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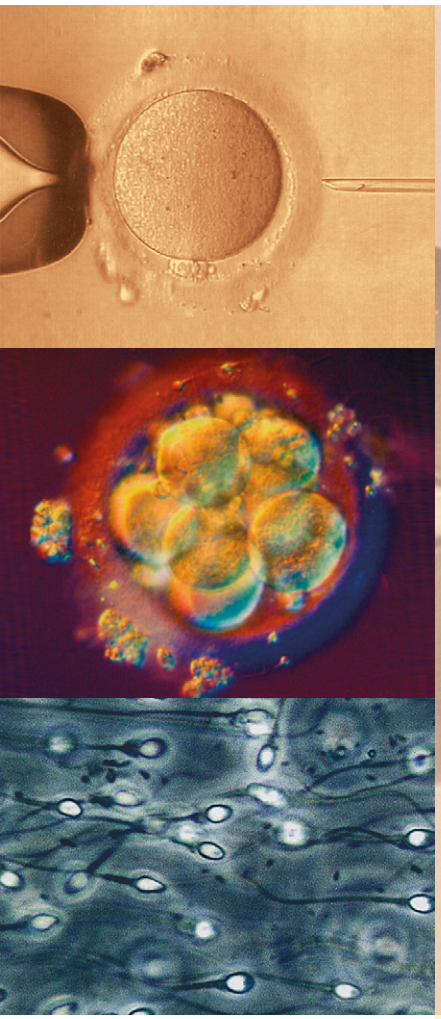

Obituary: J. Michael Bedford – Gamete Biologist and Lifelong Student of Mammalian Fertilisation 21. May 1932–24. February 2018

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J. Michael Bedford – Gamete Biologist and Lifelong Student of Mammalian Fertilisation

21. May 1932–24. February 2018

R. H. F. Hunter

Introduction

Soon after the death of J. Michael Bedford in February 2018, a series of short contributions from his students and post-doctoral associates appeared on the Internet. In diverse ways, they all expressed thanks for his guidance and support as a mentor and for his loyal friendship down the years. Each of these tributes struck an appropriate note at the time, yet none of them tried or was able to set Michael's overall career in a balanced and meaningful perspective. By definition, they were written by people younger, often far younger, than their subject. In the present instance, an attempt has been made to place his training and various spheres of interest in their historical context. Not quite a contemporary, the hope is nevertheless that the author can justify this stance by being a member of the same Cambridge University college, having shared a laboratory with him in 1967, and having been good friends since 1966 – although with one small hiccup referred to below.

Home and Background

Mike (as he will henceforth be named), was born in Sheffield, Yorkshire, in May 1932. He remained in the northern half of England throughout his younger years, moving home quite frequently due to his father's developing career as a bank manager. Cities such as Bradford, Newcastle and Manchester became familiar to him, and in later life he could still impersonate the speech of Bradford mill workers as they passed his home in the very early morning; most of those mill workers were wearing wooden clogs. Despite any impression given subsequently, Mike's family life was not privileged in those days. This fact may have influenced his long-standing social views, for his inclinations were always towards the left, towards the underdog, albeit from a progressively more comfortable personal lifestyle.

Mike's early years were spent in the company of a much appreciated sister, but there were no brothers. To his mother, there was a life-long devotion, whereas he saw less of his father due to long hours of work and extensive travel. Nonetheless, the stability of home life meant much to the young Mike yet this was soon to be interrupted by conditions imposed during the Second World War (1939–1945). Because of the German offensive taken to Britain by the formidable "Luftwaffe", and the increasingly intensive bombing of northern industrial cities, many school-age children were evacuated to the safety of the countryside. In Mike's case, this was to the Lake District in north-west England, to a farm called Castlerigg Manor, overlooking the market town of Keswick and nearby Lake of Derwentwater. Despite initial homesickness, Mike soon settled in, appreciated the beauty of the location, and – of later significance – began to take an interest in farm animals. The worst of the bombing was over within three years, enabling a full-time return to Bradford, but not for long. His parents had decided that he might benefit from a boarding school education, his father's salary was now sufficient to cope with the fees, and Mike was sent to Blundells, near Tiverton, in south-west England. Blundells was a long-established independent school (founded 1601), but it was not a major public school as Mike tended to convey when rehearsing his stock of anecdotes!

Schooling at Blundells

Mike spent all of his secondary schooling at Blundells, became increasingly gregarious, formed many close friendships, and adapted perfectly to the ethos of the school and its diverse activities. Outside the classroom, and as a hallmark of British boarding schools, ability on the cricket pitch or rugby field strongly influenced one's standing in schoolboy hierarchies. Having a good eye for the ball, Mike did well in both these sports and also became proficient in tennis and squash, the latter sports continuing to give pleasure well into middle age. A key part of life at a British boarding school was performance in the dormitory, wherein one could be exposed to much mischief, even temporary persecution. Already a tall and strong schoolboy, Mike gained an extra layer of protection by developing remarkable skills as a raconteur. He could hold an audience spellbound with wildly exaggerated anecdotes, often pure imagination, an aptitude that was to be perfected throughout his long life.

Teaching and coaching at Blundells were careful and conscientious, as permitted in a boarding school with extended hours of contact with one's teachers, and Mike found himself attracted to the sciences, with a special focus on biology. In the latter regard, his interest became more and more in animal life, not least in the evolution of species as taught in the late 1940s before the key role of DNA was revealed. Taxonomy grew to fascinate him, and throughout his career he remained a master of family, genus and species. As will be noted, this was to influence the orientation of some of his future research pursuits.

Military Training

One other aspect of life at an independent boy's school was the Combined Cadet Force (CCF). In essence, this was an introduction to military training, usually occupying one full afternoon per week,

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as well as long hours of preparation the previous evening dealing with one's uniform and highly-polished black boots. The thoroughness of such preparations would be noted during formal inspection on the parade ground the next day. Any 'slackness' led to diverse penalties, but Mike was highly enthusiastic and clearly imagined himself as 'officer material'. This was not least because in post 1945 British boys' schools, many of the masters were returning from active war service and were seen as models for military life. Furthermore, there was compulsory conscription ('call-up') in those days for 2 years of military service, invariably straight after the end of one's schooling, as was the case for Mike. In due course, he was commissioned as a Second Lieutenant in the Royal Corps of Signals.

First, however, there were some weeks of basic training at Catterick, North Yorkshire, a period that Mike described as pretty desperate. His two much repeated anecdotes from those days involved (a) his first afternoon's release from' imprisonment' at Catterick to enjoy freshly-baked scones with homemade jam and cream in the nearby market town of Richmond; and (b) in a purely military context, being on manoeuvres with a tank regiment in North Germany. Mike readily confessed to not being on the wavelength of such activity and of not understanding the procedures, so he placed the tank under control of his sergeant throughout the manoeuvres. No matter what he may have thought of public schoolboys, the very British sergeant – a seasoned professional soldier – remained loyal and his officer's incompetence was not rumbled. Overall, Mike was not suited to military life and, although enjoying social activity in the Officers' Mess, he viewed his two years in uniform as time not well spent.

Onwards to Cambridge (1952–1958)

He was more than ready to resume his academic studies and, with his biological enthusiasms and interest in farm animals, he opted for a course in Veterinary Medicine. Obtaining entrance to a veterinary school was highly competitive in those days – as so it remains – and Mike's school examination grades were not good enough for selection at one of the five established British veterinary schools. However, Cambridge University had recently opened a new veterinary school, just to the west of the city and well-known colleges, and was attracting applications by means of relaxed entrance requirements. As Mike readily confessed, he was to benefit from this arrangement and commenced his university studies in October, 1952. Not all readers of this memoir will appreciate that entrance to Cambridge University also necessitates acceptance by a college. Mike secured entrance to Sidney Sussex College (founded 1596), a college with which his school (Blundells) had long-standing links.

As was the case for Cambridge medical students, potential veterinary graduates were required to study Natural Sciences for 3 years on the university science campus (the Downing Site) before proceeding to 3 years of clinical instruction at the Veterinary School premises. Mike was a diligent but not outstanding student, although he was particularly inspired during the pre-clinical years by Dr Alex Bangham who lectured on cell physiology. This inspiration led to an original publication concerning sperm surface charge changes during epididymal passage in rabbits (Nature, 1963).

During his 3 preclinical years, Mike lived a full college life and was prominent in Sidney's sporting activities. These, of course, included rugby and cricket and he managed several trials for the university rugby team, that is for a Cambridge 'Blue'. Although not successful in this regard, he was elected a member of the prestigious Hawks Athletic Club (narrowly missed Blues) and he was a leading member of Sidney's first 15, a formidable rugby team in those days. He was also a key member of the cricket 11, and played squash and tennis to a high standard. Bearing in mind his substantial work commitments during the Natural Sciences courses, it is astonishing that he managed so much; he simply would not have found time also for the College Boat Club and activities on the river.

Being highly sociable, Mike enjoyed all aspects of College life and retained an enduring affection for Sidney Sussex throughout his future career. He had a warm relationship with his College tutor, Dr Otto Smail and kept in touch by correspondence and regular visits until the latter's death. Mike was privileged to be in College with a group of public school contemporaries who went on to become prominent in British public life, notably in the Law, in Politics and in Education as school headmasters. Throughout his life, he remained diligent in 'networking' (ghastly modern jargon) with all of those Sidney chums.

His clinical years at Madingley Road were also full, and involved ever-increasing responsibilities for animal management and health. These were supplemented with vocational work in practice and led to attractive assignments in the West Country. After graduating as a registered British veterinarian in 1958, there were the twin questions of what to do next and where to go? Leaving the magic of Cambridge with considerable reluctance – it was magical in those days, free of the modern saturation with students, tourists and traffic – Mike opted to remain in the university world and obtained a one year assignment as Fellow in Veterinary Surgery at the University of Bristol (1958–1959).

Bristol interlude and subsequent departure to USA

After the flat landscape close to Cambridge, Mike was pleased to be back in the West country and made a series of visits to his old school; he had retained happy memories of his time there. In Bristol Veterinary School, he found that he had an aptitude for teaching, and particularly enjoyed demonstrating surgical techniques to small classes of students. Although not naturally gifted in this regard, Mike developed considerable dexterity with scalpel and forceps, skills that he was to employ in his future career.

Of course, with his one year appointment at Bristol, the clock was ticking and there was the question of what to do next. Mike had gradually appreciated that he was not destined to be a practising veterinarian. Rather, he found his mind focussing on physiological questions, some of which had been touched on in Cambridge tutorials. He had also been scanning journals in the university library and, after discussion with colleagues, had decided to pursue a career in biological research if a suitable opening could be found. Noting an earlier trans-Atlantic move by one John Marston, MRCVS, a London-trained vet a couple of years

ahead of Mike, he made contact with Dr M.C. Chang at the Worcester Foundation for Experimental Biology in Massachusetts. M.C. Chang was well known in Cambridge and Mike had heard frequent mention of his name in a research context. In due course, and doubtless noting the Cambridge University training, Dr Chang was pleased to offer this unknown Englishman a 2-year post as research assistant. Dr Chang valued having an Englishman close by, partly to reminisce about his six war-time years spent there, but principally for assistance in the writing of scientific manuscripts. Mike moved to the Worcester Foundation in 1959, with that classical British question hanging over him: how would he adapt to life in the United States?

Worcester Foundation for Experimental Biology (1959–1961)

The Foundation was not located in the city of Worcester, but close to the small New England town of Shrewsbury. Situated on a hillside and looking down over a large lake and onwards to Worcester, Mike found much that appealed to him, not least the immensely friendly Shrewsbury community. In addition, Boston was only an hour away and, within the Worcester Foundation, there was a significant British presence. Under the inspiring leadership of Dr Gregory Pincus, the Worcester Foundation (established in 1945) had expanded vigorously during the 1950s and was on the verge of its greatest impact with the launching of a steroid contraceptive pill. There were also prominent courses on steroid biochemistry for young medical doctors and research scientists, generating a valuable international atmosphere.

Dr Chang and Mike quickly formed a good working relationship, not least because Mike took pains to try to follow Chang's more subtle thoughts, expressed as they were in his still somewhat limited version of the English language. After his war-time years in Cambridge, Chang had gone to the Worcester Foundation in 1945 to learn about the process of fertilisation from Pincus, and mammalian gametes were to remain Chang's primary focus throughout the 1950s. Although developing an interest in storage of spermatozoa and eggs, Chang remained transfixed by the so-called process of capacitation. As revealed independently by Austin and Chang in 1951, and named as such by Austin in 1952, this final maturation of spermatozoa in the female genital quickly caught the attention of Mike.

Shortly before Mike joined the Worcester Foundation, Chang had published observations on what he termed 'decapacitation 'of rabbit spermatozoa. In essence, this was the demonstration that putatively capacitated spermatozoa could be rendered non-capacitated by the addition of homologous seminal plasma. The question therefore arose as to what component(s) of seminal plasma might be involved. Chang was out of his depth in this context, and Mike was able to introduce valuable analytical procedures. Together they demonstrated that after high-speed centrifugation, the decapacitation factor resided in a 105,000 G precipitable fraction of whole seminal plasma. Because the topic of capacitation had been widely noted by the reproductive biology community, joint publication of this study gave Mike an early flavour of the attention that good research could generate. Despite his background in veterinary medicine and clinical studies, the two years of introductory work with Chang indicated to Mike where his future career would lie – in fundamental studies in reproductive biology, probably involving gametes.

One other research sphere involving Mike at this formative phase of his career was the procedure of in vitro fertilisation – the attempted fertilisation of mammalian eggs outside the body using relatively simple laboratory procedures. Chang was already active in this sphere, not least because of a long-standing claim by Pincus that he had achieved successful in vitro fertilisation (IVF) with rabbit gametes. Using the same procedures as Pincus, Chang was unable to endorse the work and remained sceptical, not least since Pincus had known nothing of the requirement for capacitation. Exploiting this knowledge enabled Chang & Mike to achieve early success with rabbit gametes and prompted others to enter the field of IVF. Not least amongst these was a fish gamete biologist from Japan called Ryuzo Yanagimachi, who was a contemporary of Mike's in Chang's small research group and with whom there were endless discussions. It was the beginning of a lifelong friendship.

Return to England: Royal Veterinary College, London

Well before completing his 2 years with Chang, Mike had appreciated that a research qualification, a doctorate, was essential if he was going to continue in his chosen direction. By good fortune, an opening became available at the Royal Veterinary College in London. It would take the form of a Junior Lectureship with sufficient time available to work towards a PhD. In the event, and with his conscientious approach to teaching duties, Mike required 4 years to complete his substantial PhD studies. Needless to record, these concerned mammalian reproductive biology and focused on spermatozoa. There were two principal themes. Maturation of spermatozoa in the epididymis had attracted Mike's attention, seemingly because details of the maturation process in the male might offer clues to understanding the final maturation – capacitation – in the female tract. He was not plunging into unknown territory, having been influenced by key chapters in two of the most prominent reproductive volumes, Sex and Internal Secretions and Marshall's Physiology of Reproduction. Furthermore, there were personalities in the research community especially interested in epididymal function. In the UK, there was T.D. Glover who had been closely associated with J. Hammond and T.R.R. Mann in Cambridge. And in France, there was M-C. Orgebin-Crist who was working under R. Ortavant in a research institute S.W. of Paris, but to move upon marriage to Vanderbilt University in the U.S.A.

Her elegant series of publications stimulated Mike's own experimental programme whilst, at the same time, acting as a prominent source of competition. Mike and Orgebin-Crist were not close and did not reveal in advance their experimental plans to each other. Rather, they awaited each other's publications with some trepidation, a situation that continued throughout the late 1960s and 1970s.

Mike demonstrated originality in an unusual direction. For most of his career, he was intrigued by the relocation of mammalian testes via the inguinal canals into the scrotal sac, a descent that also involved relocation of the adjoin-

ing epididymis. And, with his interest in surgical procedures, one of his early studies was to explore the influence of restoring rabbit testes and thereby each epididymis to an inguinal or abdominal location. This approach was to be refined during his post-doctoral years, and enabled Mike to comment meaningfully on spontaneous cryptorchidism and the associated sperm cell modifications.

However, the principal focus during his PhD studies involved ultrastructural modifications to ejaculated spermatozoa during progression within the female tract, in theory during capacitation. Application of electron microscopy to reproductive tissues was still at a relatively early stage of development, although C.R. Austin in London, (later to move with A.S. Parkes to the new Marshall Laboratory in Cambridge), was enthusiastically using the technique in an effort to clarify fertilisation of the mammalian egg. Mike was soon interacting closely with Austin, an Australian veterinary graduate with an established reputation in research, and 'Bunny' Austin was to become a source of guidance and much-appreciated friend. He and Mike considered that an ultrastructural understanding of membranous changes during sperm maturation might reveal subtleties of the capacitation process.

In addition to Austin, it is worth noting that there was already a flourishing reproductive community in the UK and this was invaluable to Mike, not least since his PhD supervisor at the Royal Veterinary College had no particular interest in mammalian fertilisation. Diverse individuals were willing to discuss his research with him, and these included some of his former teachers in Cambridge and members of the Agricultural Research Council's Unit of Reproductive Physiology and Biochemistry led by the distinguished Professor T.R.R. Mann. Particular mention should also be made of M.W.H. Bishop who was immensely helpful and knowledgeable, not least having contributed two key chapters to Marshall's Physiology of Reproduction.

During Mike's years back in London, there was likewise the British Society for the Study of Fertility, constituted formally in 1951 and going from strength to strength. It provided a forum for biologists, medical doctors and animal scientists/veterinarians to discuss diverse aspects of reproduction. It held a university-based conference each summer and an annual Winter Meeting at the London Zoological Society. Attendance at these meetings enabled one to be exposed to the views of authorities such as A.S. Parkes, S. Zuckerman, G.W. Harris and F.W. Rogers Brambell. There were also up-and-coming personalities such as R.A. Beatty, R.G. Edwards, R.V. Short and A. McLaren. It was an invaluable means of seeking advice on one's own research projects and of establishing future collaborations. The Society for the Study of Fertility published its own research journal, the Journal of Reproduction and Fertility, soon to be a leader in the field and edited to a consistently high standard. Those were the days when editors read every paper recommended for publication and imposed consistency of spelling and agreeable turns of phrase – all a far cry from the frenetic, computer driven, cosmopolitan world of today. Mike began to submit his own well-illustrated manuscripts to the Journal of Reproduction and Fertility and continued to support it loyally down very many years and after its change of name to Reproduction. During most of the 1960s the corresponding American society and journal were not yet in existence.

Having successfully completed his PhD studies by the end of 1965, Mike was considering his future direction, both geographically and in terms of research topics. Much to his own surprise, not least since he was so conspicuously English with a large circle of English friends from school and university, his thoughts returned to the United States, especially to the eastern seaboard thereof. During his last year at the Royal Veterinary College, one Dr John Biggers – himself a London-trained veterinary graduate – had expressed an interest in Mike's work and held out the prospect of a post with him in Philadelphia, but this was not to materialise.

Back to the Worcester Foundation for Experimental Biology

Mike had certainly appreciated both the freedom and the research facilities in Chang's well-funded group at the Foundation and also the proximity of Boston with notable experts at Harvard and at Tufts University. So, somewhat to the amusement of staff at the Worcester Foundation – who had not forgotten his potent views on most aspects of American life – Mike returned to Massachusetts as a Staff Scientist in Chang's group. Apart from hoping to secure a university post in due course, he had two overriding objectives: (1) to shed further light on the process of capacitation and (2) to demonstrate the nature of membranous changes around a fertilising sperm head as it progressed towards and then confronted the egg surface (the oolemma). Chang was liberal in the allocation of experimental animals and technical support, and imposed only one requirement. Could Mike please dream up and undertake an experiment involving X-irradiation. At that time (1966) and for most of the 1960s, Chang was in receipt of substantial research funding to study the influence of irradiation on reproductive processes, especially on mammalian fertilisation, and needed to produce publications.

Sharing a laboratory with either Dr M.J.K. Harper or Mike – the two Mikes as Chang called them – I was newly arrived at the Foundation in January 1967 and promptly enlisted by Mike in Chang's requirement for an irradiation experiment! We came up with a simple design that was to produce intriguing results in rabbits. Because we repeated all the experiments and were confident in both the X-irradiation dose and our observations on fertilisation, it was troubling that our findings strongly disagreed with those in an earlier publication by Amoroso and Parkes. Mike's comments on this apparent contradiction are not to be repeated!

In pursuit of his twin overall research objectives, Mike had honed his skills in electron microscopy under the guidance of colleagues at near-by Tufts University, and was able to generate valuable images of the rabbit sperm head as it approached and then fused with the egg surface. Vesiculation between the sperm plasma membrane and underlying outer acrosomal membrane was revealed, more or less at the same time as Dr Claudio Barros working in Austin's laboratory (Bunny Austin was now at Tulane University, Covington, USA) was finding a similar vesiculation reaction just before fertilisation by hamster spermatozoa. I well remember Mike's excitement upon receipt

of a letter from Bunny Austin proposing a joint publication on this membrane vesiculation reaction. The two laboratories were also able to report a critical role for the sperm head equatorial segment in the process of gamete fusion.

One other line of investigation was being pursued by Mike at this time. He wished to define both the location and the endocrine conditions in which rabbit spermatozoa could become fully capacitated. In large measure, these projects followed preliminary studies by Chang but Mike built on earlier experiments in the golden hamster by using egg transplantation procedures to resolve whether or not rabbit spermatozoa were fully capacitated in a particular site. Such studies were warmly appreciated by Chang and gradually led to an impressive series of publications and likewise invitations to lecture.

Despite the agreeable community at the Worcester Foundation and abundant social life, Mike did not wish to remain there for long. He very much wanted a university post, knew he possessed gifts as a teacher, and would value moving on to a professorial salary. He was after all, a Yorkshireman, his father was in banking, and Mike was always conscious of his financial situation and the attractions of the stock market. In the event E.W. Dempsey, who was Head of the Department of Anatomy in Columbia University College of Physicians and Surgeons in New York had noted Mike's work and was keen to bring him to Manhattan. Mike had already sampled the intellectual and social excitement of New York life, and when Columbia was able to offer an Assistant Professorship and a conveniently situated apartment, Mike readily succumbed and moved there in the late summer of 1967.

Career development in New York: Columbia

Mike's formal duty at Columbia involved teaching gross anatomy to medical students and, soon after his arrival he also had to give lectures in cell biology. These activities appealed to him, not least in their setting of a well-recognised medical school. He also enjoyed interacting with motivated young Americans. In the other direction, a majority of such students relished the input and performance – yes, 'performance' – of this impressive and somewhat unusual Englishman. Lectures were never dull, thought processes were stimulated, anecdotes found their place.

One other requirement for Mike was to obtain independent research funding and build up his own research group. Separated from Chang's liberal, almost endless supply of experimental animals, Mike was to discover the significant cost of rabbits and rats. As an independent researcher, the learning curve was steep, but Dempsey was fully supportive. Having established his own laboratory, Mike's major themes during his time at Columbia University involved (1) the epididymal maturation of spermatozoa, (2) ultrastructural changes in a sperm cell, especially in the sperm head as a consequence of presumed capacitation, and (3) membranous modifications enabling sperm penetration of the zona pellucida and fusion with the egg plasma membrane. Rabbits were his principal model species since the block to polyspermy is established at the vitelline surface, enabling multiple sperm penetration to be examined during passage through the zona pellucida and within the perivitelline space

In addition to these major themes, he continued to be interested in cell surface charge, not least in a context of sperm agglutination as noted when flushing actively-motile spermatozoa from different regions of the female tract soon after mating. Mike was joined at Columbia by J.W. Overstreet, in due course to graduate in medicine. During his PhD work in Cambridge, UK, Overstreet had developed an interest in sperm transport within the female tract and in capacitation, and these topics were pursued in New York. Mike never lost his own interest in capacitation, but he and Chang now recognised that incisive research would need to be biochemical and that neither of them, possessed appropriate skills. For example, the fact of a cholesterol efflux from the sperm head membranes during capacitation, would not have come to light in their laboratories nor the key involvement of Ca^{2+} ion entry into capacitating sperm cells. Nonetheless, Mike and Chang remained closely involved spectators, frequently offering a valuable biological perspective when biochemists over-interpreted their findings.

A key direction of Mike's thinking involved changes in sperm cells during transit along the epididymal duct and what consequences such changes might have for sperm passage in the female tract and at the site of fertilisation. He was stimulated by the presence in his NIH-sponsored group of H.I. Calvin and G.W. Cooper, post-doctoral fellows who possessed special skills in relation to Mike's overall objectives. Henry Calvin demonstrated that there was an increase in disulfide bonding within the sperm nucleus during passage along the epididymal duct, conferring rigidity on the sperm head of ejaculated cells. George Cooper was interested in cell surface charge and changes in charge density during the events of fertilisation. Mike's research group began to attract notice.

Sperm penetration of the zona pellucida had long been considered to involve enzymatic digestion of a pathway in conjunction with increased flagellar activity, characterised as whiplash flagellar propulsion. However, Mike never fully subscribed to the concept of lysis and, largely as a consequence of Calvin's findings on disulfide bonding, became persuaded that zona penetration by a hyperactive spermatozoon depended purely on physical force or thrust, that is cutting activity by a rigid sperm head, uniquely shaped according to species. Somewhat surprisingly, he would not compromise and view sperm penetration of the zona as requiring both enzymatic digestion and propulsive force. This was disappointing to those biochemists who had invested much time and effort to the study of acrosomal enzymes and their potential for zona lysis. It was also puzzling since Mike himself had noted the acrosome reaction – vesiculation of the outermost sperm head membranes to release acrosomal enzymes usually occurred at or close to the zona surface.

Gradually Mike's thoughts developed on changes in the sperm cell as representing a counterpart to changes in the ovulated egg, so called coevolution of mammalian gametes. Here, as inferred above, he was primarily concerned with sperm penetrability of the egg coats, especially the zona pellucida, and supportive photographs and diagrams were produced covering diverse species. Mike had first been prompted to think about evolution at school and he remained an expert in

taxonomy and loved reciting (competitively!) the specific details in any given instance. This evolutionary orientation was strongly influenced by the writings and illustrations of C.R. ('Bunny') Austin in his invaluable books on fertilisation. Indeed, Austin remained the most generous and modest of colleagues, strongly supportive and yet discreetly in the background as his own work was developed by others. Soon Mike was to extend his gamete work to marsupials and then, tentatively, to monotremes. He travelled widely to gather evidence from both marsupials and monotremes.

Mike's interest in epididymal function was referred to above, but an unusual strand began to feature from the mid-1970's onwards. Evolutionary modifications remained an underlying theme. During undergraduate studies, Mike had been exposed to conventional teaching on relocation of the mammalian testes to a scrotal sac as primarily for purposes of temperature regulation: abdominal temperature was not suitable for spermatogenesis and would act to destroy the germinal epithelium. In his clinical studies in Cambridge Veterinary School, cryptorchid animals were presented in which bilateral failure of testicular descent was noted. However, the degree of testicular relocation would vary from full abdominal retention to arrest within the inguinal canal, either unilaterally or bilaterally. This clinical teaching came into focus when Mike used surgical 'restoration' of testes to the abdomen as an experimental model in studies of sperm maturation and their potential for fertilisation.

At the same time, other lines of thought were slowly gestating in his mind. The late T.D. Glover and L. Nicander had presented a novel concept at the Annual British Society for the Study of Fertility meeting in Liverpool in July, 1970. This was that rather than the testes drawing the adjoining epididymis down during relocation to the scrotum, it was the epididymis that had taken the initiative and each testis had necessarily followed. As the author participated in the 1970 Liverpool meeting, it can be reported that this concept attracted considerable excitement and discussion, but soon slipped from view. This was probably due to the sudden death of L. Nicander and T.D. Glover's move to Brisbane, Australia. However, it was clearly gestating in Mike's mind – he attended the Liverpool meeting – and in due course he was to embrace the Glover-Nicander proposal and compose elegant essays with titles such as "Anatomical evidence for the epididymis as the prime mover in the evolution of the scrotum". Unfortunately, the origin of this novel concept was soon allowed to slip from view, and some years later I wrote to Mike on behalf of Tim Glover; (we had connections from the Animal Research Station in Cambridge). Mike was not in the least pleased to be ticked off in this context, and probably had not been taken to task since his days as an English schoolboy! These facts should clarify the last sentence of the Introduction.

Having stated the above, it is important to record that Mike went on to develop the Glover-Nicander proposal in a series of evolutionary-based investigations. These showed flair and imagination and underline a recurring theme: that is, that Mike himself was seldom the originator of completely novel ideas or concepts. However, as a gifted and painstaking investigator, he would go to extraordinary lengths to gather evidence and then present it in memorable publications.

Associated with Dempsey, Mike's 5 years at Columbia went well. His career had developed impressively, both in terms of his own research and in building a National Institutes of Health (NIH) – sponsored research group. The names of Calvin, Cooper and Overstreet have already been mentioned, but there were various other research colleagues and post-doctoral fellows whose names can be noted in his publications for that period. By 1970, he had been promoted from Assistant to Associate Professor of Anatomy and his overall input to reproductive research was formally recognised by his appointment to national committees, through connections with the World Health Organisation (WHO) in Geneva and some early invitations to Beijing, doubtless prompted by his association with M.C. Chang.

An indication of a growing reputation was his organisation of an NIH-sponsored workshop in Bethesda (January, 1973) when he was able to attract an array of prominent national and international scientists to thrash out the latest views on sperm maturation, capacitation, and the earliest stages of fertilisation in mammals. He presided over the Workshop with a light touch and conspicuous enthusiasm, and went on to produce a keynote report for NIH. Other such hallmark achievements were to follow, and Mike came to feel that his career path was being acknowledged and rewarded. Nevertheless, and as has happened to others dedicated to university teaching and research, there was a growing awareness that moving from a comfortable established post might be appropriate. The university committee structures that inevitably embrace and restrain one's primary activities might thereby be given the slip, at least for a few years.

Move to Cornell University Medical College

Medical colleagues at Cornell were aware of Mike's research and growing reputation, and they knew of his earlier studies with Chang. There was the vision that their clinical work on fertility and infertility would benefit from the presence of a talented gamete biologist in their midst. Mike himself certainly appreciated the status of Cornell University, both at its campus in Ithaca and at its medical campus in Manhattan. In the event, he left Columbia and moved across town to the prestigious Cornell Medical Center in 1972, becoming Professor of Reproductive Biology in the Department of Obstetrics and Gynecology and of Cell Biology in the Department of Anatomy. Although he briefly considered a return home to London in 1980, Cornell was to retain his skills and enthusiasm for the rest of his career. As one form of reward for not succumbing to the temptations of England, he was granted an endowed post as the Percy and Harold Uris Professor of Reproductive Biology at Cornell University Medical College.

Even though not medically qualified, Mike wished to pursue questions underlying human fertility and was developing a broad interest in the gametes of primates. The prospect of being able to examine human oocytes and spermatozoa on a regular basis was a powerful attraction. Conscious of his own training and painstaking attention to microscopic detail, he was confident of being able to stimulate the clinical work of medical colleagues and perhaps catalyse the development of an IVF programme. He

might also be able to further his own views concerning sperm penetration of the egg investments and first stages of fertilisation if he could secure suitable specimens from the clinics.

As had been the case at Columbia, postdoctoral fellows and more seasoned scientists were attracted to Mike's Cornell laboratory; their names can be found in his list of publications. Colleagues who contributed on a longer-term basis included J.J. Rasweiler, already established at Cornell. His principal focus remained with members of the bat family (Chiroptera), and such creatures became attractive to Mike with his broad interests across species. Another close colleague was D.M. Phillips whose skills with electron microscopy attained a very high standard in a reproductive sphere in which the benchmark had already been set by D.W. Fawcett at Harvard University Medical School. Other colleagues or visitors associated with Mike's Cornell laboratory are too numerous to list comprehensively, but the following names could be noted – in no particular sequence: P. D. Temple-Smith, N. L. Cross, J. M. Rifkin, M. Berrios, P. Saling, J. C. Rodger, S. S. Wilkin, P. Esponda, P. S. Cuasnicu, H. H. Kim, T. Mori and S. Oda.

During his years at Cornell, Mike's major research themes remained largely as before. There was consolidation, although details of gamete biology were always being sought from an ever broader range of mammalian species. Two of his favoured themes are worth returning to, for there is a clear suggestion of some inflexibility creeping into his views. These were presented in his unique style of writing, frequently with flourishes of exotic vocabulary, the latter perhaps being more appreciated by his British contemporaries than by a younger international audience.

First, concerning descent of the testes and associated epididymal tissues into a scrotal sac, Mike declined to embrace the twin functions of a mammalian gonad – generation of gametes and synthesis of steroid hormones and other key molecules. In his long-standing opinion, the endocrine functions of a testis and related issues of fluid movements and transport of molecules had no relevance in explaining relocation of the gonad. This polarisation found parallels in his interpretation of sperm penetration of the zona pellucida. He did not care for the notion that strong propulsive forces generated by flagellar hyperactivity working in conjunction with the influence of acrosomal lytic enzymes enabled penetration of this outer egg coat. Such seeming inflexibility was unusual in an investigator who was a systematically-educated and wide-ranging animal biologist. Perhaps this was an expression of one of M.C. Chang's more mischievous sayings: 'Always disagree – it's more rewarding'!

Two new involvements need to be mentioned at this point. Having discussed with friends and colleagues a substantial body of published work concerned with oviduct physiology, especially in domestic farm animals (sheep, pig, cow), Mike began slowly to appreciate its relevance to his own work; afterall the oviduct was the location of final gamete progression and maturation before the specific events of sperm-egg interaction. Indeed, the most conspicuous event before fertilisation was usually a phase of sperm head binding to the oviduct epithelium. Although not much interested in endocrinology, the concept of pre- and peri-ovulatory ovarian hormone changes acting locally to regulate gamete progression and maturation began to find a place in Mike's thoughts. Thereafter, his written work, not least on various exotic species, made reference to features of sperm storage and orientation in the oviduct.

However, of far greater importance during Mike's time at Cornell was his input to the development of the IVF laboratories, of which he was the scientific director from 1986-1990. Following the key work of Edwards & Steptoe and the birth of Louise Brown in 1978, there was a surprisingly rapid development of IVF laboratories in many countries of the 'western' world. These were initially within medical schools and acted to promote collaboration between the relevant clinicians and suitably qualified scientists. In this context, Mike was of supreme value, being an excellent performer – almost an artist – in the laboratory and with meticulous powers of observation. No one devoted more time to examining events under the microscope and no-one came up with better-informed proposals for modifications to the in vitro and associated clinical procedures. In collaboration with his gifted gynaecological colleague, Z. Rosenwaks, the Cornell IVF laboratories achieved high standards and worked fruitfully with a large number of couples. In reality, no part of Mike's career was more important and, in significant measure, it stemmed from his early association with M.C. Chang and lifelong friendship with R. Yanagimachi.

Seemingly of potential practical significance, there were repeated reports during Mike's time at Cornell of a reduction in human sperm counts, that is the total number of spermatozoa per ejaculate by putatively healthy men, principally in Europe and North America. Although these reports were sensationalised in some quarters, Mike believed there could be potentially serious underlying issues. Prompted by the observations of N. Skakkebaek and colleagues in Copenhagen, he focussed on sartorial considerations and accepted that modern styles of dress, especially tight underwear, might be a critical factor: the ability of a scrotal sac to facilitate cooling of the testes would be seriously compromised. A strong argument could be mounted if ejaculates from men with traditional 'hunter-gatherer' lifestyles revealed significantly higher sperm counts and a lower incidence of morphological abnormalities. Never short of enthusiasm for an exciting project and related travels, Mike wrote several funding proposals for such a study. Doubtless due to the sensitivities involved, these were not successful and there remain unresolved questions.

Mike retained a keen interest in primate sperm morphology and one of his very last publications highlighted his views on the influence of elevating scrotal temperature.

JMB in science and society – a perspective

This memoir has attempted to give a flavour of Mike's background and early life, his formal education at school and university, and the development of his principal lines of research. It has avoided too much specific detail on individual projects, for his publications are available for all to download and read as appropriate. In this last portion of the memoir, some broader aspects of Mike's scientific and social life can be mentioned.

As alluded to above, Mike repeatedly stated to the author that his various gifts did not include having strictly original ideas. Rather, his strength lay in developing such ideas, frequently in exhaustive detail, and not least by seeking evidence from a broad range of mammals. He paid little regard to the geographical inconvenience this caused him and searched widely for new evidence, for example on the gametes of marsupials and monotremes. In a number of instances, these activities were combined with official Leave of Absence from Columbia or Cornell. Sabbaticals were spent at Jouy-en-Josas (France), Edinburgh (Scotland), and of course with his special friend and source of inspiration from their days together at the Worcester Foundation, Ryuzo Yanagimachi, now fully established in Hawaii. There was also a fruitful relationship with an Englishman, Bill Breed, by then permanently settled in Adelaide.

At home in the States, Mike continued to pull his weight on committees, sat on the editorial board of several professional journals and was invariably helpful to authors as a diligent and well-informed referee. His overall contributions to research on mammalian gametes were recognised by the award of the Marshall Medal from the British Society for Reproduction and Fertility yet not recognised by the American Society for the Study of Reproduction. He had acquired American citizenship in 1993 but had retained his British status and was certainly not seen by many of his colleagues as a fully-integrated American. Indeed, his invariably excellent lectures were quintessentially English in nearly all aspects except in use of the first person singular which he had adopted by mid-career.

As already brought out, Mike placed a high price on friendship. He kept up with school friends for many years after leaving Blundells, and contemporaries from Sidney Sussex College days remained friends for life. On occasions he would fly to London to attend one of the Sidney Sussex December reunions and was able to recapture the magical days of his youth. When travelling either in the States or in Europe, his substantial 'address book' was an essential item of luggage and upon arrival at distant locations, he would promptly be on the telephone to arrange meetings or, better still, hospitality. In his long years as a bachelor, no-one was more skilled at procuring invitations for lunch or dinner at short notice, and frequently also a bed. Hosts and hostesses were amply rewarded by Mike's endless supply of anecdotes and, if there were children in the house, he would make himself interesting and amusing to them as well. In brief, he was a 'character' – in the best sense of the word.

Mike was well able to charm females of all ages, but apart from the briefest of flings, he did not permit any potentially serious romantic attachments. His first love had become his research activity, and nothing was permitted to distract him from his chosen path for long. Even so, many contemporaries were puzzled by the fact that such an attractive personality was destined to be a life-long bachelor, and thereby arose the usual mischievous questions from male colleagues. However, Mike was able to maintain his professional focus because, in his own words concerning his manliness, "he needed very little".

All this was to change when, in his mid- forties, Mike was introduced to, and absolutely captivated by, an elegant, cultured and gifted painter, one Rita Reinhardt. She herself also had a European background, but her early circumstances were dramatically different from those of Mike. She had escaped from her homeland and lethal Nazi persecution on one of the last "Kinder-Transport" trains to the West, and found sanctuary and schooling in England. In due course, she joined a relative in the United States and, by the time she and Mike first met, she had been resident there for many years.

Mike and Rita achieved and sustained domestic harmony by respecting each other's individuality and by continuing to devote long hours to their own research and painting activities. They came together for family life in the evenings, frequently as perfect hosts for colleagues or visitors. During many years of their married life, they were quite actively involved in the New York social scene and were often to be found dining with a wide circle of gifted friends. By way of contrast, they acquired a rural property in upstate New York and this enabled useful exercise and time for relaxation. Sadly for Mike, this was not to be a permanent acquisition because of the problem of tick infestation and thereby a serious risk of catching Lyme disease.

Despite frequent travels, life in the big city gradually secured a strong hold and for the former sportsman (Mike), problems of health began to surface. Most serious of all, a heart bypass-operation became necessary and as a sequel to successful surgery, there was an inevitable slowing down, physically but not intellectually. In due course, travels were cautiously resumed, lecture invitations responded to, and perhaps most pleasing of all, there was a special invitation to China to unveil a statue to M.C. Chang. By that time, Mike and Rita had moved home from New York to the agreeable surrounds of Rittenhouse Square in Philadelphia. Rita set up her own studio and continued painting and Mike travelled once a week or so up to Cornell Medical Center. Although no longer involved in experimental work, he kept in touch with various colleagues and remained interested in developments within the IVF Unit.

Whereas Mike's own sporting activities had long since ceased, he was an enthusiastic follower of American football, baseball and tennis. He continued to read avidly, not simply the news and weekly or monthly periodicals, but also a wide range of solid books. His approach to various bouts of insomnia was to read well into the small hours whilst enjoying the soothing contents of a whisky glass.

As to their new life in Philadelphia, Mike assured the writer that he and Rita were pleased to be there but that they did not yet have as large a circle of friends as they had formerly enjoyed in New York. One feels sure it was only a matter of time but, alas, this was not available. Mike died peacefully at home on 24th February, 2018. To say that he will be much missed sounds trite, but that is indeed the case, as can be noted from many tributes on the internet. Such tributes come from only a small proportion of the people whose research was illuminated and lives enriched by their interactions with this remarkably special Anglo-American personality.

Acknowledgement

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Most eminent publications of Mike Bedford (a selection):

– Bedford JM. The status and the state of the human epididymis. Hum Reprod 1994; 9: 2187–99.
– Bedford JM. Enigmas of mammalian gamete form and function. Biol Rev Camb Philos Soc 2004; 79: 429–60.
– Bedford JM. Puzzles of mammalian fertilization--and beyond. Int J Dev Biol 2008; 52: 415–26.

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