Reflections

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Memoirs of a Biochemical Hod Carrier

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An invitation to contribute to a series of articles “authored by biochemists whose contributions have helped mark the many advances in biochemistry and molecular biology since 1905” raises a variety of emotional responses. First is, of course, a feeling of surprised pleasure that I should have been considered worthy to participate in this endeavor; as Lewis and Randall pointed out in their preface to Thermodynamics and the Free Energy of Chemical Substances (1), the edifice of science is akin to a cathedral built by the efforts of a few architects and many workers, and I have certainly never regarded myself as anything other than a hod carrier on that construction site. Indeed, I note wryly that the two contributions with which my name is (occasionally) associated, the glyoxylate cycle (2) and the formulation of the concept of anaplerotic sequences (3), occupy less than 0.6% of a widely used textbook of biochemistry (4), and much of that space is used for diagrams rather than text.

Second comes the awesome realization that my own career as a practicing biochemist already spans more than half of the century these articles are intended to celebrate; I echo Horace’s lament to his friend Postumus: “eheu fugaces, Postume, Postume, labuntur anni” (5). So, what did I do to advance biochemical knowledge in the 54 years since I embarked on obtaining my Ph.D. and my life’s work?

The Beginnings

I began my research career under the benevolent (though mostly indirect) eye of my beloved teacher, Hans Krebs. He had stimulated my interest in biochemistry by hiring me as a junior technician when I left the United Kingdom equivalent of high school in 1945 and by encouraging me to take a university degree. Although he offered me a place in his department to work for a Ph.D. after I graduated, he thought it best that I should work with his colleague Robert Davies rather than in his own group; I have recounted this previously elsewhere (6).

My chosen topic was to investigate the nature and physiological role of the urease present in mammalian gastric mucosa. Using (and first synthesizing) $^{15}$N- and $^{14}$C-labeled urea, I demonstrated that there was indeed a significant breakdown of urea to CO$_2$ and ammonia if this substrate was injected into cats and that the site of this hydrolysis was confined to the stomach but that it was totally abolished by the prior administration to the animals of a mixture of antibiotics. With the help of a bacteriologist colleague, I isolated acid-resistant bacteria that were rich in urease activity from the mucosa of cats not thus medicated (7), but I did not pursue the matter further and thereby missed the opportunity to be the first to identify *Helicobacter pylori*.

The First Taste of America

Although at the time I failed to perceive the significance of my findings to the etiology of gastric ulcers, my work was adjudged to show sufficient promise to qualify me for the award of a Commonwealth Fund Fellowship, which enabled me to work for 2 years in the United States. I had originally been invited to work at Yale by Joseph Fruton, but after I arrived in his department, he selflessly agreed to my joining Efraim Racker’s laboratory rather than his.
own and after a year to my accompanying Ef on his translocation to the Public Health Research Institute of the City of New York. This move occupied the better part of 3 months. Rather than cart equipment from New Haven to New York, I selfishly utilized this interval to put into effect a requirement of the terms of the Fellowship, which was that the holder travel extensively throughout the United States and write an essay on some topic unconnected with his/her work. I chose to investigate and write about American regional cooking and set off in my newly acquired 1940 Buick to eat my way across 39 states, but I interrupted my odyssey at frequent intervals to spend some time in various centers of biochemical research en route. Neatly bisecting my trip was a wonderfully fruitful and enjoyable period of 2 months in the laboratory of Melvin Calvin, who had generously allowed me to foist myself on him (under the impression, I later discovered, that I was Arthur Kornberg!). I was warmly welcomed also by his colleagues, particularly Andrew A. Benson, Al Bassham, Clinton Fuller, and J. Rodney Quayle, who taught me the techniques used for the isolation and analysis of labeled products formed after incubating microorganisms with $^{14}$C-labeled substrates for very short time periods. These techniques enabled me, in later years, to undertake studies on the metabolism of $C_2$ compounds in bacteria (8), fungi (9), and algae (10) that also propelled me into paths I still follow.

In New York, I continued work on the pentose phosphate pathway that was then being intensively investigated by Bernard Horecker and his colleagues (as Bernie so elegantly recounted in the Reflections article published last year in the Journal of Biological Chemistry (83)) and in Ef Racker’s laboratory. My friend Paul Srere, with whom I shared a laboratory, isolated and studied yeast transaldolase while I concentrated on transketolase. We were able to demonstrate that these two enzymes, highly purified, were able to effect the conversion of pentose phosphate to hexose phosphate (11) and that erythrose 4-phosphate was an intermediate in that process (12).

The Oxford Years

On returning to England in 1955, I was offered a 1-year appointment by Hans Krebs, who had in the mean time been awarded a Nobel Prize and had moved into the Whitley Chair of Biochemistry at the University of Oxford. After an abortive start (I had been asked to investigate a problem, the solution of which was published shortly after I arrived) I decided (with Krebs’ blessing) to investigate a question that had been originally posed to me by Ef Racker. The tricarboxylic acid (TCA) cycle yields oxidative energy by effecting the total combustion of $C_2$ units (as acetyl-coenzyme A) to $CO_2$ and water, yet the cycle also provides the precursors of many cell components. How can the cycle fulfill both functions and allow microorganisms to grow on, e.g., acetate or ethanol as sole carbon source? From my cousin Margot Kogut, who had been working in Sidney Elsden’s laboratory in Sheffield, I obtained a culture of a pseudomonad known to grow readily on acetate (13). With some guidance from knowledgeable colleagues, I managed to grow this organism on a defined medium containing acetate as sole carbon source, to harvest and wash the cells, and to expose them to $[2-^{14}C]$acetate for brief times; the products were then analyzed by the techniques I had learned in Calvin’s laboratory. The only materials that acquired $^{14}$C after even the briefest exposure (3 s) were intermediates of the TCA cycle (mainly citrate and malate) or amino acids directly derived therefrom (such as aspartate and glutamate); phosphorylated products did not become labeled until later, which ruled out the operation of autotrophic pathways (14). However, although these data apparently indicated that only the TCA cycle was involved in acetate utilization, the distribution of isotope among the labeled products was not in accordance with that cycle; after the briefest exposure to $[^{14}C]$acetate, 30% of the radioactivity incorporated appeared in citrate but over 40% in malate, with only 10% in [succinate + fumarate], although once the steady state had been reached, labeled malate contributed less to the total radioactivity than did citrate. This could be explained only by postulating a second point of entry of acetate into the TCA cycle, in which its carbons appeared in malate without first passing through succinate and fumarate (8).

A mechanism that satisfactorily accounted for this was demonstrated by a postdoctoral visitor, Neil Madsen, and myself with cell-free extracts of the acetate-grown pseudomonad which, when supplemented with coenzyme A and ATP, formed $[^{14}C]$acetyl-coenzyme A and produced labeled citrate when oxaloacetate was also added; when either isocitrate or glyoxylate was supplied, labeled malate was produced (16). When incubated in the absence of air,
extracts supplemented to form acetyl-coenzyme A catalyzed the stoichiometric net formation of malate when glyoxylate was also present, and of malate and succinate when isocitrate was added (17). The enzyme effecting the postulated cleavage of isocitrate to glyoxylate and succinate, then termed isocitritase (18), had been shown previously to be present in extracts of the same pseudomonad (19), and the “malate synthetase” that catalyzed the condensation of acetyl-coenzyme A and glyoxylate to form malate had been discovered in extracts of Escherichia coli (20); both were shown to be present and highly active in extracts of the acetate-grown pseudomonad and to be quantitatively capable of accounting for the growth of these bacteria on acetate (21). Moreover, the distribution of label in alanine and aspartate, isolated from cells grown in the presence of labeled CO₂ or specifically labeled acetate, supported the simultaneous operation of the TCA cycle and the “glyoxylate bypass” (22); the joint operation of these routes was therefore termed “the glyoxylate cycle” (2). These two pathways are illustrated in Fig. 1. However, definitive evidence for the necessary and sufficient participation of the key enzymes in microbial growth on C₂ compounds had to await studies on their adaptive formation (23–25) and on the isolation of mutants lacking one or another enzymic activity (26–28).

There are, all too rarely, occasions when a person with a solution but no idea to which problem it might apply meets a person with a problem but no knowledge of the solution. This happy conjunction occurred in 1957 when Harry Beevers was spending a sabbatical in Oxford and told Krebs of his interest in the possible mechanisms that might account for the almost stoichiometric conversion of oil to storage carbohydrates in germinating castor bean seeds. Harry and I met and immediately recognized that the glyoxylate cycle might well provide that route. The next day, Harry appeared with castor beans; we disrupted them in a blender and by late afternoon had demonstrated the presence of a highly active isocitrate lyase (as isocitritase is now more properly called). Incubation of the cell-free extract with [¹⁴C]acetate,
ATP, coenzyme A, and isocitrate yielded malate as the sole labeled product; clearly, the sought mechanism had been found (29, 30). This laid the foundation for Harry's later distinguished work that identified a novel intracellular particle (the "glyoxysome") as the location of these enzymes in plants (31); a similar compartmentation had been observed also in *Tetrahymena* (32) and in a strain of *Chlorella* (10).

Because enzymes of the glyoxylate cycle provided a route for the production of glyoxylate from acetate, the question immediately arose how microorganisms could effect what in principle was the reverse process: to grow on C₂ substrates (such as glycolate, glyoxylate, or glycine) more oxidized than acetate. I was fortunate at this time to be joined by two graduate students, Jack Sadler (who died tragically young in a climbing accident only a few years later) and Tony Gotto (who was to have a distinguished career in medicine after completion of his Ph.D.).

Jack and I were able to show that the provision of energy from glycolate could occur via a dicarboxylic acid cycle, in which an isoform of malate synthetase catalyzed the condensation of glyoxylate and acetyl-coenzyme A as the first step in a sequence of reactions that led from malate via oxaloacetate and pyruvate to the loss of two carbons as CO₂ and to the reformation of the acetyl-coenzyme A acceptor (34). Measurement of the levels of citrate and malate synthetases during growth on acetate or glycolate dramatically illustrated the relative roles of the TCA and dicarboxylic acid cycles in the oxidation of these C₂ compounds (24) and lent confidence to the view that this latter cycle might, under the right circumstances, actually be physiologically significant (35).

However, just as the oxidative TCA cycle could not, on its own, account for growth on acetate, so the dicarboxylic acid cycle could not explain how microorganisms synthesized cell components from glyoxylate or its precursors. Some ancillary route must operate to replenish the intermediates of the TCA and dicarboxylic acid cycles as they are withdrawn in the course of biosyntheses, and it was Tony Gotto and I who were so fortunate as to be able to discern such a pathway (36). It gave us particular pleasure to publish this novel route as one of three adjacent papers, the second of which complemented ours in reporting the reactions that enabled growth to occur on glycine (37) and the third of which explained how organisms grew on oxalate (38), an example of fruitful collegiate collaboration and sharing of information that appears to be regrettably rare nowadays.

The novel biosynthetic pathway we described involves: (a) the condensation of 2 mol units of glyoxylate with elimination of 1 mol unit of CO₂ to form tartronic semialdehyde; (b) the reduction by NADH/H⁺ of this C₃ product to glycerate; and (c) the interaction of glycerate and ATP to yield 3-phosphoglycerate, which is then utilized via well established glycolytic and gluconeogenic reactions.

Step (a) had been previously described (39, 40), but step (b) was catalyzed by a hitherto unknown enzyme, tartronic semialdehyde reductase (41), that we succeeded in crystallizing (42). The two pathways are diagrammed in Fig. 2.

### Independence in Leicester

Although my employers, the United Kingdom’s Medical Research Council, had tolerantly extended my initial 1-year appointment to 4 and had indeed offered to make this permanent, I felt that the time had come to leave the warm shelter of Hans (since 1958, Sir Hans) Krebs’ laboratory and test my wings elsewhere. The University of Leicester, founded as a University College in 1921 and achieving independent university status only after World War II, had only small Departments of Zoology and Botany (the latter hosting one eminent but lone geneticist) to teach the biological sciences but now decided to add a Biochemistry Department. I was offered the Chair in 1960 and together with a colleague (Gareth Morris), who was the first Lecturer to be appointed, a graduate student (John Ashworth), and a secretary I took possession of our laboratories (converted to scientific use from a previous incarnation as wards in the municipal lunatic asylum) late one summer afternoon in 1961 by climbing in through a fortunately open lavatory window; we had been most generously equipped with almost all we needed except a key to the building. I say “almost all” as we had not yet received any incubator shakers that would enable us to grow bacteria in aerated batch cultures; we therefore decided to grow what would grow readily in stationary culture on C₂ compounds in Roux bottles. By a happy accident, we chose a *Micrococcus* species as a test organism and thereby uncovered another novel route for growth on glycolate (43).
Micrococcus denitrificans, the utilization of glyoxylate proceeds by a sequence involving an initial condensation of this C₂ compound with glycine to form erythro-β-hydroxyaspartate, which undergoes transamination with a second molecule of glyoxylate to reform glycine and to yield oxaloacetate (44).

The Concept of Anaplerosis

In October 1964, the Gesellschaft für Physiologische Chemie invited me to give a plenary lecture at their fall meeting in Cologne. I chose to discuss the various pathways that serve to maintain the central metabolic routes during the growth of microorganisms on C₂ compounds. Although these pathways differ greatly in their component reactions, they nevertheless serve a common physiological purpose. It was a friend and colleague, Professor A. Wasserstein (then Professor of Classics at Leicester), who suggested the term "anaplerotic" (from the Greek for "filling up again") as a generic term and I gratefully accepted his suggestion (3).

It is seductively easy to write sequences of reactions that might fulfill some desired metabolic function; to demonstrate that they play a necessary and sufficient role requires more than paper chemistry. Fortunately, this is feasible with E. coli; the organism has but one chromosome, and a mutation in a gene that specifies some enzyme crucial to the functioning of some metabolic route would be expected to result in a readily distinguishable altered phenotype. An instance of this was provided by a happy collaboration between Ed Adelberg, who was running a summer course at the Marine Biological Laboratory, Woods Hole, and John Ashworth and I, who were running a similar course in an adjacent laboratory. Ed’s students isolated a number of auxotrophic mutants of E. coli as part of their practical work, and we garnered all that looked biochemically novel. One such mutant was particularly intriguing and together with one of our students (R. L. Ward) we established that although the mutant contained a number of enzymes that in theory might have effected the net synthesis of oxaloacetate or malate from CO₂ and pyruvate or phosphoenolpyruvate (PEP), they were unable to do so because they lacked a specific PEP carboxylase (45, 46).
In collaboration with the late Jose-Luis Canovas, I demonstrated at a later date that the enzyme required acetyl-coenzyme A as an allosteric activator (Fig. 3) (47), which illustrated beautifully the manner in which a branch point in a metabolic pathway serves also as a site of control.

The realization that the anaplerotic function is exclusively borne by the carboxylation of PEP immediately raised the question of how *E. coli* can grow on C3 compounds such as alanine, lactate, or pyruvate because direct reversal of the pyruvate kinase reaction is unlikely to occur under physiological conditions. Once again, mutants supplied the answer; my colleague Ron Cooper and I isolated a mutant that, although unimpaired in its ability to utilize glucose or intermediates of the TCA cycle, could not grow on C3 compounds. This mutant was found to be still rich in pyruvate kinase activity but to lack a hitherto unknown enzyme, PEP synthase, in which the interaction of ATP with pyruvate yields PEP, PI, and AMP; the energy barrier is surmounted by using two of the “energy-rich” bonds of ATP (48–51).

The dual roles of pyruvate kinase and PEP synthase led us to study also the properties of the former enzyme in *E. coli*. It was known (52) that the pyruvate kinase activity of *E. coli* B was stimulated by fructose 1,6-bisphosphate (FBP); what surprised Massimo Malcovati and myself (53) was that there were two forms of this enzyme present in extracts of *E. coli*, K12, one of which was similarly stimulated by FBP but the other one was not. We later showed (54) that this duality was demonstrable in cells rendered permeable by treatment with dilute chloroform in ethanol (55) just as it was in cell-free extracts.

**Ad Eundem**

In 1973, I was unexpectedly offered the Sir William Dunn Professorship of Biochemistry at the University of Cambridge to succeed the incumbent (Sir Frank Young), who was due to retire in 1975. My immediate response was to refuse; the University of Leicester had treated me with extraordinary generosity, enabling my colleagues and me to build a flourishing School of Biological Sciences in a brand new building and even to initiate a new Medical School, whereas I knew the department in Cambridge to be rich in a great tradition but housed in buildings whose grandeur was not matched by their utility. However, two events changed my mind. One was a simultaneous visit from two giants of British science, Sir Alan Hodgkin and Lord Todd, both of whom were Nobel laureates, Professors in the University of Cambridge, and...
President or President-to-be of The Royal Society; I was as clay in their hands and weakly consented after all to accept the Chair, a decision I never regretted.

The second event removed the last scintilla of doubt from my mind: a phone call from Ernest Gale, then Acting Head of the Department, announced that that portion of the department in which I was to occupy laboratory space had burned down overnight! This gave me the opportunity, before I moved, to rebuild the previous warren of little rooms as the large open laboratories to which I had been accustomed in Oxford and in Leicester.

The move to Cambridge marked also a major shift in the main thrust of my work. Although I had retained my interest in microbial metabolic pathways and (with a number of students and postdoctoral fellows) had inter alia been able to elucidate the main routes whereby E. coli utilize gluconate (56–60) and fructose (61–63) as sole carbon sources for growth, I had also become increasingly aware that considerations of metabolism are incomplete if one ignores the first essential step, the mechanisms whereby substrates cross the cell membrane to enter metabolic sequences and the factors that regulate this process. This awareness had been heightened by analysis of mutants that were impaired specifically in the uptake, but not the catabolism, of C4 dicarboxylic acids (64, 65) and in the uptake, but not the catabolism, of glucose 6-phosphate (66, 67). It had been given additional impetus by the recognition of a “pecking order” in the sequence in which different hexoses are taken up by E. coli. For example, as little as micromolar amounts of glucose will powerfully inhibit the continued uptake of fructose, even though the cells are fully induced for fructose utilization and that ketose is present in great excess (68); however, mutants can be isolated in which this preference for glucose has been abolished (69). The site of one such mutation lay not in a gene for glucose utilization but was co-transducible with the gene(s) specifying the fructose operon, the major route of fructose uptake. We therefore undertook to sequence two of the three genes that comprise this gene cluster, fruA (70), which specifies the membrane-spanning transport protein, and fruK (71), which codes for a 1-phosphofructokinase, the third member of this operon (fruB) having been sequenced by Milton Saier and his colleagues (72). Because the preference for glucose over fructose was also abolished in mutants that formed the proteins of the fructose operon constitutively and in great activities, we (and virtually simultaneously, the late Pieter Postma and his colleagues (73)) also located on the E. coli linkage map the regulatory gene involved (74).

Availability of mutants in these and other genes made it feasible to recognize the numerous alternative routes for fructose utilization that can operate in E. coli (Fig. 4).

My long time colleague Maurice Jones-Mortimer and I had already shown that mutants unable to use fructose via the proteins of the fructose operon could nonetheless grow by taking up this ketose via a constitutive membrane-spanning protein involved in mannose transport (75), and when that route was also closed, further mutants would arise in which fructose was
now taken up via a gene normally involved in the uptake of sorbitol (76); later work showed that the constitutive formation of the mannitol uptake system could likewise facilitate growth on fructose.

Having been raised in the biochemical tradition that it is essential to be able to measure independently both substrates and products of any reaction under study, I had deliberately chosen to study in depth only carbohydrate transport processes that involved the glycose:phosphoenolpyruvate phosphotransferase (PT) system (77), in which the uptake of the hexose was accompanied by its phosphorylation at the expense of PEP. Quantitative measurements could thus be made by a spectrophotometric assay of pyruvate formation in cells rendered permeable by treatment with toluene in ethanol,

\[
\text{Sugar}_{\text{out}} + \text{PEP} = \text{Sugar}_{\text{in}} - \text{pyruvate}\]  
\text{Pyruvate} + \text{NADH} + \text{H}^+ = \text{lactate} + \text{NAD}^+ 
\]

which had been worked out by my late friend Dick Reeves, who spent a period of postdoctoral work in my laboratory (54, 78), as well as by techniques involving radioactively labeled materials. The consensus view arising from a variety of investigations was that transport of PT-sugars was necessarily linked to their phosphorylation (79) and that the membrane-spanning proteins could not effect entry of their substrates into the cells by facilitated diffusion. However, this conclusion was not in accord with our finding (80) that, under certain conditions, galactose could enter \textit{E. coli} cells via the principal transport protein for the PT-dependent uptake of glucose but without phosphorylation; this was later observed also with other substrates (81).

In 1995, I reached the mandatory (in the United Kingdom) retirement age and thus had to face the prospect of abandoning research. However, unexpectedly and doubtless undeservedly I was invited to join Boston University as a “University Professor” and Professor of Biology; within a month of arrival and accompanied by my colleague Linda Lambourne, experimental work was once more under way. Being fascinated by the flexibility by which \textit{E. coli} can overcome all manner of metabolic handicaps by evolving alternative routes for fructose utilization, I chose to make this general area the focus of my work, hoping thereby to gain an insight into the mechanisms by which this unicellular organism senses what is “out there” and adjusts its intracellular machinery accordingly. So far, this has shown us that the principal fructose transporter FruA can also admit mannose (82) and that the principal glucose transporter can mutate to effect the facilitated diffusion of fructose (33), this latter process being also the first step in a novel route for fructose utilization that does not involve the PT system (15). I am currently studying further mutants in which fructose supports growth despite the absence of the components of the PT system and of a functioning glucose carrier, profoundly grateful for the opportunity still to carry (and occasionally drop) bricks as small contributions to the grand edifice of biochemistry.

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