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William Herdman Elliott 1925–2012

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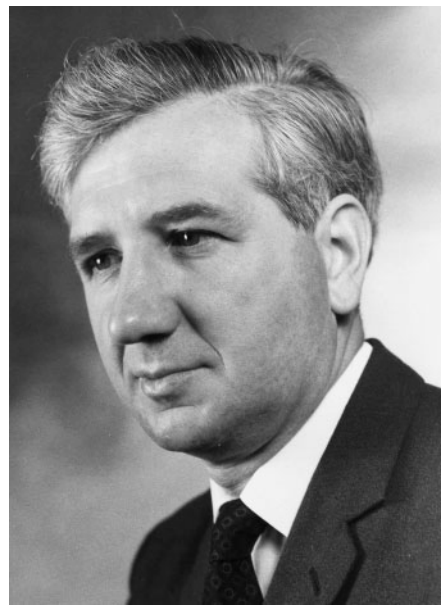
Bill Elliott graduated in Biochemistry at Cambridge and gained his PhD with enzymologist Malcolm Dixon in the Biochemical Laboratories. Following research appointments at Harvard, Oxford and the Australian National University, he became Professor of Biochemistry at the University of Adelaide in 1965. He was an outstanding scholar and stimulating teacher who profoundly influenced the lives of students and staff of his Adelaide department. Early in his career he made important contributions to the understanding of enzyme reactions driven by phosphoryl group transfer from adenosine triphosphate (ATP) and discovered the glutamine synthetase enzymes in plant and animal tissues that utilize that mechanism. He later worked on mechanisms of enzyme secretion by certain microorganisms, before turning to the biochemical mechanisms of porphyrin synthesis that lead to the formation of haem and thence haemoglobin, research that he pursued for the rest of his academic life.

Early Years, Family and Education

William ('Bill') Herdman Elliott was born on 5 June 1925 in Spennymoor, a small town with a population of ~20,000 in County Durham in the north of England. His parents, Norman Webster and Hannah (née Herdman) Elliott were married in February 1919, towards the end of Norman's five-year service during the First World War as a gunner in the Royal Garrison Artillery. Both of Bill's parents came from large families and he was the youngest of four brothers. His paternal grandfather, Joseph, had been a police inspector in Spennymoor and married to Margaret Wilson, a daughter of a farming family near Chester-le-Street. His mother's family were farmers in Weardale although his mother's father William Herdman was a paymaster for the scattered mines owned by the London Lead Co. in the Tees valley.

Bill's wife Daphne Elliott (née Davison) was born in Campbelltown, New South Wales. Her father also served in the First World War, for four years, at Gallipoli and on the Western Front. Both Bill and Daphne had come from middle-class, hard-working families with successful businesses. In many ways their values and interests were similar. Bill's parents, Norman and Hannah, owned two butcher's shops in Spennymoor. Daphne's parents, Arthur and Stella Davison, owned an old colonial hotel, the Commercial, in Picton, New South Wales.



Both Bill's parents were firm believers in the value of education. Despite the difficult conditions of the 1930s in the north of England, Bill started at the Rosa Street Primary School in Spennymoor in 1930, and in 1936 entered the Alderman Wraith Grammar School in Spennymoor. In July 1943, he obtained the Higher School Certificate with Distinctions in most subjects as a result of which he was awarded

State and County scholarships and accepted as an undergraduate at Trinity College, Cambridge. His admission to Cambridge was celebrated with a half-holiday by the students at his grammar school in Spennymoor. He studied for the Biochemistry Tripos. After completing his undergraduate degree, Bill undertook his PhD in 1946 in the Biochemistry Department at Cambridge where his supervisor was the famous enzymologist Malcolm Dixon. Bill was elected to a Fellowship of Trinity College in 1949. During his time in Cambridge the professors were A. C. Chibnall (1943–1949) followed by F. G. Young. The Biochemical Laboratories, as they were then called, led the world in the years after the Second World War. It was a stimulating environment for Bill's early career. Many of the staff at the time had been appointed by F. Gowland Hopkins who held the chair from 1914 to 1943, and during Bill's years there he was surrounded by young researchers who had stellar careers ahead including Fred Sanger, Ernest Gale, Peter Mitchell, Kenneth Bailey and Edwin Webb. Two of them, Sanger and Mitchell, were later awarded Nobel prizes.

Postdoctoral Years 1948–52

On completion of his PhD, Bill remained in Cambridge for about three years doing postdoctoral work in the Biochemical Laboratories, supported by a personal grant from the Medical Research Council. He was an early investigator of biochemical reactions that are driven by phosphoryl group transfer from adenosine triphosphate (ATP), and he used paper chromatography—a new technique developed in 1947 by Martin and Synge that earned them the Nobel Prize in 1952—for separating reaction products in many of his experiments (Fig. 1). He was the first to demonstrate that glutamine synthesis in brain tissue depends on ATP as the energy donor (1, 4) and he later isolated glutamine synthetase from green peas (8). He also worked with his future wife Daphne Davison in the Cambridge laboratory and they jointly published a major paper in *Nature* on the synthesis of argininosuccinic acid from arginine and fumarate in both animal and plant tissues (5). Daphne at the time was studying for her PhD with Robert Hill, having arrived in 1948 with BSc Hons and MSc degrees from the University of Sydney and a 1851 Exhibition

Figure 1. Bill Elliott in the Biochemistry Department at ANU, examining a paper chromatogram, a technique he used earlier in Cambridge.

science research scholarship. That year was the first year that women were admitted to study for a degree at Cambridge.

Bill and Daphne both recorded that the time spent in Cambridge was among the happiest of their lives, both scientifically and socially. They discovered that they had many common interests. The Biochemistry Department in Tennis Court Road was a very lively place, buzzing with young postgraduate students, and at the Wednesday afternoon Tea Club meetings they frequently enjoyed first-hand information from visitors from all over the world of biochemistry, especially the USA. The status of biochemistry at Cambridge was attested by the holding of the First International Congress of Biochemistry in Cambridge in 1949, an occasion of great excitement. These triennial congresses continue and in 1982 Bill chaired the Scientific Programme Committee at the 12th International Conference held in Perth, the first to be held in Australia.

Bill's time in Cambridge ended when he arranged to work in the laboratory of Fritz Lipmann (Nobel Laureate, 1953). Bill obtained a Rockefeller Fellowship and spent 1951 at the Harvard Medical School. The move to Lipmann's laboratory was a natural choice, given Bill's significant work on ATP reactions. Lipmann discovered the structure of coenzymeA (CoA) and the role of phosphoryl group transfer in biochemical reactions—he introduced the term 'high energy phosphate bonds' and the shorthand symbol ~P, sometimes referred to as 'squiggle-P'—and demonstrated the ATP-dependent formation of acetylCoA that plays a central role in carbohydrate and fat metabolism. In the meantime

Daphne had completed her PhD and returned to Australia to a position in CSIRO. By April 1952, however, it was decided that she should join Bill at Harvard and she resigned her post and returned to the USA by ship where they were married shortly after her arrival. They returned to the UK later that year for Bill to take up a demonstratorship in the Biochemistry Department at Oxford offered to him by Sir Rudolf Peters, Head of the Department. Bill worked with Sir Hans Krebs (Nobel Laureate, 1953) who succeeded Peters in 1954.

Oxford 1953–7

Bill's appointment in Oxford gave him more opportunity to advance his research on the activation of ATP-dependent biochemical reactions in important metabolic pathways and this led to several significant papers. Daphne, through her expertise in plant biochemistry, had obtained funding from the Nuffield Foundation and with W. O. James recognized the interesting phenomenon of cyanide-resistant respiration in the mitochondria of the spadices of the woodland plant *Arum*. She continued with this work until the birth of their first child, Caroline Jane, in 1955. Two more children (Michael and David) were added to the family after they settled in Australia. In 1968 Daphne returned to biochemistry after being appointed to the School of Biological Sciences at Flinders University. She was awarded the Chancellor's Medal from Flinders University in 1994 for her contribution to the education of women and girls in science and mathematics. Her extracurricular interests extended to the Australian Federation of University Women of which she was Federal President, 1997–2000. She was appointed a Member of the Order of Australia in 2002 for services to the promotion of women and as an advocate for improving the status and human rights of women.

Bill's research in Oxford focused on the mechanism of conjugation of bile acids, cholic acid in particular, with glycine and taurine to produce the so-called bile salts that are water-soluble and facilitate the digestion of ingested fats by forming micelles in the intestine. He demonstrated that the conjugation with the amino acids occurs with liver microsomes (from endoplasmic reticulum) via activation with CoA and is dependent on ATP as the energy source for the reaction (9, 11, 12). Similarly nicotinic acid (the B vitamin, niacin) is conjugated with glycine to produce nicotinuric acid (7, 15). He was invited to review the literature from his studies and those of others on the mechanism of activation and conjugation of bile acids (20).

Emigration to Australia: Canberra 1957–65

Bill's move to Australia came about as the result of a visit to Oxford by Professor Hugh Ennor FAA (later Sir Hugh Ennor), foundation professor of biochemistry at the Australian National University (ANU), who offered Bill a Senior Fellowship in his Department. Bill at first declined because he had a tenured post in the Oxford department but he later changed his mind, accepted the Fellowship and emigrated to Australia with his family in 1957. It surprised his Oxford colleagues that he would travel so far to further his career but he never regretted his decision. Over the following eight productive years at ANU, Bill conducted a range of novel experiments that were in some respects an extension of his earlier work with ATP-dependent enzyme reactions. His training in enzymology in Cambridge and Oxford was always evident through the precision with which he conducted experiments. It was also clear from his research that he possessed considerable chemistry skills. He isolated and purified compounds in the biochemical reactions that he investigated. Another ingredient apparent in his research was his objective to understand cellular activity in biochemical terms. A prime example of this was his discovery that washed suspensions of *Staphylococcus aureus*[1] produced aminoacetone from either glycine in the presence of glucose or, more rapidly, from the hydroxyamino acid, threonine. He isolated, purified and fully characterized this metabolic product. He proposed a metabolic cycle in which α-amino-β-ketobutyric acid is formed from glycine reacting with acetyl-CoA (Fig. 2) (14, 17) or by dehydrogenation of

[1] Washed cells were used to remove culture medium, preformed products and growth factors, so as to place the cells in a stable state for the experiments to be conducted. This requirement was applied in the later studies on enzyme secretion.

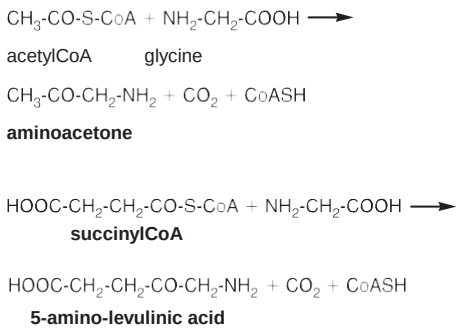


Figure 2. The synthesis of aminoacetone and 5-aminolevulinic acid result from the activity of specific cellular synthases and require the participation of coenzymeA and ATP to activate the acetyl and succinyl moieties.

threonine. The decarboxylation of the keto acid gives rise to aminoacetone.

Subsequent work (Fubara *et al*. 1986) has demonstrated that Elliott was essentially correct, including his suggestion that the glycine reaction was analogous to the synthesis of 5-amino-levulinic acid, also an amino ketone, from glycine and succinylCoA instead of acetyl-CoA. He also showed that aminoacetone is produced via a threonine dehydrogenase in animal tissues and can be metabolized. The synthesis of 5-aminolevulinic acid is the initial reaction in the pathway to the synthesis of porphyrins, a research area that Bill subsequently investigated intensively in later years in Adelaide.

He went on to study other systems and this was at the exciting time when the fundamentals of the processes of DNA replication, gene transcription and protein synthesis were rapidly becoming understood. Bill's publications from this period demonstrate his transition into these rapidly advancing areas and his research continued in that direction thereafter. An early set of experiments was directed to producing a more reliable method for measuring amino acid activation and charging of transfer RNAs (tRNAs) (23). However the phenomenon that attracted his serious interest was the ability of many bacteria to secrete extracellular enzymes to degrade macromolecular materials in the external medium. He chose to investigate *Bacillus subtilis*, which was known through the work of other researchers to secrete the enzyme α-amylase that degrades starch for an energy source. Washed cells will secrete the enzyme when carbohydrate is present in the medium but there was conjecture as to whether the secreted enzyme was from new synthesis, the conversion of a precursor protein, or cell lysis. Bill's experiments (21) showed that the production of the enzyme favoured new synthesis of α-amylase because an energy source was required and the process was compromised by compounds known to inhibit bacterial protein synthesis. In another study, Bill found that extracellular ribonuclease secretion similarly was the result of enzyme synthesis and not the release of preformed enzyme. A surprising finding and difference from α-amylase was that the antibiotic actinomycin D, an inhibitor of gene transcription, markedly stimulated the formation of ribonuclease (24)—an observation that was also made for penicillinase (Pollock 1963). Bill offered several explanations of the phenomenon and concluded that although the effect of actinomycin D was unclear at the time, his experimental results indicated that the effect was not caused by a direct stimulation of production of the ribonuclease messenger RNA (mRNA). An explanation for the effect of actinomycin D was not forthcoming until Bill moved to Adelaide and Brian May undertook further experiments, as Bill's first Biochemistry Honours student and later as a staff member.

In 1962 Bill took study leave from ANU and worked in Ernest Gale's MRC Unit for Chemical Microbiology in the Department of Biochemistry at Cambridge. Since he had used certain inhibitors of protein synthesis in the studies of α-amylase and ribonuclease enzyme secretion in *B. subtilis*, he examined the inhibitory activity of actinomycin D at the enzyme level (22). He confirmed that the concentration of actinomycin D required to inhibit DNA polymerase (discovered by Kornberg in 1957) and synthesis of DNA was much greater than that required to inhibit cell growth and hence accords with views of other researchers that actinomycin D inhibits DNA-dependent RNA synthesis (gene transcription) by binding to DNA. On his return to the ANU, Bill continued his research on the mechanisms of enzyme secretion by *B. subtilis*, and he took these investigations with him upon his appointment to Adelaide three years later. Prior to his moving to Adelaide, Bill's contributions were recognised by his appointment in 1964 to a Personal Chair at the ANU.

The Move to Adelaide: 1965 and Thereafter

The Darling Building and the Biochemistry Department

In 1919, T. Brailsford Robertson, an Adelaide graduate who had held posts in the Universities of California (Berkeley) and Toronto, was appointed to the Chair of Physiology at the University of Adelaide. However, in 1926, through an internal rearrangement, Robertson took up what was the first Chair of Biochemistry in Australia. Through Robertson's efforts the Darling Building was erected in 1922 to house the departments that taught the preclinical subjects of Physiology, Biochemistry, Pathology and Histology for the medical degree. T. B. Robertson was innovative and highly productive but his prominence in biochemical research and teaching came to a sudden end when he died from pneumonia in 1930. The Chair was then vacant until the appointment of Professor Mark Mitchell (later Professor Sir Mark Mitchell) in 1935. Mitchell remained in the Chair until his retirement in 1962. Under him the department was not as vital in research as it had been in Robertson's time although it saw some research and postgraduate training after the Second World War through the contributions of Peter Nossal and Eric Holdsworth. When the retirement of Mark Mitchell was imminent, Robert ('Bob') Morton FAA, who was then Professor of Agricultural Biochemistry at the University's Waite Agricultural Research Institute, suggested to Bill that he should apply for the position. Bill declined and the Chair was taken up by Morton himself during 1962. Sadly, the Department was again confronted with tragedy with Bob Morton's death in a chemical fire in the Darling Building in September 1963. The department functioned for the next two years with just four academics—two longer-serving staff, Bruce Keech and Beth Neville, and two newcomers, Bob Symons and George Rogers, both of whom had moved to Adelaide from Melbourne during 1962–3 specifically to join Morton. Fortunately, the University offered Bill the opportunity to apply for the vacant chair. He reconsidered his position and was duly appointed from February 1965, becoming the fourth Professor of Biochemistry in the University of Adelaide. The prospect of a fresh start with a new vision was warmly welcomed by those already in the Department.

In his new appointment, Bill confronted many challenges. The Darling Building was over forty years old and required the long-needed refurbishment and modification of research and teaching laboratories that had begun under Morton and continued in subsequent years (Fig. 3).

The Biochemistry curricula in Science, Medicine and Dentistry courses had to be reviewed to include the new molecular biology, research programmes had to be initiated and strengthened, appointments had to be made of new staff appropriate to the needs of new teaching and research directions, and secretarial and managerial appointments had to be made. By 1967 the essential changes had been implemented and the staff had increased with the arrival of molecular biologist Barry Egan and three postdoctoral fellows, John Wheldrake (Oxford), JohnWallace (Sydney, with postdoctoral experience at Cleveland, Ohio) and Julian Wells (Queen Elizabeth II Fellow, Adelaide). They were all biochemists by training and by 1970 they were full members of the staff and in time moved into molecular biology. The ensuing years saw Biochemistry at Adelaide achieve prominence nationally and internationally.

Molecular Biology in the Department of Biochemistry

Bill brought a new vision to the teaching and research in his department by introducing a strong bias towards molecular biology. With the advent of gene cloning and DNA sequencing in the early 1970s, the world of biological science was rapidly changing. Big leaps in science stem from new techniques. In biochemistry this meant the ability to study and manipulate nucleic acid and protein molecules; this profoundly influenced biology in the range of problems that became amenable to study at the molecular level. An overlap of the traditional disciplines occurred. Animal embryonic development is an example where the concepts and techniques of cell biology, genetics and biochemistry have led to a greater understanding of the processes of differentiation from egg to organism. The global broadening of biochemistry to embrace molecular biology and the fields of genomics and proteomics was reflected in a gradual renaming of

Figure 3. Bill Elliott with son David in the courtyard entrance to the Darling Building during drainage renovation and paving (1982).

many departments or schools of biological disciplines, including biochemistry, with an emphasis on 'biomolecular'.

In his Adelaide department in those early years, Bill fostered training in molecular biology, including establishing the physical facilities for gene cloning. This was an expensive enterprise, given the new regulations of the time concerning biological hazards, more perceived than real, that required the construction of a closed biohazard cloning room serviced by a self-contained autoclave for sterilizing used materials. After meeting these initial and expensive requirements, by 1978 virtually all the research groups were involved in some aspect of gene manipulation and technology. In 1982, as a result of gene research in the department, Bill was awarded the Australian Government's first Centre of Excellence, for research devoted to gene technology.

This was one of Bill Elliott's great achievements and it provided an enormous boost to research funding, not only for his academic colleagues immediately associated with the Centre (Fig. 4) but for the whole department, providing the capacity for achieving outcomes not possible with normal funding. The department's involvement in gene technology led to Bill becoming an early member of the organization now called the Office of the Gene Technology Regulator that was set up by the Australian Government to oversee applications of techniques for gene manipulation by researchers nation-wide. He also served as a member of the Research Grants Advisory Panel for the National Biotechnology Programme from 1982 to 1988.

Bill's Adelaide Research

In Adelaide Bill continued his research on the mechanisms of enzyme secretion in *B. subtilis* and expanded the work to include *B. amyloliquefaciens* which had the advantage that washed-cell suspensions of these organisms secrete large amounts of α-amylase, ribonuclease and a protease. His student John Smeaton from Canberra completed his PhD and a flow of PhD students including, B. K. May, G. Both, A. R. Gould and J. C. Paton made it possible over time to investigate the secretion mechanisms in detail. The results obtained by his group were

Figure 4. Bill Elliott with the three co-recipients of the Special Centre for Gene Technology, R. Symons, J. Wells and G. Rogers.

the subject of several papers. They concluded that there was no accumulation of preformed enzyme and that the secretion of the enzymes into the surrounding medium required continuous synthesis of mRNA (32). Their findings were applicable to all three enzymes, α-amylase, ribonuclease and protease (44, 45). In 1968 Brian May with Bill conducted more experiments on the effect of low levels of actinomycin D (<2 ug/mL) that curiously stimulates the synthesis of ribonuclease in washed cells of *B. subtilis*. At the core of the phenomenon was the finding that ribonuclease production was inhibited by inorganic phosphate (Pi) (end product inhibition) and was greatly stimulated in phosphate- starved cells. The effect of actinomycin D was inhibited by Pi after a 30 min lag, a property that indicated an accompanying process of some kind (32). The most likely explanation (Brian May personal communication) is that ribonuclease production is under the control of Pi that acts as a co-repressor of ribonuclease expression. The action of actinomycin D is to inactivate expression of the regulator gene for an apo-repressor protein. It can also be postulated that the expressed regulatory protein has a life-time of 30 min which is the delay before repression occurs.

From their studies May and Elliott postulated that the production of extracellular enzymes occurs on ribosomes bound at special translational-extrusion sites on the inner wall of the cell membrane (41). This extrusion model accommodated their experimental findings including the immunity of the cells to the degradative activity of protease and ribonuclease and the finding that removal of the cell wall from *B. subtilis* inhibited extracellular secretion (31). The model required that the nascent chain of protease is refolded in the periplasmic space

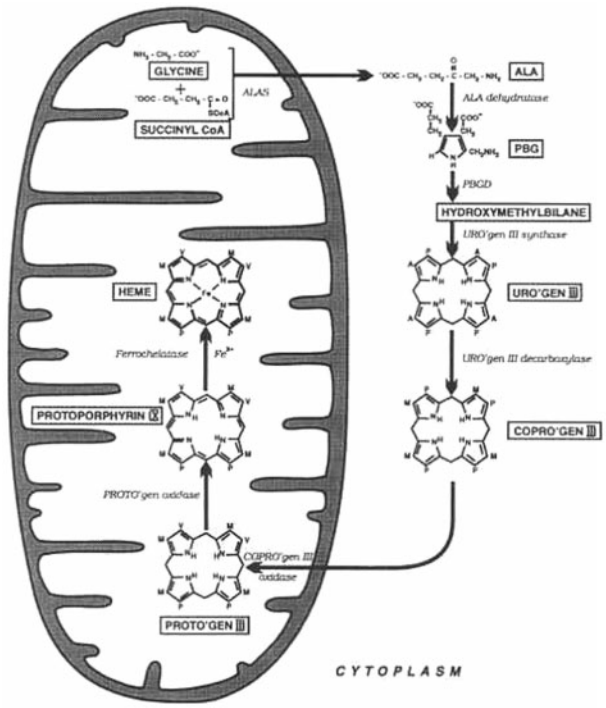


Figure 5. The pathway of haem biosynthesis showing the first step of formation of 5-aminolevulinic acid in the mitochondrion, the synthesis of the porphyrin intermediates in the cytoplasm, followed by the last three steps that again occur in the mitochondrion, including the insertion of iron to form the haem molecule (reprinted from May, B. K. *et al.*, *Progress in Nucleic Acid Research and Molecular Biology*, Vol. 51, 1–51, 1995, with permission from Elsevier).

or after secretion. Moreover, with the model of translation at the cell wall, the cell could secrete active ribonuclease despite the presence of an irreversible ribonuclease inhibitor (28) that is present in the cytoplasm of the cell.

Around 1970, Bill embarked on a new direction to focus on the synthesis of haem, the iron-tetrapyrrole that is essential for the health and function of most cells. Familiar examples are the haemoproteins, haemoglobin, myoglobin, cytochrome C of the mitochondrial electron transport chain and cytochrome P450 that functions in the metabolism of hydrophobic compounds in liver cells and solubilises them for excretion.

The first step in haem synthesis is the synthesis of 5-aminolevulinic acid (5-ALA) that takes place in the mitochondria as do the last three steps, the intervening ones occurring in the cytosol (Fig. 5). The synthesis of 5-ALA is an ATP–dependent reaction between succinylCoA and glycine catalysed by 5-aminolevulinic acid synthase (ALAS). Bill was familiar with this type of reaction because it was analogous to the formation of aminoacetone involving acetylCoA and glycine, the reaction he found in his earlier research (see Fig. 2). The haem programme became his most intense interest up to the time of his retirement in 1988 and, jointly with his collaborator Brian May and many research students, Bill made major contributions to the field.

Their investigations over the years centred on ALAS and its regulation in hepatic and erythroid tissues. The regulation of the level of haem is critical, given that the requirement varies with different cell types and responses and any excess is toxic through the accumulation of intermediates of the pathway, with the development of disorders called porphyria. The research strategy was to purify the liver ALAS protein, chicken liver being the favoured source and then, in the following years, the isolation of ALAS

genes, gene sequencing and examination of the control of expression at the transcriptional and post-transcriptional levels.

It was established by the Elliott/May team that two pyridoxal phosphate-dependent ALAS isoenzymes are expressed in birds and animals, one being the housekeeping or 'hepatic enzyme' ALAS-1 expressed not only in liver cells but in all cells to provide haem for haemoproteins and the other being ALAS-2, that is specifically expressed in erythroid cells to provide haem for haemoglobin. The hepatic ALAS-1 enzyme was the first to be examined in detail and a radioactive assay for it was published early in the work (35) followed by purification of the enzyme from liver mitochondria (42); however, later studies showed this was an active but degraded form of the native enzyme. Since the level of enzyme activity in the liver is relatively low, the administration of so-called porphyrinogenic drugs such as phenobarbital or 2-allyl-2-isopropylacetamide was routinely used to greatly increase the level of the enzyme in the liver mitochondria. Early studies of the drug induction of ALAS in rat liver suspensions were published (49, 50).

The biological significance of the induction of ALAS-1 by porphyrinogenic drugs was not initially recognised but later, with the identification of a sub-family of cytochrome P450s inducible by drugs, the following working model was adopted: drugs induce liver P450s so that they can be removed from the body, these proteins require haem, hence ALAS-1 is also induced.

The native form of mitochondrial ALAS-1 was first isolated from the livers of drug-induced chick embryos by Borthwick *et al.* (68) and antibody raised. Electron microscopy (71) showed the purified enzyme was a homodimer of two identical subunits. Subsequently a cDNA clone for the chicken ALAS-1 was isolated for the first time and confirmed by sequence comparison with the purified protein. Complementary DNA (cDNA) clones for the rat and human ALAS-1 followed. Likewise, cDNA clones were also isolated for the drug-induced liver cytochrome P450 in chick embryos and rats. Armed with these molecular tools, the following was found.

1. ALAS-1 is initially synthesised in the cytosol as a larger precursor protein with an N-terminal signal sequence (74) that enables migration into the mitochondria after which the sequence is removed to yield the mature enzyme (this was found to be true for ALAS-2 except that the signal sequence differed). The transport of the protein into the mitochondria is likely to be by the mechanisms that have since been elucidated.
2. Drugs simultaneously increase transcription of the P450 and ALAS-1 genes (Srivastava *et al.* 1988), notably in the liver.
3. Haem, the end product, tightly controls the rate limiting ALAS-1 protein by acting both transcriptionally and post-transcriptionally, the latter through altering mRNA stability and preventing import of the precursor protein into mitochondria (see Fig. 6). It was postulated that haem is bound to the N-terminal signal sequence of the ALAS-1 protein precursor.

A detailed examination of the genomic exon-intron organization was obtained for the chicken ALAS-1 gene (78) and the human gene was localized to chromosome 3 (Sutherland *et al.* 1988). Studies aimed at localizing the drug responsive sites in the ALAS-1 promoter were not possible because hepatoma cell lines did not respond to drugs and primary cultures could not be transfected. One study did locate a promoter region that directed haem repression when ALAS-1 promoter constructs were tested in a Leghorn hepatoma cell line.

After Bill retired in 1988 he retained his interest in the ALAS work as it continued under Brian May's direction until his own retirement in 2003. Work continued on the mechanisms of regulation of ALAS gene expression but the emphasis was on ALAS-2, the erythroid enzyme. A cDNA clone for human ALAS-2 was obtained and the human gene isolated and the genomic organization determined (Conboy *et al.* 1992). The promoter displayed many sites specific for erythroid transcription factors that underlie its tissue specificity.

Unlike ALAS-1, the erythroid ALAS-2 enzyme was not controlled by haem. Interestingly, an iron-responsive element was discovered in the ALAS-2 mRNA (but not in the ALAS-1 mRNA) that bound a specific protein and prevented translation; thus production of ALAS-2 was influenced by iron levels.

During the Elliott era, porphyria diseases with accompanying mutations in haem pathway

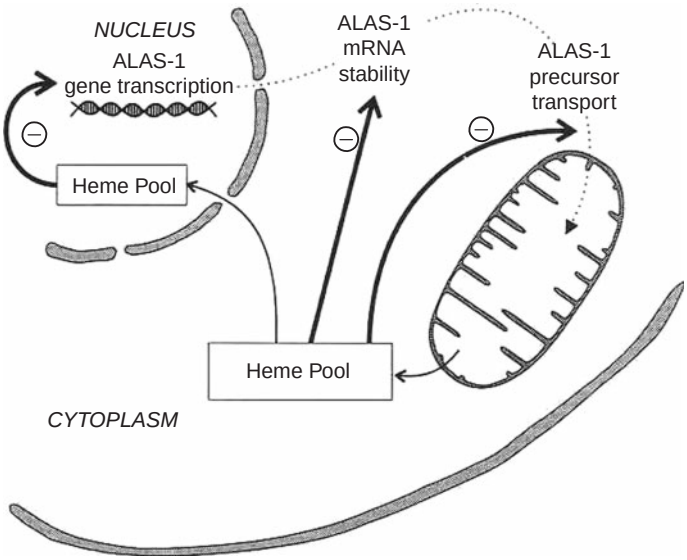


Figure 6. Diagram showing the involvement of cytoplasmic haem in controlling the level of haem synthesis in the hepatic cell by several mechanisms. The transcription of the ALAS-1 gene is repressed by haem as is the transport of the synthase into the mitochondrion and reduction in the stability of the mRNA encoding ALAS-1 (reprinted from May, B. K. *et al.*, *Progress in Nucleic Acid Research and Molecular Biology*, Vol. 51, 1–51, 1995, with permission from Elsevier).

enzymes were identified by other groups, with the characteristics of these diseases arising from the overproduction of intermediates for porphyrin synthesis. One of the porphyrias was the 'mad King's disease' from which King George III suffered and according to all available information the affliction was acute intermittent porphyria. Significantly, no mutations in ALAS-1 are known since this is the rate-limiting enzyme and such mutations presumably would be fatal. However, it was shown by the Elliott/May group that ALAS-2 was located on the X-chromosome (Cox *et al.* 1990) and mutations in this gene were responsible for the disease X-linked sideroblastic anaemia, a condition affecting the bone marrow. The primary pathogenesis of sideroblastic anemia is the failure to form haem completely and leads to deposits of iron in the mitochondria that form a ring around the nucleus of the developing red blood cell. In most cases it is an X-linked inheritance and occurs mainly in males. Several mutations were detected in the ALAS-2 mRNA and genomic DNA of a human patient (Bottomley *et al.* 1992). The consequences of these mutations have been embraced in a model in which activity of a defective ALAS-2 in erythroid cells would be lowered and consequently the production of protoporphyin and haem reduced. The continuing importation of iron into the mitochondria would lead to its accumulation because of the reduced levels of protoporphyrin to incorporate it.

In summary, Bill's research into the control of expression of ALAS has contributed greatly to the understanding of how haem levels are tightly regulated in different cell types in response to different signals, such as drugs and those of erythropoiesis.

Teaching

Bill had achieved many successes in his virtually full-time research at Cambridge, Harvard, Oxford and the ANU but he was eager to teach biochemistry to undergraduates. One of his early initiatives after arriving in Adelaide was negotiating to teach some principal aspects of molecular biology in the then Biology I course that was a standard mix of zoology, botany and genetics. In four to five lectures he succeeded superbly and over subsequent years he protected his small lecture slot with determination. His

lectures were extraordinarily successful because they were about new advancing fields of DNA-RNA-protein, genes and the control of their expression in *Escherichia coli*. The function of the Lac operon in *E. coli* was at that time a central example of gene control. Professor Peter Rathjen, who was a student in Biology I at the time, observed that Bill 'shouldered the more difficult task of seating biochemical understanding within biology instead of using the relatively easy mission of teaching biochemical facts'. The lectures were given with such skill and enthusiasm that over the years he captivated numerous students and caused many to take Biochemistry as a major subject in the second and third years for the Science degree. Several of Australia's leading researchers have credited Bill as being a pivotal inspiration in their decision to pursue a career in the life sciences. In those initial years the student numbers taking Biochemistry in second and third years increased remarkably (numbering ~200 and ~80 respectively) and stretched the capacity of the department's resources. Through the respect from the staff that he generated, mapping out new Biochemistry courses according to the individual strengths and interests of the staff proceeded relatively smoothly. Former students and staff recall that his mentoring skills were outstanding. Bill was impressed with the idea of aiding self-learning by students and he obtained sufficient funds to set up part of the teaching laboratory as a 'dry laboratory' in which there were cubicles for listening to tapes of recorded lectures from various parts of the second-year course accompanied by slide diagrams; this initiative was a forerunner of the audio-visual teaching now conducted more efficiently 'on line'.

Contribution to University and Professional Affairs

Bill made many contributions inside and outside the University of Adelaide. He commanded the highest respect throughout his time as Professor and Head of Department. His friendliness but firm leadership had a strong influence on members of the Department: academic and research staff, postgraduates, postdocs and general staff alike. In running the Department he would seek and consider opinions from staff and for the most part he governed by consensus, although always aware that the outcomes were his responsibility. Although he maintained his primary role in the Department, he also held the position of Dean of the Faculty of Science in 1972–3.

A very important move that gave scientific prominence to his department and the University was his leadership in establishing BRESA, a University of Adelaide biotechnology company, in 1982. In the 1960s the late Bob Symons, the nucleic acid expert in the Department, developed synthesis pathways to produce efficiently ^{32}P-labelled deoxyribonucleotides and ribonucleotides for labelling polynucleotides in his research (84, 85). He supplied these materials to research groups within the Department and in other institutes and universities at low cost. Bill recognized that this facility for radioactive products and related products would rapidly develop into a major activity and needed to be properly commercialized. As a result of his effort, and in collaboration with Bob Symons, the BRESA venture became the first Australian company to market products for molecular biology research. It later became the larger Bresagen establishment, a precursor to the present-day GeneWorks Pty Ltd that produces and markets a wide range of research materials.

Bill was elected to Fellowship of the Australian Academy of Science in 1965, the year he moved to Adelaide, and participated actively for over thirty years in the affairs of the Academy, including as a member of Council (1969–72); as a member and, twice, Chair of the Molecular and Biological Sectional Committees (1966–93); and as a member of the Science Policy Working Group (1988–97). Bill also served on national advisory committees, serving as a member of the Research Grants Advisory Panel for the National Biotechnology Programme from 1982 to 1988.

In 2003 he was awarded the Centenary Medal for service to Australian society and science in molecular biosciences. The University of Adelaide holds an annual lecture, the W. H. Elliott Lecture, to celebrate his work and achievements.

Bill was a long-standing member of the Australian Society of Biochemistry and Molecular Biology (ASBMB, formerly the Australian Biochemical Society or ABS), having joined in 1957 when he was at the ANU. He served as President between 1972 and 1974, and had previously served as State Representative, first for the ACT

Figure 7. Bill and Daphne Elliott relaxing in the South Australian bushland (1978).

and later for South Australia. He was elected an Honorary Member of the society in 1992.

Family Life

Bill's family life was very important to him and he ensured that he spent as much time with his wife and children as he could. When they first moved to Adelaide, Mark Mitchell introduced the Elliott family to Kangaroo Island. After holidaying there a couple of times, in 1971 they persuaded him to sell them one of his properties, Narimba, a stone settler's cottage (built 1884) with 20 acres of surrounding bush, subdivided off from what was to become the Pelican Lagoon Conservation Park. This was to prove a soul-restoring refuge for the next forty years, and looks like continuing so for the next generation.

Bill enjoyed taking breaks in the Australian bush (Fig. 7). On Kangaroo Island he often went fishing and walking. He was not interested in competitive sports as either a participant or a follower and once remarked to Robert Richards when Rob was a PhD student that his only exercise 'was jumping to conclusions'. He read a lot and was a devotee of classical music, especially Mozart.

Retirement and Textbook Writing

After Bill had taken up his appointment in Oxford he perceived the need for a compendium to make a broad range of biochemical information readily available to researchers. Bill and Daphne enlisted K. M. Jones, Bill's first PhD student, and R. M. C. Dawson, a Beit Memorial Fellow in the Biochemistry Department at Oxford, as co-authors. The compilation and printing of biochemical data was an enormous task and incorporated assistance from many biochemists who judged the type of content and who later substantially contributed to the compilation of material. The publication was taken on by Oxford University Press and the first edition of *Data for Biochemical Research* appeared in 1959. The work went to three editions, the last in 1986, and is still used despite the Internet.

In the 1980s Bill planned a new venture that stemmed from his long experience in teaching biochemistry. He decided to write a textbook of biochemistry that was strong on concepts and written in a narrative style that would enthuse students to read a textbook. Today's texts on the subject are generally confronting and weighty tomes that are impossible for students to carry around. To construct the kind of text he envisaged that adequately covered the whole of biochemistry and molecular biology was a monumental task. With Daphne's important co-authorship Bill began serious writing by 1988 and the first edition was published in 1997. The result was a signal success and the book has reached its 4th edition, with translations into other languages.

Bill retired in 1988 and was awarded the title of Emeritus Professor by the University Council. His many outstanding qualities, that included enabling others to achieve, are celebrated annually by the W. H. Elliott Lecture given at the University of Adelaide. The Discipline of Biochemistry also funds a research fellowship in his name.

Bill passed away in Adelaide on 25 July 2012 and is survived by Daphne, children Jane, Michael and David and grandchildren Laura, Hannah, Hugh and Katherine.

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