. With her "characteristic thoroughness" [56] she embarked with A.R. Trim in 1937 on a study of the changes of adenine compounds in the presence of some cellular enzymes of *E. coli* [57]. Her first paper on nucleic acids started with a statement: "**The importance of nucleic acid derivatives in cell metabolism is becoming increasingly apparent…**" [57, p. 1740] (see footnote 24). Though Stephenson seemed to have a great desire to explore these new areas, the outbreak of World War II brushed aside her studies on nucleic acids until nearly ten years later.

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Chapter 4
Between the Medical Research Council and the Biochemistry Department

Scientific advance at the beginning of the 20th century also brought new hope in battle against diseases, namely infectious diseases. The Medical Research Council (MRC) [1, 2] was created in 1913 as a British government agency responsible for promoting research in the biomedical fields to improve human health through world-class medical research. Over the years the MRC has become the leading national body responsible for coordinating and funding medical research in the United Kingdom. The flagship of British biomedical research became the MRC National Institute for Medical Research established in the same year as the MRC, and besides this, the MRC endeavoured to promote research through setting up organised teams of external staff under the general title of 'research units'. In Cambridge, the MRC created new opportunities for research outside the clinical field—nutrition and bacterial chemistry which made use of the inspiration and guidance of F.G. Hopkins who had been associated with the MRC from the very beginning also formally.[1] In principle the research units were built round a chosen leader and a host institution which provided accommodation for the respective unit.[2] The "chosen leader" of the Cambridge MRC laboratories, both the bacterial chemistry and the nutritional[3] ones, was no doubt Hopkins, and the Biochemistry Department acted as host institution.

Stephenson was in a peculiar position being attached both to the Biochemistry Department and the MRC which equally shaped her career as of a biochemist and a woman scientist. Cambridge University was characterized by male domination in the scientific community, where there were ten times as many men as women.

[1]F.G. Hopkins was member of the Medical Research Committee in the years 1913–23, 1926–30, and member of the Medical Research Council 1926–1930 [1, p. 269 and 282–283].

[2]"In some instances there has been no host institution, the unit being maintained by the Council as a separate establishment" [1, p. 139].

[3]The Dunn Nutritional Laboratory, later the MRC Dunn Nutrition Unit, was set up as an offshoot of Hopkins' Department of Biochemistry in 1926 [3, pp. 64–66].

S. Štrbáňová, *Holding Hands with Bacteria*, SpringerBriefs in History of Chemistry, DOI 10.1007/978-3-662-49736-4_4

This imbalance became even more visible at the senior staff positions. At the top of the hierarchy were heads of major departments and laboratories: "Their authority was rooted in scientific prestige, paternalistic in character […]" [4, p. 22]. Stephenson was lucky to work under Hopkins who was "a less dominating figure of authority than, say, Rutherford"[4] and the Dunn Laboratory's organisation was "less hierarchical and formalised than the Cavendish's" [4, p. 25], nevertheless Hopkins was perceived as a liberal father-figure by most of his co-workers who affectionately called him "Hoppy". Hopkins' unique quality was his personality [5, p. 198]:

> His courtesy was almost Chinese in perfection. He received students, colleagues and visitors with extraordinary kindness, and listened politely and with genuine interest to all […] He was accused, in his kindness of heart, of regarding his geese as swans. But through his solicitous inspiration his geese were liable to be transformed into swans.

Stephenson speaks of "…tenacity of somewhat at variance with his gentle slightly hesitating, courteous manner" [6, p. 169].

In the period of Hopkins's chairmanship of the Department, the breadth of research activity was simply astonishing for what today would be considered to be a small laboratory. Although part of the research community worked on a permanent basis, the turnover of co-workers was in Hopkins' lifetime tremendous; at the lab benches had taken turns about 370 people—researchers, students, foreign visiting scientists, technicians.[5] Due to Hopkins' fame, his laboratory became a Mecca that attracted students from Britain, Europe and overseas. Getting in touch with mostly young scientists from different countries with a broad spectrum of research interests was a particular bonus for Stephenson.

In Cambridge, women were a suppressed and gifted minority assembling mainly in biological disciplines.[6] Nearly 15 % of Hopkins' collaborators were women[7]; during the Second World War the Institute housed even more women who replaced men serving in the army, but very few received university appointment. The unusually high proportion of women at Hopkins' laboratory and the high degree of intermarriages among co-workers was often target of tease or even nasty remarks (Fig. 4.1). For instance the journal *Chemistry and Industry* published an irritated comment on this circumstance already at the time of the Institute's opening [3, p. 46]:

> …it [the new Institute] is probably too much the resort of women students, who cannot be expected to bring to the study of the subject that breadth and originality of outlook and the acute powers of observation that are essential to progress.

[4]Ernest Rutherford, 1st Baron Rutherford of Nelson (1871–1937), British physicist, pioneer of nuclear physics, 1908 Nobel Prize winner.

[5]An almost complete list of Hopkins' coworkers was compiled for the Hopkins memorial volume issued in 1949 [7].

[6]For details of the conditions of women's scientific education and status in Cambridge see e.g. [8, 9].

[7]Calculated from [7].

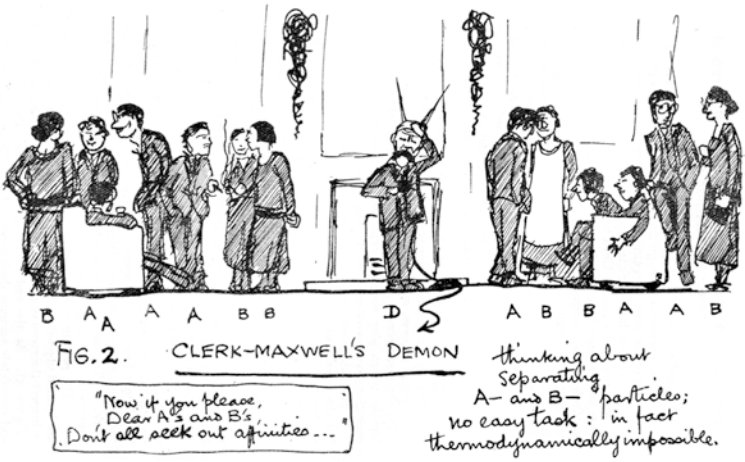

Fig. 4.1 Cartoon from *Brighter Biochemistry* (No. 2, 1924, p. 16) shows a laboratory scene with the high proportion of women, while the accompanying text points to the pairing tendencies of the local males and females. The man in the centre is F.G. Hopkins depicted as Clerk-Maxwell's Demon who is "thinking about separating A- and B- particles [that is men and women]; no easy task; in fact thermodynamically impossible"

It was often said that the Biochemistry Department reminded of a family. This impression was intensified by the fact that several married couples worked there side by side. Unlike most women at the Department, however, Stephenson did not marry, and her single status not only helped her to retain independence, but also improved her chances of a career both at the University and the MRC. Stephenson's position at the Department was more autonomous than that of her colleagues also because she was fully paid from MRC's budget. Nevertheless she and her collaborators were integrated into the activities of the Department as also demonstrates their regular participation in the Department of Biochemistry Tea Club, where members of the Department featured with lectures on their research [10]. Stephenson profited from the Department's intellectual wealth and largely contributed to it. In the course of the years Hopkins even "came to depend, to an extent that was not always fully recognised, on M.S. for advice and support with the social and strategic problems of the department" [11, p. 329].

Stephenson took full share in teaching of both practicals and lectures in Part I and Part II biochemistry [12]. From 1925 onwards she gave courses on bacterial metabolism to the Part II Tripos advanced biochemistry class. Her lectures were popular, but apparently not due to her rhetorical skills, as Ernest Gale remembers [13, p. 2]:

> Instruction in bacterial metabolism came as a course of lectures to the part II biochemistry class given by MS, but, revere her as we may, no one could call her a brilliant lecturer. The lectures might well begin in the middle and end at the beginning but at least we gathered that someone had done something terrific.

Also Woods testifies that Stephenson [14, p. 378]:

> did not much enjoy formal lecturing; lectures provided the facts, but it was the informal chat during the practical class that she got in real touch with the student. Her success may be measured by the steady flow of recruits from the Part II Class to her research team. It was the guidance of the young research worker that Marjory Stephenson had her greatest influence. […] Though always ready with […] advice, she never 'spoon-fed' […]. She encouraged persistence and insisted on the degree of thoroughness characteristic of her own work. Of Marjory Stephenson it may truly be said that 'infection not instruction is the secret of education'.

Cambridge University awarded Stephenson the Doctor of Science degree in 1936 for her outstanding research, but offered no appointment until 1943 when she became University Lecturer in biochemistry, after teaching for eighteen years.

The position of Stephenson between the Department and the MRC was not as simple considering that she had close ties to both institutions, while the MRC was her employer who was approving of her programme and to whom she had to report. To understand better the situation, we must recall the origins of Stephenson's laboratory at the MRC.[8] Initially, the MRC planned to establish in Cambridge a permanent research unit in bacterial chemistry consisting of a director and a small team but the candidate for this job, the organic chemist Harold Raistrick, left the Biochemistry Department in 1921 and the MRC did not consider Stephenson appropriate nominee for the position of a director. Eventually the plans of the Unit narrowed to a one-story laboratory which was placed behind the Biochemical Department and one person—Stephenson employed first on annual grants and since 1929 as permanent staff without being officially assigned to any position. Stephenson herself was very pleased that her laboratory remained appended to the Department as she also mentioned in her letter to Fletcher written in March 1929 [15]: "The change from a temporary to permanent basis leaving me attached to Professor Hopkins' department offers a combination peculiarly attractive…".

The laboratory progressed under the informal leadership of Stephenson [16]. She gradually assembled an outstanding small team (Fig. 4.2) and retained her autonomy in choosing problems to be investigated and doing first-rate goal oriented research. As shown in the previous chapter she had a number of collaborators who were paid from different sources (only exceptionally paid by the MRC), but her annual reports to the MRC indicate that the laboratory used to house even more individuals: PhD students of Stephenson (some of them financially supported by Stephenson herself, like John Yudkin), colleagues from the Biochemical Department, local and foreign visitors eager to work on joint projects or learn new techniques. Stephenson exerted a pull on collaborators especially since 1930 when her famed monograph *Bacterial Metabolism* [17] first appeared; however, it was not only the uniqueness of her field which attracted researchers to her laboratory. The originality of Stephenson's research extended beyond bacterial biochemistry and promised to investigate general phenomena of the cellular life. In the years 1922–1948 collaborated with Stephenson at least 58 persons (Table 4.1), many of

[8] See Chap. 3.

Fig. 4.2 The staff of the biochemistry laboratory in 1930. Several persons mentioned in this book are in the *front row*: from the *left* D. Needham (*second one*), J. Needham next to her, J.B.S. Haldane (the *fourth*), next to him F.G. Hopkins and S.W. Cole. Stephenson is sitting second from the *right* next to Muriel Wheldale (Archive of the Department of Biochemistry, University of Cambridge. Picture reproduced with the permission of the Archive)

Table 4.1 Collaborators of Marjory Stephenson 1922–1948

Collaborators at the MRC Research Unit	20
Collaborators - Members of the Biochemistry Department	22
Loosely attached collaborators	10
Others	7
Total number of collaborators	58
Number of women collaborators	15
Percentage of women collaborators	26

The Table was compiled from the list of collaborators in Supplement 1

whom later became notable scientists or even Nobel Prize winners.[9] Personal testimonies suggest that people were eager to work with Stephenson also because of her personal qualities, working style and competence [14, p. 378; 18]:

[9]The list of Stephenson's collaborators in the Appendix is far from being complete, but may give us an idea of Stephenson's far reaching influence.

> Her great enthusiasm for chemical microbiology was infectious… her whole attitude towards scientific research was an excellent model for the beginner. Her insistence upon thorough and well-controlled experimental work and upon a really full investigation before rushing into print were a discipline that might well be followed by far more research supervisors. She was always far more interested that her young people should achieve a good training and sound experience than that her Unit should produce a constant flow of papers. […] She was never dictatorial about the research to be undertaken and was very happy for people to develop a research line of their own.**[…]** Not only her Ph. D. students but also many visiting research workers from abroad appreciate these qualities.[10]

> Another characteristic was that her name never appeared on a paper unless she had been responsible for a full share of the actual work at the bench. It is therefore difficult to assess completely her direct influence in the development of this subject [chemical microbiology] by reference to her papers alone; much more work published independently by younger members of her team was suggested by her and its successful prosecution made possible by her counsel and aid.

These remarks might imply that she did not care too much about writing up her results, but the wide-ranging bibliography of publications that stemmed from her laboratory testifies about the intensive experimental and publishing activity taking place under her guidance. By far not all of those papers were signed by Stephenson, even if she encouraged teamwork and participated in most experiments at least with inspiration and advice.

Over the first ten years of Stephenson's engagement with the MRC, a specific relationship had developed between Stephenson and her superiors. Stephenson was a loyal employee, hard working and dependable, but at the same time she always evinced a certain degree of autonomy in choosing problems to be investigated in her laboratory and selecting her collaborators (Fig. 4.3). On the whole, the correspondence between Stephenson and the MRC officials reflects mutual respect and appreciation of Stephenson's scientific accomplishments and services to the MRC. Her salary was regularly increased and special grants enabled to purchase adequate laboratory equipment.[11]

The MRC supported also some of Stephenson's study trips, like the one in autumn 1926 which she spent in Manchester with W.C.C. Topley[12] to acquire some basic microbiological techniques [21, p. 170; 22]. In 1926, Stephenson accessed along with other Hopkins' associates the 12th International Congress of Physiology in Stockholm, where Hopkins presented one of his conceptual lectures pleading for the establishments of specialized institutes of general biochemistry [23, 24]. There is no evidence about any Stephenson's paper delivered at the Congress [see 23], but in *Brighter Biochemistry* she (and the Needhams) humorously reported about their visit

[10]Robertson almost word for word quotes this letter in her obituary; see [19, p. 575].

[11]E.g. correspondence related to the purchase of Warburg manometers, see Mellanby to Stephenson, October 8, 1935; Stephenson to Mellanby 10 October, 1935; purchase of grinding mill, Stephenson to Mellanby 27 May, 1936, and others. MRC Archives 2036/2/I.

[12]William W.C. Topley (1886–1944), leading British bacteriologist and imunologist, established in 1927 at the University of Manchester probably the oldest taught postgraduate medical microbiology in the world [20].

Fig. 4.3 8th Annual Dunn Dinner 1934. F.G. Hopkins sits at the *head table*, next to him to the *right* Mrs. L.J. Harris and Boris Chain. Stephenson is at the *left table*, the second on the *right side*. One of MS's collaborators, L.H. Stickland, is the third at the *right table* (Archive of the Department of Biochemistry, University of Cambridge. Picture reproduced with the permission of the Archive)

at the Congress [25] and Stephenson's fictitious communication *On the Spontaneous Generation of the Fruit Fly out of Sterile Banana Pulp* which got so much attention that [25, p. 22]:

> other meetings were abandoned this morning…. and room could scarcely by found for the Royal Family, which had telephoned its intention to be present at so historic an occasion. The success of the meeting was greatly enhanced by the spectacular suicide of a geneticist, who… committed harikari with a micromanipulator at the conclusion of the address.

The article also caricatures Stephenson's leadership tendencies [25, p. 23]:

> At the Congress banquet […] one of us (M.S.) conducted the orchestra in the absence of the conductor, owing to illness… On the journey home the 'B.B' Travelling Fellows were able to demonstrate how valuable the man of science is to the community. […] the steamship rode into a storm […] The crew were soon washed overboard […] Dr. Stephenson made her way to the engine-room, where, in the short space of five minutes, she had everything under control.

To the USA Stephenson travelled, as far as we know, twice. In February 1931, she started to make plans to spend part of her holidays in America: "I hope to be able to acquire some new techniques and to get hold of some current line of research and especially to meet some workers", wrote Stephenson to Fletcher [26]. Her trip was well prepared also thanks to several letters of recommendation which Fletcher sent to his American friends asking them to assist Stephenson during her US stay. His letter to Henry Dakin[13] [27] may surprise us for its harsh criticism of Hopkins:

[13]Henry Drysdale Dakin (1880–1952), British born American biochemist.

> She [Stephenson] has an agreeable personality […]. She is really the permanent part of the little centre we have consistently tried to support under Hopkins upon bacterial chemistry. I will confess that I have never been satisfied with the degree to which work has been fostered by Hopkins or linked with the bacteriologists next door. But anyhow, Miss Stephenson has done her best.

During her journey July to October 1931 [28], Stephenson visited several laboratories in New York and Ithaca: "R. Chambers[14] in Washington Square, where I learnt the use of his micro-dissecting apparatus […] Dr. Morton Kahn of Cornell,[15] who is an expert in the application of the apparatus to the isolation of the single bacterial cell […]" Henry Dakin introduced her to Avery at the Rockefeller Institute (Fig. 4.4) and Heidelberger at the Columbia University[16] who showed her methods used to treat chemical problems of immunology, according the Stephenson "the most significant move in biochemistry now being made" [28]. Kohler highlighted the fact that the trip to the US possibly inspired Stephenson to start her programme of adaptation studies [21, p. 177]:

> In the fall of 1930 René Dubos[17] and Oswald Avery had discovered a most remarkable case of adaptation: a soil bacterium that produced, in the presence of a specific substrate, an enzyme that digested the capsular carbohydrate of type III pneumococcus. […] Stephenson was having long talks with the Rockefeller Institute group in November, when Dubos was writing up his work for publication, and within a month she was reading Karström's dissertation and recalling that she, too, […] may have witnessed a case of adaptation. Stephenson went to New York to get a technique; she returned with a big new research project.

In New York (probably at Avery's department), Stephenson met Hugh L.A. Tarr, a Canadian student from Montreal and invited him to work with her after he expressed a wish to "investigate biochemically the difference in two strains of the same organism exhibiting rough and smooth type colonies especially where such types show differences in pathogenicity" [28].[18] Stephenson suggested him

[14]Robert Chambers (1881–1957), American biologist who was pioneer in micrurgy (dissecting living cells); he invented the micromanipulator for "cell surgery". At the time of Stephenson's visit he worked at the New York University.

[15]Morton C. Kahn was a professor at Cornell University Medical College involved with public health and tropical disease.

[16]Oswald Theodore Avery (1877–1955), Canadian born American bacteriologist who presented the first strong evidence that DNA was the molecule of heredity; he worked at the Rockefeller University Hospital in New York. Michael Heidelberger (1888–1991) American immunologist, one of the founders of modern immunology who spent most of his career at the Columbia University in New York.

[17]René Jules Dubos (1901–1982), French born American microbiologist and humanist-philosopher. He researched on antibiotics, immunity and other topics; isolated antibacterial substances from soil microorganisms—this pioneering studies led to the discovery of several antibiotics. Dubos spent most of his career at the Rockefeller Institute for Medical Research in New York.

[18]It is only too well known that Avery through solving this issue in 1944, was first to unveil the role of DNA in heredity.

Fig. 4.4 Stephenson with Judith in front of the Institute. The large Dalmatian dog used to accompany her to the laboratory and became its favourite member (Archive of the Department of Biochemistry, University of Cambridge. Picture reproduced with the permission of the Archive)

"to adopt for this purpose the haemolytic streps [Streptococcus] associated with puerperal fever in view of the fact that the MRC was inaugurating and attack on this disease" [28]. This way she hoped perhaps to meet MRC's requirement to focus more on medical problems, but Tarr instead explored in Stephenson's laboratory biochemical reactions related to sporulation in Bacilli.[19]

[19]Tarr stayed several years at the Department but probably only experiments for his first paper [29] were done under Stephenson's direct supervision.

We have no details of Stephenson's other trips, like to Russia in 1936 and a "very successful riding tour with a group of friends in Hungary" [19].[20] In 1939 Stephenson attended the Third International Microbiological Congress in New York and accessed some laboratories at the Universities of Wisconsin and Iowa [30].

However, let us go back to the early 1930s. The MRC management was apparently quite satisfied with the results of Stephenson's American trip in 1931 which also was intended to stimulate the progress bacterial chemistry in England with which the MRC was greatly displeased [31]:

> "The impression made upon you about all this significant work in bacterial chemistry in U.S.A. is what I expected. It is the sort of activity and progress some of us fondly hoped ten and more years ago might be made in England, and not least in Cambridge. […] It saddens me to think that there is no work at all of this kind even beginning in either of the two great palaces for bacteriology in Cambridge and Oxford", wrote Fletcher in reaction to Stephenson's report. "Your own work […] is among the really bright spots that relieve the gloom elsewhere".

In spite of this flattering statement, however, Stephenson had to defend permanently the direction of her research that did not have, compared with the MRC's scheme, adequate ties to practical medical problems.

In 1930, when Stephenson and Stickland were studying anaerobic bacteria taken from the polluted River Ouse, "the MRC was somewhat bemused by her choice of work and Marjory received a letter from Sir Landborough Thomson (…) suggesting that this might be a matter for the Committee on River Pollution of the Department of Scientific and Industrial Research rather than MRC". Only thanks to Hopkins' support "she could tell MRC that he was fully in favour of her taking the work a little further before taking it to the Committee on River Pollution." [32] Fletcher in his letter of 1931 urged Stephenson to reduce the "purely abstract biochemical point of view" with a threat that the MRC will only support investigations that are "likely to assist the progress of medicine" [31]. In this point, however, MRC was evidently unjust to Stephenson as also reflects her readiness to cooperate with Dr. Florey in investigating lysozyme[21] and especially her collaboration with the MRC Unit for Medical Bacteriology founded in 1934 at the initiative of Fildes[22] at the Middlesex Hospital in London. Fildes' Unit was focused on pathogenic bacteria and function of antibacterial agents and soon between the teams of Stephenson and Fildes a close liaison had evolved in research into the nutritional needs and metabolic activity of bacteria. Fildes, who was Secretary of the MRC's Bacteriology Committee, suggested nominating Stephenson for

[20]The trip to Hungary was probably organized by her former colleague, the famous Hungarian biochemist Albert von Szent-Györgyi who was back in Hungary from his stay in Cambridge.

[21]Florey, Howard Walter (1898–1968), Australian born British pathologist know especially for his penicillin investigations. 1927–1931 he was at the Pathology Department in Cambridge, where he investigated antibacterial agents, especially lysozyme, discovered by Fleming in 1922.

[22]Sir Paul Fildes (1882–1971), foremost British pathologist and bacteriologist who devoted his life to the study of pathogenic bacteria, was author of the monumental *System of Bacteriology* published (1930–1931) by the MRC and founder of the *British Journal of Experimental Pathology*.

member of this Committee in 1934 [33], which further tightened the ties between the two Units.[23] In 1939, Stephenson recommended her pupil D.D. Woods to Paul Fildes. As evidenced by Woods' words, he accepted the new position [34, p. 688]:

> with alacrity…because it had always been Marjory Stephenson's philosophy that problems in our field would be most likely to be solved if attacked at all levels of investigation, which meant of course the nutritional and more biological approaches as well as the more purely metabolic ones I had used so far.[24]

In spite of Stephenson's apparent willingness to meet MRC's requirements, and regardless of verbal recognition of her work, permanent tension between Stephenson and her employer could have been sensed over the years. It often came through in daily operating problems. Due to the breadth of exacting research going on in her laboratory and a number of collaborative ventures, Stephenson badly needed technical assistance, but for many years the MRC had not considered important to provide the unit with adequate staff. Stephenson expressed her annoyance with this situation, for instance in her letter to Fletcher where she reacted to Fletcher's criticism regarding the absence of medical aspects for her research [38]:

> I do heartily agree about the necessity for justifying my existence by work with a medical trend but about my 'colleagues' that you mention I wonder whether we are a little at cross purposes; as a matter of fact since Miss Whetham departed I don't think the MRC has financed one; I never had more than one person working with or under me and for the past 2 years this has been Mr. L.H. Stickland who has drawn his money from other sources.

Although Stephenson repeatedly appealed for some paid assistance which she urgently needed,[25] it was only in 1937 that the MRC appointed her first full-time assistant E.F. Gale who eventually became Stephenson's successor after her death. This modest help was assigned to Stephenson after 15 years service with the MRC, when she had already acquired wide international reputation.

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[23]According to Woods: "…the fine record of this country [with regard to the development of bacterial chemistry in Britain] in the years between the wars did to large extent derive from the parallel development of the M.S. [Stephenson] group (working mostly on 'metabolic' lines) and of the Fildes' group (from the bacterial nutrition standpoint). The greatly accelerated rate of progress in recent years [that is after WW2] has probably resulted largely from the inevitable fusion of these lines of approach." [18].

[24]At Fildes's laboratory Woods' pioneering work on PABA was carried out. He discovered in 1940 hat the antibacterial action of sulfonamides is caused by the fact that they interfere with an essential metabolite necessary for the growth of the bacterial cell. This metabolite turned out to be the p-aminobenzoic acid (PAB or PABA) a hitherto unknown vitamin with which sulfonamides compete by reason of similarity of structure. When the drug "wins this competition" the bacteria stops to multiply. Woods' explanation was rapidly and widely accepted, and came to be known as the Woods-Fildes theory. The theory, later known as competitive inhibition, has become one of the principal concepts of modern chemotherapy and served as point of departure for the production of anti-metabolites [35, p. 207; 36]. It is necessary to add, however, that the theory was in reality a special application of the phenomenon which emerged from the paper of Quastel and Woolridge published in 1928 [37] as mentioned in Chapter 3.

[25]For instance [39].

A permanent source of disagreement between Stephenson and the MRC was also her undefined role as an informal head of the laboratory and the vague position of the laboratory within the MRC's structure. Stephenson's situation became untenable in the late 1930s when the MRC authorities put her in a responsible position and demanded results without formal authority of decision. As her position within the MRC and in the British scientific community strengthened, especially during World War II (her wartime activities will be treated separately), she more and more pressed upon the MRC for the official recognition both of the laboratory as a Unit and herself as its head. In March 1944 Stephenson in her letter to Sir Edward Mellanby, the successor of Fletcher at the MRC, asked whether it might be a good plan if papers from the unit were in future described as coming from the '**Medical Research Unit for Microbiology, The Biochemical Laboratory, Cambridge**' [40, 41] In the absence of a reply to the query, Stephenson and Gale went ahead with their plan [41]: Gale published a letter in *Nature* on 16 June 1945" [42] in which his affiliation was given as the MRC Unit of Chemical Microbiology, etc."[26] Other tactics Stephenson applied since 1944, was a demonstrative use of the unauthorized heading without the approval of the MRC on her reports to the MRC.[27] In addition, the report for the period October 1, 1945—September 1, 1947 was signed by Stephenson's name with the addition "Director of the Unit", while in the final version submitted by the MRC to the Parliament the "Director" was absent and the "Unit" remained intact [44]. Even more amusing is the correspondence on this matter disclosing the somewhat nervous reactions of the MRC as well as the University officials, to Stephenson's delicate but permanent insistence to be officially nominated Director of the Unit. J.T. Saunders, the Secretary General of the Faculties, University of Cambridge wrote to Landsborough Thomson, the MRC's Second Secretary, on 3 July 1945 [45]:

> Last term the General-Board decided to review the question of units and pseudo-units [sic!]. After the Board's review I shall be in a position to suggest what arrangements should be made to regularise Dr. Marjory Stephenson's position. I agree with you that it would be better to regularise the position because exception would certainly be taken by the University to the establishment of a unit by a process of infiltration.

Nonetheless, the MRC did not arrive to any concrete decision even after many-years lasting discussions.[28] Under the pressure of Stephenson's obstinate routine in using the terms "Unit" and "Director", the MRC representatives quietly surrendered at least at the level of semi-official correspondence. A few months before her death, she obtained a letter from Landsborough Thomson who wrote her that the Council does not object against the term "Unit", but the matter should be reconsidered by University authorities [48]. The problem passed like a hot potato between the University and the MRC, and the irrationality of the situation

[26]The address "Medical Research Council Unit for Microbiological Chemistry" had appeared in some modifications for several years also on other printed publications coming from the laboratory.

[27]The first of these held the date 30 September 1944 [43].

[28]See for instance [46–49].

demonstrates also the fact "that the words Medical Research Council Unit for Chemical Microbiology have long been painted on the door of her laboratory in the School of Biochemistry" [49]. Stephenson did not give up her campaign even facing death, like in one of her last letters announcing her final resignation because of advanced cancer: "Will you please accept my resignation from the directorship of this unit as from Christmas 1948" [50].[29] The answer of Mellanby indicates that the MRC finally gave up the battle [51]:

> I was very grieved indeed to see your letter of October 5th, offering your resignation from the directorship (sic!) of the Unit […] Would you agree to stay on, not as head of the unit, but in some part-time working capacity…?.

The MRC Minutes of 19 November 1948 stated Stephenson's "whole-time established appointment as director replaced from 1.1.49 by a part-time appointment at £500" [52] (See footnote 29).

We may only guess why the MRC hesitated for such a long time to grant Stephenson's laboratory the status of a unit and to appoint Stephenson for its Director. One of the answers could be the MRC's elusive discriminative policy toward women. In 1948 there was only one woman at the MRC who held the position of a Research Unit Director, namely Constance A.P. Wood,[30] Director of the Radiotherapeutic Research Unit in Hammersmith Hospital, London, one of the pioneers in modern cancer radiotherapy. The two other women in leading positions were casually called "Head of Research Group"—besides Marjory Stephenson this also included Ann Bishop[31] who was in charge of the Group for Research in Chemotherapy at the Molteno Institute of Cambridge University [53].

The MRC sometimes implemented even more open forms of gender inequality, like in the case of Dorothy Moyle Needham, prominent biochemist known for her pioneering work on the biochemistry of muscle. Dorothy and her husband Joseph Needham[32] belonged among those extraordinary scientific married couples whose social, personal and scientific lives were closely intertwined; they both started their careers with F.G. Hopkins and both had introduced new directions in biochemistry, some of them hand in hand, like embryology. In 1945, when the couple returned to Cambridge after their stay in China, Dorothy Needham received a grant from the MRC to work on the biochemistry of muscle contraction, but was repeatedly refused permanent position and her small personal grant had to be prolonged every year. The MRC officials were not willing to change their minds even after repeated interventions of prominent scientists like A.C. Chibnall (Hopkins' successor at the Biochemistry Department) or M. Dixon, and tried to justify their humiliating conduct by the MRC's policy, which "usually regarded married

[29]Underlined by SŠ.

[30]Constance Annie Poyser Wood (1897–1985), director of Radium Beam Therapy Research (RBTR), MRC Radiotherapeutic Research Unit (formerly London Radium Institute), 1934–1962.

[31]Ann Bishop (1890–1990), protozoologist and parasitologist; she examined chemotherapy for treatment of amoebic diseases. One of the few women Fellows of the Royal Society.

[32]There exist many biographies of Dorothy and Joseph Needham; see e.g. [54, 55].

women in rather a different light from unmarried and did not give them the full salary of the latter" [56]. The high proportion of women scientists and their frequent marriages with their colleagues at Hopkins' laboratory offered a dubious excuse to such attitudes. The undignified correspondence[33] in this matter continued until 1952, when the MRC even refused to renew Dorothy Needham's grant.

Let us add an epilogue of the many years lasting quiet struggle for formal recognition between Stephenson and the MRC. Even the official histories of the MRC misconstrue the facts of the above described occurrences. F.H.K. Green in his 1948 article on the origin, constitutions and functions of the MRC [53] calls Stephenson's laboratory "Group for Research in Chemical Microbiology", while the more recent voluminous history of MRC asserts that the Chemical Microbiology Research Unit was formally established in 1944 and its directors were Marjory Stephenson (1944–1948) and E.F. Gale (1948–1962) [2, p. 354]. In reality, in Stephenson's lifetime the Unit had never been officially established although many articles and documents bear the name of the Unit. Stephenson was never officially appointed Director, although she is attributed this title in various documents, as well. After Stephenson's death in December 1948, Ernest F. Gale, her successor, was immediately appointed Director of the Unit for Chemical Microbiology. The officially listed staff listed then two more people compared to 1947, that is 6 researchers with Ph.D. or M.A. [57]. The Unit was transferred to University of Cambridge in 1962 [2, p. 354]. Stephenson's work on microbial metabolism was followed up by her pupil Ernest H. Gale who became Professor of Chemical Microbiology in 1960 and remained a member of the department until his retirement in 1981 [58].

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Chapter 5
The Rise of Nazism in Germany and the Second World War

After the Nazis came to power in Germany in 1933, not only the careers, but also the lives of thousands of German academics, especially those with Jewish roots, became in serious peril. In a few years, the outbreak of World War II and the German occupation of most European countries evoked an unprecedented persecution and exodus of millions of people, including scientists and scholars of all nations. The British scientists were among the first in Europe who understood that not only science, but also the whole human civilization found itself on the edge of abyss and that fast action was inevitable.

"*Aid for Displaced German Professors*." Under this title appeared on June 3, 1933, in *The British Medical Journal* an article which announced the establishment of the organization which ever since has supported, funded and helped refugee academics from all over the world [1]:

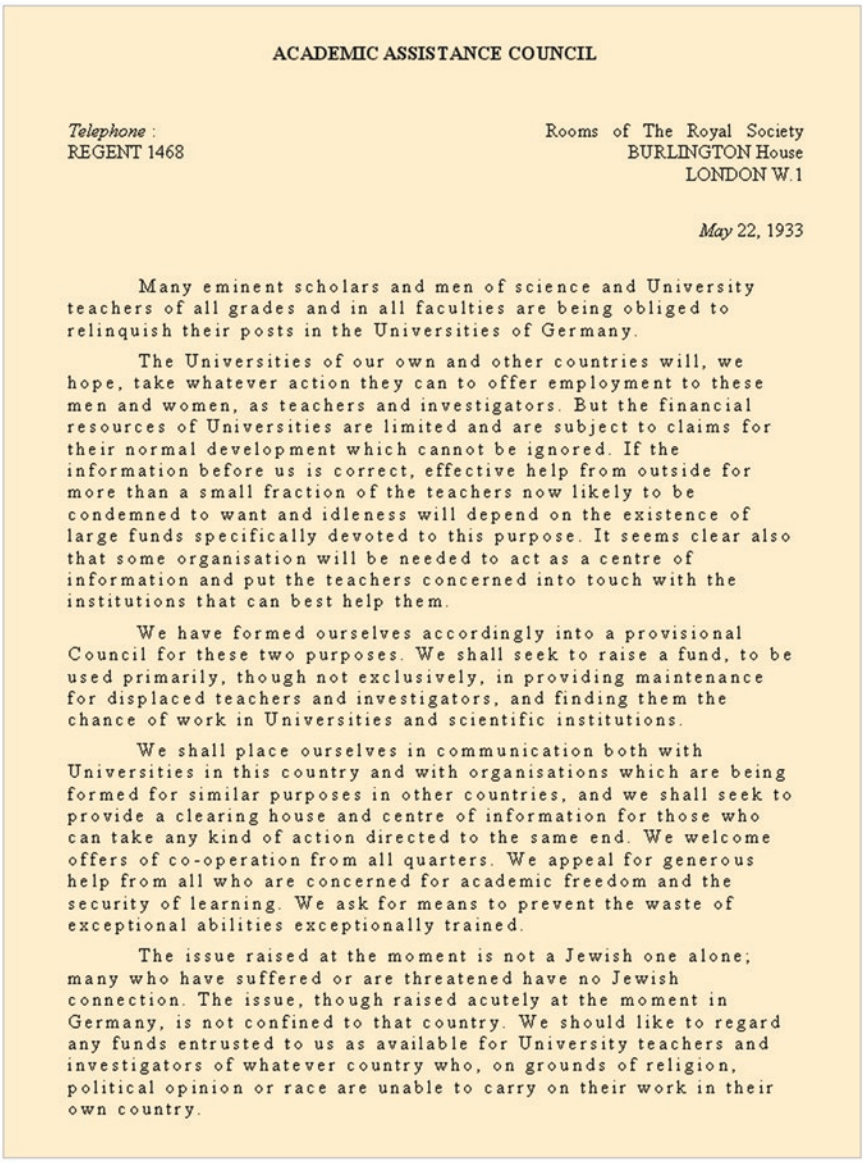
> A group of forty-one men and women holding high positions in the intellectual life of Great Britain have formed themselves into an Academic Assistance Council, and have issued a public appeal for funds to assist university teachers on the Continent who 'on grounds of religion, political opinion, or race, are unable to carry on their work in their own country.' […] The immediate concern of the council is to assist teachers and investigators who have been displaced under the present regime in Germany.

The *Academic Assistance Council* (AAC)[1] initiated by Lord Beveridge[2] was founded on May 22, 1933 (Fig. 5.1). The signatories of the founding statement

[1]In 1936 the AAC was transformed into the Society for the Protection of Science and Learning (SPSL); it was renamed in 1999 Council for Assisting Refugee Academics (CARA) which exists until today. Its current name since 2014 is Council for At-Risk Academics. For its history, as well as the experiences of post-war academic refugees see [12] where earlier literature is given, as well.

[2]William Henry Beveridge, 1st Baron Beveridge (1879–1963), British economist and social reformer.

S. Štrbáňová, *Holding Hands with Bacteria*, SpringerBriefs in History of Chemistry, DOI 10.1007/978-3-662-49736-4_5



ACADEMIC ASSISTANCE COUNCIL

Telephone :
REGENT 1468

Rooms of The Royal Society
BURLINGTON House
LONDON W.1

May 22, 1933

Many eminent scholars and men of science and University teachers of all grades and in all faculties are being obliged to relinquish their posts in the Universities of Germany.

The Universities of our own and other countries will, we hope, take whatever action they can to offer employment to these men and women, as teachers and investigators. But the financial resources of Universities are limited and are subject to claims for their normal development which cannot be ignored. If the information before us is correct, effective help from outside for more than a small fraction of the teachers now likely to be condemned to want and idleness will depend on the existence of large funds specifically devoted to this purpose. It seems clear also that some organisation will be needed to act as a centre of information and put the teachers concerned into touch with the institutions that can best help them.

We have formed ourselves accordingly into a provisional Council for these two purposes. We shall seek to raise a fund, to be used primarily, though not exclusively, in providing maintenance for displaced teachers and investigators, and finding them the chance of work in Universities and scientific institutions.

We shall place ourselves in communication both with Universities in this country and with organisations which are being formed for similar purposes in other countries, and we shall seek to provide a clearing house and centre of information for those who can take any kind of action directed to the same end. We welcome offers of co-operation from all quarters. We appeal for generous help from all who are concerned for academic freedom and the security of learning. We ask for means to prevent the waste of exceptional abilities exceptionally trained.

The issue raised at the moment is not a Jewish one alone; many who have suffered or are threatened have no Jewish connection. The issue, though raised acutely at the moment in Germany, is not confined to that country. We should like to regard any funds entrusted to us as available for University teachers and investigators of whatever country who, on grounds of religion, political opinion or race are unable to carry on their work in their own country.

Fig. 5.1 Founding Statement (first page) of the Academic Assistance Council (1933), today Council for At-Risk Academics (CARA Council for Assisting Refugee Academics, digitalised files)

The Royal Society have placed office accommodation at the disposal of the Council. Sir William Beveridge and Professor C.S. Gibson, F.R.S., are acting as Hon. Secretaries of the Council, and communications should be sent to them at the Royal Society, Burlington House, W .1. An Executive Committee is being formed and the names of Trustees for the Fund will shortly be announced. In the meantime cheques can be sent to either of the Hon. Secretaries.

Our action implies no unfriendly feelings to the people of any country; it implies no judgment on forms of government or on any political issue between countries; it implies no judgement on forms of government or on any political issue between countries. Our only aims are the relief of suffering and the defence of learning and science.

LASCELLES ABERCROMBIE	A.D LINDSAY
S. ALEXANDER	LYTTON
W.H. BEVERDIGE	J.W. MACKAIL
W.H BRAGG	ALLEN MAWER
BUCKMASTER	GILBERT MURRAY
CECIL	EUSTACE PERCY
CRAWFORD & BALCARRES	W.J. POPE
WINIFRED C. CULLIS	ROBERT S. RAIT
H.A. L FISHER	RAYLEIGH
MARGERY FRY	CHARLES GRANT ROBERTSON
C.S. GIBSON	ROBERT ROBINSON
M. GREENWOOD	RUTHERFORD
J.S HALDANE	MICHAEL E. SADLER
A.V. HILL	ARTHUR SCHUSTER
GEORGE F. HILL	C.S. SHERRINGTON
W.S HOLDSWORTH	GEORGE ADAM SMITH
F.GOWLAND HOPKINS	G. ELLIOT SMITH
A.E. HOUSMAN	J.C. STAMP
J.C. IRVINE	J.J. THOMSON
F.G. KENYON	G.M. TREVELYAN
J.M. KEYNES	

Fig. 5.1 (continued)

were distinguished British scientists, among them J.S. Haldane,[3] A.V. Hill, E. Rutherford, W.H. Bragg,[4] and also F.G. Hopkins who was highly aware of the seriousness of the political events. In the 1930s and 1940s the Council contributed to the rescue and placement of some 2600 scholars and scientists from Nazi Germany and Nazi- occupied Europe. Eighteen of them became Nobel Prize winners, and hundred and twenty were elected as Fellows of the British Academy or the Royal Society [3]. Under Hopkins's auspices fled Germany for Cambridge Hans Adolf Krebs, Ernst Friedman, Ernst Chain, Hans Weil, Max Rudolf Lemberg, Hermann Lehmann, Stefan Joseph Bach and other biochemists[5] who found their temporary or permanent asylum at the Biochemistry Department. The second wave of refugees hit Britain when Hitler annexed Austria and subsequently occupied Czechoslovakia and other European countries. Three Czechoslovak refugee biochemists Jan Herbert Waelsch, Arnošt Kleinzeller, and Kateřina (Katja) Sgalitzerová—Ošancová found haven in the Department of Biochemistry, Waelsch and Kleinzeller in Stephenson's laboratory.[6]

First in this long line of exile biochemists was Hans Krebs who had deliberated of fleeing to England immediately after he was placed on leave of absence from the Freiburg University on April 12, 1933 [7, p. 418]. According to Holmes, Krebs wrote to Hopkins a letter dated April 26, 1933, in which he asked him about the possibility of getting employment in Cambridge. "In the meantime", tells Holmes,

[3]John Scott Haldane (1860–1936) Scottish physiologist, researched the physiology of breathing. During World War I he invented the gas-mask.

[4]Sir William Henry Bragg (1862–1942), British physicist, inventor of X-ray crystallography. In 1915 he shared the Nobel Prize with his son William Lawrence Bragg (1890–1971).

[5]E. Friedmann (1877–1956), formerly professor of biochemistry University of Strassburg; H. Weil-Malherbe, neurochemist, friend of Krebs, adopted the name of his wife (Rosanne Malherbe), Krebs and Stephenson acted as witnesses to their wedding; M.R. Lemberg (1896–1975), biochemist, came from the University of Heidelberg, left for Australia, researched animal pigments; H. Lehmann (1910–1985) clinical biochemist and human geneticist, came from Kaiser-Wilhelm-Institute of Physiology in Heidelberg; S.J. Bach (1898–1973) did cancer research and investigated the metabolism of amino acids. Hopkins' institute probably embraced even more refugees than are mentioned in this chapter as suggest some names and dates in the list of Hopkins' collaborators and colleagues [4].

[6]Jan Herbert Waelsch (born 1909), was a biochemist, who worked with Stephenson in the years 1939–1941, but we have not much information about his background and further destiny. Arnošt Kleinzeller (1914–1997) got his Ph.D. with H. Krebs in Sheffield and in 1941 came to Hopkins' department, where he cooperated first with the Needhams and since 1942 with Stephenson. From 1943 till the end of the war he acted as advisor of the Czechoslovak exile government. In the after-war Czechoslovakia he became known especially for his research on cellular membrane transport. He emigrated again in 1967 and spent the rest of his life at the University of Pennsylvania [5]. Kateřina (Katja) Sgalitzerová—Ošancová (1920–2003) who also is on the list of Hopkins' associates, worked until 1943 at the Dunn Nutritional Laboratory with another Czechoslovak refugee biochemist Egon Hynek Kodíček (1908–1982) and John Yudkin. Since 1943 she also served the exile Czechoslovak government. After returning to Czechoslovakia, she became a highly regarded nutrition expert for the rest of her life. For more details on the Czechoslovak refugee biochemists see [6].

"Hopkins had written to Warburg[7] enquiring about the 'details' of Krebs's present situation" [7, p. 425]. In reality, it was Stephenson who wrote on April 25 a letter to Otto Warburg and expressed her concern about Krebs' fate (Fig. 5.2): "Several of my colleagues and myself would like to get in touch with your former student Dr. H.A. Krebs of Freiburg University…." She then asked Warburg for Krebs' address and "any particulars of his present situation. A very early answer would be of great service to us" [8].

Shortly after he was definitively dismissed from the University, Krebs landed in England on June 20, 1933 and eight days later settled in Cambridge [9, pp. 3–4]. He carried with himself also 30 Warburg manometers and "associated vessels" which started the "Manometry Period" in the Cambridge laboratory [11, p. 204][8] shortly before the time when Warburg's manometric method became the most widely used technique in biochemical laboratories. In 1934 Krebs got the position of University Demonstrator and remained in Cambridge until 1935 when he was appointed Professor of Biochemistry at the University of Sheffield. As Holmes reminds, Krebs got particularly well with Stephenson with whom he was most impressed of all the researchers in the Cambridge laboratory [9, p. 44]. "Marjory Stephenson was, in his view, not only a highly effective, imaginative investigator, but an extremely warm, friendly and helpful colleague" [7, p. 190]. He could judge her from his first-hand experience because in 1935, before he moved to Sheffield, he started to collaborate with Stephenson on the metabolism of bacteria. The question they attempted to resolve at that time with the aid of the manometric method was whether or not the action of hydrogenlyases (the enzyme group she discovered with L. Stickland) was reversible. These experiments were mutually beneficial for both as Stephenson was introduced to the manometric method, which then became a standard procedure in her laboratory, and Krebs became more familiar with the techniques used in the specialized subfield of bacterial metabolism. The experiments were carried on in cooperation with D.D. Woods, Stephenson's graduate student, who by application of the manometric method demonstrated the reversibility of the enzyme system

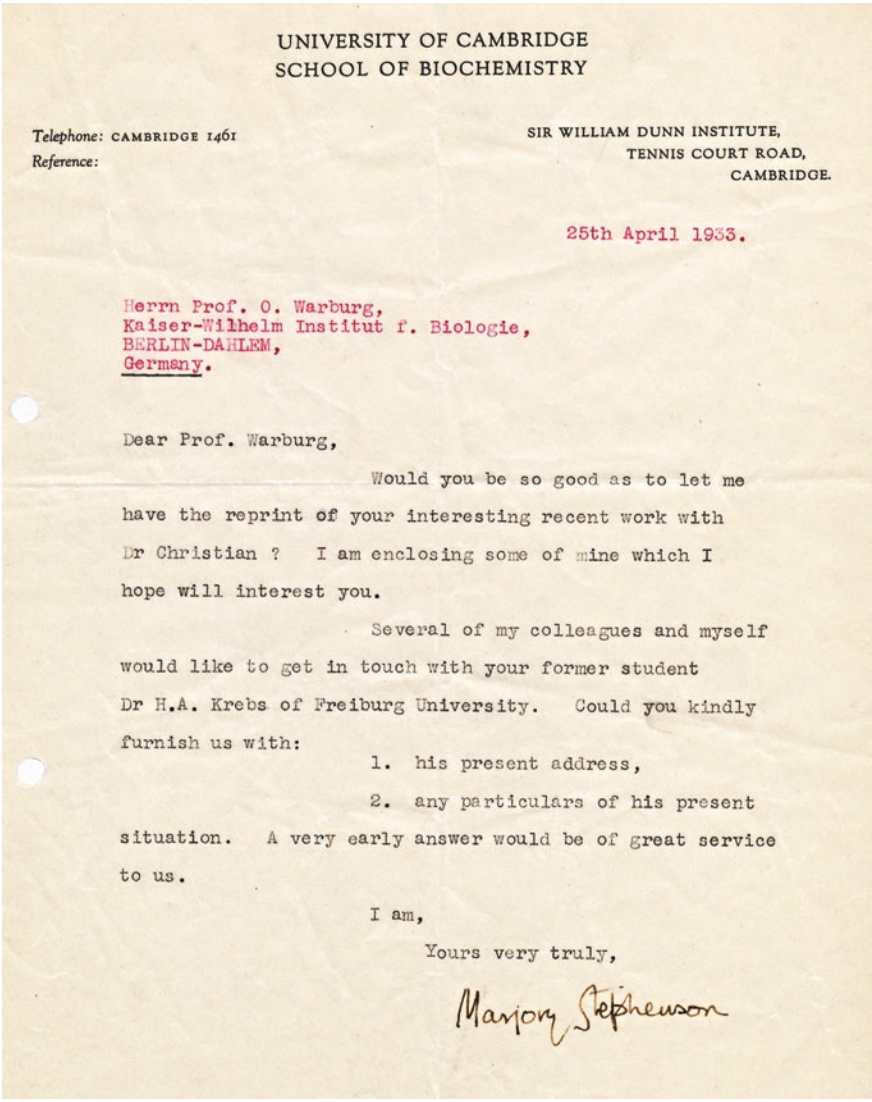
$$HCOOH \leftrightarrow H_2 + CO_2$$

and at the same time the phenomenon of carbon dioxide fixation in a biological non-photo-synthetic system [11, pp. 204–205].

Cooperation and warm friendship between Stephenson and Krebs was not interrupted even after Krebs left for Sheffield in 1935, as also evidenced by the correspondence between the two which was going on between 1936 and 1948 [12]. In 1936, Stephenson sent her student Sydney Elsden to spend five weeks "working under Krebs' supervision on problems relating to the formation of

[7]Otto Heinrich Warburg (1883–1970), belonged among the leading biochemists in Germany and worldwide. He was awarded Nobel Prize in 1931.

[8]Woods and Kleinzeller, formerly Krebs' student, belonged after the war to the leading exponents of the manometric method. Kleinzeller published in 1965 the comprehensive widely used manual of manometric methods with the introduction of Hans Krebs [10].



UNIVERSITY OF CAMBRIDGE
SCHOOL OF BIOCHEMISTRY

Telephone: CAMBRIDGE 1461
Reference:

SIR WILLIAM DUNN INSTITUTE,
TENNIS COURT ROAD,
CAMBRIDGE.

25th April 1933.

Herrn Prof. O. Warburg,
Kaiser-Wilhelm Institut f. Biologie,
BERLIN-DAHLEM,
Germany.

Dear Prof. Warburg,

Would you be so good as to let me have the reprint of your interesting recent work with Dr Christian ? I am enclosing some of mine which I hope will interest you.

Several of my colleagues and myself would like to get in touch with your former student Dr H.A. Krebs of Freiburg University. Could you kindly furnish us with:

1. his present address,
2. any particulars of his present situation. A very early answer would be of great service to us.

I am,

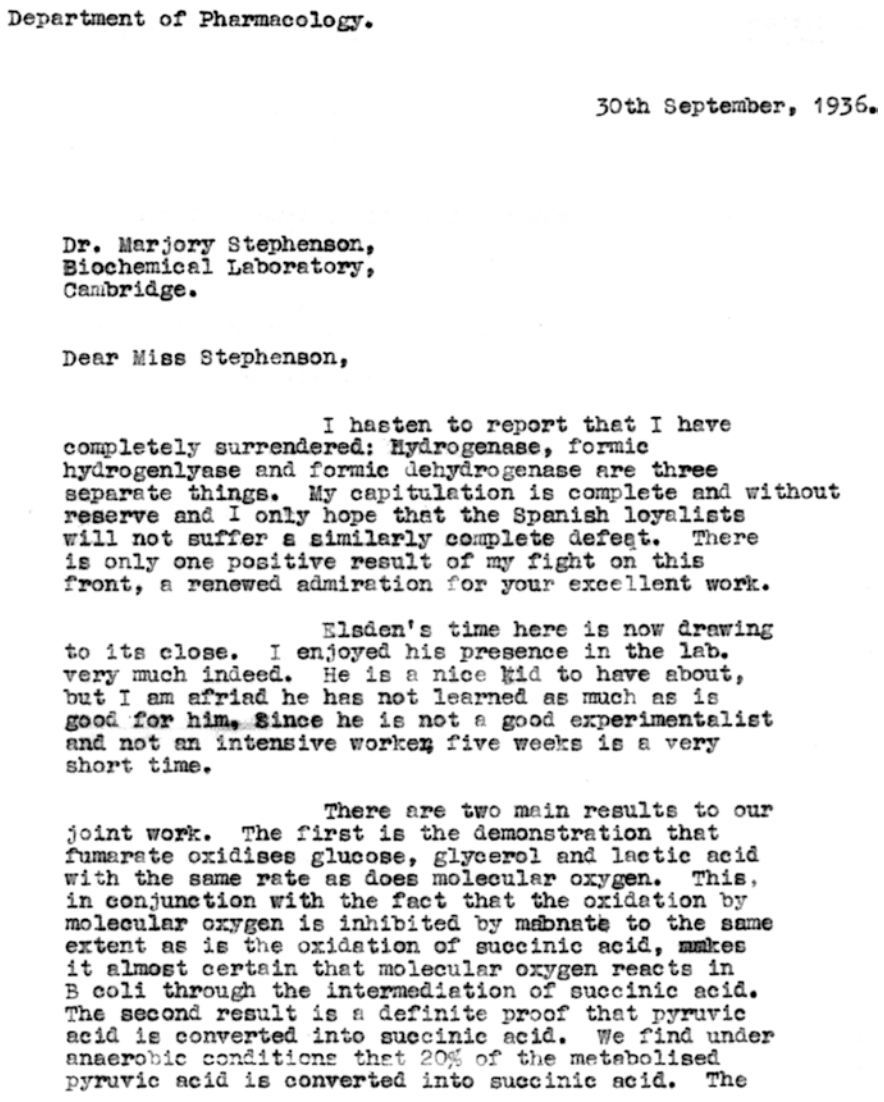
Yours very truly,

Marjory Stephenson

Fig. 5.2 Letter of Stephenson to the leading German biochemist E. Warburg dated April 25, 1933, in which MS expressed her concerns about the fate of Hans Krebs (Archiv der Berlin-Brandenburgischen Akademie der Wissenschaften. Image reproduced with the permission of the Archive)

succinic acid by various bacteria" [9], 319. Krebs in his letter of September 1936 (Fig. 5.3) admits half-jokingly that their experiments had confirmed some former Stephenson's results of which Krebs had had doubted about:

> I hasten to report that I have completely surrendered: Hydrogenase, formic hydrogenlyase and formic dehydrogenase are three separate things. My capitulation is complete and



Department of Pharmacology.

30th September, 1936.

Dr. Marjory Stephenson,
Biochemical Laboratory,
Cambridge.

Dear Miss Stephenson,

I hasten to report that I have completely surrendered: Hydrogenase, formic hydrogenlyase and formic dehydrogenase are three separate things. My capitulation is complete and without reserve and I only hope that the Spanish loyalists will not suffer a similarly complete defeat. There is only one positive result of my fight on this front, a renewed admiration for your excellent work.

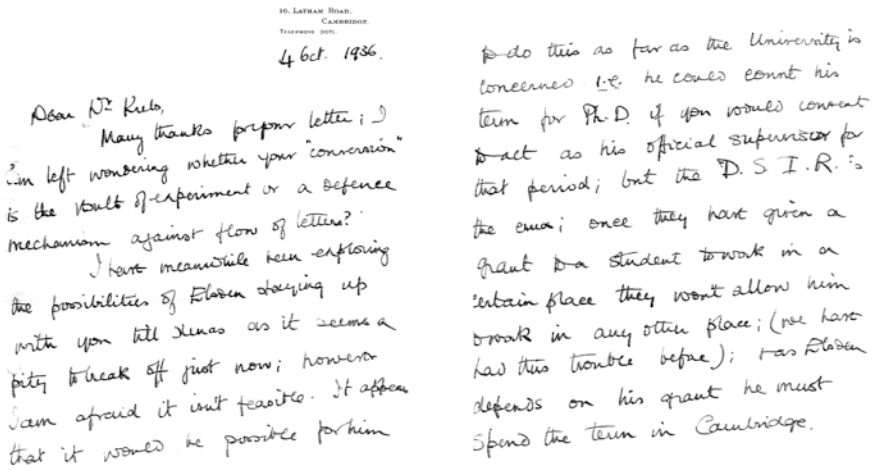
Elsden's time here is now drawing to its close. I enjoyed his presence in the lab. very much indeed. He is a nice kid to have about, but I am afriad he has not learned as much as is good for him, since he is not a good experimentalist and not an intensive worker; five weeks is a very short time.

There are two main results to our joint work. The first is the demonstration that fumarate oxidises glucose, glycerol and lactic acid with the same rate as does molecular oxygen. This, in conjunction with the fact that the oxidation by molecular oxygen is inhibited by malonate to the same extent as is the oxidation of succinic acid, makes it almost certain that molecular oxygen reacts in B coli through the intermediation of succinic acid. The second result is a definite proof that pyruvic acid is converted into succinic acid. We find under anaerobic conditions that 20% of the metabolised pyruvic acid is converted into succinic acid. The

Fig. 5.3 First page of a teasing letter of Krebs to Stephenson concerning the enzymes hydrogenase, formic hydrogenlyase and formic dehydrogenase (Krebs to Stephenson 30 September, 1936) (University of Sheffield, The University Archives Special Collections. Image reproduced with permission of Professor Lord Krebs and the Archives)

without reserve and I only hope that the Spanish loyalists will not suffer a similarly complete defeat.[9] There is only one positive result of my fight on this front, a renewed admiration of your excellent work.

[9]Allusion to the Spanish Civil War 1936–1939.


16, Latham Road.
Cambridge.
Telephone 3091.

4 Oct. 1936.

Dear Dr Krebs,
Many thanks for your letter; I am left wondering whether your "conversion" is the result of experiment or a defence mechanism against flow of letters? I have meanwhile been exploring the possibilities of Flosdorf staying up with you till xmas as it seems a pity to break off just now; however I am afraid it isn't feasible. It appears that it would be possible for him to do this as far as the University is concerned i.e. he could count his term for Ph.D. if you would consent to act as his official supervisor for that period; but the D.S.I.R. is the snag; once they have given a grant to a student to work in a certain place they won't allow him to work in any other place; (we have had this trouble before); Flosdorf depends on his grant he must spend the term in Cambridge.

Fig. 5.4 Joking answer of Stephenson concerning the enzymes hydrogenase, formic hydrogenlyase and formic dehydrogenase (Stephenson to Krebs 4 October, 1936) (University of Sheffield, The University Archives Special Collections. Image reproduced with permission of Professor Lord Krebs and the Archives)

Stephenson answers in a similarly amusing tone (Fig. 5.4): "I am left wondering whether your 'conversion' is the result of experiment or a defence mechanisms against flow of letters?" Krebs replied: "My conversion was genuine and the result of experiments" [13]. A description of the work follows.[10] From the correspondence in the subsequent years we can infer that Krebs frequently discussed with Stephenson his experimental and private matters and went to see her when visiting Cambridge.

In September 1938, just before the Munich Agreement, when Europe found itself on the threshold of the war, the staff of the Biochemistry Department held two emergency meetings which resulted in a document on "Work which should be undertaken in time of war" [14].[11] The document was presented to the authorities who were entrusted with the co-ordination of the expected war-time research: to the Secretary of the MRC A. Landsborough Thomson, and to the Vice-Chancellor of the University [15]. It contained proposals for research, using the Department's special skills that might be of service to the nation in case of war. In the first place was listed research work "on the use of micro-organisms for the production of substances of industrial or medical importance or for dietary purposes" and on "general problems of fermentation (cf. acetone and glycerine during the last war)." These tasks concerned especially Stephenson and her team.

[10]For details of the related experiments, see [9, pp. 313–328].

[11]The emergency meetings were held on Sept. 28 and Sept. 30, 1938 [14].

The outburst of the Second World War affected all aspects of academic life. The MRC, as well as the Cambridge Department of Biochemistry, were anxious, like most of the British institutions, concentrate all their resources in support of defence and war work. The operations of the Biochemistry Department became significantly affected as only about two of the academic staff was left, therefore some lectures and demonstrations were temporarily consigned to people further afield. Research activities shifted almost entirely to the wartime programme foresightedly prepared a year ago. The Department also joined new affiliates who were to become famous in the future. In 1940, Fred Sanger came on a Beit Memorial Fellowship and in 1943 Peter Mitchell became member of Dixon's team. Hopkins retired in 1943 and was succeeded by the plant biochemist Albert Charles Chibnall[12] who had been professor of biochemistry at the Imperial College. A typical consequence of the war was increased participation of women in academic and industrial life [16, p. 58]:

> There were Girton and Newnham graduates in almost every government department…. One of the social features most sharply distinguishing Britain from Germany….was the participation of women in the war effort.

The wartime activities of the Stephenson team were fully shifted to the needs of defence defined by MRC's official policy.[13] New knowledge in medical science, including microbiology and biochemistry, gained in the interwar time, and the well-established network of clinical and basic research units covering a wide range of fields, made the MRC well prepared to react to the wartime needs. The Council's strategy was to continue ordinary research work during the war as far as possible, but to adapt it increasingly to topics connected with warfare needs. In bacteriology, the diagnosis and treatment of wound infections was of special importance; particular attention was paid to gas gangrene and other infections caused by anaerobic bacteria, which do not grow or grow poorly in the presence of oxygen. The MRC emphasized in the first place healthcare, especially the various urgent measures in hospitals evoked by the war situation. This is evidenced by numerous memoranda issued by the MRC related to cross infection, prevention of gas gangrene, "hospital infection", etc. These actions were managed by the Preventive Medical Committee of the MRC and the respective sub-committees. Stephenson was invited by the MRC to become a member of its Committee on Chemical Microbiology. The significance of bacteriology increased during the war also thanks to the discovery of penicillin which became a wonder drug that helped the allies to win the war.[14]

Stephenson's organizing talent combined with her authority in the field of chemical microbiology and inexhaustible energy could be fully utilized during the

[12]Albert Charles Chibnall (1894–1988), British biochemist who specialized in plant biochemistry. He researched especially plant proteins. He was appointed in 1943 Sir William Dunn Professor of Biochemistry in succession to F. G. Hopkins, but resigned in 1949.

[13]For the MRC's activities during WW2, see [17], pp. 292–332.

[14]For detailed account of the history of penicillin see [18].

Fig. 5.5 Staff of Biochemistry Department in wartime 1943–1944. From the *left* E. Baldwin, D. Bell, D. Needham, A.C. Chibnall, M. Dixon, M. Stephenson, R. Hill (Archive of the Department of Biochemistry, University of Cambridge. Picture reproduced with the permission of the Archive)

Second World War. After Gale was awarded Ph.D. in 1939, Stephenson recruited a new assistant Ronald Davies who became one of her closest collaborators. Stephenson's report of work accomplished in the war years 1939–1945[15] indicates that the number of the laboratory staff subsequently increased to about 12 people paid by the MRC and from various grants. The laboratory also cooperated with members of the Biochemistry Department (Fig. 5.5) and various British institutions, like the Lister Institute, National Institute for Medical Research, Oxford University, Sheffield University, Edinburgh University and others. The working programme considerably changed compared to the past: even the so called basic research focused on possible medical or industrial applications. Ernest Gale with Helen Epps[16] and other associates, published in the years 1940–1945 almost 20 papers which dealt in large detail with the control of the formation of enzymes involved in the deamination of amino acids and reported about the discovery and

[15]The facts on the work of Stephenson's laboratory during World War Two are taken mostly from [19].

[16]Helen M.R. Epps (Mrs. Tomlinson) worked with Stephenson 1941–1945.

isolation of six enzymes—amino acid decarboxylases. They extracted and purified the co-decarboxylase from yeast and the "combined results obtained by this Department and the Cornell University U.S.A. showed that the coenzyme is identical with pyridoxal phospate" [19] (what we call today vitamin B_6). These studies, indeed, also had medical applications, for instance in treating wound infections by Clostridia and prompted Stephenson to call together "a number of workers with experience in the most varied aspects of pathogenic spore-bearing anaerobes (notably *Cl. welchii*) into an informal conference under the chairmanship of Professor Dalling in 1941." [20, p. 572]. The conference resulted in a decision to set up a group of specialist who would work on the group of pathogenic anaerobes.[17]

In 1940, Gale detected in the intestinal flora of infants suffering from neonatal diarrhoea a strain of streptococci possessing high activity of tyrosine decarboxylase. This finding contributed to better understanding the aetiology of neonatal diarrhoea whose epidemic erupted in the years 1941–1942 in several British hospitals. Due to this calamity, part of Stephenson's staff worked on a secret project of experimental rat diarrhoea. The top secrecy of the work is also emphasized in Stephenson's letter to J.G. Crowther written in 1941 [21]:

> I feel I must write and emphasize what I mentioned when you were with us last week that we work on Experimental Rat Diarhoea must not be mentioned to anyone as it has its origin from the Medical Services and is regarded by them as secret; any chat will involve us in serious trouble and destroy in prospect of further liaison with them.

Ernest Gale was integrated into larger interdisciplinary teams of microbiologists, biochemists and pathologists co-ordinated by Stephenson under the auspices of the MRC.[18] In the years 1941–1943 a major project directed by Stephenson aimed at developing active immunisation against gas gangrene,[19] in which workers of the Cambridge Institute of Animal Pathology (J. Keppie), National Institute for Medical Research, the Royal College of Surgeons, the Lister Institute (Muriel Robertson), and the Cornell University (USA) participated. Medical implications also had Stephenson's cooperation with Hugh K. King and the Czechoslovak refugee biochemist Herbert Waelsch on research into the action of urea as a germicide in connection with wound-healing [23] and the production of the enzyme urease in the *E.coli* strains causing cystitis (urinary tract infection).

The other projects directed by Stephenson concerned strategically important biotechnological production of organic compounds, namely solvents for the synthetic rubber industry (like acetone and butanol) and nutritives. The shortage of rubber and the "probable extension of the synthetic rubber industry stimulated

[17]Robertson who wrote about this meeting referred probably to Sir Thomas Dalling (1892–1982), British veterinarian, Chief Veterinary Officer for the United Kingdom in the years 1948–1952.

[18]To this issue relates extensive correspondence kept in MRC 2036/2/II, for instance [22].

[19]Members of the team from Stephenson's laboratory were W.E. Van Heyningen, R.N. Beale, E.E. Sampson, D. Herbert and P.H. Herbert.

M.S. to study the mechanism of butanol fermentation, with a view of increasing the yield of solvents" [24, p. 334]. Stephenson with Ronald Davies published 1941–1942 several papers on acetone-butyl alcohol fermentation in *Clostridium acetobutylicum* with promising results that would have enabled biotechnological production of acetone on a large scale. However, correspondence of Stephenson with Krebs [28–35] (who enthusiastically supported her attempt to implement the research findings into practice) and Mellanby [36][20] suggests that Stephenson could not push through either patenting the acetone production by fermentation or its industrial production perhaps due to inflexibility of the MRC and the government officials. "You are right", writes Krebs in one of these letters [28], "no one seems to have the initiative. In my experience the worse offenders are not the politicians or administrators but scientists, inside and outside the Government. They are afraid of making fools of themselves, or of being accused of defeatists attitude if they support measures that might possibly prove unnecessary." The disinterest of the industries was another reason why the acetone project failed. In Krebs' words: "the industries concerned, especially the Distillers Company, Ltd. are far too powerful […]. These firms, of course, do not want any outside interference with their business and the work in their scientific laboratories." [32].

In the nutrition part of her biotechnological programme Stephenson also engaged the Czech refugee biochemist and medical doctor Arnošt Kleinzeller who came to her laboratory in 1941 after he got his Ph.D. with Krebs in Sheffield. It was his own idea [37] to study with Stephenson and R. Hill[21] the fat metabolism and fat formation in the food yeast *Torulopsis lipofera* [38] as part of the wartime research which was exploring alternative sources of nutrition also in metabolic products of microorganisms. Linked to nutrition was also Stephenson's contribution to a project of microbiological assay of vitamins of the B group where she participated in large-scale trials of various methods. "She did not enjoy this work, though the full-cream dried milk left over from the experiments was some compensation" [24, p. 334].

Even this short survey can convince the reader about the remarkable productivity of the teams directed by Stephenson during the war. Such broadly conceived endeavour was vital for the success of the fight against disease and famine in time of the war and Britain's defence against the threat of German invasion as emphasized by Stephenson: "Every bit of conjoint work of this kind […] has […] a twofold value; (1) its own and (2) as an advance on the 'get together' front, which is the only hope of solving the difficulty of increased technical specialisation." [39]

[20]In Stephenson's letter to Mellanby dated October 20, 1941 [29], we may find an intriguing remark witnessing the wide scope of Stephenson's contacts: "You may be interested to hear that the mysterious group of workers Dr. Fox and Professor Heilbron referred to as "Grosvenor" is Professor Weizmann's" (Chaim Weizmann, 1874–1952, biochemist and Zionistic politician who lived in England and in 1948 became the first Israeli President).

[21]Robert Hill (1899–1991), plant physiologist and biochemist from the MRC Unit of Plant Biochemistry in Cambridge.

Fig. 5.6 John Yudkin with his wife Milly and Milly's parents in Cambridge c. 1934. From *left* Selma Himmelweit, John, Milly, Felix Himmelweit (Personal archive of Prof. Michael Yudkin. Image reproduced with permission of Prof. Yudkin)

This "get together" also had great moral importance in the most difficult years of the Second World War. We should not forget, however, of the humanistic aspect of her wartime activities. She was helping wherever she could, unpretentiously and discreetly, so that even her various biographies do not mention many instances of people in need whom Stephenson lent her hand. About Stephenson's humanitarian ideals writes Robertson [20, pp. 567–568]:

> The tyranny and oppression of scientific workers, particularly of the Jews, that began in Germany in 1933 after the accession to power of the Nazis, were extremely repugnant to Marjory Stephenson's generous nature. There was also an almost unconscious liberalism of outlook which no doubt belonged to the principles in which she had been reared, that made her to resent the absence of mental freedom for others just as much for herself. She was, therefore, an active and helpful person in getting support for refugee scientists…

Professor Michael Yudkin,[22] son of Stephenson's collaborator John Yudkin [40], told me the story of his parents and grandparents (Fig. 5.6). In 1933, John Yudkin married Michael's mother Milly Himmelweit, a young German-Jewish girl, who had recently escaped with her parents from Berlin when the Nazis came to power [41]:

> I think I didn't tell you, however, that when my mother and father married in 1933, my father was only 23 years old, and MS [Stephenson] offered to let them stay in her house

[22]Michael Yudkin (born 1938) is Emeritus Professor of Biochemistry, University of Oxford.

for a while. My mother's mother and father[23] arrived in England from Berlin in the summer of 1933, and while they were living temporarily in London, started to build a house in Cambridge where my parents would live on the ground floor and my grandparents on the first floor. But for some time until the house was ready my parents were living in MS's house. I think in a way MS thought of herself as a senior member of my father's family—to say she regarded herself as his mother would be an exaggeration, but perhaps as an aunt—and was happy to 'look after' the young couple and help them. I am sure too that MS was very much aware of the problems of Jewish refugees and was deeply sympathetic to the situation of my mother and her parents.

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Chapter 6
Post-war Activities. Recognition and Honours

After Hopkins' retirement in 1943, A.C. Chibnall, Professor of Biochemistry at Imperial College, was appointed head of the Department of Biochemistry. One of his first moves was to change its loose internal organization and "establish formal sub-departments of enzyme biochemistry under Malcolm Dixon, and chemical microbiology under Marjory Stephenson" [1, p. 427]. In January 1944, quite long before the end of the war, Chibnall compiled a memorandum [2] in which he analyzed the present situation in biochemistry and its implications for the future development of the Department after the end of the war. He stated that the war research in biochemistry had

> "shifted appreciably in favour of the U.S.A. to an extent that cannot but cause uneasiness to those in Great Britain responsible for the training of students and research workers, and for initiation of research. It is vital therefore that in the immediate post-war years a determined effort should be made to reassert the position of Great Britain in this new and flourishing science" and to re-establish fundamental research "which have had to remain dormant […] on account of war work."

Chibnall paid in this context separate attention to the situation in chemical microbiology which

> has now reached that stage of advancement when it is directly applicable to veterinary science, agriculture and industry. This is the outcome of work done during the last twenty years on fundamental problems of microbiological […] chemistry, much of what has been done in this Department.

Such rewarding results had been obtained, as pointed out by Chibnall, in spite of the fact that the "microbiological group here has so far consisted of one permanent worker only [Stephenson, SŠ], who is a member of the scientific staff of the M.R.C., and who has acted as Director [sic!] to a group of research workers at various levels", supported from various sources. "Hitherto the University has given no official recognition to this subject [chemical microbiology] in spite of the "demand for microbiological workers trained in biochemical methods", which

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"has been intensified by recent successes in the biochemical attack on bacteriological and immunological problems." Hence "the contemplated expansion in the programme of teaching and research needs provision for more than double the existing accommodation" [2, p. 3].

Chibnall's memorandum reflected the fact that the new field of chemical microbiology had become increasingly recognized not only among biochemists and microbiologists, but also in medical and industrial sphere, and quite unexpectedly also in political circles. Shortly after the war, a Parliamentary Advisory Committee was set up to investigate why penicillin, a British discovery, was further researched and eventually produced in the United States. It stated that Britain had lacked specialists trained in both chemical and biological handling of microorganisms and to bridge this gap, a centre should be established which would offer training for students and advanced research into the biochemistry of microorganisms. Sir Paul Fildes, who was a member of the Committee, suggested that Marjory Stephenson and her group associated with the MRC Unit for Chemical Microbiology in Cambridge could provide a suitable base for such development [3, pp. 154; 4, p. 79–88]. This decision foreshadowed the expansion of chemical microbiology in Cambridge. In 1947 was built from the money of the Rockefeller Foundation,[1] government funds and the MRC[2] a new modest temporary edifice nicknamed the "Bug Hut", which stood behind the Biochemistry Laboratory. Stephenson moved here with E.F. Gale, R. Davies, J. Tosic,[3] two technical assistants and a few research students [5, p. 82].

In the few years left to her, Stephenson continued her research and training a new generation of microbial biochemists. Among her students was Peter D. Mitchell, the future Nobel Prize winner, who had failed to defend his first unconventional Ph.D. thesis in 1948[4] and then received his Ph.D. in 1951 under Gale's supervision for a much more conformist work on the mechanism of action of penicillin.[5] Between Mitchell and Stephenson had developed a mutually appreciative relation, which influenced Mitchell's future career, more than it is generally known. Stephenson intervened twice in Mitchell's career. In 1948 she was organising a meeting on the bacterial surface for 1949 and asked Mitchell, though still a graduate student, to give a major talk, in which he identified the osmotic barrier of bacteria

[1]In 1946 the Rockefeller Foundation gave the Department a grant of total $ 9500 to build two "huts"—the "Bug Hut" and the "Protein Hut", "with the proviso that the equipment be bought in the United States" [5, p. 82].

[2]For some details on the preparation of construction see [6].

[3]According to [7], Tosic, researcher from Yugoslavia, was at the Unit only from August 1949. This is a mistake since MS mentions in her letter to Elsden written on 11 March 1947 that Tosic left for Edinburgh. However, Stephenson's remark hints that Tosic might have been in the "Bug Hut" only shortly.

[4]That time he was Ph.D. student of J.F. Danielli [8].

[5]Mitchell became known not only for his scientific achievements, but also by his non-traditional way of life as independent researcher in his private laboratory built in a mansion in Cornwall. His only co-workers were the biochemist Jennifer Moyle (born 1921) and one technician [8].

with their cytoplasmic membrane, a topic which he afterwards pursued throughout his scientific life. According to Weber [10]:

> Stephenson did not live to preside at this meeting, but before she died she intervened again in Mitchell's career in a way that had a lasting effect. She suggested that Jennifer Moyle, who was a research assistant in her laboratory,[6] work with Mitchell. This began a formidable and productive collaboration that lasted, with one brief interruption, until Moyle's retirement in 1983. Both Mitchell and Moyle felt that Stephenson had real insight into their unique and complementary strengths, Mitchell as an imaginative and brilliant theorist and Moyle as a meticulous and superb experimentalist. Together they pursued a line of research on bacterial transport informed by Mitchell's increasingly more precise and articulated theoretical speculations and tested by Moyle's careful experimentation.

The fame of the laboratory also attracted foreign students like the Canadian-American Roger Stanier who became one of the most influential post-war microbiologists.[7]

In 1947, after complicated negotiations, the subject chemical microbiology was recognized by the University as a discipline in its own right and Stephenson was appointed the first University Reader in Chemical Microbiology. She set up a special new third-year Part II course in Chemical Microbiology which used the third edition of her *Bacterial metabolism*, as the main text for the subject. As H.H. Dale[8] explained to the University's Vice Chancellor H. Thirkill in a letter written in 1947,[9] the introduction of the new discipline at the University had been motivated among other things by the great and growing national need "[…] for scientists who have had a training in the fundamental science suitable to equip them for research in the general field of microbiology, with its growing range of technical applications".

Towards the end of her scientific career, Stephenson's research was limited to two topics. First was the production of acetylcholine during fermentation of plant juices by lactobacilli. She attacked this problem jointly with E. Rowatt and K. Harrison by studying sauerkraut fermentation. Stephenson and Rowatt identified the bacteria which during fermentation produced acetylcholine as *Lactobacillus plantarum*, and made a full study of its biochemical behaviour. This was Stephenson's last article published in her lifetime [14].

Stephenson's final project was rooted in the pre-war period when she had decided to undertake a general investigation of the function of nucleic acids in bacterial metabolism as she rightfully anticipated the significance of this group of

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[6]Jennifer Moyle was a biochemist, sister of another biochemist Vivian Moyle. She came to work with Stephenson in 1947 as follows from Stephenson's letter to Elsden dated 11 March 1947: "I have a sister of Miss Moyle for my assistant and could ask nothing better" [9].

[7]Roger Y. Stanier (1916–1982) [11, 12].

[8]Sir Henry Hallett Dale (1875–1868), British pharmacologist and physiologist, 1936 Nobel Prize Winner. H.H. Dale was at that time President of the Royal Society and member of the Scientific Advisory Committee to the Cabinet.

[9]The letter belongs among the correspondence reprinted in [13]; the documents reflect the complexity of one year lasting negotiations.

compounds. Stephenson's and Trim's paper of 1938 on the metabolism of adenine compounds [15] remained, however, isolated as she had to focus on her war-related research, and she only could return to this exciting topic after World War II. Her first post-war report to the MRC suggests that she had planned detailed metabolic studies of nucleic acids: "Work is in progress on the changes occurring in the nucleic acids of the bacterial cell in various metabolic conditions." [16] Together with her assistant Jennifer Moyle, the future closest co-worker of Peter Mitchell, she investigated the breakdown of nucleic acids by cellular enzymes and prepared some of these enzymes in cell-free condition "I have got on to the most interesting piece of research I have ever done and where it's going to turn next I just don't know", wrote Stephenson to Elsden in 1947 [17] about her very last piece of work which has never been published.[10]

On 22 March 1945, Marjory Stephenson and Kathleen Lonsdale[11] became the first two women elected Fellows of the Royal Society. Most Stephenson's biographers pay only little attention to this achievement, although it represented a real historical breakthrough at the times when substantial barriers still impeded election of women to national academies of sciences in Europe and overseas. Joan Mason has shown in her detailed account [19], that the act of election was culmination of a lengthy process commenced by the campaign of J.B.S. Haldane[12] in 1943 which had evoked two years lasting heated discussions in the British scientific community related to the very nature of conservative traditions, democratic principles, prejudice and discrimination against women scientists in the academic world. Stephenson's name was from the very beginning at the top of the list of the potential candidates, supported not only by Haldane, but also by Henry Dale, F.G. Hopkins and others. According to Haldane [19]:

> I think that the strongest claim is that of Dr. Marjorie [sic!] Stephenson who was the first person in the world to do work on bacterial metabolism as exact as that on mammalian metabolism, and who has continued to do good work in this field, discovering, for example, a number of new enzymes, in particular those dealing with the production and consumption of hydrogen.

Obtaining the most prestigious British scientific title must have brought Stephenson great satisfaction, but as pointed out aptly by Elsden and Pirie she probably had mixed feelings about this award [20, p. 337]:

> "As a feminist she was pleased when the old anomalous rule that women could not be Fellows of the Royal Society was abolished and she was human enough to be gratified that she was one of the first to be admitted." In general, however, "she was unsparing in

[10]Woods [18, p. 383] refers to a paper of Stephenson and Moyle published in the Biochemical Journal in 1949, but I could not find it in any number.

[11]Kathleen Lonsdale (1903–1971) was a crystallographer, pupil of W.H. Bragg, first woman tenured professor at the University College London. She was a pioneer in the use of X-rays to study crystals.

[12]John Burdon Sanderson Haldane (1892–1964), British physiologist, geneticist, evolutionary biologist and mathematician, one of the greatest thinkers of his time.

> her condemnation of secretiveness, personal vanity and competitiveness in scientists and for this reason jeered at most of the medals and awards that scientists on occasion confer on one another. […] Each year when a new list of Fellows was published she would remark '…that means a few more scientists can settle down to their work instead of fussing about their reputations'. In this context another comment of hers should be preserved: 'These young men fuss about their reputations as if they were ageing virgins in a Victorian novel.' "

Stephenson's position of a worldwide recognized leader in her field highlights her invitation in 1946 to the International Congress of Pasteurian Sciences in Paris [21] commemorating the 50th anniversary of Pasteur's death; this was also a celebration of the reunion of French scientists with their foreign colleagues after the years of occupation. Among the invited honorary guests were, for instance, W.A. Engelhardt[13] from Russia, a number of British scientists (B.C.J.G. Knight,[14] J.D. Bernal,[15] E.B. Chain and others), Ø. Winge from Denmark, J. Quastel representing Canada, A.J. Kluyver[16] from the Netherlands, Marc-Henri Van Laer[17] from Belgium, the Americans M. Heidelberger and W.M. Stanley and others [21] Stephenson in her talk entitled "The Debt of Biochemistry to Biology" [22] demonstrated the extraordinary capacity of microorganisms to serve as model organisms for biochemical investigations and contribute to the progress of biochemistry. "It is in the study of intracellular mechanisms that microorganisms provide such convenient material for biochemical investigation" [22, p. 138]. Her conclusion where she anticipates the future directions of biological sciences enabled by the progress in biochemistry of microorganisms sounds almost prophetic [22, pp. 139–140]:

> The outlook for the progress of the twin sciences of biochemistry and microbiology has never been brighter. We are now moving with the same velocity as in the Golden Days of Pasteur, but at a different level. This is due not only to the impetus given by the development of new technical methods […] but to a change in the most important of all tools, the mind of the scientist. […] We have now reached the stage when the biochemist feels ready to attack any type of biological problem. The realisation that the border-line between the living and the non-living is very blurred encourages the attack on the chemical processes involved in growth and heredity, an attack already begun. This stage would certainly have been reached much more slowly if at all, had not the biochemist had to his hand the flexible and tolerant material presented to him in the form of the microbial cell.

[13]Wladimir Alexandrowitch Engelhardt (1894–1984), foremost Russian biochemist, whose studied led to the concept of ATP as universal source of energy in the cell.

[14]Bert Cyril James Gabriel Knight 1904–1981, British microbiologist known for his work on bacterial nutrition and as the editor of the Journal of General Microbiology.

[15]John Desmond Bernal (1901–1971), British scientist, pioneer in x-ray crystallography and molecular biology, philosopher and thinker with controversial political positions.

[16]Albert Jan Kluyver (1888–1956), Dutch microbiologist and biochemist. More on him in the next chapter.

[17]Marc-Henri Van Laer (1893–1951), Belgian microbiologist involved in research into fermentation.

It appears that Stephenson much enjoyed her trip to Paris, but the honours and ceremonies seemed to her ridiculous. In her letter to Sidney Elsden she unleashed her love of gossip [23]:

> Paris was the greatest possible fun. The Etat did us proud (too proud!) we lectured ourselves (mine you will be surprised to learn was considered a success) & listened to interminable speeches, accessed ancient monuments in Paris (also the Opera); Vallery-Radot[18] must have delivered himself of 20,000 words at least; we went down to Dole & Arbois in a special train & laid endless wreaths on statues of Pasteur (birthplace and childhood home), got in 2 banquets within 14 h & as this district is a noted centre of wine industry I leave you to imagine the effect on the congresistes; in the special train coming home Knight established a local Black Market in bismuth and bicarbonate […]. Fildes distinguished himself by being v. cross [tiny "smiley" picture of Fildes]. 1. he was not invited to speak & 2. at the Paris banquet he was not at the High Table ('who—are—all –these—fellers in—places—of honour—boom—boom'); he relieved his spleen by telling to Gale & ? scurrilous gossip about Pasteur. Really he is[19] rather an old horror.

Although in the final years of her life (Fig. 6.1), as we also will see in the next chapters, Stephenson has gained the recognition she deserved, she did not fully enjoy her new situation not only because of her serious illness hanging over her head as a sword of Damocles; she was apparently unhappy and concerned about the developments in the Department which under Chibnall's management was on decline and losing its leading position, as she confided to Elsden in January 1947 [24][20]:

> I am worried about the Department, it is beginning to disintegrate owing to the absence of a real Professor. People come here to work and no one knows they are here or what they are doing and no one knows what anyone else is working on or whom to discuss his problems or difficulties with: Dophi[21] and I are trying to organise a series of coffee parties or some other device for putting people in touch. Malcolm[22] is only useful as a methodologist; but something will have to be done. I wish you would come home.

A few months later she complained again [26]:

> The lab goes from bad to worse; Wing [?] the new store keeper is now returning to Zoology whence he came and Baker threatens similarly; Chibs[23] droops more than ever and does nothing about anything. I now look forward to Joseph's return[24]; he is our only hope.

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[18]Louis Pasteur Vallery-Radot (1886–1970), French physician, grandson of Loius Pasteur, his biographer and editor of his complete works.

[19]Underlined by Stephenson.

[20]Elsden was at the time working in America. See also [25] where she talks about the biochemistry teaching as "disaster".

[21]Nickname of Dorothy Needham.

[22]Malcolm Dixon (1899–1985), British biochemist.

[23]Albert Chibnall.

[24]Joseph Needham was since 1942 in China as the Director of the Sino-British Science Co-operation Office.

Fig. 6.1 M. Stephenson and D. Needham in 1948, on the occasion of the assumption of the Chancellorship of Cambridge University by General J. Smuts (1870–1950) (Archive of the Department of Biochemistry, University of Cambridge. Picture reproduced with the permission of the Archive)

Noteworthy testimony of this unfavourable atmosphere in the Biochemistry Department is offerred to us by the biographer of Roger Stanier [11, p. 256]:

> …it was with relief that in 1945 he [Stanier] accepted a Guggenheim Fellowship to work in Marjory Stephenson's laboratory in Cambridge. He must have had high hopes indeed of that visit; his wish, yet again, to improve his knowledge of biochemistry was probably fortified by tales related by his mother of that ancient University as a fount of culture as well as of distinguished science. It is evident that he was personally disappointed by what he found there. Perhaps, with Britain only just emerging from the traumas of the war, life in an unusually austere Cambridge with its shortages of food and fuel was less than attractive to a visitor from North America.

Elsden commented that the situation in the Biochemistry Department as caused by poor quality of the organic chemistry and the worry that "the Biochemistry was scared of being 'eaten' by Todd[25] who, incidentally had been offered the Chair of Biochemistry, but had been 'encouraged' to turn it down" [27]. Nevertheless, the essence of the problems lay apparently elsewhere, namely in the post-war multifaceted changes in the whole field of biochemistry associated with its transformation into molecular biology. The golden era of Hopkins' dynamic biochemistry was over and for the time being, the new leadership could not offer any vision or strategy that would have reacted to the onset of ground-breaking changes and enlivened the Department's declining intellectual activity.[26]

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[25]Alexander R. Todd (1907–1997) organic chemist, Nobel Prize Winner 1957.

[26]Chibnall resigned from the chair in 1949; the official reason was that he wanted to concentrate more on research, but apparently he was disinterested in the concept of dynamic biochemistry as coined by Hopkins and could not offer a new one instead [1, pp. 427–428].

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Chapter 7
From Chemical Microbiology to General Microbiology

Most biographers acknowledge Stephenson for opening and establishing the new interdisciplinary field of chemical microbiology. Let us look at the main stages of Stephenson's work which in the years 1930–1948 stimulated formation of chemical microbiology and simultaneously also general microbiology [1], on the boundary of biochemistry, microbiology and bacterial physiology.[1]

7.1 The Bacterial Metabolism Monograph

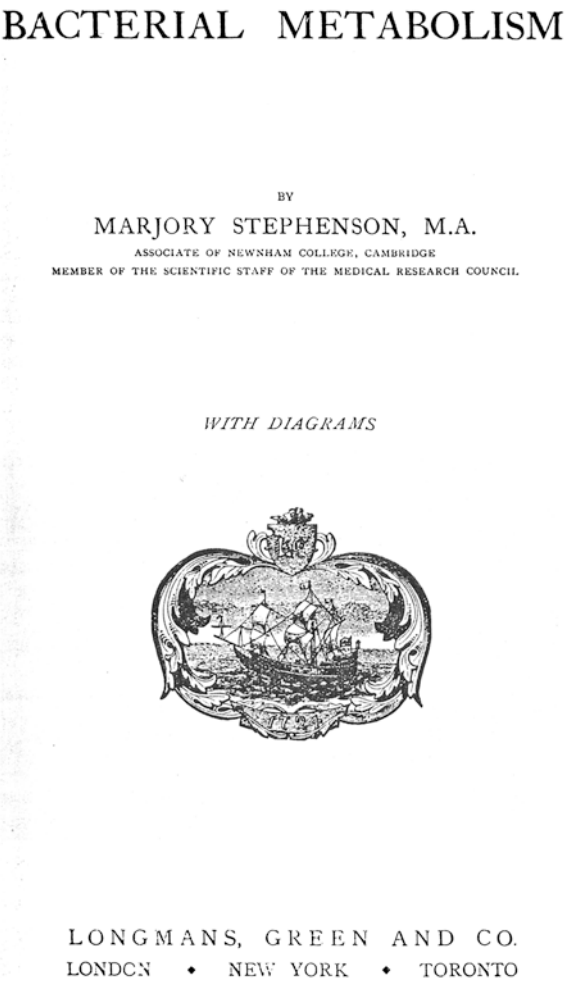
The field of chemical microbiology was defined and demarcated in Stephenson's most significant and popular work, the monograph *Bacterial Metabolism* (Fig. 7.1), written at Hopkins' suggestion [3] whose first edition published as early as in 1930 [4] greatly enhanced her international reputation. The aim of this book which was published by Longmans, Green in the series *Monographs on Biochemistry* had been, as explained by Stephenson [5, p. xi]:

> to choose from the mass of data on the chemical activities of bacteria facts which may help us to gain an insight into the essential chemical processes accompanying the life of the organisms concerned. […] In the selection of material for consideration in this book doubtless much has been omitted […]; but it is time that an attempt should be made to arrange the scattered data in order to appraise our knowledge of bacteria as living organisms apart from their rôle as disease germs or the bearers of commercially important catalysts. […] Perhaps bacteria may tentatively be regarded as biochemical experimenters.[2]

[1]The "physiological" aspects of Stephenson's contribution were accentuated by Kohler, who considered Stephenson's agenda a "coherent and distinctive program for bacterial physiology […] a mixture of Cambridge-style enzymology, comparative physiology and evolutionary biology. No one ingredient was novel, but the combination was groundbreaking." [2, p. 170–171]. "Bacterial biochemistry had come of age, in large part, because of the intellectual program that Stephenson had evolved in the 1920s and 1930s" [2, p. 180].

[2]All highlights in this chapter were done by SŠ.

S. Štrbáňová, *Holding Hands with Bacteria*, SpringerBriefs in History of Chemistry, DOI 10.1007/978-3-662-49736-4_7


BACTERIAL METABOLISM

BY

MARJORY STEPHENSON, M.A.

ASSOCIATE OF NEWNHAM COLLEGE, CAMBRIDGE

MEMBER OF THE SCIENTIFIC STAFF OF THE MEDICAL RESEARCH COUNCIL

WITH DIAGRAMS

LONGMANS, GREEN AND CO.

LONDON • NEW YORK • TORONTO

Fig. 7.1 Title page of the first edition of Bacterial Metabolism (1930)

The monograph endeavoured to treat systematically and in their entirety the basic types of biochemical reactions taking place in the bacterial cells (as they were known in the 1930s)[3] in the spirit of Hopkins' "dynamic biochemistry", and organize the scattered research literature; the bibliography itself took up 32 pages. It also described the new modern methods (mostly conceived in Stephenson's laboratory) of investigation of enzymes and various chemical changes in the microbial cell, and showed a number of actual experiments which led to the new findings. This approach made the book exceedingly useful not only as a summary

[3]The individual chapters were called "Energy Relations and Fermentation", "Respiration", "Growth and Nutrition", "Carbohydrate Breakdown", etc.

of knowledge, but also as a handbook.[4] It also served as a textbook for Stephenson's lectures in advanced biochemistry, and as such, encouraged students to use bacteria in the laboratory to investigate basic biochemical problems.

The contemporary reviews published in journals with wide range of readers reflect the response which the monograph of the yet unknown researcher evoked in the scientific community. The review of Harold Raistrick [6], at that time professor of biochemistry at the London School of Hygiene and Tropical Medicine and acknowledged expert in biochemistry of moulds, was essentially positive, but slightly critical, observing that the "subjects which the author has discussed are treated in a most exhaustive fashion", but some areas of bacteriological chemistry were omitted:

> […] The most serious defect of the book is the almost entire lack of reference to the work of Kluyver and his Dutch school of microbiological chemistry in Delft. These workers have brought new and inspiring viewpoints into so many of the subjects dealt with by Miss Stephenson that omission of their work is very regrettable.

An anonymous review published in the *British Medical Journal* [7] deliberated about the "relationship in which bacteriological chemistry stands to medicine" and expressed the hope that bacterial cells will serve soon as tools for studying metabolic processes in animal cells:

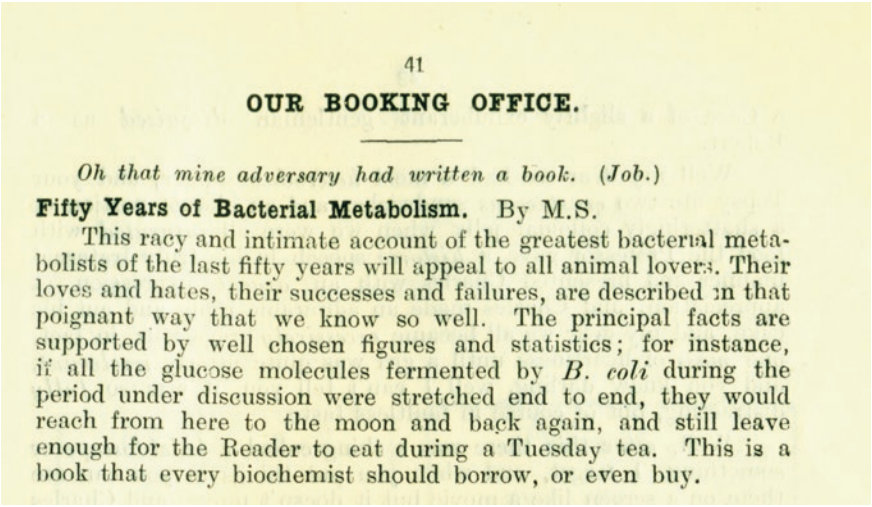
> if from such experiments we could safely draw inferences as to the activities of animal cells, we should have at our disposal a most valuable means for studying metabolic processes […] A recent monograph by Miss Marjory Stephenson […] gives an admirable view of the ground already won, and indicates some of the lines along which fresh advances are likely to be made. So far […] there is no other book from which may be drawn such concise and adequate information about the chief phases of bacterial metabolism.

Reviews appeared also in America. H.A. Matill [8] from the Iowa State University, which hints that the monograph had been read also overseas, praised the "immense amount of material most ably organized" and anticipated that the "book will be eagerly welcomed by biologists and chemists alike for its clear and critical exposition of the fundamental chemistry and physics of bacterial life." Stephenson herself reviewed her own monograph in *Brighter Biochemistry* (Fig. 7.2) in her typical humour [9].

In spite of some critical voices, most reviews of the monograph agreed that it established bacterial metabolism as a new field in biochemistry. Stephenson's pupil Ernest Gale reminds [10, p. 1]:

> In 1930 she published her monograph, and at one and the same time established Bacterial Metabolism as a branch of experimental science, and herself as its outstanding authority. The book attracted many workers to the new subject, and knowledge of microbiology began to grow so rapidly that new editions of the book became necessary every few years.

[4]For instance, in an appendix the reader can find the most frequently used media for different types of microorganisms.



41

OUR BOOKING OFFICE.

Oh that mine adversary had written a book. (*Job.*)

Fifty Years of Bacterial Metabolism. By M.S.

This racy and intimate account of the greatest bacterial metabolists of the last fifty years will appeal to all animal lovers. Their loves and hates, their successes and failures, are described in that poignant way that we know so well. The principal facts are supported by well chosen figures and statistics; for instance, if all the glucose molecules fermented by *B. coli* during the period under discussion were stretched end to end, they would reach from here to the moon and back again, and still leave enough for the Reader to eat during a Tuesday tea. This is a book that every biochemist should borrow, or even buy.

Fig. 7.2 Stephenson's "review" of *Bacterial Metabolism* in *Brighter Biochemistry* (No. 7, 1929–30, p. 41) which shows that she did not take herself too seriously

Thanks to the increasing reputation and the fast development of the new field, and last but not least, Stephenson's matter of fact style and practical comprehensible treatment of the subject, the book became highly popular and the overall demand prompted publishing of new editions. The substantially revised and expanded second edition of *Bacterial Metabolism* of 1939 [11] and the third edition which came out posthumously in 1949 [12] became classic texts and reference works for several generations of biochemists and microbiologists all over the world. Usually are quoted only these three editions, however, meanwhile also reprints of the editions appeared in 1940, 1943, 1952; even as late as in 1966 the M.I.T. Press reissued the 1949 edition as a paperback [13].[5] The Russian translation in 1951 [14] made accessible the monograph to readers in the Communist Block.

The nine years that had passed between the first (1930) and second (1939) editions of the *Bacterial Metabolism* were Stephenson's scientifically most productive period (treated in Chap. 3). The tremendous progress in bacterial chemistry to which Stephenson substantially contributed, reflected the new version of the book quite convincingly, while its focus slightly changed. As Stephenson indicated in the Preface of the second edition [11], the publishers agreed to remove the book from among the monographs and re-issue it as an advanced textbook. The volume increased by 70 pages (this time the bibliography extended 50 pages!)

[5]For the overview of the various editions and impressions see http://www.worldcat.org/title/bacterial-metabolism/oclc/2366730/editions?.

captured the essential progress in the field, especially in the newly added chapters "The Metabolism of Nucleic Acid", "Bacterial Photosynthesis" and Stephenson's strongest theme "Enzyme Variation and Adaptation".

J.H. Mueller,[6] American bacteriologist and immunologist, undisputed authority in the field of bacterial metabolism, gives evidence of how the second edition of Stephenson's book was received by her contemporaries. In his review he floridly characterized the rather blurry situation that had developed in the interdisciplinary field where Stephenson's work attempted to introduce order and lucidity [15, p. 266]:

> **Somewhat chemical, perhaps, for the average bacteriologist, and rather bacteriological for many biochemists, the book illustrates well the position of the worker in this field.** Welcomed to neither group by its prophets, yet impelled to be on speaking terms with the subject-matter and disciplines of both, he is blessed with an abundance of problems, theoretical and practical, whose solutions frequently become incorporated in the thought of one or the other of the basic sciences, and in any event supply comfort to the discoverer in his academic solitude. Perhaps the picture is not quite so dreary, for if one may judge from the bibliography […], great number of investigators […] have invaded this scientific no-man's-land. Many of these have clearly returned unharmed to their own lines. Others have remained as prisoners […] in the other camp. **But a third group […] have elected to continue as Miss Stephenson herself has done, in the somewhat nebulous, but none the less fruitful field of bacterial chemistry, or chemical bacteriology, and to make contributions of general and far-reaching importance.**

Once Mueller favourably commented the details of most chapters, he concluded [15, p. 267]:

> In short, it is not too much to say that the biochemist or bacteriologist who reads this book will not fail to derive profit from the variety of facts now available in this borderline field, and to see many applications of possible new methods to his own particular problem […] It is replete with excellent charts and tables, which illustrate many of the actual experiments of those workers who have contributed to the **establishment of bacterial metabolism on a basis where it may now perhaps be considered to represent a science in its own right.**[7]

The third edition of *Bacterial Metabolism* [12] was Stephenson preparing in the hectic post-war circumstances when she was immersed in organizing work, teaching and fighting with her disease. As the preface testifies, she was well aware of the "startlingly rapid" progress of bacterial metabolism "due partly to the greater number of workers in the field, partly to the introduction of new techniques,

[6]John Howard Mueller (1891–1954), foremost American bacteriologist and immunologist, head of the Department of Bacteriology and Immunology, Harvard Medical School, Boston, Mass.

[7]Even into this article had crept Stephenson's subtle self-irony recalled by Mueller: "Miss Stephenson recently told the reviewer that [the book] was full of errors of omission and commission, but to the casual reader, at any rate this would appear to be an over-statement." [15, p. 267].

but most of all to the evolution of new concepts involving fresh experimental approaches." It was the time of transition from biochemistry to molecular biology in which she could not participate anymore, but was well aware of the onset of the new paradigm in which the microorganism as a model will play a decisive role [12, p. vi–vii]:

> This **new stream of knowledge** has its origin in several sources: microbial genetics, nucleic acid metabolism, adaptive enzyme formation, function of growth factors, the intracellular changes resulting from chemotherapeutic agents, antibiotics and other cell poisons, and interference with metabolism resulting from the introduction into the cell of chemical analogues of essential cell metabolites. All these are contributing to produce a picture—at present incomplete and patchy—of the biochemical machinery of growth. We seem, in fact, to be witnessing a transition from katabolic to anabolic studies, **made possible only by the use of the microbe as experimental material. […] Bacterial metabolism is now such a wide study that it is no longer convenient for one person to attempt to cope with all its branches;** I can confidently assert that this is the last edition which will appear over the name of the author.[8]

Stephenson's correspondence reveals that the manuscript of the third edition went to press on February 28, 1947,[9] but the publisher was so slow that she did not live to see the printed book.[10] Therefore, her former student Roger Stanier could not tell her about his disappointment of the 1949 edition which he articulated in his critical review [17]. He objected that Stephenson did not react properly to the

> "facts and concepts that have emerged in the decade since the previous edition" and "instead the framework of 1939 has been preserved intact and new information has been inserted piecemeal. The result is a lack of integration so great as to obscure many important principles. […] **Omissions are most serious in the chapter on enzymic variation and adaptation, where the author failed to consider the implications of recent work on bacterial genetics and on adaptive enzyme formation**." Nevertheless, according to Stanier, the book "in spite of the criticisms […] **still remains by far the best presentation of the subject.**"

Stanier was probably right that Stephenson did not manage to follow the latest developments in biochemistry and genetics, nevertheless his admonition was not fully justified. Boris Magasanik[11] not so long ago drew attention to the fact that Stephenson and her pupil Gale were the first scientists who mentioned in their textbooks Avery's transformation experiment of 1944 which identified DNA as the

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[8]Stephenson wrote the Preface to the 3rd edition in 1948 a few months before her death.

[9]Robertson remarks in Stephenson's biography [16, p. 570] that Stephenson "had finished the work upon the third edition in 1946 and it was a source of considerable disappointment to her that the publication was so long delayed".

[10]We can learn this from Stephenson's letter to Elsden dated 11 March 1947, where Stephenson complains about the slowness of the publisher: "B.M. [Bacterial Metabolism] went to press on the last day of Feb. but so far no proof; I expect Longmans will print an edition of 100 copies in 2 years by which time I hope to be living in Uganda in some locality out of reach of the postman." Newnham College Archives, Papers of M. Stephenson.

[11]Boris Magasanik (1919–2013), American biologist whose career was linked most of his life to the Massachusetts Institute of Technology. He researched primarily on microbial physiology and gene expression in yeast and bacteria.

genetic material of the cell at the time when most researchers had still expressed their doubts about the significance of Avery's finding [18, p. 357]. While Gale was cautious to interpret it in his monograph [19], Stephenson, in the third edition of the Bacterial Metabolism described the transformation experiment and unambiguously asserted [12, p. 296] that the

> **importance of [Avery's] observation is that it carries irrefutable proof that nucleic acid controls enzyme production**, a fact toward which converging evidence already pointed. It also shows that […] a dividing cell can use a portion of **nucleic acid polymer from a related organism to control the synthesis of a substance alien to itself and characteristic of the cell from which the nucleic acid was derived**.

Stephenson's monograph [4, 11, 12] which was based to a large extent on research of her laboratory, offered new systematized knowledge in biochemistry of microorganisms and unified its methodical base; this way it helped to build up a solid foundation for the future development of molecular biology. The three editions signified the individual stages of development of chemical microbiology, as well as the culmination of the past progress resulting in the emergence of molecular biology which recast the findings of bacterial biochemistry into an entirely new quality. Besides the *Bacterial Metabolism*, it is necessary to mention the role of other widely read publications of Stephenson, namely her reviews "Chemistry of Bacteria" she was writing for the *Annual Review of Biochemistry* from 1932 to 1935 [20–23]. These works which were summarizing, classifying and disseminating advances in the field, helped to prepare the ground for the emergence of molecular biology, as well.

Well-received treatises and reviews were not the only means which stimulated the circulation of ideas, knowledge and methods of chemical microbiology. In 1946 Stephenson with her collaborators prepared under the auspices of the Medical Research Council a Cambridge Summer School Course in Bacterial Chemistry [24] with lectures, demonstrations, and colloquia in order to propagate knowledge of "*biochemical approaches to bacteriological problems and… some techniques involved*" [25]. Scientists of different specializations from all over the country attended the School both as listeners and speakers; besides the members of Stephenson's laboratory and the Biochemistry Department also such notable authorities like Sir Paul Fildes, David Keilin[12] and Sir Alexander Fleming.[13]

> "Fifty five people attended the course, which was the limit we could cope with in the demonstrations, we could gave filled the course at least twice over; the lectures were attended by a good many persons not enrolled in the course. I hope it has spread a knowledge a bit and helped along the cause of microbiological development in this country," reported Stephenson to Mellanby [26].

[12]David Keilin (1887–1963), parasitologist and biochemist, was most of his life affiliated to the Molteno Institute in Cambridge. He became famous especially for his rediscovery of the respiratory pigment cytochrome. His subsequent life-long research aimed at elucidation of the function of the cytochromes in cellular respiration and the production of cellular energy.

[13]Sir Alexander Fleming (1881–1955), British physician, bacteriologist and immunologist, best known for the discovery of the enzyme lysozyme (1953) and the first known antibiotic penicillin which he found in the mould *Penicillium notatum* in 1928. For his discoveries he received the Nobel Prize in 1945 with H. Florey and E.B. Chain.

The zealous success of the Cambridge Summer School resulted in its repetition in 1948 in Oxford, where it was organized by D.D. Woods. Stephenson "played a full share in the second edition of the School in Oxford and was herself present throughout." [27].

7.2 The Society for General Microbiology

The endeavour of Stephenson and other British biochemists and microbiologists to integrate all aspects of chemistry and biology of microorganisms culminated in the founding of the *Society for General Microbiology* (SGM) in 1945. This act was preceded by several years of preparatory process full of twists and turns in which Stephenson played a key role [28–32].[14] The first, rather unforeseen impetus came from the *Society of Agricultural Bacteriologists* which proposed in 1943 at its Annual General Meeting in Leeds (also attended by Stephenson) the formation of a more general bacteriological society which could act as a counterpart of the *Society of American Bacteriologists*.[15] The organizers of the Leeds meeting, namely L.A. Allen and R.T. St. John-Brooks[16] succeeded to put together a group of about thirty leading British microbiologists (including Stephenson) representing most areas of the discipline, to assess the options. Stephenson supported enthusiastically the creation of an entirely new society "for the establishment and extension of a common ground between all forms of microbiology" [28, p. 173]. She became the member of the inaugural Committee for the Formation of a General Bacteriological or Microbiological Society (further only "Committee") which worked for almost two years to formulate the establishing of the new society [35].[17] L.A. Allen [36] recalls that:

> Her [Stephenson's] support of the project was particularly valuable. Not only was she outstanding in her own field of work but she was at that time one of the very few non-medical workers in the front rank of microbiologists. At the same time she was respected by a large number of the medical bacteriologists. She also carried with her in support of the project a number of the younger members of the Cambridge group—for example Elsden and Gale. […] There is no doubt that her wise counsel and the influence she exerted among a wide circle of microbiologists greatly contributed to its success.

[14]The history of the SGM is also treated on the web page of the SGM [33], but it does not mention at all Stephenson's role in establishing and activities of the SGM, although, paradoxically, the Society awards annually the Marjory Stephenson Prize Lecture [34].

[15]The Society of American Bacteriologists, since 1961 called the American Society for Microbiology, was founded in 1899.

[16]Leslie Alfred Allen (1903–1963) was a dairy bacteriologist who also pursued technical microbiology and hygiene. As a President of the Society of Agricultural Bacteriologists he was instrumental, together with Ralph Terence St. John Brooks (1884–1963), bacteriologist from the Lister Institute, in establishing the SGM. In the SGM's first governing body Allen was elected Secretary along with St. John Brooks.

[17]The preparatory meetings were organized by the "joint secretaries" of the Committee: L.A. Allen and R.T. St. John-Brooks.

Since 1943, Stephenson threw herself with great energy into organizing work as a prime mover behind the preparation of the new Society. She even invented the name of the Society [30, p. 1], but her effort was focused especially on its orientation and programme as we can read in the Minutes of the Committee for the formation of the Society in 1943 [37][18]:

> Dr. Marjory Stephenson thought that we should make the scope of the Society as wide as possible and include bacteriologists, mycologists, protozoologists and virologists and that we should concern ourselves more particularly with the general aspects of the subject. **The biochemical approach was becoming more and more important in each branch of the science** and there were fundamental similarities between the various microbes. She thought we should not call the new Society a 'Society of Bacteriologists' […]. **Society for General Bacteriology would be a better title and the Society should inaugurate a journal covering wide interests.**

Stephenson obviously acted as a unifying element among the leaders of various branches of microbiology who participated in the preparatory meetings. She defended successfully her conviction that the Society should cover research into all forms of microorganisms (bacteria, viruses, micro-fungi, protozoa and microscopic algae in their various biological activities) and deal "**predominantly with the more fundamental aspects of the study of these forms, including their physiology, nutrition, chemotherapy, systematics and ecology**" [31]. Stephenson's active part in the foundation of the SGM stemmed from the idea "that the most rapid development of microbiology depended on the closest liaison between those interested in the more biological and biochemical aspects" [38, p. 151] and her firm belief that neither aspect can do without the other; while the biological fields set the problems, the biochemical approach is necessary to solve them.

The first candidate for presidency was David Keilin [39] and when he declined, the Committee tried to persuade Stephenson to take this post (Fig. 7.3) [40]:

> As you probably know, professor Keilin cannot see his way to accept the office of President for the first year of our existence; so we must all reconsider the question. The Committee […] has […] come to the unanimous decision that you should be asked to permit us to put your name forward as our first President. Everyone would be very pleased if you would do this and we shall all be most disappointed if you cannot give the Society this good start on what we hope will be a very successful career. […] Please say yes!

In spite of this earnest request, Stephenson refused to accept the presidency of the SGM, possibly due to her political tactfulness and/or serious illness. Finally, Sir Alexander Fleming was elected first President of the Society for General Microbiology at the inaugural meeting of the Society 16 February 1945. In the first governing body of the SGM, Stephenson was elected member of the Committee; the other woman scientist serving at the Committee was Muriel Robertson [31, 32, 41].

[18]Stephenson's active participation in the preparatory period of the SGM is also documented by the minutes of the meetings of various committees kept at the Archives of the SGM, Reading.

SOCIETY FOR GENERAL MICROBIOLOGY

St. Loy,
Clay Hill,
Bushey, Herts.
13th July 1944

Dear Miss Stephenson,

From the time of the first meeting of the Organizing Committee of the Society for General Microbiology many of us thought of you as a very obvious Chairman and indeed, when Sir John Ledingham felt that the burden of presiding over our gatherings was too exacting for him, we persuaded you to take the chair at our second meeting. It was only at your own request that we forgave you this office at subsequent meetings! So you see you have always occupied a very important place in our thoughts with regard to the direction of the Society.

As you probably know, Professor Keilin cannot see his way to accept the office of President for the first year of our existence; so we must all reconsider the question. The Committee delegated its authority in this matter to Professor Miles and the two Secretaries and we, as well as Professor Keilin himself, Dr. Kenneth Smith, Miss Robertson and others, have thought the matter over and have come to the unanimous decision that you should be asked to permit us to put your name forward as our first President. Everyone would be very pleased if you would do this and we shall all be most disappointed if you cannot give the Society this good start on what we hope will be a very successful career. Do not let the question of an address disturb you. You could say just as much or as little as you liked. The principal thing is to have you presiding. Please say yes!

Yours sincerely,

(Hon. Secretaries)

Miss Marjory Stephenson, D.Sc.,
School of Biochemistry,
Tennis Court Road,
Cambridge.

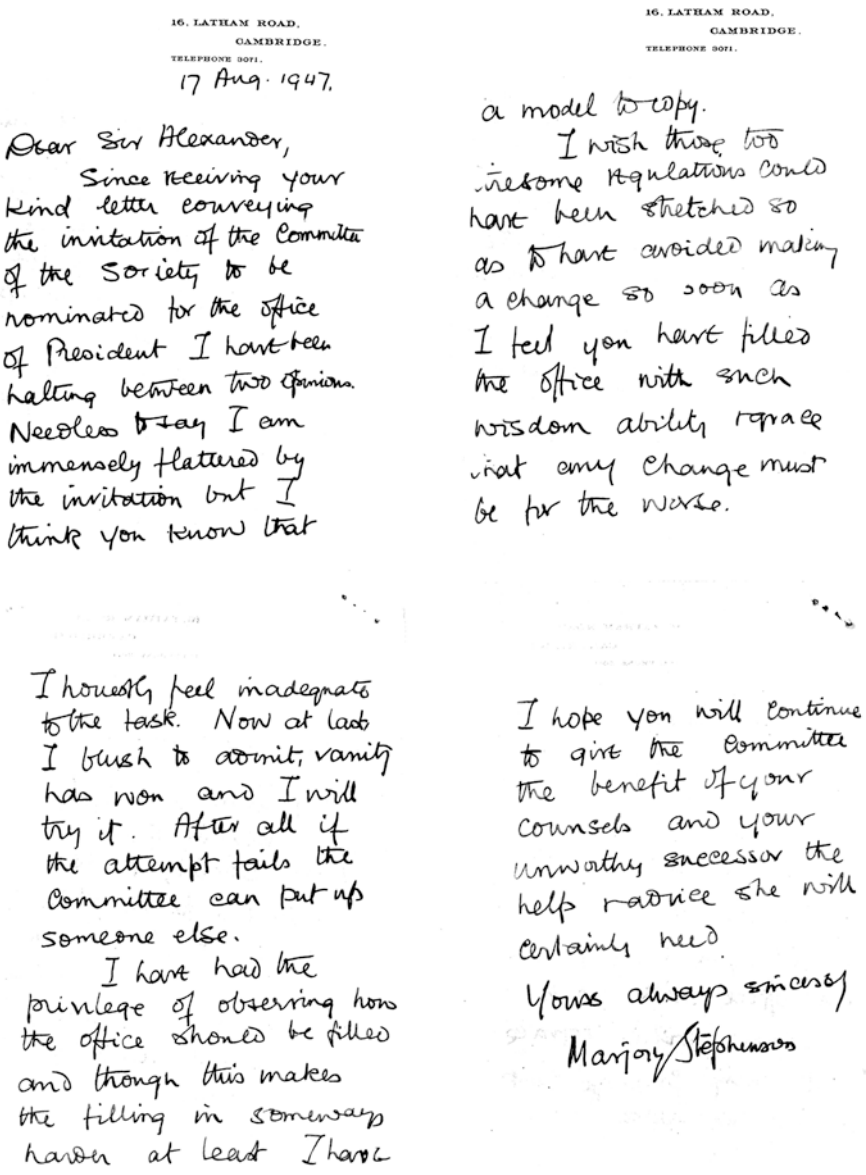
Fig. 7.3 Letter of 1944, in which the Committee for the Formation of a General Bacteriological or Microbiological Society was to persuade Stephenson to take the post of the first president (Image reproduced with the permission of Microbiology Society Archives, former Society for General Microbiology, and the Chief Executive of the Society, Dr. Peter Cotgreave)

After Fleming's term of office expired in 1947,[19] Stephenson hesitantly agreed to accept the presidency.[20] It was in fact Fleming himself who asked her to take on the office, but unfortunately his letter has not been preserved. Stephenson's answer [42], in which she expresses her acceptance, is worth quotation[21] as a testimony of her modesty and generosity (Fig. 7.4):

[19]According to the Statutes of the SGM The President shall hold office for three years, but shall not be eligible for immediate re-elections [41].

[20]Some biographies of Stephenson omit her activities in the SGM, some indicate inaccurate data on the SGM and Stephenson. J. Postgate in his history of SGM [30] does not even mention Stephenson's presidency and incorrectly states that she died in 1949.

[21]The letter was copied including the missing comas.



16, LATHAM ROAD,
CAMBRIDGE.
TELEPHONE 30711.

17 Aug. 1947.

Dear Sir Alexander,

Since receiving your kind letter conveying the invitation of the Committee of the Society to be nominated for the office of President I have been halting between two opinions. Needless to say I am immensely flattered by the invitation but I think you know that I honestly feel inadequate to the task. Now at last I blush to admit, vanity has won and I will try it. After all if the attempt fails the Committee can put up someone else.

I have had the privilege of observing how the office should be filled and though this makes the filling in somewhat harder at least I have a model to copy.

I wish those too irksome regulations could have been stretched so as to have avoided making a change so soon as I feel you have filled the office with such wisdom ability & grace that any change must be for the worse.

I hope you will continue to give the Committee the benefit of your counsels and your unworthy successor the help & advice she will certainly need.

Yours always sincerely

Marjory Stephenson

Fig. 7.4 Stephenson's letter of 1947 to Sir Alexander Fleming, in which she modestly agrees to accept the presidency of the SGM (Image reproduced with the permission of Microbiology Society Archives, former Society for General Microbiology, and the Chief Executive of the Society, Dr. Peter Cotgreave)

17 Aug. 1947

Dear Sir Alexander,

Since receiving your kind letter conveying the invitation of the Committee of the Society to be nominated for the office of President I have bee halting between two opinions. Needless to say I am immensely flattered by the invitation but I think you know that I honestly feel inadequate to the task. Now at last, I blush to admit, vanity has won and I will try it. After all if the attempt fails the Committee can put up someone else.

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Yours always sincerely
Marjory Stephenson

In 1947, Stephenson became President of the SGM while Fleming stayed member of the Committee and was elected Honorary Member of the Society [43]. The same year the *Journal of General Microbiology* was founded. Stephenson was given, however, only one year to stay in her presidential office.

In 1949, one year after her death, the *Society for General Microbiology* established in her memory the Marjory Stephenson Memorial Fund (Fig. 7.5). The subscription form states the following [44]:

The Committee of the Society are unanimous in their desire to pay a tribute to a great scientist, a great personality and a great President. […]. The Committee agreed that the most suitable memorial would be a Lecture, to be given at regular intervals […] and to be known as the Marjory Stephenson Memorial Lecture.

Since 1953, the SGM has been awarding the Marjory Stephenson Prize "for any outstanding contribution of current importance in microbiology" associated with the Marjory Stephenson Memorial Lecture. The inaugural lecture in 1953 was read by one of her pupils, D.D. Woods [38].[22]

7.3 Stephenson's Concept of Chemical Microbiology and General Microbiology

It is necessary to point out that even if Stephenson is rightly attributed the merit of establishing the field of chemical microbiology, we may to a certain extent agree with the view that "her scientific outlook was strictly empirical. In her own field she kept

[22]In 1988 the prize was renamed the Marjory Stephenson Prize Lecture. At present the Marjory Stephenson Prize Lecture is "awarded annually to an individual who has made exceptional contributions to the discipline of microbiology (…). The recipient of the Prize Lecture will receive £ 1000 and be expected to give a lecture based on the work for which the award has been made to a meeting of the Society" [34]. This web page shows Stephenson's picture and asserts that "Marjory Stephenson was the second President of the Society 1947–1949 (sic!) and a distinguished pioneer of chemical microbiology".

SOCIETY *for* GENERAL MICROBIOLOGY

MARJORY STEPHENSON MEMORIAL FUND

Dear Sir or Madam,

As you know, the Society recently suffered a grievous loss through the death of its President —Dr Marjory Stephenson.

An outstanding figure in the biochemical world, she was known to all students of microbiology for her pioneer work in the field of bacterial metabolism. The part she played in establishing the Society for General Microbiology was, perhaps, less generally realised. When the movement for the formation of the Society began it was evident that careful preparatory work would be necessary before the project could be launched. Marjory Stephenson was a member of the inaugural committee from the very beginning, and throughout the formative period and afterwards, when the Society had been founded, her balanced outlook and wise counsel, no less than her idealism and enthusiasm, contributed greatly to its success.

The Committee of the Society are unanimous in their desire to pay tribute to a great scientist, a great personality and a great President, and they appointed a sub-committee to explore the possibility of establishing a memorial. A summary of the sub-committee's report was read at the Annual General Meeting on 20th April, 1949, when it was agreed that a memorial should be established and that it should be left to the Committee to decide on the form this should take.

The Committee are agreed that the most suitable memorial would be a Lecture, to be given at regular intervals (possibly annually) and to be known as the Marjory Stephenson Memorial Lecture. It is intended that a committee to be appointed for the purpose shall on each occasion select a suitable person, preferably a member of the Society, and invite him or her to give the Memorial Lecture. In addition to payment of travelling expenses, etc., it is proposed that the lecturer should receive, as a token of the occasion, a medal or books of equivalent value. It is also proposed that the selection committee should be asked to bear in mind particularly the claims of younger members.

The cost of maintaining a memorial of this character is expected to be of the order of £30 a year, and for this a capital sum of about ONE THOUSAND POUNDS would be needed. The Committee feel that members of the Society would like to contribute to the proposed memorial and for this purpose they are opening a Marjory Stephenson Memorial Fund.

You are invited to return the enclosed subscription form to the Hon. Treasurer, Mr. H. J. Bunker, together with your subscription to the Fund. It is intended to keep the Fund open for two years. If you find it more convenient to spread your subscription over the two-year period, rather than to give the whole sum now, would you please indicate your intention on the form so that the Treasurer may have some idea of the sum he may eventually expect to receive.

J. W. McLEOD, *President*

On behalf of the Committee

SOCIETY *for* GENERAL MICROBIOLOGY

MARJORY STEPHENSON MEMORIAL FUND

TO THE HONORARY TREASURER

I enclose a subscription (£ s. d.) towards the Marjory Stephenson Memorial Fund.

I intend to subscribe the further sum of £ s. d. towards the Fund before June 1951.

Signature.....

Address .....

.....

When completed please send this form, together with your subscription, to Mr. H. J. Bunker, Research Department, Messrs. Barclay Perkins & Co. Ltd., Park Street, Southwark, London, S.E.1, or direct to the Society's bankers—the National Provincial Bank, Ltd., 12 Southwark Street, London, S.E.1. In the latter case cheques should be made payable to the Society for General Microbiology, *No. 2 Account.*

Fig. 7.5 Announcement of the establishment of Marjory Stephenson Memorial Fund in 1949 (Image reproduced with the permission of Microbiology Society Archives, former Society for General Microbiology, and the Chief Executive of the Society, Dr. Peter Cotgreave)

her attention firmly on the actual observations and was less interested in the theories that flowed from them." [45, p. 336]. This positivist and "practical" position is also apparent in her *Bacterial Metabolism* which for the same reason remained a helpful sought-after manual even in the 1960s. On the other hand, Stephenson's original and exact experimental methods, systematic mapping of the wide range of cellular biochemical reactions in bacteria and discoveries and investigations of new enzymes, enabled the use of microorganisms as cellular models. She was extremely competent in pinpointing essential problems, like the issue of biochemical adaptation, and track them systematically. New knowledge she and her collaborators produced was crucial not only in defining and demarcating the field of chemical microbiology but also had important consequences in opening new domains for science.

Stephenson's approach to examination of microorganisms stemmed from the recognition that at the cellular level there is an underlying unity in entire live nature and her research contributed significantly to confirm this affirmation. She was able to demonstrate quite convincingly that bacterial enzymes behaved similarly as enzymes in higher organisms and that cellular metabolism and its control in bacteria was governed by regularities analogous to those in higher organisms. The mass of experimental papers flowing from her laboratory and also her monographs and reviews gathered huge amount of evidence corroborating the principle of unity in biochemistry, coined by F.G. Hopkins, articulated by the Dutch microbiologist Kluyver and other contemporaries [46–48], and eventually expressed emblematically by Monod's famous dictum "what is true for *E. coli* is also true for elephant"[23] This quotation, as Friedmann reminds us [48] comes in many versions, for instance "Anything found to be true of *E. coli* must also be true of elephants." Monod was apparently not the first who had used this comparison. In 1926 the Dutch microbiologist Albert Jan Kluyver invented the catchy phrase "From the elephant to butyric acid bacterium—it is all the same!" [48, p. 58]. Although Stephenson was evidently inspired by Kluyver's principles, she surprisingly had never quoted in her writings his ground-breaking papers on the unity in biochemistry (and was criticised by Raistrick for this omission) [6][24] and only belatedly acknowledged Kluyver's influence in one of her last papers published in 1947 in the jubilee volume issued in his honour [49, p. 33]:

> Kluyver used [biological oxidation] as a basis for a unified conception of the intermediary reactions […]. Under his inspiring guidance there emerged from the Delft School during the late twenties and early thirties a series of biochemical experiments […] familiarising bacterial chemists with the view that, although the final products are so diverse, yet many of the same fundamental processes are at work in all. Certainly our views concerning the details of these processes have undergone many changes since those days but the conception of a unified pattern of events underlying very diverse phenomena was first inspired by Kluyver's teaching.

[23] In French "Tout ce qui est vrai pour le Colibacille est vrai pour l'éléphant", see http://www.pasteur.fr/infosci/archives/mon/im_ele.html, accessed November 5 2013.

[24] This neglect was for some unknown reasons mutual. Kluyver did not refer to Stephenson's works as well, not even in his book published in 1956 [47] where he brings further evidence to life's unity provided by microbiological studies.

Stephenson herself, although considered pioneer in employing microorganisms as the most suitable models of cell investigation, was quite cautious in transfer of knowledge from one type of organism to another as she admitted in this lecture [49, p. 34]:

> Now although it is true that many fundamental chemical reactions are common to animals, plants and microbes, it is easy to overestimate the unity of nature when bacteria are being considered in relation to animals and plants. It is probably true to say that whilst most chemical changes occurring in the latter are either duplicated or closely paralleled in some microorganism or other yet the converse is far from being true.

If we talk about Stephenson as predecessor of molecular biology, we must do so with a certain reserve, as well. Monod indeed in part followed the concept of environmental control of the cellular chemical reactions, namely the concept of adaptation coined by Stephenson and Yudkin, however, as E. Fox Keller brings up, he substituted "adaptation" by the term "induction" to rid biochemistry from its teleological language. Fox Keller also indicates the political motives of this move—"it became his personal crusade to save biology from the corrupting influences of Lysenkoism" [50, p. 175].[25]

It is striking for such influential scientist as Stephenson, how rarely she expressed in her writings some general concepts and ideas, visions of future developments or other general deliberations about her field. They are usually concealed; in the forewords to the individual editions of *Bacterial Metabolism* or in a few presentations prepared for occasional festive performances, like the one mentioned earlier [49]. Perhaps she was too shy or modest to articulate some universal wisdom, or she just preferred subjects where she felt strong—experiments, results and their interpretation. Also Woods, one of her former students, observed that [51, pp. 382–383]:

> Marjory Stephenson was essentially an experimentalist; it is really remarkable how few of her papers contained a section formally labelled 'Discussion'; when such did occur it was devoted rather to practical matters, or to the relation of the work to other fields, than to hypothesis. […] She wrote comparatively few reviews and these were largely factual

The essential (and perhaps the only) conceptual paper of Stephenson, namely her speech at the inaugural meeting of the Society for General Microbiology in February 1945, has paradoxically, never been published and its ideas have circulated just in "secondhand" interpretation [38,[26] 45, 51]. The paper is sometimes presented under the title "**Levels of Microbiological Investigation**", but the preserved archival typewritten version [52] with Stephenson's handwritten remarks, bears no heading. This manuscript, which is with great probability the authentic

[25]Trofim Denisovich Lysenko (1898–1976) was a Russian biologist and agronomist, Stalin's follower, who through his political power entirely dominated Soviet biology. He rejected classical genetics and replaced it by pseudoscientific false theories of Lysenkoism which transferred to practice had disastrous effect on Soviet biology and agriculture.

[26]Detailed analysis of Stephenson's speech from the perspective of chemical microbiology.

version of Stephenson's lecture, has most likely not been known earlier, not even to Woods as follows from his words which characterize Stephenson's memorable lecture [38, p. 151]:

> Stephenson summarized her own experience and thought and drew for us a simple overall picture of the various methods of approach to research in microbiology, and especially chemical microbiology. **I have always felt this to be one of those clear-sighted and simple statements of general principles which remain indefinitely helpful** and become, so to speak, **part of the commonlaw of a science**. Unfortunately, we have no published account of this actually from her own pen.

The "secondhand" descriptions of Stephenson's paper usually omit the introduction where she emphasizes that the hopes she builds around the new society are contacts and motion. The second issue (topical until today) she puts forward is the line between pure and fundamental science [52, p. 1]:

> I should like to confess that in the labelling of microbiological work I am somewhat of a heretic. […] Pure science for example implies the existence of an impure variety whilst fundamental research suggests that someone else is occupied in superficial activities. Such terms are apt to introduce discord in the family, which is not one of the aims of our society.[27]

Stephenson knew what she was talking about as the new Society hoped to accept into its ranks a wide spectrum of specialists in microbiology, and certain conflicts of interest, especially between the medical bacteriologists and the rest of the membership were to be expected.[28] For this reason she had wisely selected for her introductory lecture a topic that she thought might unify the audience and would be shared by all members of the SGM.

In her reflection Stephenson generalized her own and other scientists' experience in the field of bacterial metabolism and applied it to the differentiated field of general microbiology which encompasses diverse types of microorganisms and their various biological manifestations, including metabolism, morphology, ultra-structure, genetics and others. She pointed out that there exist various ways of approach to research in microbiology and especially chemical microbiology. The microbiologist's work can proceed in different levels labelled A, B, C, D, E, related to certain historical periods in the development of microbiology starting with Pasteur's first paper on fermentation in 1858:

---

[27]Underlined by MS.

[28]Stephenson's intuition was apparently right as it follows from her letter to Elsden written in July 1948: "I find it very depressing that after some 30 years of works and 2 editions of B.M. [Bacterial Metabolism] the medical bacteriologists are as uneducated biochemically as ever." In her letter to Elsden dated 9 November 1948 (that is in the period of her presidency) she mentions certain controversies in the classification and nomenclature subcommittee of the SGM Committee stirred up by the medical bacteriologists who apparently wanted to dominate the SGM: "I don't really expect it [the committee] to achieve a new classification but I do hope it will prevent the medical bacteriologists from running away with British bacteriology and upsetting it into a deep ditch; it must insist on Bacteriology being treated as a whole not as medical Bacteriology only; so everyone must be prepared to stand to" [53].

(A) mixed cultures of organisms growing in natural environment,
(B) pure growing cultures in complex media,
(C) pure growing cultures in highly purified chemically defined media,
(D) non-proliferating cells in pure cultures containing chemically defined substrates,
(E) cell-free enzymes and coenzymes on pure substrates.

These individual levels represent different degrees of complexity and simplification, but no level by itself is adequate for complete understanding of bacteria as they are found in Nature and (in Woods' words) "no one level is more important than another; they represent a spectrum rather than a ladder." [38, p. 151] Therefore research must occur at all levels with the workers at each level depending upon each other [52, p. 2]:

> But it is obvious how dependent on each other are the workers at different levels. Facts established at A and B provide the starting point for work at C, D and E. But movement must be in both directions […] Unless work is to grow first stale and then sterile it must be refreshed by contacts with work at other levels. Moreover as knowledge increases and technique becomes more difficult interdepartmental [we may say rather "interdisciplinary", SŠ] collaboration is strongly indicated, a development which this society may do much to foster.

Stephenson's research strategy introduced to the community of microbiologists was exceptional from several standpoints. Firstly, because it invited scientists experimenting at different levels to interdisciplinary collaboration. Secondly, because it called attention to studying microbial cells at various levels to obtain complex knowledge of the cell's chemical activities. Last, but not least, because this way Stephenson declared her recognition and respect to Nature's complexity and appealed for better understanding of microorganisms as they are found in Nature. Such attitudes are often disregarded by the contemporary science which prefers research on levels C-E and tends to ignore level A. In Stephenson's call for investigation of living objects, even so small as microorganisms, in their natural circumstances, we may notice her respect for the integrity of Nature contradictory to the stereotype of studying Nature through domination and disintegration.

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Chapter 8
Stephenson's Personality

Stephenson's scientific achievements have already been treated in detail, but her personal qualities only marginally, though the attentive reader could already get some impression of her exceptional individuality. To write about Stephenson's personality is not a simple task. There exist no interviews with Stephenson we know about and she evidently did not like to talk about herself. Therefore, her individual portrait assembled from the fragments of correspondence, personal memories of her collaborators, and various archival documents will only look like an incomplete mosaic.

It is necessary to reiterate that in the 1930s, Stephenson as an indisputable leader in her laboratory (although without official appointment), gradually attracted a wide circle of collaborators. This distinguished her from most contemporary women scientists who were doing high quality research, but mostly without leadership ambitions which were not tolerated anyway by the male dominated scientific community. Stephenson was one of the very few who got the determination and courage to overstep this invisible line. Also thanks to the fact that she found a free niche for her research, where she was able to generate a new field and fill it systematically with knowledge, she won the necessary respect and independence and over the years also followers and subordinates. Stephenson never married, so the lab became her second home and her students, collaborators and assistants her family (Fig. 8.1). Some of them got to know her quite closely and their (sometimes perhaps idealizing) testimonies can bring us nearer to Stephenson as an individual.

Stephenson's co-workers are unanimous in describing her enthusiasm for chemical microbiology, thorough experimental work and care for the professional development of the young adepts of science who gathered around her. Donald Woods, Stephenson's graduate student, who started his research career as a Beit Memorial Research Fellow in Stephenson's laboratory in 1936, was so much impressed by her charisma that he remembered every detail of his first encounter with Stephenson long before he met her in person [1, pp. 203–204]:

S. Štrbáňová, *Holding Hands with Bacteria*, SpringerBriefs in History of Chemistry, DOI 10.1007/978-3-662-49736-4_8

Fig. 8.1 Stephenson entertains friends in her house. From the left: Unidentified person, P.B. Armstrong (USA), D. Wrinch, Judith, M. Stephenson. Photo taken around 1935 (Archive of the Department of Biochemistry, University of Cambridge. Picture reproduced with the permission of the Archive)

> I became interested in this subject (chemical microbiology) at 8:30 p.m. on Friday 9 May 1930. At that time the late Dr. Marjory Stephenson gave a broadcast talk in a series entitled 'Biochemistry: what it is and what it does'. Her particular topic was 'How microbes live or some aspects of bacterial physiology'. This short talk made a deep impression upon me: I was 18 at the time, which is no doubt an impressionable age…In the course of this broadcast she said: 'I don't know whether I have persuaded any patient listener to think that microbes are an interesting study on their own account, but I can assure you that those of us who spend our time trying to persuade these little people to disclose their secrets, find our lives full of interest and often excitement.' Well, she had at least one convert, for since that broadcast the whole of my scientific life has been devoted either to preparing myself for, or actually studying, the biochemistry of micro-organisms.

Although, as was mentioned in this book several times, Stephenson was leaving her collaborators at all times freedom of choice, in many instances she followed up (and sometimes endorsed) their further careers and must have been happy to learn that most of her "offspring" proved to be high achievers on their career paths (see Supplements). For instance, in a letter to her pupil and friend Sidney Elsden [2] she confesses her concern about the future of her young biochemistry student Jane Pinsent: "I feel like a parent sea gulf and long to knock her [Jane] off her rock and make her fly".[1]

[1]Stephenson had been mentor of the biochemistry student Audrey Jane Pinsent (Gibson) (1924–2008) who graduated in 1946. She obtained her Ph.D. degree in 1949 at the Lister Institute, worked with Elsden in Sheffield where she met and married the biochemist Quentin Gibson. Jane and Quentin spent most of their lives at Cornell University (New York, USA), see [3].

People who used to work with Stephenson agree about her fair and co-operative behaviour towards her associates, her readiness to help and advise not only in the laboratory, but also in privacy and her straight nature devoid any insincerity and pretence. These virtues are depicted by one of her closest friends the foremost biochemist Dorothy Needham [4, p. 202]:

> Dr. Stephenson was greatly sought as friend and adviser. She was always ready to pay sympathetic attention, and her advice, usually given quickly and with decision, was based on a deeply considered philosophy of life. One of her great characteristics was her intense interest in people and a favourite theme in her conversation was the influence of character upon scientific achievement or, conversely, the effect of certain types of results upon the psychology of research workers […] One of her great qualities was her hatred of any form of cant, hypocrisy, pretention or slovenliness; she was ruthlessly outspoken in her condemnation of any such suspected defect. But this personality, so lively and so gifted with the capacity for leadership, had another characteristic: a fundamental humility, which enabled her to listen, learn, and, if need be, change her mind.

Donald Woods confirms the image of Stephenson's as a friendly, sympathetic, charismatic and high-principled person [5, p. 378]:

> Marjory Stephenson… had a vivid and arresting personality: her feelings—and the expression on them- about people and affairs were always positive. She was intolerant of all forms of pretentiousness, whether scientific or personal.

Sidney Elsden, who got his Ph.D. with Stephenson in 1941, and the virologist Norman W. Pirie, Hopkins' collaborator go into more depth when characterizing her behaviour towards her colleagues [6, pp. 336–337]:

> Marjory Stephenson adopted much the same attitude towards people as she adopted towards science. She was concerned with what they were actually doing and with their motives rather than with what they said they were actually doing and why. This pursuit of personal information and discussion of motive, especially when undertaken by someone with her infectious gaiety, could become formally indistinguishable from gossip and the pejorative word was sometimes used by those whose activities were being analysed.

Especially Elsden's opinion should be taken seriously. Judging from Stephenson's 16 preserved letters she wrote to him in the years 1946–1948[2] they had had a long-standing friendship and in the last years of Stephenson's life they became very close. The letters she wrote to him about various scientific and personal issues reflect an almost motherly attitude and profound trust (Fig. 8.2) so that they represent a fascinating and informative collection allowing us a more intimate and less idealized insight into Stephenson's views and character. The letters are written in a typical "Stephenson style" combining pragmatism, dry humour and self-irony. Stephenson's pleasure in gently mischievous gossip is

[2]The collection of Stephenson's letters to Elsden is kept at Newnham College Archives. Valuable are Elsden's hand-written notes to each letter which comment the circumstances and people mentioned in the letters [7].

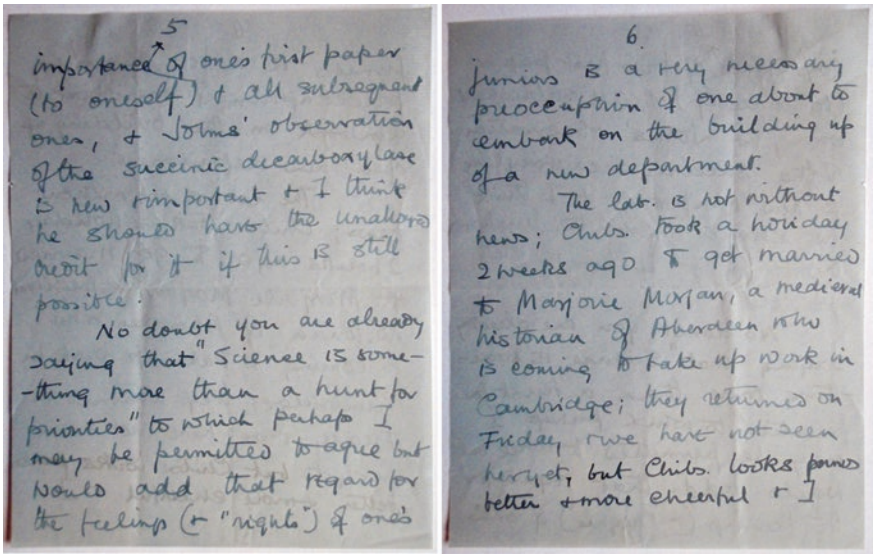

Fig. 8.2 "No doubt you are already saying that 'Science is something more than a hunt for priorities' to which perhaps I may be permitted to agree but would add that regard for the feelings (or 'rights') of one's juniors is a very necessary preoccupation of one about to embark on the building up a new department." Stephenson to Elsden in her letter dated 15 June, 1947 (Newnham College Archive. Image reproduced with the permission of the The Principal and Fellows, Newnham College, Cambridge)

evident, for instance, in her description of her good friend and prominent biologist Muriel Robertson's[3] visit in Stephenson's house in 1947 [8]:

> I survived Muriel's visit by the use of several expedients; for one thing she had several visits to pay which she took her off for several mornings and most afternoons; then I made her read Prof. Butler's rather dull book on the man and tell me what was wrong with it, she found it as an irresistable [sic!] challenge.

Elsden's commentary to the letter points out [7, p. 7]:

> Muriel Robertson […] was a great friend of MS, the one problem with her was her continuous conversation—very interesting always, but exhausting. M.S. play ws feed her with books on controversial subjects.

But Stephenson's letters to Elsden are far from being just jokes and chitchat. She confided to him her personal and professional problems and also (as shown in the previous chapters) her concerns about the situation in the Society for General Microbiology or the prospects of the Cambridge Biochemistry Department. She also discussed with him his future career and careers of her former students.

[3]Muriel Robertson (1883–1973), British protozoologist and bacteriologist, worked at the Lister Institute. Cooperated with Stephenson during WW2 and wrote Stephenson's official obituary published by the Royal Society [13].

Elsden, after getting his Ph.D., with Stephenson joined in 1942 the ARC[4] Unit of Animal Physiology in Cambridge, and then in 1946/47 was working for a year at the Hopkins Marine Station in Pacific Grove, California, so that about half of the letters were written during his American sojourn. Caring attention emanates from Stephenson's letters she wrote to Elsden the US especially because she was concerned about the brain drain which threatened Great Britain after World War. Although she understood how important had been the American experience for her talented pupil, she warned him in harsh words of the temptations of big money [9]:

> Werkman[5] was in Paris and attempted to seduce Gale; $ 6000 was his price; EFG[6] pushed him up to that figure and then cut the rope – bump –. Industry in the USA is sucking science dry and the academic potentates are adopting a policy of kidnapping in Europe. […] In my view for young men to leave reasonable conditions in their own country to grow rich quick in the USA equates them to Quislings.

In spite of her disapproval of the brain drain tendencies, however, Stephenson was a dependable tutor and the future of her students was for her above politics. At the beginning of 1947, when Elsden had raised a question about staying in the USA,[7] she advised him not to come back because of the unsettled working conditions in Britain [10]:

> "Dear Sidney, don't come home; you will only hang about doing nothing for weeks and weeks; the A.R.C.[8] won't make up its mind yet and won't be influenced by your presence anyway; and you will only have wasted a good [?] opportunity for working with van Niel[9] and greatly increasing your scope of usefulness:" At the end she repeats in capital letters: "DONT COME HOME. Ever yours MS."

Even in her letters Stephenson could not deny her teaching temperament, like in a painful lesson of lecturing she gave Elsden after he returned home in 1947 and was appointed in 1948 Senior Lecturer in the University of Sheffield. It is worth quoting it in full length with the underlining and missing punctuation [11]:

> Meanwhile I propose to explode a rocket under your chair because I realise that if I don't no one will. It is this (dear Sidney) your lecturing habit has become very bad and I must be remedied because we cannot afford to let it go on. Briefly it is this: you take at least 3 times too long to say what you have to say, first you now talk at dictation speed this is literally true this means you decrease your rate by at least a factor of 2-probably more-. next you give the most enormous pauses so that the interval between one sentence and the next

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[4]Agricultural Research Council.

[5]Chester H. Werkman (1893–1962) American microbiologist from the Iowa State University specializing in physiological and chemical microbiology.

[6]Ernest F. Gale.

[7]Elsden's commentary: "Following Sir Joseph Barcroft's death I did raise the question of coming back from the U.S." [7] J. Barcroft (1872–1947) was British physiologist, since 1941 head of the animal physiology unit of the Agricultural Research Council in Cambridge (Dunn). Elsden apparently aspired to his position.

[8]Agricultural Research Council.

[9]Cornelius B. Van Niel (1897–1985), American Dutch microbiologist with whom Elsden worked in the US.

> is sometimes equivalent to length of other sentences. Truly you pad out with the free use of such material as 'in my opinion', 'the importance of this consideration can hardly be exaggerated'; 'as has many times been remarked before' etc. etc. I do beg you to take this seriously: comes you not for a bit write out your lectures and addresses and then prune out the undergrowth. It is far far better to read a lecture than to go on like this.[10]

She later must have felt sorry for her tone as she was aware of the fact that her pupils did not perceive her as a brilliant lecturer [12]:

> You are very sweet to take my hurtful remarks about your lectures though in the end I expect the prickly pear will bear figs. I must clear up, I do not ask you to imitate Ernest's[11] *Multum in parvo*[12] style; though I regard his lectures as a notable achievement. I am often doubtful whether they are optimal for students; but I have always been so slow witted myself that even at the best I was never any rule of the rate at which clever modern students could absorb.

We only have random knowledge about Stephenson's political views and her participation in social movements. Although she belonged to the political left [13, p. 568], she did not adhere to any 'party line' [5, p. 378], but in the 1930s was active in the *Cambridge Scientists' Anti-War Group*, together with her left-wing friends Dorothy and Joseph Needham, Norman Pirie and his biochemist wife Antoinette (Tony, née Patey), Dorothy Hodgkin,[13] and others. She did her best to assist European intellectuals whom the fascist regimes forced out from their countries and who found refuge in Great Britain. After World War II, Stephenson was also elected vice-president of the *Association of Scientific Workers* (of which Hopkins had been president before) [14].

An important question is, whether Stephenson was a feminist. In Robertson's opinion "Marjory Stephenson had worked for women's suffrage in her youth", but later she "lost her interest in feminism as such. All her life, nevertheless, she was a warm supporter of women's education and encouraged their work in many fields" [13, p. 567]. Of her co-workers listed in Supplement 1 at least 25 % were women, mostly in research positions, whom she helped as much as she could to pursue a successful scientific career, which was not always the case when a woman achieved an elite position within the scientific community.

In this context we may ask whether Stephenson's research and problem-solving style may also be understood as gender-related. We can certainly find a parallel between her concept of general microbiology and Barbara McClintock's

[10]Elsden commented Stephenson's criticism of his lecture in the following way: "A beautiful example of M.S. at her [?] forthright. I had delivered an appalling lecture to the Biochemical Society Symposium on Chromatography and wrote to agree with her" [7, p. 9].

[11]Ernest Gale.

[12]Latin expression which means "much in little".

[13]Dorothy Mary Crowfoot Hodgkin (1910–1994), chemist and crystallographer, confirmed the structure of penicillin and vitamin B12. She was awarded Nobel Prize in 1964 "for her determination by X-ray techniques of the structures of important biochemical substances".

"feeling for the organism".[14] According to E.F. Keller, McClintock's biographer, "to McClintock, nature is characterized by an a priori complexity that vastly exceeds the capacities of human imagination" [16, p. 162]. Stephenson respected this complexity as we can notice, for instance, in her famous lecture on *Levels of Microbiological Investigation*[15] where she called attention to the necessity of studying cells at various degrees of complexity and pleaded for better understanding of bacteria as they are found in Nature, a view that has been neglected both by biochemistry of the 1950s and contemporary molecular biology. We may ask together with Keller, whether such perception of science and nature reflects McClintock's and Stephenson's gender. Keller rightly argues against such a simplified view, which confirms "our most familiar stereotypes of women." Stephenson, as well as McClintock would [16, p. 173].

> disclaim any analysis of her work as a woman's work, as well as any suggestion that her views represent a woman's perspective. To her [and to both of them, SŠ], science is not a matter of gender, either male or female; it is, on the contrary, a place where (ideally at least) 'the matter of gender drops away'.

Although Stephenson's life was inseparable from her work, she also had many hobbies and interests. She read widely and could not imagine her life without books. She appreciated good food and wine and loved to cook for friends invited to her house. Travelling, listening to classic music, riding and painting in oil were other forms of her distraction [17]. But above all, Stephenson's love of nature found its expression in her passion for gardening in which she believed as a "cure for social ills" [14]. She had a garden at Romsey House, Mill Road, where she lived until 1935. Her new house which she built in 1935 at 16 Latham Road (Fig. 8.3)[16] [13] had a large garden where she planted many fruit trees, "including an apple-tree of the same variety as that from which Isaac Newton saw the apple fall" [19, p. 57]. Robertson, who used to be Stephenson's frequent guest, recalls in her obituary that [13, p. 568]:

> In [gardening] she took an increasing interest, as time went on, so that she became extremely well-informed about grafts and scions and the attractive mysteries connected with them. […] This house was of some importance in the growth and development of her personality. […] Her informal hospitality could be given scope here so that she would entertain the most various people. […] The atmosphere of this house and the pleasant rather casual kindness that seemed always to inform it have given happy memories to many of her friends and to many people who would hardly claim the title.

No wonder, some amusing notes about gardening also crept into Stephenson's correspondence dealing mostly with professional matters, although even in this context she could not deny her inclinations to instruct people. In her letter to

[14]Barbara McClintock (1902–1992), American geneticist, Nobel Prize winner (1983), whose life and work was brilliantly elaborated by Keller [15].

[15]See Chap. 8.

[16]According to Cope, Stephenson lived in Latham Road from 1934. She was able to build the house thanks to the inheritance from her father who died in 1929 [18].

Fig. 8.3 The house in Latham Road that Stephenson built in 1935 (Personal archive of Prof. Michael Yudkin. Image reproduced with permission of Prof. Yudkin)

Sidney Elsden written in October 1948, she reacts to his and Erica's (Sidney's young wife) invitation [2]:

> I should like to visit you very much and see your garden. I should also like to bring you a young apple tree on No [November] 9 which you can train as a dwarf pyramid so please leave room for one.

About three weeks later, she returns to the apple tree issue (Fig. 8.4) [12]:

> I hope your house and garden give satisfaction. I expect you may have planted your fruit trees by the time I come up be sure to plant with the swelling which denotes where the young tree was first budded at least one clear inch above the ground [a picture is included]. Any fruit growing manual will tell you how to plant; it is v. [very] important in all details.

It is hard to believe that all these letters we have quoted from, factual and caring, humorous and matter of fact, were written in the shadow of terminal cancer.

We do not know exactly when Stephenson noticed for the first time the outbreak of her breast cancer. Elsden mentions her mastectomy[17] which she had around 1943,[18] while according to Cope "in September 1944, at the age of 59, Marjory was diagnosed with breast cancer for which she was treated with surgery in the Evelyn Nursing Home, returning to work before the end of the year" [18].

[17]Surgical removal of breast.

[18]We can only deduce this from Elsden's remark to Stephenson's letter dated 15 October 1948 [7, p. 8].

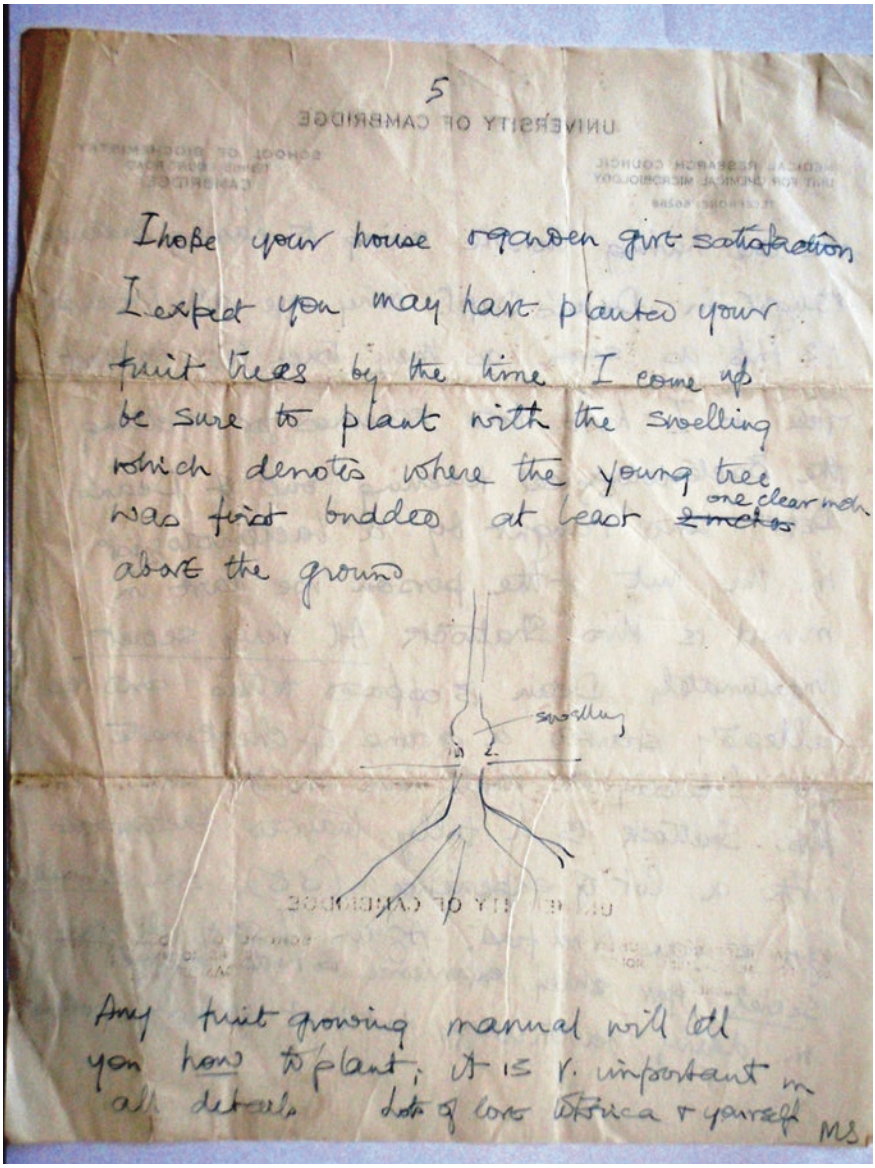
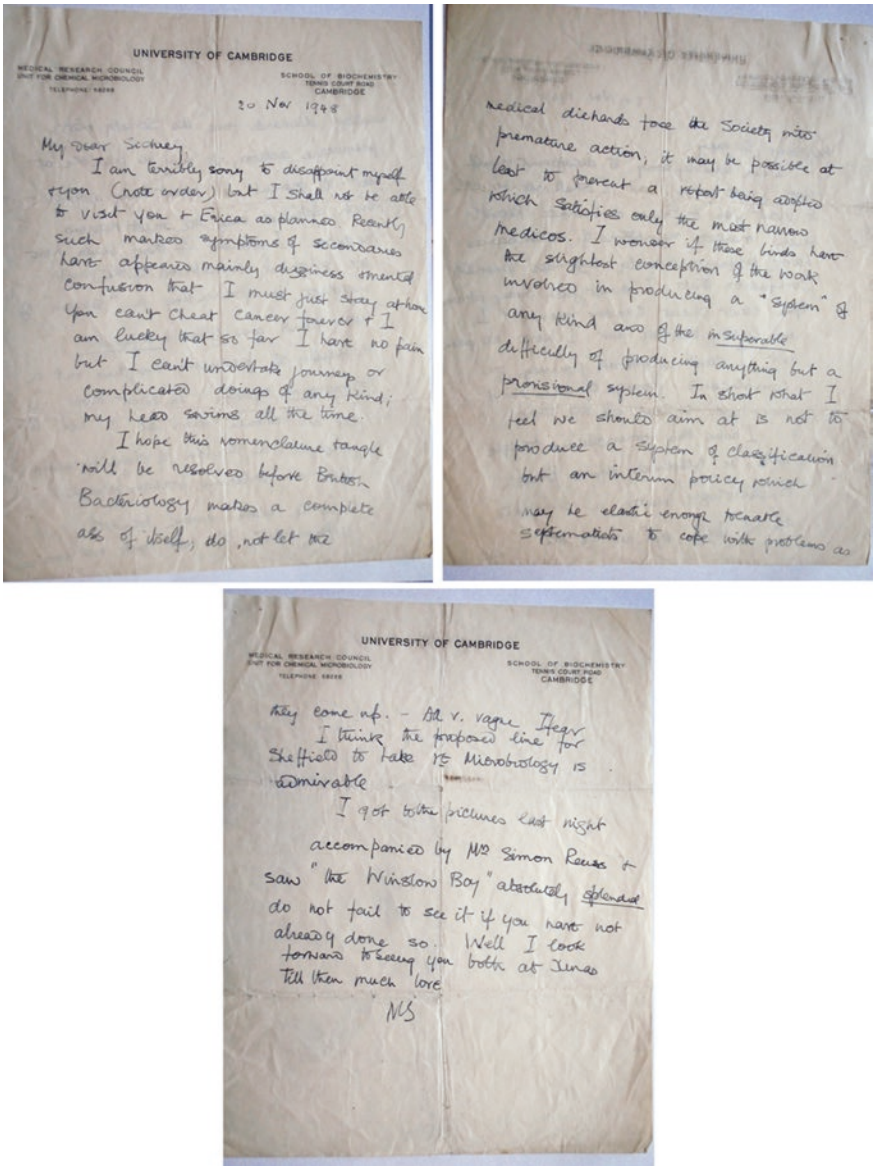


Fig. 8.4 Stephenson explains to Elsden how to plant an apple tree (letter of 9 November 1948) (Newnham College Archive. Image reproduced with the permission of the The Principal and Fellows, Newnham College, Cambridge)

Anderson points out that "her health was impaired since 1945" [19, p. 56]. All in all, it appears that Marjory did not confide with her illness even to her close collaborators. Stephenson's resignation letter she sent Mellanby on October 5, 1948



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TELEPHONE 54248

SCHOOL OF BIOCHEMISTRY
TENNIS COURT ROAD
CAMBRIDGE

20 Nov 1948

My dear Sidney

I am terribly sorry to disappoint myself & you (note order) but I shall not be able to visit you & Erica as planned. Recently such marked symptoms of secondaries have appeared mainly dizziness & mental confusion that I must just stay at home. You can't cheat cancer forever & I am lucky that so far I have no pain but I can't undertake journeys or complicated doings of any kind; my head swims all the time.

I hope this nomenclature tangle will be resolved before Enteric Bacteriology makes a complete ass of itself, do not let me

medical dictators force the Society into premature action, it may be possible at least to forecast a report being applied which satisfies only the most narrow medicos. I wonder if these kinds have the slightest conception of the work involved in producing a "system" of any kind and of the inseparable difficulty of producing anything but a provisional system. In short what I feel we should aim at is not to produce a system of classification but an interim policy which may be elastic enough to enable systematists to cope with problems as

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they come up. – All v. vague I fear.
I think the proposed line for Sheffield to take is Microbiology is admirable.

I got to the pictures last night accompanied by Mrs Simon Reuss & saw "The Winslow Boy" absolutely splendid do not fail to see it if you have not already done so. Well I look forward to seeing you both at Xmas Till then much love

MS

Fig. 8.5 Stephenson's last letter to Elsden dated 20 November 1948 (Newnham College Archive. Images reproduced with the permission of the The Principal and Fellows, Newnham College, Cambridge)

testifies [20] that the second outbreak of lung cancer which is "so far controlled satisfactorily" occurred in May 1947. She is still trying to depreciate her illness when she writes: "Actually my bad memory and slow mental processes are more

trouble to me than the aforesaid cancer, so please do not picture me as an invalid or unable to carry on normal avocations" [19]. On October 15, she mentions her disease in the P.S. of her letter to Elsden: "I have sent in my resignation both to the University and the MRC to take effect at Xmas a proceeding I know you will bless. My memory is worse than ever and general health poor." [2] Stephenson's health was rapidly deteriorating and at the end of November 1948 she complained in her very last letter to Elsden of dizziness and mental confusion which made her to stay at home (Fig. 8.5). "You can't cheat cancer forever and I am lucky so far I have no pain but I can't undertake journeys or complicated doings of any kind" [21]. In spite of facing the inevitable end, Stephenson continued working and even prepared a paper for press shortly before her death on December 12, 1948 [19, p. 56]. The same day she died in the Evelyn Nursing Home in Cambridge [14]. The Memorial Service was held in the presence of her friends, collaborators and many distinguished personalities at King's College Chapel on 15th January 1949.[19]

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10. Stephenson to Elsden, 16 April 1947. Newnham College Archives, Papers of M. Stephenson
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[19]Cope [17] mentions among the personalities who came to pay tribute to Stephenson, for instance, Sir Alexander Fleming; Sir Edward Mellanby, Secretary of the MRC; Charles Raven, Master of Christ's College; Dame Myra Curtis, Principal of Newnham College; representatives of the Society for General Microbiology as well as many research institutes and academy departments with which Stephenson had connection. Documents related to the Memorial Service are kept at the Newnham College Roll Office, File on M. Stephenson.

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21. Stephenson to Elsden, 20 November 1948. Newnham College Archives, Papers of M. Stephenson

Chapter 9
Conclusions: What Is Left Behind

Stephenson (Fig. 9.1), whose research built on the strategic programme of dynamic biochemistry of F.G. Hopkins, is considered founder of chemical microbiology, a field which investigated biochemical events in microorganisms to get a deeper understanding of cellular biochemistry and its organization. Experimental results of her laboratory indicated that metabolism in microorganisms and its control is governed by regularities analogous to those in higher organisms, an observation which had multiple consequences. It supported the principle of unity in biochemistry which justified using various microorganisms not only as objects of research, but also as models enabling deeper comprehension of general cellular phenomena and their organisation in all types if cells, including the cells of higher organisms. Introducing microorganisms as models also paved the way towards research into enzymatic adaptation (later known as enzymatic induction) in bacterial cells which culminated in the years 1936–1938 in the so-called mass action theory of enzyme formation advanced by J. Yudkin. These new principles, along with some methodical innovations designed in Stephenson's laboratory, were taken up by molecular biology as a point of departure for the theories of cellular regulatory mechanisms and protein synthesis developed in the 1950s and 1960s. Besides, Stephenson and Gale as early as in 1948 fostered the idea that microbial models might resolve how genes act in the cell and were among the first who accepted the Avery–MacLeod–McCarty experiment as a valid proof of the essential role of DNA in heredity [1, p. 306]:

> The microbe thus supplies ideal biochemical material for the study of anabolic processes, giving results which may prove to be valid for both animals and plants. **It also promises to provide a clue to the mechanism by which the gene controls the production of enzymes and so controls the development of the cell.** In the brilliant work of Avery, MacLeod & McCarty (1944) it has been shown that the rough (non-encapsulated) Type II pneumococcus can be transformed permanently into a new type producing the polysaccharide capsule characteristic of Type III. This has been done by incorporating into the growth-medium of the rough form of the Type II organism minute amounts of a

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Fig. 9.1 Stephenson in her final years. Photo by Walter Stoneman. (Newnham College Archive. Image reproduced with the permission of the The Principal and Fellows, Newnham College, Cambridge)

rigidly-purified desoxyribonucleic acid obtained by the disintegration of the Type III organism. This transformation seems to be equivalent to the incorporation in the Type II cell of a new gene controlling the the enzymic production of the Type III polysaccharide.

During World War II, Stephenson and her collaborators were involved in projects related to strategically significant biotechnological production of organic compounds and this way contributed also to the fast advance of British post-war biotechnology.

Chemical microbiology as a new interdisciplinary research field introduced by Stephenson evolved stepwise in the years 1930–1948. Among its "parent" disciplines we may include microbiology, biochemistry, bacterial physiology, physical and organic chemistry. The "field" acquired gradually some features of a scientific discipline: an explicit strategic programme envisioned in Stephenson's monographs; a well-defined subject and objective of research, (including specific methods); specialized institutional and educational base; institutionally anchored scientific community; and adequate social acknowledgement. Stephenson also actively participated in the establishment of the institutionalized interdisciplinary field of general microbiology which integrated research into diverse forms

of microorganisms at various levels of organization on common grounds, encompassing aspects of chemical microbiology, microbial physiology, nutrition, chemotherapy, systematics and ecology. The sources indicate, however, that she had to defend the research programmes of chemical microbiology and general microbiology against traditional medical bacteriology both within the MRC as well as the Society of General Microbiology.

Another circumstance which obviously interfered with the free expansion of Stephenson's ideas was the ambivalent position of her laboratory which had never acquired the official status of a Unit within the MRC, and her own indeterminate position of an "unappointed director". In spite of such unfavourable state of affairs, Stephenson's research programme attracted to the laboratory a great number of collaborators and pupils both from Britain and abroad and she herself became an international authority in the field of bacterial metabolism. The laboratory also cooperated with other research establishments especially during World War II when Stephenson supervised several British warfare related projects. However, regardless of such impressive circle of co-workers, pupils and trainees she never created what we may call a "scientific school". They acquired her methods and working style but sometimes applied their knowledge and education also in various other related domains or themselves opened new fields[1]; her direct successor became Ernest Gale as a director of the officially MRC Unit of Chemical Microbiology established in 1948 and Professor of Chemical Microbiology at Cambridge University appointed in 1960.

In spite of her unquestionable essential contribution to the development of several scientific fields in the first half of the 20th century, Stephenson not only did not leave a visible trace in the form of a scientific school, but became one of the forgotten or nearly forgotten scientific personalities being rediscovered only recently. Although her methods and findings became firmly incorporated into the foundations of molecular biology, practically no history of molecular biology has mentioned her important contribution to its formation. Not even Magasanik's paper which explicitly points to a "small number of microbiological discoveries in the 1940s (that) were responsible for the dramatic transition from microbial biochemistry to molecular biology and consequently for the movement of microbiology from the periphery to the center of biology" [2, p. 357]. Although this statement in fact characterizes the essential contribution of Stephenson's team to the rise of molecular biology, Magasanik mentions in this context neither Stephenson nor any of her collaborators. One explanation why Stephenson's role in the development of molecular biology has been omitted might be her research style which focused more on designing methods and accumulation of hard data than on advancing theories and hypotheses. Another clue might be the absence of a scientific school whose members usually carry on the ideas of its founder and further nurture the reputation of their teacher. In Stephenson's case we also should consider the role of the sharp paradigm shift from biochemistry to molecular biology which was taking place in the 1940s and 1950s; she paved the way for the emergence of molecular biology, but was absent during it formation.

[1]For instance, John Yudkin became one of Britain's leading nutritionists.

Such episode of a typically "forgotten" scientist raises, however, a more general question what conditions might be determinative in recognition of a scientist in his/her lifetime and permanent acknowledgement by the future generations. Historians and sociologists of science have unearthed cases of "forgotten" scientists who fell into oblivion in spite of their important contributions to the treasury of world science. mostly because they did not fit into the category of the "famed" scientists.[2] No doubt that most of the "forgotten" scientists are women, even those whose scholarly contributions are unquestionable. The reasons and circumstances of undervaluing of women's contribution to science (as well as medicine, arts, literature and other fields) and their omission from histories and dictionaries has been highlighted and analyzed by Margaret Rossiter and named *Matilda effect* [4].

The story of Marjory Stephenson, a prominent woman scientist of the first half of the 20th century, also raises the issue of position of women scientists in male dominated scientific communities, in this case in Britain. Although Britain was in many respects more progressive in offering qualified job opportunities to women and accepting women in scientific societies than Central and Eastern Europe or even France, only a few women had reached in Stephenson's lifetime top university or research positions. Women mostly remained in lower posts not only in universities but also in government controlled institutions like the MRC and had to face various discriminatory practices. Stephenson's career was from this perspective exceptional as she was able to attain higher achievements: design and realize her own research programme; achieve managerial and decision-making post in the MRC and teaching position in the Cambridge faculty hierarchy, and take a prominent status in the British and international scientific community. Although the MRC obviously discriminated its qualified women employees, Stephenson herself was faced with open intolerance or prejudice associated with her scientific and managerial activities only very rarely. Her superiors, colleagues and co-workers unanimously recognized her competence and charisma. It was the official status symbolized by posts, titles and adequate technical assistance which made the difference between the acceptance of a man and a woman scientist of similar qualities.[3] That is why Stephenson's laboratory was never officially acknowledged *de iure* as an independent MRC Research Unit (although in reality it functioned as

[2]The opposite of the "forgotten scientist" is the "famed scientist" who is characterized according to Merton and Rossiter [3, 4] by charisma, previous reputations, positions in large institutions or research schools and well-placed disciples which help them to get even more fame.

[3]We can even find in recent history of science a number of examples which illustrate the difference between the official reception of a man and woman scientist of comparable qualities. The story of John Needham and Dorothy Needham was already mentioned in this book. As another instance could serve the case of the biochemist Gerty Theresa Cori (1896–1957) who shared the Nobel Prize with her husband Carl Cori (1896–1984) in 1947. The spouses had the same university education and scientific background and worked during Gerty Theresa's lifetime in equal cooperation. In spite of that Gerty Theresa could for a long time get only the job of an assistant at the New York State Institute for Study of Malignant Disease in Buffalo and the Washington University School of Medicine in St. Louis, and was appointed professor only in 1947, 16 years after her husband.

such) and only had a few staff on the MRC's payroll. Also her delayed nomination for Reader at the Cambridge University and election for Fellow of the Royal Society or President of the SGM was apparently motivated by the fact that she was a woman; an experience still not uncommon to women scientists in the present times, particularly in some countries.

It is not so simple to decide what circumstances and personal qualities made Stephenson so different of most contemporary women scientists and motivated her to break the vicious circle and take a for a woman an unusually prominent position in the scientific community. Apparently her extraordinary skills and courage to stand up against prejudice and devote her life to science were awakened by her open-minded family education, the first-rate Newnham College instruction and women-friendly environment in Hopkins' laboratory with a very high concentration of brilliant personalities. Pnina Abir-Am told me recently about an interview with John Edsall (1902–2002) the outstanding American biochemist and historian of biochemistry, who met Stephenson in Cambridge in 1924 and was impressed by her "reparteeing with the very clever JBS Haldane" [5]. Such behaviour must have been very unusual for a woman in those times if Edsall remembered it after almost 70 years. In 1924, Stephenson, although 17 years older than Edsall, was only starting her research career while Haldane was a star in biochemistry and biology, a polymath, considered one of the most brilliant minds in the 20th century known for his sharp and ironic way of conversation. Edsall's remark indicates Stephenson's communication ability, charisma, healthy self-esteem, sense of humor and courage which predestined her to the position of leader and organizer. These features along with her thirst for knowledge, meticulousness and her image of a pragmatic, friendly, sympathetic and high-principled person with deep humanitarian ideals were confirmed repeatedly in the memories of her friends and coworkers. Stephenson evidently did not suffer of the "Curie complex" observed by Rossiter [6][4] and found her way to social networks of her men contemporaries as well as she became a new type of role model to her numerous women and men collaborators.

Stephenson acted in a period that was to become a milestone in a number of scientific disciplines and should be ranked among the scientists who lead the way to new territories. At the same time, she herself represented a milestone being a representative of a rare genre of women scientists who deliberately and resolutely penetrated also into new social circles of which they used to be excluded.

[4]To characterize this phenomenon I will use the words of Julie Des Jardins who has approached the problem recently: "The historian Margaret Rossiter noted an inferiority complex in women after Curie's tours of the United States in the 1920s, and for generations the Curie complex has continued to allow men to disqualify women—and women to disqualify themselves—from science. Women scientists have felt as though they cannot measure up to Curie, and of course how could they, when this mythical measure of female competence has morphed in the American mind over and over again?" [7, p. 5–6].

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Supplements

Supplement 1. Collaborators of Marjory Stephenson in the Years 1922–1948

The following list represents an attempt to prepare an overview of people who worked with Marjory Stephenson not only in her Cambridge MRC laboratory, but also under other circumstances. As sources of information have served Stephenson's annual and other reports submitted to the MRC[1]; lists of workers in the University of Cambridge supported by the MRC[2]; Stephenson's correspondence kept at the MRC Archives; Stephenson's bibliography[3] (for co-authors), biographies cited in Note 4; list of workers of the Hopkins laboratory[4]; and other sources cited separately. The collaborators are listed in each subdivision roughly in a chronological order according to the years when they worked with Stephenson. The following data (if available) are given with each name: years in which the person was attached to Stephenson; details of position, salary, etc. years in which he or she was affiliated to Hopkins' Department (if known, e.g. H. 1938–1940), and a short notice on immediate further career. Some data might be incomplete or even erroneous, but in spite of this I consider them useful for the orientation of the reader.

1. Collaborators at the MRC research Unit in Cambridge (Staff paid by the MRC and other fellowships, researchers attached to the Unit paid from other sources, graduate students, technical assistants).

[1]MRC Archives 2036/1/I, 2036/2/I-III.

[2]MRC Archives 2036/1/I.

[3]The most complete bibliography of Stephenson's works can be found in Robertson, Marjory Stephenson, op. cit., pp. 576–577.

[4]Collaborators, Colleagues, op. cit.

S. Štrbáňová, *Holding Hands with Bacteria*, SpringerBriefs in History of Chemistry, DOI 10.1007/978-3-662-49736-4

Margaret Dampier WHETHAM
1921–1927, MRC grant; married A.B. Anderson 1927; 5 children, in the years 1948–57; abstracting work.[5]

Hugh L.A. TARR
1931–1934; student from Montreal, Australia.

Dorothy MOYLE–NEEDHAM
1931 and 1945–1952, small personal MRC grants; H. 1919—at least 1948.

Donald Deveraux WOODS
1933–1939; 1933 Ph.D. student of MS, DSIR Grant, Beit fellowship;
1939 attached to P. Fildes London and Middlesex Hospitals.

John YUDKIN
1931–1935 Ph.D. student; part-time Department of Colloid Science; 1945 Prof. of Physiology, King's College of Household and Social Science in London.

Ernest GALE
1936–1948; 1936–1939, Ph.D. student; 1937–1939, MRC full-time personnel as assistant to MS; 1939–1948, 1851 Exhibition and MRC grants; 1948 successor of MS as Director of the Unit; 1960 Professor of Chemical Microbiology Cambridge University.

David Ezra GREEN
1938, MRC Grant for expenses; H. 1932–1940, American Beit Fellow; Columbia Univ., New York; Professor of Biochemistry, University of Wisconsin, Madison Wisconsin.

Ronald DAVIES
1941-?; MRC staff member.

Helen M.R. EPPS (Mrs. Tomlinson)
1941–1942; H. 1941–1945, research grant.

W.E. van HEYNINGEN
1941–1943, MRC maintenance and expenses grant.

R.N. BEALE
1941–1943, technical assistant.

E.E. SAMPSON (Miss)
1941–1943, associated worker; Streatfield Research Scholar, Royal College of Surgeons Scholar.

J. Herbert WAELSCH[6]
1941; H. 1939–1941; refugee scientist from Czechoslovakia.

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[5]Newnham College Register, op. cit., p. 38; Newnham Roll Office, File on M.D. Whetham (Mrs. Anderson).

[6]Soňa Štrbáňová, Czechoslovak Biochemists, op. cit.

Arnošt KLEINZELLER[7]
1942–1943, MRC grant; H. 1941–1944; refugee scientist from Czechoslovakia; 1943–1945 advisor to Czechoslovak Health Council, UK; after 1945 Dozent of Biochemistry Technical University and Charles University, Prague and Czechoslovak Academy of Sciences, Prague.

Jennifer MOYLE
1944-?; later collaborator of P. Mitchell.

Margaret Patricia HORLICH
1944, research assistant.

M.E. SIDAWAY
1944, research assistant.

Edith S. TAYLOR
1944–1945; H. 1946-?

J. TOSIC[8]
1946–1947?; left for Edinburgh

2. Collaborators—members of the Biochemistry Department; external co-authors of papers.

Juda H. QUASTEL
1924–1926; H. 1921–1927; 1947 Professor of Biochemistry McGill University, Montreal, Canada.

Herbert I. COOMBS
1926; H. 1923–1927; Australia.

Robert P. COOK
1927–1928; H. 1926–1932, 1935–1940; Lecturer in Biochemistry, Univ. of St. Andrews, Dundee.

Leonard H. STICKLAND
1928–1934; H. 1928–1934; Lecturer in Biochemistry, University of Leeds.

Joseph NEEDHAM
1931; H. 1922–at least 1948

Malcolm DIXON
1936; H. 1921–at least 1948; Reader in Enzyme Biochemistry Univ. Cambridge.

Perry W. WILSON
1936; H. 1936; Professor of Agricultural Bacteriology, Univ. Wisconsin, Madison, Wisconsin, USA.

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[7]Ibid.

[8]It is not clear how long and when did Tosic work with Stephenson. Around 1945 he was at the University of Sheffield as shows his address in a publication in the Biochemical Journal in January 1946.

David J. BELL
1936; H. 1936–at least 1948; University Lecturer in Biochemistry, Univ. Cambridge.

Charles E. CLIFTON
1936–37; H. 1936–1937, American visitor; Professor of Bacteriology, Stanford University CA, USA.

Arthur R. TRIM
1938; H. 1937–39; 1942 Senior Scientific Officer ARC Unit of Plant Biochemistry, Cambridge.

Jack L. STILL
1940; H. 1938–1940, student from the University of Sidney, Australia; Lecturer in Biochemistry, Univ. of Sidney.

Elsie WATCHORN
1941; H. 1924–at least 1948; University Demonstrator of Biochemistry, Cambridge Univ.

Hugh K. KING
1941; H. 1939–1941; Lecturer, Department of Bacteriology, Edinburgh Univ. Medical School.

Denis HERBERT
1941–1943; H. 1938–1943; Scientific Officer of the National Institute of Medical Research, UK.

Philippa H. HERBERT
1942–1943; H. 1942–43; Research worker, Department of Human Anatomy, Oxford Univ.

Ruth E. Van HEYNINGEN
1942; H. 1940–1943; Research worker Oxford Univ.

Hans A. KREBS
1941/H. 1933–1935; Professor of Biochemistry Sheffield Univ.; Nobel Prize 1953.

Margaret E. ROWATT
1944–47; H. 1944–1947; Department of Biochemistry Sheffield Univ.

Peter D. MITCHELL
?; H. 1942–1955; Zoological Institute Univ. Edinburgh; Glynn Research Labs. Bodmin; Nobel Prize 1978.

Norman Wingate PIRIE
?1945–1948; H. 1929–1940; Head of Department of Biochemistry, Rothamsted; Agricultural Res. Station, Harpenden.

J. BADDILEY
1945.

K. HARRISON
After 1945

Roger Y. STANIER, 1945–1947 Guggenheim Fellow

3. Loosely attached collaborators, mostly from outside the Biochemistry Department.

L. COLEBROOK

A. STANLEY GRIFFITH, MRC Field Laboratory, Cambridge.

Paul FILDES, London and Middlesex Hospitals.

Dorothy JORDAN-LLOYD, 1923–1924/H. 1915–1920; Research Labs. Leather Trade Association Director 1927.

William W.C.C. TOPLEY, 1926; Manchester.

Howard W. FLOREY, 1931; Pathology Department, Cambridge Univ., Nobel Prize 1945.

T.R. PARSONS, 1941–1942.

J.B.C. KNIGHT, 1941–1943, Lister Institute.

Muriel ROBERTSON, 1943; Lister Institute; biographist of Stephenson.

M.R. POLLOCK, 1944; National Institute for Medical Research, London.

4. Others (Names appearing in various connections and unclarified cases).

M. SMITH, 1931; co-author of a paper with the Needhams and Stephenson.

J. SHEPARD, 1931; co-author of a paper with the Needhams and Stephenson.

Patricia GREEN (Mrs. CLARKE), 1939; distinguished biochemist, pupil of Stephenson who influenced her in specializing in biochemistry and genetics of bacteria.[9]

ELSTREE, 1941–1943; listed among collaborators of the gas gangrene project.

James KEPPIE, 1943; co-author of paper with M. Robertson, listed among collaborators of the gas gangrene project.

E. RODAN, listed in Report 1939–1945 as assistant to some nutritional work.

A.W. RODWELL,? 1948; Australian CSIR travelling fellowship; 1949 listed as attached worker to the MRC.

[9] http://www.theguardian.com/science/2010/feb/15/patricia-clarke-obituary, accessed 12 December 2015.

Supplement 2. Chronology of Stephenson's Life and Work

1885	Born 24 January at Burwell to Robert Stephenson and Sarah née Rogers
1897	Boards Berkhampsted High School for Girls in Hertfordshire
1903–1906	Studies chemistry, zoology and physiology at Newnham College in Cambridge
1906	Teaches and studies at Gloucester School of Domestic Science and also
1908	Visiting Lecturer at Cheltenham Ladies' College
1910	Teaches at King's College for Women, in London (Kensington)
1911	Invited by R.H.A. Plimmer to teach advanced classes in the biochemistry of nutrition at the University College London and join Plimmer's research group
1912	Publishes her first paper in the *Biochemical Journal* on the enzyme lactase in dog intestine
1913	Receives a grant from the Newnham College and the Beit Memorial Fellowship for Medical Research
1914	First World War starts
1914	Volunteers for war service with the Red Cross
1916	Serves the Red Cross in Salonika (Greek Macedonia)
1918	Completes her service and is decorated Member of the Order of the British Empire (M.B.E.) and Associate of the Royal Red Cross (A.R.R.C.) 2nd Class awards
1918	Takes up her Beit Fellowship
1919	Joins F.G. Hopkins in the Biochemical Laboratory in Cambridge and becomes an associate (later a fellow) of Newnham College
1921	Switches her research to microbial biochemistry
1922	The Medical Research Council offers her a grant renewed on annual basis
1922	Publishes (jointly with M. Whetham) her first papers on bacterial metabolism
1925	Begins lecturing on bacterial metabolism to Part II (third year) biochemistry class
1925–1935	Stephenson's laboratory publishes the most papers on new experimental techniques, bacterial enzymology and bacterial cell metabolism
1926	Attends the 12th International Congress of Physiology in Stockholm
1929	Becomes permanent "external" member of the MRC's staff
1930	First edition of *Bacterial Metabolism*
1931–1937	Enzyme adaptation studies jointly with Yudkin, Gale and other collaborators

1931	First visit to the USA (July–October)
1933	Nazis come to power in Germany
1933	On April 25 writes a letter to O. Warburg where she expresses her concern about the fate of H. Krebs; Krebs settles in Cambridge in June
1935–1936	Collaborates with Krebs
1935 (1934?)	Builds a house in Latham Road
1934	Member of the MRC's Bacteriology Committee
1936	Doctor of Science of Cambridge University
1936	Trip to Russia and Hungary (?)
1936–1938	Yudkin articulates the mass action theory of adaptive enzyme formation
1937	Starts studying nucleic acid derivatives
1939	Second edition of *Bacterial Metabolism*
1939	Second World War starts
1939	Attends the 3rd International Congress for Microbiology in New York
1940	J. Monod gets acquainted with Stephenson's and Yudkin's adaptation studies
1939–1945	Engaged in top secret projects related to warfare; coordinates work of British interdisciplinary teams
1943	Secretary to the MRC Committee on Chemical Microbiology
1943	Formal university sub-department of chemical microbiology is established under M. Stephenson
1943	University Lecturer in Biochemistry
1943	Participates in organization of the Society for General Microbiology as a prime mover
1943 (1944?)	Breast cancer is diagnosed; undergoes mastectomy
1945	The Society for General Microbiology (SGM)[10] is founded under the Presidency of Sir Alexander Fleming; Stephenson elected as member of the Committee and reads at the inaugural meeting her key lecture "Levels of Microbiological Investigation"
1945	Elected Fellow of the Royal Society
1946	Invited to the International Congress of Pasteurian Sciences in Paris
1946	First Cambridge Summer School Course in Bacterial Chemistry
1947	The third edition of *Bacterial Metabolism* goes to press
1947	President of the Society for General Microbiology
1947	SGM starts *Journal of General Microbiology*
1947	Chemical microbiology is recognized by the University as a discipline in its own right; Stephenson appointed first University Reader in Chemical Bacteriology

[10]Today Microbiology Society.

1947	Stephenson's laboratory moves to the new temporary edifice "Bug Hut"
1947	Starts regular investigation of nucleic acid metabolism in bacteria (with J. Moyle)
1947 (May)	Second outbreak of lung cancer
1948	Summer School in Bacterial Chemistry takes place in Oxford
1948 (October)	Stephenson sends her resignation sent to both the University and the MRC
1948	Dies December 12 in Cambridge
1949	Memorial Service on January 15 for Stephenson at King's College Chapel in Cambridge
1949	Third edition of *Bacterial Metabolism*
1949	The Society for General Microbiology establishes the *Marjory Stephenson Memorial Fund*
1953	The Society for General Microbiology starts awarding the *Marjory Stephenson Prize* "for any outstanding contribution of current importance in microbiology" associated with the Marjory Stephenson Memorial Lecture
1988	The Marjory Stephenson Prize is renamed the *Marjory Stephenson Prize Lecture*

Supplement 3. Main Sources to the Biography of Marjory Stephenson

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Newnham College Register 1871–1971, Volume I, 1871–1923, p. 177
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