History of ASA
Publications

Journal of Andrology

Andrology

Handbook of Andrology
HISTORY OF THE JOURNAL OF ANDROLOGY

First Editor of J. Andrology 1980: Andrzej Bartke, Ph.D.

First Editors of Andrology 2013: Douglas T. Carrell Ewa Rajpert-De Meyts

Erv Goldberg’s collection

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The American Society of Andrology was formed in 1975. Only five years later, the *Journal of Andrology* has come into existence as an expression of the efforts of individuals in this field. We believe that the Journal will be an important source of information for all investigators and clinicians interested in male reproduction.

In recent years, andrology has been a rapidly expanding area of scientific inquiry and now includes the clinical and experimental aspects of such areas as animal husbandry, biochemistry, developmental genetics, endocrinology, family planning, histology, immunology, molecular biology, pathology, pediatrics, pharmacology, physiology, psychology, and urology.

One may object to specialized journals because they restrict exchanges of ideas across interdisciplinary lines. However, we believe that the Journal will expose a diversity of investigators to new basic and applied research on normal and pathologic reproductive processes as well as on the regulation of fertility. We hope that the Journal will provide a forum for the presentation of data on comparative aspects, clinical applications, current methods, differential diagnoses, and safe therapeutic approaches to the problems of male infertility and fertility.

The willingness of members of the Editorial Board and Dr. Andrzej Bartke, Editor, to accept the additional responsibility of publishing a scientific journal is evidence of our members' commitment. Many other individuals, too numerous to name, have generously worked toward the actualization of this journal. I wish to thank them on behalf of the Society. Dr. Eugenia Rosemberg, Chairman of the Publication Committee, deserves special recognition for her tireless efforts.

Let us all work together to make this an excellent journal. Your participation in this venture, through manuscripts and comments, is welcomed.

NANCY J. ALEXANDER, President
*The American Society of Andrology*
Early Years of the Journal of Andrology

Andrzej Bartke

2002

From the time when the American Society of Andrology (ASA) first came into existence, there were debates about creation of a specialty journal. Some members of the council and the Society felt that a U.S. andrological journal would be important for the development of the field of Andrology in North America. Others, including myself, felt that the field of andrology was too small to support yet another Journal in this field. It was argued that rather than creating a new journal, ASA should become co-sponsor of the International Journal of Andrology, which was published in Europe. However, in 1978 when the ASA Council decided to launch a new journal and offered me a chance to be its first editor, I accepted this challenge. The Publication Committee chaired by Dr. Eugenia Rosenberg negotiated a contract with Lippincott Co. and the Journal of Andrology was born.

The first editorial board consisted of Drs:

Nancy J Alexander
Rupert P Amann
Richard D. Amelar
Rudi Ansabacher
Marie-Claire Orgebin-Crist
C. Alvin Paulsen
Kenneth L. Polskoski
Eugenia Rosenberg
Martin Dym
Stuart S. Howards
Fernand Labrie
Richard J Lobl
Richard J Sherins
Emil Steinberger
Philip Troen.

I selected this group hoping that these prominent figures in the field of Andrology would be reassuring to prospective authors.

Most members of the Council appeared very confident that the journal would be successful. However, there was also a tangible feeling of concern and suspense. Would we receive enough manuscripts to allow timely publication of scheduled issues? Would the manuscripts be of high quality? I knew Dr. Frank Comhaire, editor of the International Journal of Andrology, through a common interest in distribution of testosterone in different compartments of the testes. We both felt strongly that neither of us would consider doing anything to undermine the activities of the other journal, and thus our 'competition' was friendly from the very beginning.

The first issue appeared in January 1980. It consisted of papers provided by members of the Council and the Editorial Board, or submitted in response to our solicitations. Support provided by Society officers and Editorial Board members continued to be very important during the first years of the existence of the journal, but naturally, our success hinged on submission of manuscripts from outside this small group. I sent many letters to members of ASA and others soliciting manuscripts for the Journal of Andrology. These included many individuals whom I was able to "sign is" as members a few years earlier when ASA was created and I took on chairmanship of the Membership Committee. Although manuscripts initially trickled in at a fairly low rate, it was very clear to all of us that the journal would not succeed if we did not maintain high standards of peer review and acceptance. I vividly remember the task of composing rejection letters that would hopefully not offend the authors or discourage them from submitting other manuscripts to the Journal.

We quickly developed a list of reliable reviewers. Those who were tardy and unresponsive to reminders will never know that they may have received a "black testis award" initiated by Lynn Rudloff, Editorial Assistant, duly marked on their index card in our address file.

I had a great deal to learn, including some technical aspects of journal production. We enjoyed excellent working relationship with Lippincott. On several occasions, when the number of accepted manuscripts was particularly low, I had to find out from Lippincott what was the "real," i.e. the absolute rather than our standard deadline for assuring that the new issue of the journal would appear on time.
Early Years of the
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Looking back at this exciting period, it is difficult not to be amazed by how much everything has changed since the early days of the Journal. Did the editorial office really function without e-mail and Fax? Many younger members of ASA might find it hard to believe when our journal was started, microsurgery of the male reproductive system was an exciting novelty, research on inhibin was considered controversial, automatic systems from analysis of sperm motility were yet to be developed, and if anyone had the foresight to contemplate the use of intracytoplasmic sperm injection, it certainly would have been labeled science fiction.

Gradually, the Journal of Andrology found its niche and a group of loyal supporters. We were certainly helped by the decision of the Institute for Scientific Information to include us in "Current Contents" almost from the start. Happily, our citation index quickly placed us at the top of the list of andrology journals.

In 1983, I resigned from the editorship because of election to vice-presidency of the ASA. In the hands of my successor, Dr Marie-Claire Orgebin-Crist, the Journal of Andrology grew in size, quality, and prestige, a trend that continues to this day.

Andrzej Bartke
Department of Physiology
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Parting Messages From Current and Former Editors of the Journal of Andrology (just the first and last printed here)

First Editor’s Memoir

... The first issue appeared in January 1980. It consisted of papers provided by members of the council and the editorial board or submitted in response to our solicitations.... Did the editorial office really function without e-mail and fax? Many younger members of the ASA might find it hard to believe that when our Journal was started, microsurgery was an exciting novelty, research on inhibin was considered controversial, auto- matic systems for analysis of sperm motility were yet to be developed, and if anyone had the foresight to contemplate the use of intracytoplasmic sperm injection, it certainly would have been labeled science fiction....

Andrzej Bartke, Editor-in-Chief, 1980-83

Last Word

In 2007, it was our turn to take responsibility for the editorship of the Journal. We came aboard as 3 co-editors-in-chief, a new arrangement for the Journal, which had continued to grow in size and activity....Among our most honored rewards in service to the Journal was the continual interaction we had with Marvin Meistrich, chairperson of the ASA Publications and Communications Committee....He contributed as much to the success of the Journal during our tenure, as he did through his work to create the new journal, Andrology, which was considerable....Looking back over the history of the Journal, we are pleased to have seen a steady increase in its ISI impact factor, which was 3.14 in 2011....As we pass the baton to Doug Carrell and Ewa Rajpert de Meyts, editors-in-chief of Andrology, we wish for them the same rewards and satisfaction that we have enjoyed working together in trust for the Journal of Andrology.

Arthur L. (Bud) Burnett, Sally P. Darnay, Jay Sandlow
Co-Editors-in-Chief, 2007–12
Editorial

“ANDROLOGY”—The New Journal of the American Society of Andrology and the European Academy of Andrology

This article will be jointly published in the Journal of Andrology and the International Journal of Andrology.

History

Andrology is the study of health issues specific to males, with a focus on basic aspects of their reproductive system (gonads, endocrine, and accessory organs), and diagnosis and treatment of medical problems associated with infertility, sexual dysfunction, and urological problems. In medicine, the development of Andrology as a specific specialty is rather recent; it had often been considered a subspecialty of urology or endocrinology. The field of Andrology, emerging over the past 40 years, has produced several specialty journals covering both the basic scientific and clinical areas. The International Journal of Andrology (IJA) began publication in 1978 and became the official journal of the European Academy of Andrology (EAA) in 1992. The American Society of Andrology (ASA) launched the Journal of Andrology (JA) in 1980. These 2 journals have been the leading journals in the field of Andrology, with current impact factors of 3.6 (IJA) and 3.1 (JA).

Merger

Andrology remains a small and specialized field, and the size of both journals has been modest, each publishing about 600 pages per year. With the goal of increasing the visibility, impact, and prominence of both journals, and to better promote the field of Andrology, the EAA and ASA have decided jointly to create a single, even more prominent journal, Andrology. The international spirit of cooperation between the 2 societies and the enhanced availability of worldwide electronic communication has made it possible to jointly publish this new journal. The 2 societies will share equally in the management and editorial decisions of Andrology and in profits and losses from journal revenues and expenses.

Transition Period: Journal of Andrology and the International Journal of Andrology

The 2 original journals will actively continue to publish throughout 2012, with the last issues being published as November/December 2012 issues. New papers submitted to these journals will be accepted for review through March 31, 2012. We encourage members of the 2 societies to continue to send their best work to JA or IJA so that we can keep the journals strong as we go into the merger. It is possible that some papers submitted to the original journals that need to be sent back to authors for significant revisions might not be accepted in time. If they are accepted later, they will appear in Andrology. Starting in late 2012, the back issues of both JA and IJA will be hosted on-line at the Wiley Online Library.

Andrology

The EAA and ASA are pleased to announce that a contract has been signed with Wiley-Blackwell, publisher of the IJA, for publication of Andrology. The journal will be published both in print and on-line, bimonthly, with accepted articles published on-line shortly after acceptance. We believe that there will be cost savings to both societies by eliminating duplications of effort in publishing and that the merged journal will result in increased profitability and income for the benefit of both societies. Ewa Rajpert-De Meyts, MD, PhD, of the Rigshospitalet of Copenhagen University, and Douglas Carrell, PhD, HCLD, of the University of Utah Medical School, have been chosen as Co-Editors-in-Chief. Members of the ASA (including trainees) and EAA will receive on-line subscriptions to Andrology with print subscriptions available at a modest extra charge. The greater distribution of the new journal will be a benefit...
to authors; also, society members will now have access to the content that would have been in separate journals.

We believe that this larger, merged journal can more effectively compete with other journals and attract better articles. This more prominent journal should increase the prestige of the discipline of Andrology. Andrology will continue to publish basic, translational, clinical, and epidemiological research in andrology and will include all topics emphasized in both of the original journals. These include, among other areas, hormonal regulation, spermatogenesis, reproductive tract, accessory sex organs and external genitalia, sperm function and quality, prostate diseases including cancer, and male sexual physiology. Studies using mammalian and nonmammalian model systems and molecular and cellular investigations to understand male reproductive health and function in humans and important animal species will be considered. In addition, guidelines in clinical andrology and andrology laboratory science, as well as ASA and EAA society information, will appear in Andrology.

Impact Factor

Journal impact factors are published annually (June of each year) by the Institute for Scientific Information (ISI) in Thomson Reuters Journal Citation Reports. Although it will take several years for Andrology to fully establish its own impact factor, the combined impact factor of IJA and JA and Andrology can be computed to obtain an Impact Factor that authors can use to document the Impact of the Journal in which they are publishing. The June 2014 ISI Impact Factor report will list IJA and JA separately and represent the number of citations in 2013 to articles in the journals in 2011 and 2012 divided by the number of articles published in those 2 years; the numerators and denominators can be easily combined to calculate an overall impact for the 2 original journals. The 2015 ISI impact factor will list IJA, JA, and Andrology. For IJA and JA, the number will represent the citations in 2014 to articles published in 2012 divided by the number of articles published in that 1 year; for Andrology the impact factor will represent citations in 2014 to articles published in 2013 divided by the number of articles published in that 1 year. Again, an overall impact factor can be calculated by combining all 3 numerators and denominators. Thus, an effective impact factor of the original and merged journals can be obtained during the transition. From 2016 onward, only the impact factor of the new journal Andrology will appear in the ISI database. Based on our goals for the merged journal, strong support of ASA and EAA for the merger, and an outstanding Editorial and Publishing team, we expect the eventual impact factor of Andrology to surpass those previously achieved by JA and IJA.

Launch

The first issue of Andrology will be published in January 2013. A submission site using the ScholarOne Manuscripts on-line submission and peer review system will be open at the start of April 2012 for submission of new manuscripts of original research in andrology. The Editors will be soliciting potentially outstanding review articles, and individuals with suggestions for reviews should contact one of the Editors-in-Chief. We encourage ASA and EAA members to support the launch of Andrology by submitting their best papers, especially during these most important first several years of the journal.

Marvin L. Meistrich
Department of Experimental Radiation Oncology
University of Texas MD Anderson Cancer Center
Houston, Texas

Ilpo T. Huhtaniemi
Department of Reproductive Biology
Imperial College London, United Kingdom

Co-Chairs of Journal Oversight Committee for Andrology
We hope you will enjoy this special commemorative section of the *Journal of Andrology*’s final issue. It opens with an article written by all previous and current editors-in-chief to provide highlights of the *Journal*’s history for each editorship, and thereby show how the field and the *Journal* progressed over time. We tried to convey our collective perspectives on the editors’ roles in building an outstanding *Journal* and working with authors to ensure scientific credibility and integrity. Next, we provide a series of reviews selected to represent some “hot-button” research areas that have emerged in both the basic science and clinical practice of andrology during the lifespan of the *Journal of Andrology*, and that we expect to continue to motivate research in the future. We invited several notables of the American Society of Andrology (ASA) to write about them. Rather than writing exhaustive reviews, we asked these scientists to capture the major breakthroughs made to date in addressing the area, using a limited number of seminal references, and then to pose critical unanswered questions that await andrologists to resolve in the future. These reviews span the field to include the principles of genetics in male fertility, the scope of study of spermatogonia, the role of reactive oxygen species in sperm function, the evolution of erectile dysfunction management, and the scientific nexus of aging and declining testosterone. Finally, we invited Marvin Meistrich, chair of ASA’s Publications Committee, and Douglas Carrell, North American co-editor of *Andrology*, to combine in relating the story of how the *Journal of Andrology* and the *International Journal of Andrology* have come together and introducing the visions and goals for our new bigger and better journal.

Arthur L. (Bud) Burnett, MD  
Sally P. Darney, PhD  
Jay Sandlow, MD  
Co-Editors-in-Chief
Parting Messages From Current and Former Editors of the *Journal of Andrology*

The proposal to produce this final commemorative issue for the *Journal of Andrology* arose during our regular discussions as current editors soon after it was announced that the *Journal* would complete its own life course and merge into a new publication (to be named *Andrology*) with the *International Journal of Andrology*. We considered the momentous occasion to be one that should be celebrated with an enduring tribute in recognition of the *Journal*’s exceptional 33-year existence. Among the various contributions sought for inclusion in this issue, we envisioned an article assembling collected short essays from all living former editors drawing on notable events and highlights, if not less well-known challenges and successes arising during their editorship eras. We thought that any such production of musings, viewpoints, and most of all words of wisdom from those who have had major roles in the direction and accomplishments of the *Journal* would offer an illuminating read for the society’s members and friends and provide all readers another venue to share in and enjoy the *Journal*’s great history.

We are enthralled to have gathered these collections, all personal compositions of the former editors-in-chief, and for their effort that has helped us complete this special endeavor we express to them our tremendous gratitude. Serving as the *Journal*’s last editors, we are also grateful to contribute our essay at the very end as part of this joyous chronicle.

First Editor’s Memoir

From the time that the American Society of Andrology (ASA) first came into existence, there were debates about creation of a specialty journal. Some members of the council and society felt that a US andrological journal would be important for the development of the field of andrology in North America. Others, including myself, felt that the field of andrology was too small to support yet another journal in this field. It was argued that rather than creating a new journal, ASA should become cosponsor of the *International Journal of Andrology*, which was published in Europe. However, in 1978 when the ASA Council decided to launch a new journal and offered me a chance to be its first editor, I accepted this challenge.

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DOI: 10.2164/jandrol.112.017475
Excerpts presented with permission; Bartke, 2004.

Andrzej Bartke
Departments of Physiology and Internal Medicine
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Editor-in-Chief, 1980–83

The Early Years
The Journal of Andrology first appeared in January 1980. 5 years after the ASA was founded with 179 charter members. The wisdom of creating a new journal was vigorously debated by council. The assets of the society were only $20,042 as of December 1979, but a poll of the membership indicated that 59.6% of the members wanted the ASA to have its own journal.

Dr Bartke accepted the daunting challenge to become its first editor-in-chief. In 1982 he was elected vice president of the society and announced that, at the completion of his 3-year term as editor, he could not be reappointed for a second 3-year term. I was very sorry that he could not continue to guide the growth of the Journal because he had done so much to get it off the ground.

I was asked to be the second editor of the Journal of Andrology. Honestly, looking back, I do not know why I accepted this task: the membership had grown from 179 in 1975 to 500 in 1983, but the number of manuscripts submitted between 1980 and 1983 hovered around 80, the finances of the society were tight, and this conditioned the terms of the contract with the Lippincott Publishing Company. However, I agreed with Andy Bartke that the Journal of Andrology was important for the society and that “the contents of the Journal were critical to its future success.” I accepted the challenge, hoping that I would not destroy what Andy had already achieved and with one goal in mind: insure the credibility of the Journal by publishing papers of high quality.

Dr Benjamin Danzo agreed to serve as associate editor, and we served a first 3-year term from 1983 to 1985 and were reappointed for a second 3-year term from 1985 to 1988. After that, council probably felt that it was too cumbersome to change editorial offices after a 3-year term and adopted a nonrenewable 5-year term for all subsequent editors. During our tenure the number of manuscripts received increased from 84 in 1983 to 110 in 1987. The rejection rate from 1983 to 1988 ranged from 32% to 55%, averaging 43%. The ISI citation index for the Journal of Andrology was 2.2 for papers published in 1987 and 2.17 for papers published in 1988.

There were problems, of course. The percentage of human-related manuscripts received in 1983 and 1984 was 49% and 40%, respectively. The council felt that a clinical associate editor should be appointed to clearly send the message that the ASA encompasses both basic and clinical studies. I agreed and Dr Spyros Pavlou was appointed associate editor in 1986. This policy has been maintained to this day.

A worrisome aspect of publication was the length of time between reception of a manuscript and publication. It grew from 8.3 months in 1983 to 12.5 months in 1988. There were several reasons for this: There were only 6 issues published per year; the number of pages negotiated in the initial contract with Lippincott (400) was based on an estimation, a good estimation because the number of pages published in 1980, 1981, and 1982 were 320, 370, and 416, respectively. Although at the beginning sending an issue to the publisher required a leap in faith because I did not know if we would have enough accepted manuscripts for the next issue, soon there was a backlog of manuscripts. When the contract with the publisher was renegotiated in 1983, the number of contracted pages was increased to 448. At first this solved the problem, but as the membership grew to 698 and the number of manuscripts increased to 110, the backlog crept up again. In the initial contract Lippincott had agreed to cover the losses of the Journal in the first 3 years, but by the time the Journal moved to Vanderbilt, it was imperative that the Journal be solvent. Keeping in mind that pages contracted but not used would still be charged to the society, it was a difficult task for the Publication Committee to predict the number of pages needed for the next 4 years. Although in 1986 32 more pages were negotiated, we ended in 1988 with a backlog of 2 issues. This, of course, was unacceptable and it was solved by negotiating a new contract and increasing the number of contracted pages to about 900. Balancing the number of manuscripts with the number of contracted pages was the most frustrating aspect of my tenure as editor-in-chief.

During our tenure, we were confronted with several thorny ethical issues. With advice from the Publication Committee and the Officers of the Society, we tried to resolve each issue as fairly as possible. I was glad that in 1988 in consultation with the Publication Committee Guidelines for Ethical Standards were adopted for the Journal of Andrology.

Finally, I was very concerned with the fact that I was operating as editor-in-chief without liability insurance covering the society and the Journal. This was brought to the attention of the council in 1983 and figured as new business in each council meeting until 1988. It was slightly unnerving.

Looking back on these 6 years, I am grateful to the associate editors, Drs Benjamin Danzo and Spyros Pavlou; the editorial assistant, Carol Walter; the chairs of the Publication Committee, Drs Martin Dym, Anita Hoffer, and David Hamilton; and the officers of the
society. This was clearly a collective effort. Personally, I was pleased to see the ISI citation index at 2.2 in 1987. This was higher than all other andrology journals as well as the Journal of Reproduction and Fertility, and slightly lower than Fertility and Sterility (2.35) and Biology of Reproduction (2.3). To achieve this in a short 8 years was certainly what I was most proud of. I felt that I had not let down Andy Bartke and the society that had entrusted me with the Journal.

Marie-Claire Orgebin-Crist  
Center for Reproductive Biology Research  
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Editor-in-Chief, 1983–88

Bully for Andrology

The merger of the Journal of Andrology and the International Journal of Andrology into a single crosscutting publication presents an unprecedented opportunity to advance andrology as a discipline, promote investigative collaborations among andrologists, and augment the fiscal fitness of the editorial enterprise. From the standpoint of a former editor, it is gratifying to witness the commitment on the part of andrologists, European and American, to band together for the purpose of establishing a vehicle to publish important new findings across all aspects of basic and clinical andrology. The new journal sharpens the resolve of the founders of the European and American societies to publish manuscripts offering novel insights spanning all domains of andrology. The opportunity to disseminate scientific and clinical advances so widely through digital technologies promises to expand the boundaries of andrology and facilitate the application of basic and clinical advances to a far broader set of global constituents. Given the progress made in andrology over recent decades, few if any would be willing to predict the scale and scope of future advances made in this discipline. The new editors, nevertheless, have a substantial platform to extend the mechanistic integration of processes directing reproductive success, and ultimately improve the clinical outcome of patients suffering from reproductive disorders.

On a personal note, the opportunity to serve as editor of the Journal of Andrology provided a clinic for learning about the economic, ethical, legal, social, political, and scientific aspects of serving as proxy for the Journal’s readers. Within the crucible of editorial responsibilities resides the reality that each manuscript embodies the sweat, blood, and tears of one or more authors whose promotion, tenure, compensation, and funding may rest on an editorial decision. The task of providing for the fair, prompt, and thorough review of manuscripts coupled with the need for editorial adjudication, with reasoned suggestions for revision and clarification, provided a prism to view all facets of scientific scholarship.

If past is prologue, the new editors should prepare themselves to deal with scientific indiscretion (Jasny et al, 2011). The problems are not new, but they are unnerving to uncover and manage on one’s editorial watch. The disturbing rise in the number of manuscripts retracted from journals, across all fields, serves to remind investigators, reviewers, and editors of the imperative that manuscripts contain scientific findings that are novel, replicable, and untainted by conflicts of interest (Cressey, 2012). Sustaining scientific progress and preserving the public trust requires vigilance on the part of all who obtain scientific data and publish their results.

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Editor-in-Chief, 1988–93

Expansion to Co–Editors-in-Chief, Reflection of the ASA

In 1993, we were very excited to take over the editorship of the Journal of Andrology. We knew that we had some big shoes to fill from the outstanding achievements of previous editors. We believed that having a basic scientist and a clinician as co–editors-in-chief would better reflect the strength of the ASA. We selected 3 associate editors to broaden the expertise of the Journal and expanded the editorial board to reflect the diverse disciplines of the society. Our tenure began with a new publisher, Allen Press. This self-publishing model with Allen Press as a printer and distributor instituted by the Publication Committee has provided an excellent example for other societies for managing a journal. Our new editorial assistant, Denise Lecy, attended a journal editorial seminar sponsored by Allen Press in preparation for this new process. Over the years, Ms Lecy attended all of our annual meetings in order to interact with and become familiar with the members. Ms Lecy proved her value to the Journal in many ways. Thus, we depended on her to ensure that the Journal met the high standards expected from the society.

Our initial goal was to introduce more rapid processing of papers and reviews. A computer software program was installed to track papers more efficiently. We instituted a
Editors' Messages

Change is in the Air

David and I became co-editors-in-chief in 1997, following the Ron Lewis and Don Tindall era...big shoes to fill. Fortunately, Ron and Don got us off to a good start by spending hours going over what worked and did not work during their tenure. As we reflect back on the challenging yet rewarding 5 years as co-editors, there are several highlights that come to mind:

• Within the editorial office David and I decided to split editorial duties by reproductive site. So instead of one of us reviewing all manuscripts on the front end and the other doing editorial work on the back end, David worked on submissions regarding testis, sperm, and epididymis from submission to publication, and I did the same for the prostate and penis. The benefits of this change in workflow was if one of us was gone for any extended period of time, the other person knew the entire process from start to finish and could easily fill in.

• We changed the function of the editorial board from primary reviewers to advocates and advisors of the Journal. In addition, to improve the quality of the board, we revised the board member policy from an automatic 5-year term to renewable 1-year terms; we kept on the members who participated in a meaningful way and rotated out those who just wanted the title.

• Because we now were not using the board as extensively for reviewers, we worked hard to reach out to new reviewers, thinking that those who participated were more likely to submit manuscripts in the future.

• We added several new sections to the Journal: a Bioethics/Law Forum, Andrology Lab Corner, and Androlog online discussion.

• The net result of all of this is that the Journal nearly doubled in size during our tenure.

• There is one more significant focus of our tenure as co-editors—we worked extensively with the authors to get good articles that were not particularly well written ultimately accepted. It would have been easy to reject many of these manuscripts, but the science behind these selected manuscripts was of high quality. The extra effort required a lot of going back and forth with the authors, but both of us felt great pleasure seeing many of these articles in print. We
thank our editorial assistants, the editorial board, and all the authors who submitted articles that helped us take the Journal to the next level.

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Co–Editors-in-Chief, 1997–2002

The Penultimate Journey

The Journal moved to the Big Apple in 2002, making the Population Council and Weill Cornell Medical College its new home. Matt and I were ecstatic to continue the tradition of co-editors from basic and clinical backgrounds to the Journal. If we were to recognize what changes the next 5 years would make in our lives, I’m not sure we would have been so excited.

At the time the Journal moved to New York, we were primarily buried in paperwork (old manuscripts, reviews of manuscripts, etc) that was completely gone by the time our editorship ended. Certainly, the entire publishing business was changing dramatically—to the point where I don’t think any of us were certain that paper journals as we knew them would continue to exist in the future. When the Journal of Andrology left the University of Minnesota and Jon and David’s capable hands, the FedEx budget for processing reviews and manuscripts alone would have dwarfed our editorial office budget. We were grateful to Jennifer Bellask for coordinating our initial shift to electronic communication with authors that was completed with the transfer of physical office activities to Jansen Editorial Services and HighWire Press’ manuscript tracking system. The input of the Publication Committee, Drs Bernard Robaire and Marvin Meistrich, was instrumental in facilitating these changes—as daunting as they initially seemed to be.

We began the difficult job of balancing the new sections of the Journal with the core, peer-reviewed manuscripts alone would have dwarfed our editorial office budget. We were grateful to Jennifer Bellask for coordinating our initial shift to electronic communication with authors that was completed with the transfer of physical office activities to Jansen Editorial Services and HighWire Press’ manuscript tracking system. The input of the Publication Committee, Drs Bernard Robaire and Marvin Meistrich, was instrumental in facilitating these changes—as daunting as they initially seemed to be.

We began the difficult job of balancing the new sections of the Journal with the core, peer-reviewed manuscripts. We loved the sections of the Journal introduced by the prior co-editors that brought new perspectives: Andrology Lab Corner (a site for new techniques & lab-oriented insights), Androlog Summary (an overview of the very active Androlog Listserv so ably coordinated by Andy Meacham and Craig Niederberger), and Bioethics and Law Forum (a wide-ranging set of discussions relevant to andrology that Susan Benal Kerr brought new insights to), as well as reviews and minireviews that are critical to the reputation of the Journal. We shared with prior and subsequent editors the challenges of getting an adequate number of able reviewers for manuscripts in the relatively small field of andrology, as well as the delight of supporting a journal that provided a critically important niche in our field.

The challenges of editorship were compounded when I was named chair of urology at Cornell; Matt carried the challenges well as co-editor, demonstrating great flexibility of scheduling and extended sharing of duties. Never once did Matt complain of having to take on a broader role, and it was his work that allowed the Journal to grow in quality of manuscripts published during this time. A major emphasis of this time was to increase the number of scientifically sound but clinically relevant papers, especially those with a focus on the genetics of male infertility. We were pleased at the number and quality of those papers that were published, but sadly also realized that impact factor ratings were driven more by review papers than solid peer-reviewed manuscripts.

Sadly, Matt passed away as our tenure as editors was completed, an untimely death that brought a tremendous amount of sadness to all of us, and a great loss to our field of andrology. A talented researcher and a dynamic, thoughtful investigator with boundless enthusiasm for teaching, life, and love for his wife, Dianne, the loss of Matt stunned us in ways that could not have been predicted. His loss will be forever commemorated at Weill Cornell Medical College by the Matthew P. Hardy Distinguished Professorship, an endowed chair currently occupied by Dr Marc Goldstein, his close friend and colleague. We still miss him tremendously.

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Co–Editors-in-Chief, 2002–07

Last Word

In 2007, it was our turn to take responsibility for the editorship of the Journal. We came aboard as 3 co–editors-in-chief, a new arrangement for the Journal, which

1 Deceased.
had continued to grow in size and activity. We distributed responsibilities to a large extent based upon each of our areas of academic expertise for reviewing manuscripts and steering them through the manuscript review process. Bud handling sexual medicine and prostate diseases both at basic science and clinical levels, Sally handling andrological basic science broadly, and Jay handling male reproductive medicine and andrological clinical science. Our collective position also took on a new dimension resonant with the modern era of electronic communication and publishing. Although each of us was geographically situated in different cities (Baltimore, Research Triangle Park, and Milwaukee), we worked together in a virtual editors’ office. Regular teleconferences, now fashionable in the conduct of journalistic business, enabled us to discuss editorial issues, including several very interesting publication ethics questions.

Among our most honored rewards in service to the Journal was the continual interaction we had with Marvin Meistrich, chairperson of the ASA Publications and Communications Committee. From the start, Marv was actively engaged in our monthly conference calls. Much of our effectiveness is owed to his boundless energy in exchanging ideas, offering guidance, and constantly executing necessary chores that assisted greatly in our editor roles. He contributed as much to the success of the Journal during our tenure, as he did through his work to create the new journal, Andrology, which was considerable. Together with input from Marv, the Publications and Communications Committee, and our editorial board, we also implemented new procedures and policies surrounding manuscript submission, review processing, and peer review, which heightened the efficiency, transparency, and accuracy of these activities.

Much as our predecessors had done, as editors we strived for excellence and quality in the Journal, a foremost objective to preserve its high impact and recognition. Looking back over the history of the Journal, we are pleased to have seen a steady increase in its ISI impact factor, which was 3.14 in 2011. During our tenure, we maintained its breadth of content, welcoming research articles that represented all areas of andrology laboratory science, clinical and epidemiologic studies, reproductive genetics and endocrinology, sperm biology and assisted reproduction, and spermatogenesis and male reproduction. We maintained the Journal’s special sections and beyond research articles sought to include case reports, andrology lab corner submissions, memorials and perspectives, and editorials. We expanded its features as well, such as soliciting more scholarly review articles, including those based on presentations at the ASA annual meeting. We also published a number of special editions, which will serve as lasting resources in the field, including Proceedings of the 2008 ASA Workshop, “Therapeutic Strategies for Male Sexual and Hormonal Health” (Burnett, 2009); Proceedings of the 2009 XXth North American Testis Workshop, “Testicular Function: Levels of Regulation” (McCarry and Eddy, 2010); and Proceedings of the 2011 Fifth International Conference on the Epididymis, “The Epididymis: Present Progress, Future Directions” (Avellar and Cuasnicu, 2011).

As expressed by the other editors, we enjoyed experiencing the progression of andrological science firsthand over the 5 years of our term. At the same time, we also learned a lot about the ever-changing publications field. Judy Jansen and her staff in Jansen Editorial Services continued to provide us with timely input and editorial support, beginning with training us in the efficient use of the Benchpress software for manuscript processing. Their oversight helped us operate effectively as “virtual editors” across time and space. We also greatly appreciate Kristen Anderson and the staff at Allen Press, who help ensure optimal organization of content within each issue, meaningful cover graphics, and timely production of each issue. These many behind-the-scenes activities all contributed to the excellence of our Journal.

Scientific credibility depends heavily upon critical and constructive peer review. Our editorial board members and ad hoc reviewers were the heroes here. They ranged from young “hotshots” in the field to established investigators who helped ensure appropriate attribution of ideas to the pioneers in the field. They took time from their own professional activities to help colleagues and the Journal to succeed. We acknowledged their invaluable input individually in the final issue of each volume.

Finally, we offer a take-home message for authors. The papers that fly through peer review are those that convey a very clear and compelling rationale up front, and conclude with how this new information will advance the field of andrology by offering new or improved methodology, by elucidating our understanding of basic biology, and/or by advancing clinical practice. We had no trouble finding good reviewers for such papers, which are exciting to read and relatively easy to critique. We have enjoyed working with all authors and hope each of you will continue to submit your best research findings to Andrology.

As we pass the baton to Doug Carrell and Ewa Rajpert de Meyts, editors-in-chief of Andrology, we wish for them the same rewards and satisfaction that we have enjoyed working together in trust for the Journal of Andrology.
References


Evolution of the Journal of Andrology and a Bright Future for Andrology

Historical Perspective

In the 1970s andrology really emerged as a specific discipline. The American Society of Andrology (ASA) was founded in 1975. In 1978, under the guidance of Dr Rune Eliasson, publication of the International Journal of Andrology was initiated, and in 1992 it became the official journal of the European Academy of Andrology (EAA). In 1980, the ASA began publication of the Journal of Andrology under the editorship of Dr Andrzej Bartke (Burnett et al, 2012). In addition to these, 3 other journals specifically devoted to andrology are also currently published.

Andrology originally was a branch of medicine treating health issues specific to males with a focus on their reproductive system, and included studies of the gonadal, endocrine, and accessory organ systems, and diagnosis and treatment of medical conditions related to fertility, sexual function, and the urogenital system. The ASA has taken a broad view and has promoted and supported basic research on model organisms that leads to an understanding of the mechanisms underlying these systems. In addition, there are parallels between research applicable to human fertility and the reproduction of animal species important for economic or conservation purposes; significant publications in these areas are also included in the Journal of Andrology.

Since 1980, there have been huge advances in biomedical science in general, and in aspects that particularly apply to andrology. Molecular biology and genome sequencing has led to the knowledge of genes that affect the development of the reproductive organs, male fertility, and disorders of the reproductive system. The addition of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) to the repertoire of assisted reproductive technologies (ART) has overcome major barriers to male infertility. Although they have diminished the importance of andrology research in aspects of sperm characteristics related to fertilizing ability, such as motility, because they bypass the natural barriers, the widespread use of such techniques has increased the need for andrology lab facilities as a component of such procedures and spawned research into genetic and epigenetic consequences of eliminating this natural selection process.

Major Contributions of Papers in Journal of Andrology

Examination of papers with high citation rates in the Journal of Andrology over the life of the journal provides a measure of the areas to which the journal has made significant contributions to the field of andrology (Table). Some of those areas may have had more impact on the development of the field of andrology over the past 32 years and others are very highly relevant to current and future issues in andrology. Although this list does not cover all the areas of contribution of the journal to the progress in andrology, and citation rates do not always give a full measure of the impact of articles, this selection nevertheless highlights areas in which the Journal of Andrology has published numerous significant studies and reviews, and honors the contributions of the authors.

Oxidative Stress in Testis and Spermatozoa—Papers in the area of oxidative stress in spermatozoa and also in testes were in general the most highly cited (Alvarez et al, 1987; Aitken and Clarkson, 1988; de Lamirande and Gagnon, 1992; Saleh and Agarwal, 2002; Turner and Lysiak, 2008). The studies in the Journal of Andrology defined mechanisms and emphasized the relationship between the generation of reactive oxygen species in the testis and sperm with infertility. Modulating reactive oxygen species generation offers the hope of improving testicular function and semen quality. Currently there is much activity in using relatively common oral, readily available antioxidant therapies for treatment of male infertility, both for the purpose of achieving natural pregnancies and in ART procedures (Aitken et al, 2012). Although these therapies have often been shown to achieve better sperm function and improve pregnancy rates, appropriate placebo-controlled clinical trials have not been performed and are still needed; trials with these antioxidants should be an important area for future research.

Sperm Chromatin—The next category of numerous highly cited papers involved analysis of sperm chromatin...
and relationship to semen quality and fertility. Since the advent of IVF and ICSI, the focus of semen analysis has expanded from just the motility and acrosomal properties of the spermatozoa necessary for accessing and fusing with the oocyte to a more detailed analysis of the quality of the sperm’s genetic material that is delivered. This concern has been heightened by the fact that in ART, defective sperm that might be carrying more genetic damage can be used for successful fertilization, transmitting the genetic defect to the next generation.

Indeed, sperm with poor semen quality by classical criteria did display DNA-strand breakage by the comet and in situ nick-translation assays (Irvine et al., 2000). The description of a rapid and practical flow cytometric assay for quantifying DNA strand breakage and chromatin packaging abnormalities in large numbers of sperm by the sperm chromatin structure assay (SCSA) in an Andrology Lab Corner paper provided a description of background and protocols to enable this assay to be more widely used in many andrology labs, where it now is an important part of semen evaluation (Evenson et al., 2002). Furthermore, this assay has proven valuable in environmental epidemiology studies on the potential impact of pollution on male reproductive health. Comparison of the different assays with others such as terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) and sperm chromatin dispersion (SCD) demonstrated a good correlation between the SCSA, TUNEL, and SCD assays, and these could be used to assess sperm DNA damage, which is higher in infertile than in fertile males (Chohan et al., 2006).

Although there is general agreement on the association between sperm DNA damage and infertility, the presence or absence of such damage does not absolutely distinguish fertile from infertile individuals; an excellent discussion of the value and limitations of those tests for patients undergoing specific procedures, including intrauterine insemination, IVF, and ICSI, was presented in a very useful review in the Journal of Andrology (Zini and Sigman, 2006). An animal study has been successfully used to experimentally test the level of DNA damage that causes failure of embryo development and determine the stage of embryo development at which developmental defects predictive of blastocyst apoptosis can be observed (Fatehi et al., 2006); these methods can be used to select more viable embryos in human ART procedures. Finally,
a well-cited paper (Aoki et al, 2006) describing variation in protamine levels in infertile men has portended greatly increased interest in the roles in embryogenesis of epigenetic factors including DNA methylation, the presence of and localization of specific residual histones on the chromatin, and the presence of activating and repressive posttranslational modifications of these histones.

Semen Cryopreservation—One of the most highly cited papers in the Journal of Andrology (Hammerstedt et al, 1990) was in the area of semen cryopreservation and involved an in-depth analysis of the membrane properties of sperm and how that affected the survival of the cells during a freeze-thaw cycle. Further studies into the initiation of capacitation-like (Bailey et al, 2000) and apoptotic-like (Ortega-Ferrusol et al, 2008) reactions as a result of the freeze-thaw cycle and their roles in the reduced life spans of the surviving populations have been widely cited. Although the data in these papers were based largely on bull, ram, and equine sperm, as semen cryopreservation and artificial insemination are economically important in those species, the general principles elucidated are also applicable to improving the cryopreservation of human sperm, which is assuming new importance with the need to preserve the viability and DNA integrity of the low numbers of testicular sperm obtained from testicular biopsies of azoospermic men.

Metabolic Syndrome, Obesity, Hypogonadism, and Erectile Dysfunction—The Journal of Andrology has published well-cited studies relating the current increases in obesity and type 2 diabetes to disorders of the male reproductive and genital systems. One such study demonstrated that increased body mass index was associated with a dramatic decrease in the numbers of normal motile sperm cells and also a decrease in sperm integrity (Kort et al, 2006). Because obesity is now considered as one factor comprising metabolic syndrome, a more recent review (Traish et al, 2009) suggested that hypogonadism (specifically androgen deficiency) was associated with and might be responsible for an increase in metabolic syndrome, and furthermore that erectile dysfunction may be a consequence of the metabolic syndrome. Both the Journal of Andrology and the International Journal of Andrology have published important, widely used recommendations resulting from collaborations between several societies to carefully outline the patient assessment and response criteria for evaluating the benefits and risks of testosterone therapy for late-onset hypogonadism appearing in aging males (Nieschlag et al, 2005, 2006; Wang et al, 2009). The mechanisms that account for age-related declines in testosterone and therapeutic hormone replacement approaches continue to be an active area of study (Zirkin and Tenover, 2012). The Journal of Andrology has also published several well-cited studies supporting the use of phosphodiesterase-5 inhibitors for treatment of erectile dysfunction (Guay et al, 2001; Hellstrom et al, 2002), as well as numerous basic research studies of mechanisms involved. Recent advances and new challenges on this topic are discussed by Burnett and Hellstrom (2012).

Merger With the International Journal of Andrology

The Journal of Andrology and the International Journal of Andrology have similar scopes and impact factors, but also have historically had unique areas of emphasis. Some particularly strong areas that are emphasized more in the International Journal of Andrology include effects of environmental toxicants and endocrine disruptors on development of the gonads and the male accessory organs and the consequences of this disruption on pubertal development, fecundity, and malignancy; pathogenesis of testicular germ cell cancer; and studies of genetic causes (eg, Y-chromosomal defects) in infertility. Conversely, the Journal of Andrology has had a greater breadth of basic science studies and animal model studies. To draw from the strengths of the 2 journals, the ASA and EAA will merge them to form a new journal, Andrology, which has begun accepting submissions and will publish its first issue in January 2013 (Meistrich and Huhtaniemi, 2012).

The major motivation for the merging of the Journal of Andrology and the International Journal of Andrology is to strengthen and improve the quality of the new merged journal. Rather than continuing in a competitive mode between the top 2 journals, the goal of the merger is to establish Andrology as the clear leading publication for studies on male reproductive science and medicine. It is the goal of the societies and editors that the merger will establish a clear first-choice journal in the field of andrology that will effectively compete with journals in related disciplines and enhance the perception of the field of andrology. With a broader base of papers to draw from, it is hoped that the quality of papers published will clearly reflect a high level of scientific investigation that will foster attention and respect for the field of andrology, thus helping to facilitate further growth and development in the field of andrology. The editorial team, composed of co-editors-in-chief from North America and Europe and associate editors and editorial board members from 6 continents and 22 different countries, carefully selected to represent all areas of study relevant to andrology, reflects the intention of establishing a truly global journal.

Although the merger provides a stronger foundation to build upon, an improvement of the stature and impact factor of the journal is not automatic, and will
be contingent on *Andrology* successfully navigating through challenges and obstacles, some of which are reflective of the current state of scientific journal publishing and some of which are specific to the merger and launching of a new journal. For example, the dramatic advances in electronic publishing, which facilitate more rapid submission, editing, and publishing of manuscripts, has enabled the launching of new journals, evidenced by the abundance of new, "low-impact" journals in many areas of biomedicine, including andrology. So there will be, and already is, a line of new journals ready to fill the void left by the *Journal of Andrology* and the *International Journal of Andrology*. Therefore, it is imperative that *Andrology* establish itself quickly and firmly as the journal of choice for top manuscripts in the field. The journal oversight committee, the editors, the editorial board, and the publisher, Wiley-Blackwell, will work hard to advance the journal by improving the review and editing process, enhancing the appearance and functionality of the journal, maximizing accessibility consistent with a business model to recoup costs, and striving to assure the highest level of publishing integrity and fairness to authors. However, ultimately the success of the journal is dependent on the submission of top-quality papers, especially by members of the ASA and EAA.

To increase the visibility and usability of the new journal, the editors are working closely with the EAA and ASA publications committees, the latter chaired by Jacques Tremblay, to enhance the flow of information from the journal through social media sites to society members and the public. Such efforts will include the highlighting of breakthrough manuscripts and online discussion of manuscripts.

**The Future of Andrology**

We expect that *Andrology* will be the leading publication in new developing areas of andrology. Although it is impossible to predict future breakthroughs in andrology, certain fields of study seem to portend high impact in the future.

For example, it is likely that there will be major advances in the genetics of infertility through complete genome sequencing of patients and controls, which will uncover structural variations and rare polymorphisms that likely account for a high percentage of male infertility (de Rooij and Griswold, 2012). These genetic tools may benefit other areas of andrology as well. Similarly, studies of epigenetic alterations have the potential to demonstrate the role of the environment and drastically advance our understanding of diseases of the reproductive tract, including cancer and infertility.

Another example of a potentially major advance in the treatment of reproductive diseases is the ongoing growth of stem cell biology and technology. The basic concepts in characterizing mammalian germ cell stem cells were clearly explained to a wide audience in a highly cited paper by de Rooij and Russell (2000), which contributed to an increase in research and outstanding progress in this area over the last decade. Nevertheless, challenges continue (de Rooij and Griswold, 2012). Stem cell studies have the potential of dramatically enhancing our knowledge of basic biological mechanisms, as well as the hope for of new treatment modalities. Such therapeutic benefits could benefit numerous areas of andrology, from improved options for patients attempting fertility preservation prior to cancer therapies to addressing various forms of abnormal spermatogenesis.

The field of ART may be an area that will benefit from recent technological advances in sperm selection procedures and sperm cryopreservation. There appear to be promising new techniques to select sperm for ICSI that contain less DNA damage than unselected sperm in the ejaculate. As our understanding of what makes a sperm competent for normal embryogenesis increases, sperm selection may become a key topic of andrology research. Also, the recent advances in recovering sperm from testicular biopsies in men with nonobstructive azoospermia have highlighted the need for enhanced sperm cryopreservation techniques for these patients with limited sperm. Sperm vitrification may be one tool for improving cryopreservation success in these men and in severely oligozoospermic patients.

Lastly, it is likely that novel pharmaceutical advances, ultimately based on progress in pharmacogenetics, will alter the way sexual dysfunction and other disorders of the male reproductive system are treated. Underscoring all the potential clinical applications will be the continued progress of understanding cellular and endocrine biology, and technological advances in cell analysis, cell separation techniques, genomics, and proteomics. *Andrology* stands ready to publish in all areas of male reproductive studies and will anxiously await the next breakthroughs and major contributions.

**Concluding Remarks**

The *Journal of Andrology* and the *International Journal of Andrology* have both independently established fine reputations of quality scientific publishing and are the top 2 journals in the field of andrology. Together they have laid an excellent foundation for *Andrology* to become a global leader in publishing studies of male reproductive health and science. We invite submission of all high-quality manuscripts, and will actively solicit reviews on cutting-edge topics from leading researchers.
We encourage active participation in the journal by submitting top studies for publication, accepting review requests, and providing the editors with your ideas and suggestions.

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Acknowledgments

We thank Drs Ilpo Huhtaniemi, Ewa Rajpert-De Meyts, Wayne Hellstrom, and Christina Wang for helpful comments.

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In the inaugural issue of Andrology, we take this opportunity to momentarily celebrate the merging of the two leading journals in the science and medicine of male reproduction. The collaboration of the European Academy of Andrology and the American Society of Andrology in the merging of their prior journals, International Journal of Andrology and Journal of Andrology, and their joint oversight of Andrology lays a firm foundation on which the advances in our field can be better disseminated and highlighted to scientists, clinicians, and the general public. In addition to celebrating the launch of Andrology, we highlight a few of the challenges ahead, with a call for the support of you, each of our readers.

The merging of two journals is a difficult undertaking under any circumstances, but particularly so when the journals represent two societies that are geographically, and in some regards culturally, different. It should be noted that the merger has been discussed previously, in fact on multiple occasions. So why was the merger accomplished now? We would suggest the following as some of the key reasons for the merging of the journals and the new creation of Andrology:

1. While the prior two flagship journals overlapped in scope, each had particular strengths that if merged together result in the potential of an improved journal in both impact factor and coverage. There should be no mistaking that all involved in the merger hope for an improved impact factor, which reflects well upon our field as a whole and attracts attention from researchers, funding agencies, academic review committees, and the broader audience.

2. The publishing industry is undergoing dramatic changes that have facilitated the easy establishment of niche journals, particularly ‘for-profit’ online journals that often provide inadequate peer review or editorial responsibilities that threaten to harm the quality of published information available to clinicians and researchers. Additionally, technological advances have revolutionized the positive options available in publishing. At this key juncture, it is imperative that the field of andrology has a flagship journal that evolves and implements technological advances from a position of strength and integrity, which the merger facilitates. In the coming issues, we will highlight some of the trends and options which all journals must navigate, but it is important that Andrology faces these challenges and makes decisions based on unwavering dedication to scientific excellence and publishing ethics.

3. The development of Andrology was ultimately due to the dedication, vision, and persistence of key members of the two societies, including Ilpo Huhtaniemi and Marvin Meistrich (former chairmen of the publication committees of the European Academy of Andrology and the American Society of Andrology), the editors of the predecessor journals, the leaders of the two societies, and the representatives of our publisher, Wiley-Blackwell. Difficult and serious questions were faced throughout the process, and will continue to arise, but the dedication of those involved in the process of ‘making it work’ for the good of all has been unusual and necessary.

The history of the merger and information concerning the impact factor of the new journal during the two-year-long transition period was described in detail in a recent editorial published jointly in Journal of Andrology and International Journal of Andrology (Meistrich & Huhtaniemi, 2012). The two journals were occupying two top positions on bibliometric lists in this field, so Andrology begins with a respectable composite.

We shall post updated information on the Andrology website (www.wileyonlinelibrary.com/journal/Andrology). We encourage you to look at this website, which has been active since April 2012. In addition to Early View of accepted papers, you can find on the website announcements of upcoming andrology meetings, highlights of the best papers and society-related information.

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The two societies and publishing committees took care to balance the influence of the andrology communities on both sides of the Atlantic: the new editorial team comprises equal numbers of Americans and Europeans, and all other continents are represented on the board. We are happy that the board includes many world-renowned experts in andrology and reproductive medicine but besides scientific excellence, the editors are distinguished by their willingness to contribute constructively to the peer-review process.

So, with the foundation strong we ask for the continued support of you, the leading andrologists of the world. Ultimately the continued success of Andrology is dependent on the submission of your science to our journal and your participation in the peer review process. We, as co-editors, have committed to honest, fair, and rapid review of your work, as well as continued creative efforts to advance the quality of the journal. With the technological and scientific breakthroughs that continue to accelerate advances in science and medicine, and with your support, we anticipate that Andrology will fulfill its mandate to better support advances in the field of andrology.

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Preface

Since the first edition of the Handbook of Andrology, published by the American Society of Andrology 15 years ago, over 20,000 printed copies, as well as uncounted numbers of electronic copies, have been distributed to colleagues and trainees around the world. The first edition was translated into Spanish, Italian and Chinese. Most of the fundamental information provided in the first edition is still valid; however, the volume of scientific literature on the various facets of the subject of andrology has expanded tremendously. This has resulted in a constantly growing body of knowledge, not only in basic science but also in the clinical management of men’s health issues.

In this edition, we have increased the number of chapters from 24 to 41, but have made every effort to retain a style that will allow trainees to be introduced to the field of Andrology and become as excited about working in this field as are the contributing authors. Our chapters encompass the wide range of topics that characterizes the field of Andrology, from molecular biology to veterinary and human medicine, from applied research to ethics. We once again have been extremely fortunate to have as authors world-renowned Andrologists who are experts in the various subjects included in the Handbook; we wish to thank each of them for their valuable contributions.

With the advances in information technology, we feel that it is time to drop the traditional format of a paper bound book and move to an electronic only version for this edition of the Handbook. With the support of the American Society of Andrology, this edition of the Handbook will be freely available to all members of the Society. The electronic version is available as a single PDF or as PDFs of individual chapters. We believe that this approach will allow for a wider scope of circulation of the Handbook, permit more frequent updates of the content, and help save a forest of trees.

It is our hope that this second edition of the Handbook of Andrology lays the foundation for basic scientists, clinician scientists, healthcare professionals, trainees, policy makers and anyone who has an interest in the discipline to acquire the relevant knowledge that they seek.

Finally, we would like to acknowledge the dedicated secretarial support of Ms. Elise Boivin-Ford and to thank all the contributors and various members of the American Society of Andrology for their assistance and support in making this Handbook possible.

Bernard Robaire and Peter Chan
Co-Editors
February 2010
Lessons Learned in Andrology

An Editorial section introduced in 2014

By invitation, leaders in the field of andrology
Submit brief essays on valuable lessons from their distinguished careers
Lessons Learned in Andrology: Seeing is believing

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Editors’ Note: With this issue of Andrology we introduce a new feature entitled ‘Lessons Learned in Andrology’. By invitation, leaders in the field of andrology will submit a brief essay that addresses valuable lessons they have learned in their distinguished career, possibly including short historical vignettes. The objective of this new feature is to assist others, especially young investigators, in considering important lessons that are learned in a successful career, providing a deeper historical understanding of the field of andrology and helping all to better appreciate the contributions of leaders of the field. In this inaugural essay, Professor Masaru Okabe recounts a valuable lesson he learned in carefully considering assumptions.

Masaru Okabe received his Ph.D. in Pharmaceutical Sciences from Osaka University and now is a Professor Emeritus of Osaka University, Japan. He studied the mechanism of fertilization by producing many gene-manipulated animals such as calmegin- and IZUMO1-disrupted mice. He also made the world’s first ‘green mouse’, transgenic for the green fluorescent protein (GFP, normally present in jellyfish), which is used in over 1000 laboratories globally.

Our lives are driven by many assumptions. When we undertake a research project, we design experiments based on various assumptions. After results are obtained, we use our knowledge and imagination to interpret the data. Some experiments provide simple data, which require no imagination for interpretation and tell us clearly, yes or no: ‘Seeing is believing’. But the application of this truism might have a pitfall. Here is my story.

Calmegin is a molecular chaperone specifically expressed in pachytene stage male germ cells. We produced calmegin-disrupted mice by homologous recombination, expecting a phenotype on spermatogenesis. Despite the fact that calmegin is expressed only in male germ cells, the disruption of calmegin did not cause any defect in spermatogenesis. The spermatozoa were morphologically normal and swam as vividly as those from wild-type mice. Ours was a typical but disappointing story of a strong candidate gene encoding a protein that initially appeared to have ‘no essential effect’. However, when mated with females, we found that the calmegin-disrupted males were infertile.

For mammalian fertilization to occur, spermatozoa must bind and penetrate the zona pellucida, an extracellular matrix surrounding the egg. The importance of zona binding observed in vitro seemed to be obvious. Moreover, ZP3, a component of the zona pellucida, is reported to induce the acrosome reaction in spermatozoa. Considering these facts together, it was widely believed that the sperm acrosome reaction must be induced by the zona pellucida when spermatozoa bound to the zona. Only the acrosome reaction induced in this manner was thought to facilitate spermatozoa to penetrate the zona pellucida and fertilize eggs (Theory A).

With Theory A in mind, we tried to examine the mechanism of infertility in the calmegin-disrupted males by observing in vitro fertilization. In wild-type spermatozoa, the eggs started to rotate with the tail beats of the many spermatozoa bound to the zona, but the spermatozoa from calmegin knockout mice bounced off the zona pellucida and were not able to bind to eggs. No wonder the calmegin-disrupted males were infertile! Seeing is believing! We took a movie of the spermatozoa bouncing off the zona pellucida and presented it at many conferences. I think we significantly contributed to strengthening Theory A.
Since then, more than 10 genes have been newly reported as essential for spermatozoa to retain their zona-binding ability. Interestingly, all of these spermatozoa shared one more phenotype: the inability of spermatozoa to move beyond the uterotubal junction (UTJ), thus failing to migrate into the oviduct. (This was attributed to the lack of ADAM3, as all of these gene-disrupted mouse spermatozoa lacked ADAM3 on their surfaces.)

However, to our surprise, we found that when we placed these infertile spermatozoa directly into the oviduct to bypass the UTJ, the eggs were fertilized! According to Theory A, the acrosome reaction should be induced upon contact with the zona pellucida. Why could the spermatozoa which lost their so-called ‘zona binding’ ability still fertilize eggs? What was the meaning of our movie showing the spermatozoa failing to bind to the zona pellucida? Perhaps the so-called ‘zona binding’ we observed in vitro using eggs deprived of the cumulus layer reflected artificial aspects of the sperm functions. We never see this many spermatozoa swarming to naked eggs in vivo.

Recently, using fluorescent protein-tagged spermatozoa, a majority of the zona penetrating mouse spermatozoa were confirmed to be acrosome reacted before reaching the zona pellucida. Moreover, the timing of the acrosome reaction in the mouse was demonstrated to be less strict than previously thought. When spermatozoa that had penetrated the zona were collected and subjected to a second round of IVF, these spermatozoa penetrated the cumulus layer and zona pellucida a second time, fertilizing a second egg.

‘Seeing is believing’ may be a golden rule in science, but magicians can make a coin seem to penetrate glass by guiding our assumptions to a wrong direction. One of my most memorable lessons learned from Mother Nature is that she sometimes behaves like a magician. Are the assumptions driving your research really correct?
Lessons learned in andrology: Learning from experience – getting it wrong is alright

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I recognize that making it to where I am today has been, and still is, a daily learning curve. The steepness of the curve varies, but it is incessant, and is an exciting and invigorating aspect of scientific research. Much of this learning is generic, not specific to andrology, but I have tried in this article to give it an andrological context wherever possible. A valuable outcome of the lessons I have learned from ‘making mistakes’ is that I routinely use these experiences to enlighten students and young post-docs – especially when they slump dejectedly in a chair opposite my desk, after a failed experiment, and complain that ‘they can never hope to reach my level’. My response is ‘you are years ahead of where I was at your age’, because I was a slow developer with an uninspiring academic track record.

When I arrived in Edinburgh in 1974 at the Medical Research Council (MRC) Reproductive Biology Unit run by Roger Short, I was already hooked on male reproduction, but oh what reinforcement awaited me! There were two visitors on a year’s sabbatical to the Unit – Niels Skakkebaek and David de Kretser. Considering the heights to which these two andrology giants were already climbing, for me to come under their guidance and inspiration at such a formative time was game changing. The fact that both are still youthfully active and energetic with their ideas, and the research to match it, despite being well beyond ‘retirement age’, speaks more eloquently than I can of how important an influence they have exerted on andrology, and on me, personally.

Advances in understanding in andrology are not about individuals but about ideas, but it is individuals who form the ideas. What sets Niels and David apart is that they always anchored their ideas. Both were practising clinicians, which meant that seeing the reality of patient’s reproductive problems always gave their ideas a practical attachment, no matter if their ideas turned out right or wrong. Basic scientists such as myself do not have this anchor, but I learnt from them to always focus on ‘real-world’ reproductive health problems, their causes and prevention (or correction); for this reason, I consider ‘keeping your feet on the ground’ a great compliment to pay to someone.

It seems remarkable (or more accurately, remarkably stupid on my part) that I had no interest in sperm counts, as opposed to spermatogenesis, until talking with Niels Skakkebaek 20 years...
ago while writing my chapter for *Physiology of Reproduction* on ‘Spermatogenesis’ (Sharpe, 1994). He told me about their studies suggesting a 50% fall in human spermatozoa counts over the previous 50+ years (Carlsen et al., 1992), a conversation that completely changed the focus of my thoughts and my research. Until then, the idea that sperm count per se was important didn’t really gel because I worked on the rat, in which highly organized, super-efficient ‘Rolls-Royce’ spermatogenesis coupled with sperm storage made such issues irrelevant. But for the human, with disorganized, highly inefficient spermatogenesis and no sperm storage it was, and is, a big issue. This also got me interested in understanding species differences so that I could select the best models for the human (Sharpe et al., 2003; Mitchell et al., 2008), something I recommend as essential to all basic researchers who use rodents ‘as human models’. Never presume that the rodent is a good model, first prove it (more evidence below).

In 1998 I was giving a talk on ‘Environmental hormones, reproductive development and human health’ to the Tyndall Forum at the Royal Institute in London, where you present to policy makers, politicians and other influential folk – an opportunity to sell your research. In a quaint English way, the presentations were followed by ‘supper’, at which I was sat opposite Lord Somebody from the UK House of Lords, who looked ancient and who I foolishly labelled (in my head) as old and dodgy. During supper he said to me ‘Thank you in your talk for taking me to the borders of ignorance’. My first reaction was that it was some sort of insult, but on reflection I thought it one of the wisest comments made to me. Indeed, I use it in talks and especially when dealing with the media. It captures the inherent problem with scientific research, namely, that our coalface is at the borders of ignorance – so don’t be surprised that much of what we discover there subsequently turns out to be wrong or only a fragment of the truth.

This is not the only lesson I’ve learnt about (my) ignorance! I have a great imagination (my only talent), which will readily construct a hypothesis if you throw a handful of facts/data at it. It has served me wonderfully well, but when I was younger, I took it very personally if my hypotheses were proved wrong. But the maxim that ‘Science makes fools of us all’ is something that I’ve now learned to enjoy. Back in 1993, the inspiration from Niels Skakkebaek resulted in me and I writing a hypothesis article for the Lancet, the so-called ‘Oestrogen hypothesis’ which proposed that increased in utero exposure of males to oestrogens (from various sources) might underlie common male reproductive disorders (Sharpe & Skakkebaek, 1993). It has become a citation classic (hint; to get high citations, never include data!). Yet time and further research has proved that the hypothesis is fundamentally flawed, because human foetal Leydig cells do not express full-length oestrogen receptor alpha (ERα) as do rodent foetal Leydig cells, and it is ERα that mediates the adverse effects of oestrogens on the foetal testis (Mitchell et al., 2013). Nevertheless, it was still a good hypothesis because it focused and stimulated research that advanced understanding. That is what hypotheses are for, vehicles for advancing scientific understanding, irrespective of whether they prove right or wrong. I now take pride in ‘being wrong 90% of the time’, as I tell my students each time I suggest one of my brilliant ideas to them! Progress comes from making mistakes, because we learn best from mistakes. I have a sign in my office that I point out to students when they have just discovered they ruined an experiment through a mistake, ‘Good judgement comes from experience; experience comes from bad judgement’.

Working for much of my earlier career on spermatogenesis inevitably led me into the path of (the late) Lonnie Russell, a giant in the field, though clearly not everyone’s cup of tea. Lonnie was someone you loved or hated, the result I’m sure of his devilish love of being provocative. Once you recognized and embraced this as ‘harmless fun’, Lonnie turned out to be one of the best catalysts I have encountered. I still smile when recollecting the hours I spent kicking ideas back and forth with him, invariably in a bar drinking beer. Truly inspirational, as his more direct trainees will tell you better than me, as all have gone on to be andrology stars themselves. Research progress inevitably needs hard work, but it is the ideas that drive progress. These ideas, once kicked around and mixed with beer, are what generates a hypothesis which then progresses as described above. At the heart of this process are the catalysts, and Lonnie was among the best.

Last, but not least, I want to emphasize the role that humour has played in my career in andrology. Research has many downs, and good humour is one way of coping. All know that I like telling jokes, but they may not realize that I learned my art from two masters in andrology – Focko Rommerts and Doug Stocco. Anyone who has heard Focko deliver his ‘Testomania’ talk at a scientific meeting will have learnt that research on the testis can be fantastic fun. Doug is simply an outstanding story-teller, who could tell jokes non-stop for 2 h, for most of which I literally cry with laughter. In my opinion, humour has a serious role to play in science and in andrology in particular. I have learnt that humour is one of the very best vehicles for communicating serious science. Virtually everyone appreciates humour, can identify with it and will remember what you tell them by association, so I try always to add humour into my talks. Andrology lends itself to humour – indeed many of the jokes you hear in pubs and elsewhere are often andrology related, none more so than in my area of ‘masculinization’, which touches on male–female comparisons which we can all identify with and laugh about. Anyone who doubts the role of humour in andrology should check out this link (http://youtu.be/xFKDjS4efS) which, believe it or not, was a UK MRC-sponsored stand-up comedy routine by yours truly to help celebrate 100 years of MRC support for research. But I think I’ll stick to the research as a career! Maybe I’ll even get it right eventually if I keep getting it wrong often enough.

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Lessons Learned in Andrology: 
Back to the future: making children in bed (at the right time)

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Manuela Simoni, MD, PhD was born in 1956 in Italy. She obtained her MD in 1982, the specialization in endocrinology and metabolism in 1985, and the PhD in the same field in 1991. Between 1990 and 2007, she worked at the Institute of Reproductive Medicine of the University of Münster, Germany, where she was professor from 1998. From 2008, she is full professor of endocrinology at the University of Modena and Reggio Emilia, Italy, where she currently holds the following positions: Chair of Endocrinology, Director of the Clinical Unit of Endocrinology at the NOCSAE Hospital, Director of the School of Specialization in Endocrinology, Deputy Director of the Department of Biomedical, Metabolic and Neural Sciences. Her research interests are gonadotropin and androgen action, testicular function, genetics of male infertility, endocrinology and pathophysiology of reproduction. She is a member of several societies, including the European Academy of Andrology (EAA) and the European Society of Endocrinology (ESE), and serves in the editorial boards of several journals in the fields of endocrinology and reproduction.

I was lucky. I had my first child at the age of 38 and the second at 45. The strange thing is that they were made in the old-fashioned, traditional way: in bed and not in the assisted reproductive technologies (ART) department. No exogenous gonadotropins, no oocyte pickup, no semen collection in a soundproof room, no intracytoplasmic sperm injection. Just fun. Not even Caesarean section. Just luck (and a good obstetrician).

For a woman in career postponing pregnancy is becoming the rule. If you want to become a physician, in most European countries you need to go through 13 years of school, 6 years of university, and 4–5 years of residency. Entering primary school with 6, you end up at the age of 30 with nothing in your hands other than a diploma. Then you start looking for a job and, depending on which country you live in, at least other 5–10 years pass until you get a permanent position. Exactly at the age between 35 and 40 you start thinking about reproduction. If you are a woman, your reproductive potential may be naturally gone. If you are a man, you may discover only then that you are infertile. Often this happens after many years of active couple contraception without having ascertained the fertility status in advance. At this point, as an established professional couple, you are ready to make the fortune of ART centres. Obviously, we cannot expect our colleagues OB&G to be active against this trend. So, perhaps we, the andrologists, should become active on multiple fronts and do something against the reproductive emergency of the Western countries.

Andrological societies are young: ASA was grounded in 1975, other national societies shortly thereafter, the European Academy of Andrology in 1992. The oldest article dealing with male infertility I could find in PubMed dates back to 1945 (Walker, 1945). In his communication to the Royal Society of Medicine, Dr Walker, a surgeon urologist, correctly identified the main clinical features and some diagnostic procedures of male infertility which are still valid today but the proposed treatment consisted of garlic extracts against infections, testosterone and X-ray applications to the testis. Meanwhile we have antibiotics, we understood the contraceptive effect of exogenous testosterone and appreciated that radiations deplete, rather than nurture, germ cells. However, our therapeutic equipment was not enriched by any really effective medicine, apart from gonadotropins in case of hypogonadotropic hypogonadism. The approach to the infertile male is still inefficient and many treatments are empirical: if sperms are lousy and the partner is over 35, the chance of natural pregnancy remains very low, irrespective of the medical treatment you try.

How to get out of this frustration? Certainly, we should diagnose and treat the male as much as possible and work in interdisciplinary teams with gynaecologists to optimize the conception probability, but it is time to widen the action spectrum of Andrology to further levels.
EDUCATION

Women do not appreciate enough that their fertility potential declines sharply after a certain age (Heffner, 2004). Men do not know about it either. Most couples ignore the importance of having intercourse with exact timing in the presence of normal cycles (Wilcox et al., 1995; Zollner et al., 2013), not an issue at young age with frequent sexual activity but a possible problem in older, busy couples. There is some inter-individual variability (my husband and I obviously belong to the very fertile end of the Gaussian distribution) and some genetic factors regulating ovarian longevity are being identified (Stolk et al., 2012). However, we do not have any test predicting the rate of fertility drop. Even if we had it, would women be willing/able to adjust their reproductive project according to it? Some ART centres start to offer ‘social’ ovarian cryopreservation to educated women willing to postpone pregnancy. As an elderly mother approaching her sixth decade of life with teenager children, I am not sure that this is the right path to follow.

Scientific societies should engage in educational programmes in schools, raising the awareness of the issue well in time, and guiding young people to find the right information in the web jungle. Men and women should be able to make an educated choice about their reproductive fate early enough not to blame themselves or anyone else later in life. Of course, one can always borrow gametes and uteri (and there is a florid market thereof), but we have too little knowledge about the long-term psychological, philosophical, medical and social consequences of such surrogate parenthood for the individuals concerned.

PREVENTION

Preserving good fertility potential across the life phases presumes that reproductive health receives the same attention as other health-related issues. While women visit a gynaecologist relatively early in life, e.g. searching advice for contraception, and thereby receive medical attention focused on reproduction, men usually go to the doctor only when they are really sick (Wang et al., 2013). Not to say about visiting an andrologist (what is andrology)? Average men talk a lot about sex, dispelling ancestral fears of untellable reproductive inadequacy, but when it comes to their own sex/fertility problem, they are often unable to cope with it. Even in the prevention of sexually transmitted diseases, men are left behind: in my country, the National Health System offers human papillomavirus vaccination to girls but not to boys, as they would be naturally immune and not vehicle of the infection.

With our Italian Society of Medical Andrology and Sexual Medicine (SIAMS) we have started some prevention campaigns in secondary schools (www.amicoandrologo.it) and during public events (www.androlife.it). Through these instruments, young men have the possibility to get information, ask questions in a confidential way and obtain a free visit. In addition, media campaigns, e.g. about erectile dysfunction, premature ejaculation, etc. are supported jointly by the scientific societies concerned, creating a new reproductive culture. These initiatives are important for the prevention of andrological diseases, as they increase awareness and result in early diagnosis of treatable conditions (e.g. infections, varicocele, and testis tumour). They are usually very well received and contribute to orientate unsure and hesitant men.

ACTING ON THE STAKEHOLDERS

There is too little support for reproductive research. Funding agencies fuelled by public money feel obliged to carry on research programmes dealing with more serious diseases, such as cardiovascular, neurodegenerative, diabetes and cancer, just to mention the best sellers. To me, it is illogical: wealth increases the epidemiological relevance of diseases partly due to overfeeding and, instead of instructing people to eat less and conduct a healthier life, we spend public money in seeking medicines to fight the consequences of having eaten too much. Life expectation increases steadily, so that ‘healthy ageing’ is a major thematic area in several finalized research programmes. In Western countries with an established social security system, as in the EU, the progressive ageing of the population is exhausting public finances at the expense of the young generations, who are jobless, frustrated and with no lust for making children: a very strange and short-sighted demographic policy indeed.

Andrologists should take the lead and act whenever and wherever possible to convince the stakeholders that reproductive health and research are as important as other fields of medicine, if not more: if cancer is lethal for the individual, infertility is lethal for the species. Recurring to ART when the physiological reproductive age is over may be an option for wealthy people but is unfair to the majority. Infertility should be recognized, researched on, prevented and treated on time. Policies supporting young couples in their family planning are essential for a sustainable vision of the future.

My personal vision of the future is that Andrology should support making children in bed at the right time in all possible ways: with medical care, research, education, prevention and political action.

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Lessons Learned in Andrology: What I have learned

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Editors’ Note: This is the second feature entitled ‘Lessons Learned in Andrology’. By invitation, leaders in the field of andrology will submit a brief essay that addresses valuable lessons they have learned in their distinguished career, possibly including short historical vignettes. The objective of this new feature is to assist others, especially young investigators, in considering important lessons that are learned in a successful career, providing a deeper historical understanding of the field of andrology and helping all to better appreciate the contributions of leaders of the field.

Niels E. Skakkebaek is a professor and former chairman, now senior researcher, of the Department of Growth and Reproduction at Rigshospitalet, Copenhagen, Denmark. He received his medical degree from the University of Copenhagen and in addition to his clinical responsibilities has been a prolific researcher and mentor. He has published more than 500 peer-reviewed manuscripts in international journals and been a leader in cutting-edge research including the areas of carcinoma in situ of the testis, endocrinological aspects of growth and development, and environmental aspects of male reproduction, including developing the ‘testicular dysgenesis syndrome’ hypothesis. Professor Skakkebaek has received numerous awards for his contributions and continues to be a mentor and inspiration to many young researchers.

What have I learned in my professional life as a scientist and clinician? Not enough to avoid continuing making errors. Perhaps my answer should be that the fact that I am still learning something every week has made me more humble and also curious to learn more. However, looking back at some events were more shining than others. I will first mention the importance of learning from giants in the field. A giant I met when I was very young was professor, Yves Clermont, McGill University, Montreal. In a few weeks he introduced me to the world of mammalian spermatogenesis, first rat, then human spermatogenesis (Clermont, 1963).

My early work describing carcinoma in situ testis (CIS) had not been possible without an intense training in Clermont’s laboratory. Before I left his laboratory, I was able to distinguish between A-dark, A-pale and B spermatogonia; spermatocytes and spermatids and used his system to analyse testicular specimens from infertile men. However, back in Copenhagen, specimens from two infertile men did not fit into the Clermont system. The nuclei of the basal layer of germ cells in the seminiferous tubules were bigger (10–11 μm nuclear diameter rather than 6–7 as the diameter of type A and B spermatogonia) and the chromatin was coarse, even more coarse than in type B spermatogonia. Our pathologist did not appreciate the significance of these cells. However, because of what I had learned from Yves, I was sure that I had picked up something important and wanted to publish it.

After initial rejection from Acta Endocrinologica (now European Journal of Endocrinology), I had my findings accepted for publication in Acta Pathologica as a cell abnormality in two infertile men (Skakkebaek, 1972a). However, before the article appeared in the journal, both men developed invasive germ cell cancer. It was detected early because one of the men had accepted a second biopsy for studies of the cells by electron microscopy and during open biopsy procedure the surgeon noted that the testicle had grown since previous biopsy and the new specimen now revealed an embryonic carcinoma. First then did I fully understand the nature of the cells and contacted the other patient with the same peculiar cells. Amazingly, also he had developed invasive tumour and I hurried up to write a second paper, appearing in the Lancet, suggesting that the abnormal cells were, in fact, precursor cells for testicular germ cell cancer (Skakkebaek, 1972b). Luckily, both men survived without spread from the tumours.

During the next 10 years I learned what many others also have experienced: It may take many, many, years to obtain acceptance of research findings. In fact, my story about carcinoma in situ testis was considered very controversial and not fully
accepted until the mid-1980s, although I was never in doubt, not a second, because of my training with Yves Clermont.

The story also taught me the importance of translational human research to obtain the full picture of a health problem. The andrologist who himself does microscopy on testicular specimens of his infertile patient has a great advantage with regard to correct diagnosis of a testicular disorder. Although we all know that ‘oligozoospermia’ and ‘azoospermia’ are symptoms and not diagnoses, in andrological literature these words are often used as surrogates for clinical diagnoses and basis for intervention. Testicular biopsy is of course neither indicated nor possible in many men with fertility problems. However, whenever a biopsy specimen is available, the clinical andrologist has a unique chance to use information from it in diagnostic work-up of the patient, particularly if the spermatogenesis and Leydig cell appearances are evaluated semi-quantitatively (McLachlan et al., 2007). The pathologists do not do that. The andrologist must acquire the skill him/herself, also for correct classification of infertile men participating in clinical research projects.

Another important mentor for me, when I was young, was the Danish epidemiologist Dr Johannes Clemmesen, who was a pioneer in testis cancer epidemiology. He started the first national cancer registry, the Danish, in 1943. He was not only the first to appreciate the increasing trends in testicular germ cell cancer; he also noted strong birth cohort effects with increasing risks among the more recently born cohorts. In addition, he pinpointed the enormous differences in incidences in testis cancer within the Nordic countries, where Denmark had four to fivefold higher rates than Finland and hypothesized that environment or lifestyle played a role (Clemmesen, 1981). He inspired me to explore these conspicuous differences between two apparently similar countries and thereby obtain information about the aetiology of testicular cancer. His own hypothesis was that mothers smoking in pregnancy could explain the differences, as Danish women smoked much more than the Finnish – even cigars. Later studies did not confirm the smoking hypothesis, but the foetal hypothesis is still very much alive and supported by evidence from studies of the CIS cell. Most likely, other environmental factors are to blame (Skakkebæk et al., 2006, 2011).

I first learned the importance of setting up a unit for translational research in andrology by visiting another giant when I was young, Mortimer Lipsett at NIH, Bethesda. I was fascinated by the idea of having clinical management of patients in one wing of the building and laboratories in the neighbouring wing with people running back and forth all the time. A similar structure became the corner stone of the University Department of Growth and Reproduction which was initiated at Rigshospitalet in 1990. Here clinical and basic research go hand in hand. It has created a wonderful research environment, now chaired by Professor Anders Juul. During my years in paediatrics and andrology, I had learned that many cases of male infertility and even testicular cancer should be seen as late onset of perinatal or paediatric problems. And to address those clinically and scientifically we needed many disciplines to work together, including people with expertise in paediatric and adult endocrinology, andrology, molecular biology, epidemiology, statistics and chemistry. We did in fact manage to bring all the expertise together and I believe that I have learned more from colleagues with such skills during the last 20 years than I picked up earlier.

In conclusion, I have learned to stand on the shoulders of giants, because nobody creates alone.

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Germ cells and fertilization: why I studied these topics and what I learned along the path of my study

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Professor Ryuzo Yanagimachi received his Doctor of Science degree from Hokkaido University in Japan in 1960. He then served as a post-doctoral fellow at the Worcester Foundation for Experimental Biology in the United States under the direction of the distinguished reproductive biologist M.C. Chang. After a brief period of working in Japan, Dr. Yanagimachi joined the faculty of the University of Hawaii, where he ultimately established and directed the Institute for Biogenesis Research until 2004. Professor Yanagimachi is responsible for many seminal studies and advances in reproductive biology, including studies in sperm capacitation, in vitro fertilization, and cloning. He has received numerous awards and honorary degrees, including induction into the U.S. National Academy of Sciences, induction into the Hall of Honor of the NICHD, the Marshall Medal (UK), and the Distinguished Andrologist Award of the American Society of Andrology.

Professor Yanagimachi is known by his many students, fellows, and colleagues not only for his creative and elegant experimental designs, but also for his genuine collegiality and friendships.

INTRODUCTION

I used to be good in preparing photo-micrographs and drawing diagrams myself, but now I am struggling with the newer electronic methods of preparing micrographs and diagrams. Most of the things that were the forefront 40-50 years ago are obsolete today. The world and technologies keep changing rapidly, but there are some things that do not change. People’s wish to pursue happiness is an example. Uncertainty and apprehensions of one’s future is just other example. Today some young, smart persons with great talent see nothing but a bright future. In my time I was certainly not one of them, in fact I was quite opposite. Despite the many handicaps I had (lacking proficiency in the English language, for instance), I managed to survive a competitive, yet enjoyable life in science. Here, I share with you: (a) how I got interested in germ cell and fertilization research, (b) what I studied and what I learned in the past, (c) what I should have known when I was young, and (d) a few other thoughts that entered my mind.
and one part of glacial acetic acid) for 5 min. Drain the slide and stain the with acetic alcohol (freshly prepared by mixing three parts of 100% ethanol formalin in PBS). Then, replace the fixative between the slide and coverslip to overnight (if glutaraldehyde is not available, fix eggs overnight in 10% paper. Leave the slide in a coplin staining jar containing the fixative 10 min – 10 min. Eggs can be examined immediately using a phase-contrast microscope. To store slides, replace the staining solution with acetic acid-water-glycerol mixture (4 : 4 : 2) and seal the coverslip with a nail polish (nitrocellulose in solvent). (B) A mixture of vaseline-paraffin-bee’s wax (9 : 1 : 0.5 by weight) is melted. Slide glasses each with four melted dots of above mixture are prepared and stored. A drop of physiological medium containing eggs is placed at the centre of four vaseline-paraffin dots and covered with a coverslip which is compressed until eggs are flattened like a thin pancake. Living eggs can be examined using a phase-contrast or interference-contrast microscope. To fix eggs, run 4% glutaraldehyde in phosphate-buffered saline (PBS) from a side of the coverslip to the opposite side using a piece of filter paper. Leave the slide in a coplin staining jar containing the fixative 10 min to overnight (if glutaraldehyde is not available, fix eggs overnight in 10% formalin in PBS). Then, replace the fixative between the slide and coverslip with acetic alcohol (freshly prepared by mixing three parts of 100% ethanol and one part of glacial acetic acid) for 5 min. Drain the slide and stain the eggs with aceto-carmine for 5–10 min. Eggs can be examined immediately using a phase-contrast microscope. To store slides, replace the staining solution with acetic acid-water-glycerol mixture (4 : 4 : 2) and seal the coverslip with a nail polish (nitrocellulose in solvent). (B-D) Phase-contrast micrographs of live zona-free hamster eggs containing swollen human sperm heads. (E) A fixed and stained hamster egg with human sperm heads before and after swelling within egg’s cytoplasm.
arrived at the WFEB he called me into his office and gave me a research project that involved the study of leucocytes in the female genital tract and sperm capacitation. He must have thought that leucocytes might have some role in sperm capacitation in vivo. He said to me: ‘This is your bread and butter. There are five work days a week. Use 3 days for this project. You may use the two remaining days for the research you want to do’. In other words, he gave me some freedom. In vitro fertilization of hamster eggs (Yanagimachi & Chang, 1963, 1964) was started by using one of these free days. I transmitted this work code to my postdoctoral fellows I had after moving to the University of Hawaii.

For many years, I was puzzled by the fact that Chang had accepted me to work in his laboratory. Several years before he died in 1991, he and Mrs. Chang came to Hawaii. While traveling through the Hawaii Volcano National Park, I asked him why he accepted me as a postdoctoral despite my total lack of research experience with mammals. His reply was brief: ‘Well, you did good work with fish’. If he had not given me a chance, I would not be where I am today.

After moving to the University of Hawaii

I joined the Department of Anatomy and Reproductive Biology of the University of Hawaii Medical School in 1966. In addition to the hamster, the guinea pig became my favourite model animal to study sperm capacitation, AR and in vitro fertilization (Yanagimachi, 1981, 1994). I knew guinea pig spermatozoa had gigantic acrosomes, but I never thought of using them for my study until my colleague – Milton Diamond – had to euthanize many guinea pigs to terminate his neuro-endrocrinological study. Even though acrosomes of hamster spermatozoa are much larger than those of mouse and human spermatozoa, guinea pig sperm acrosomes are even far larger than acrosomes of hamster spermatozoa. My colleagues and I combined in vitro sperm capacitation and fertilization techniques with light- and electron-microscopy work to study capacitation, the AR and sperm interactions with eggs.

Sperm capacitation

While I was trying to capacitate hamster spermatozoa in vitro, the spermatozoa were first moving very slowly. I thought they were going to die. However, when I re-examined them a few hours later, they were moving very vigorously as if they were going to jump out of the dish. I first called it ‘activation’ (Yanagimachi & Usui, 1974), then renamed it ‘hyperactivation’ (Yanagimachi, 1981). In a non-viscous medium, hyperactivated spermatozoa display a tortuous tail movement, while in a viscous medium they exhibit a snake-like motion. We found that hyperactivated spermatozoa have greater vigour than pre-activated spermatozoa (Katz et al., 1978). Ca²⁺ dependence of both sperm hyperactivation, the AR and spermatozoa-egg fusion was quickly established by using both the hamster and guinea pig (for reviews, see Yanagimachi, 1981, 1982).

Spermatozoa–egg fusion

To study spermatozoa–egg fusion, we first freed eggs from zonae pellucidae using enzymes (e.g. trypsin), then inseminating them with acrosome-intact and acrosome-reacted spermatozoa. We found that only live acrosome-reacted spermatozoa could fuse with zona-free eggs, suggesting that some important physiological change occurs in the sperm plasma membrane upon the AR (Yanagimachi & Noda, 1970; Yanagimachi, 1994). Proper concentrations of H⁺ and Ca²⁺ in the medium are essential for successful spermatozoa–egg fusion (Yanagimachi et al., 1980; Yanagimachi, 1988). We found that zona-free hamster eggs can fuse with not only hamster spermatozoa but also spermatozoa of various other animals including humans as long as they are acrosome-reacted (Yanagimachi et al., 1976). Even though a zona-free hamster egg fused with a single human spermatozoon develops into pronuclear stage and even into 2-cell stage, it cannot develop further, perhaps because of the incompatibility between the human sperm nucleus and the hamster egg cytoplasm (Yanagimachi, 1977). I first thought that zona-free hamster eggs could be used to assess the fertilizing ability of human spermatozoa, but what can be assessed are (i) the ability of acrosome-reacted human spermatozoa fuse with egg plasma membrane of hamster and perhaps human egg and (ii) the ability of human sperm nucleus to develop into a pronucleus. Inoue et al. (2005) used hamster zona-free eggs to study if antibodies against Izumo (spermatozoa-born membrane fusion protein) could prevent membrane fusion of human spermatozoa with eggs. Zona-free hamster eggs were also used to examine chromosome constitutions of human spermatozoa (Rudak et al., 1978). We later found that we can examine human sperm chromosomes after mechanical injection of spermatozoa into mouse eggs (Lee et al., 1996; Rybouchkin et al., 1996). Perhaps, eggs of any species can be used to examine human sperm chromosomes by microsurgical injection.

Egg activation

We found that Ca²⁺ ionophore activates eggs of a variety species (including mammal) by releasing Ca²⁺ from intracellular store (Steinhardt et al., 1974). Spermatozoa seem to bring in a factor that triggers Ca²⁺ release from the egg’s internal store. We reported that perinuclear material within the sperm head carries this egg-activating factor (at least part of it) (Kimura et al., 1998a).

Spermatozoa in vivo

While I was studying spermatozoa and fertilization in vitro, I thought that it would be important to know what spermatozoa are doing in vivo. I wanted to know how and where spermatozoa are capacitated and reach the ampullary region of the oviduct to fertilize eggs. Using the hamster and guinea pig again, we found that spermatozoa can complete capacitation in the isthmus region of the oviduct (Smith & Yanagimachi, 1989), migrate to the ampullary region of oviduct perhaps being aided by a hormone-dependent adovarian peristaltic movement of the oviduct (Battalia & Yanagimachi, 1979, 1980), with amazing reduction in the number of spermatozoa reaching the ampulla (Cummins & Yanagimachi, 1982; Smith et al., 1987). Based on this information, I made a grant proposal to the NIH to study sperm behaviour and physiology in vivo. I thought it was the best proposal I had ever made. To my surprise and disappointment, the proposal received the lowest possible score and it was not funded. One of the referees commented that ‘we cannot learn anything from in vivo study’. Of course I was very disappointed. Retrospectively speaking, I was not intelligent enough to refute this irrelevant criticism. I thus temporarily
discontinued my study along this line. Today we all know that everything on the sperm surface is not involved in the sperm interaction with eggs. Some play critical roles in spermatozoa–epithelium interaction and sperm ascent through the female tract (Okabe, 2013).

**Study of sperm nucleus**

When I began to study mammalian fertilization in 1960, only very few people were studying spermatozoa and fertilization in mammals. During next 20 years the number of researchers in this field increased exponentially. Molecular approaches to the problem were thought to be the only way to solve the problems of fertilization and reproduction. It was fashionable to study the sperm AR and spermatozoa–zona pellucida interactions at the molecular level. I was already over 60 years old. It was troublesome for me to learn rapidly evolving molecular technologies. Some of our papers were rejected by journals and ratings of my NIH grant applications became lower than before. In other words, I struck a wall. I asked myself what is the most important thing of all I have studied? What is the essence of fertilization? Is it sperm activation, the AR, sperm interaction with the zona pellucida or spermatozoa–egg fusion, and so on? ‘Aha. The heart of fertilization is the union of male and female genomes. The essence of fertilization is a creation of a new individual whose genomic makeup did not exist before and will not exist again in future’. I had forgotten about it. To my surprise, mammalian sperm nucleus itself had not been studied much by others. There was room for me, I thought.

My associate Tsuyoshi Uehara and I previously found that the hamster sperm head (nucleus) injected microsurgerically (so-called ICSI) into a mature egg was able to decondense and transform into a pronucleus even after freeze-drying of spermatozoa (Uehara & Yanagimachi, 1976). We also found that the nuclei of testicular spermatozoa were able to develop into pronuclei (Uehara & Yanagimachi, 1977). However, our study at that time was largely ignored by others. In fact, some even laughed at us. ‘Why did you inject spermatozoa into eggs? They would enter eggs anyway’.

Because I wanted to know if spermatozoa-injected eggs could develop into normal offspring with known genetic makeup, I switched experimental animals from the hamster to the mouse. My associates and I soon found that injection of isolated sperm heads (nuclei) into eggs resulted in normal development of embryos (Kuretake et al., 1996). Freeze-dried spermatozoa could produce normal offspring by ICSI (Wakayama & Yanagimachi, 1998). Because spermatids have haploid nuclei, they might be used as substitutes for mature spermatozoa to produce offspring, which we found to be the case (Ogura et al., 1994; Kimura & Yanagimachi, 1995a). When we injected nuclei of the secondary and primary spermatocytes into mature eggs, each underwent meiosis, two haploid nuclei then united and some eggs developed into live offspring (Kimura & Yanagimachi, 1995b; Kimura et al., 1998b). In the human, injection of eggs with round spermatid nuclei has had mixed results and is still considered to be experimental (Practice-Committee & the Society for Assisted Reproductive Technology of The American Society for Reproductive Medicine, 2004). At least in the mouse, we can obtain live offspring after round spermatid injection. It is important to note that mice (and common laboratory rodents) are ‘exceptional’ in that they do not need the sperm centrosome for syngamy, the union of spermatozoa and egg pronuclei. Other species, including rabbit, monkey and humans seem to require good sperm centrosome for successful union of spermatozoa and egg pronuclei (Hewitson et al., 2002; Terada et al., 2010). The centrosome in round spermatids may be too ‘immature’ to serve as the centre of microtubular aster formation necessary for orderly movement of spermatozoa and egg chromosome (Tachibana et al., 2009). However, full term foetuses were obtained by treating eggs (rabbit) with ionomycine before and after round spermatid injection (Hirabayashi et al., 2009). I do not believe in ‘exception’. Exception may be telling us something most important.

In the mouse, the readiness of male germ cell nuclei to support normal embryo development is as follows: testicular and epididymal spermatozoa > spermatids > secondary spermatocytes > primary spermatocytes. Interestingly, some spermatozoa with severely abnormal head morphology were able to produce normal offspring by ICSI (Burrue et al., 1996). Germ cells of mouse males lacking the CREM gene cannot develop beyond the round spermatid stage, yet their round spermatid can produce normal offspring by injection into eggs (Yanagimachi et al., 2004).

**Mouse cloning**

While we were studying the nuclei of spermatozoa and spermatogenic cells, the birth of a sheep, cloned from an adult somatic cell, was announced (Wilmut et al., 1997). Because ‘Dolly’, the sheep, was the only one that survived after birth, people began to wonder if this sheep was really cloned from an adult somatic cell. A scientific magazine listed 10 research Institutions that might report a second cloned animal. Our research team was not among them because we never attempted to cloning animals in our laboratory. However, we had all the equipment necessary for cloning. The instrument we were using for ICSI could be used without any modifications. A postdoctoral fellow Teruhiko Wakayama from Japan was interested in animal cloning – since his childhood – and attempted to clone mice using his free time. Wakayama showed me a midterm foetus cloned using a cell of cumulus oophorus. We were collecting mature unfertilized eggs of mice almost every day for our studies. Cumulus cells were routinely discarded. Soon, Wakayama obtained a live young which was named ‘Cumulina’. Maurizio Zuccotti and I suggested and helped Wakayama to isolate and use Sertoli cell and brain cell nuclei for cloning. The paper we prepared was quickly rejected by a journal which said ‘this is not the subject of general interest’. We then submitted the same paper (with more data) to Nature. One of the two referees approved our paper immediately, but the other was skeptical saying that mice we obtained could be parthenogenetic. It took over 6 months before a third referee approved our paper for publication (Wakayama et al., 1998). Wakayama left my group in 1999, but we continued working on cloning efficiency and epigenetic problems associated cloning in collaboration with Kunio Shiota of the University of Tokyo (Ogane et al., 2001), Randal Sakai of the University of Cincinnati (Tamashiro et al., 2002) and Rudolf Jaenisch of Whitehead Institute of Massachusetts Institute of Technology (Humphrey et al., 2001), John McCarrey of the University of Texas at San Antonio (Murphey et al., 2009) among others.
Over 10 years ago, I received a frozen cadaver of a transgenic mouse from a friend. This male mouse, died of an unexpected flood, was the sole animal with unique genotype. To make this story short, we could not clone this mouse because that time we did not know how to recover and handle cells from frozen body for cloning, which can be performed today (Wakayama et al., 2008). Nevertheless, cloning by somatic nuclear transfer should be a temporal, supplemental method for animal reproduction. Total dependence of animal reproduction to cloning, which eliminates genomic diversity among individuals in a colony, would be detrimental for long term survival of any species.

After my retirement

Although I retired from the University of Hawaii in 2005, I continue to work on mammalian fertilization at a much slower pace than before (Watanabe et al., 2013). In addition, I started to work on fertilization in non-mammalian animals (e.g. fish and insect) with big help from my friends (e.g. Yanagimachi et al., 2013). Because I was a zoology major student when I was in Japan, working with non-mammalian species is no problem. It is fun and exciting to uncover something new, even if many others think the subjects are trivial and insignificant.

WHAT I SHOULD HAVE KNOWN WHEN I WAS YOUNG

When I was a graduate student, I thought I did all the hard work and my mentor did nothing. I thought I knew new things better than the mentor. I was totally wrong. Nothing started without his direction and advice. Students should not forget about this. I know a few persons who did Nobel class research, yet did not respect each other enough and could not go along. It was a pity to see such occurrence. The subject of our scientific research is nature, but it is us – humans – who do the work. If human relationships are not good, there can be no real success in scientific research.

When I was a student, I thought everything written in scientific papers and books are facts. I did not doubt ‘well-known’ reports, theories and concepts. Now, I think the majority of the reports in papers are not reporting the truth. Of course, authors believe that they are reporting facts. ‘Facts’ are, however, authors’ interpretations and are not necessarily facts. Humans tend to see what we believe in or wish. Most of us feel comfortable by accepting currently popular concepts or ‘dogmas’. Again, the majority of dogmas are not true at all or representing only part of the whole.

We face difficulties from time to time during research. Human IVF, for example, was thought extremely difficult 50 years ago. Now it is easier than IVFs in many animals. Fifty years ago, we did not know the tricks. In other words, nothing is difficult; we just do not know necessary tricks. The late Prof. Robert (Bob) Noyes, MD (1919–2008), who was a pioneer of fertilization study and recruited me to the University of Hawaii, told me a story. At Harvard Medical School during late 1940s, he was trying to fertilize rabbit eggs in vitro without success. When he talked about this to Prof. John Rock (gynaecology professor- co-inventor of oral contraceptive), he told Bob ‘See what the rabbit is doing’. Until then, Bob was using ejaculated spermatozoa for insemination. He then thought about how rabbit spermatozoa reach the oviduct where eggs are waiting for spermatozoa. When he used spermatozoa collected from oviduct of mated females (~10 h after coitus), it was an instant success. In a meeting in Boston, Bob told this story to Drs. M.C. Chang (1908–1991) and C.R. Austin (1914–2004). According to Bob, they did not say anything. At that time Bob was busy in finishing his study of human endometrium (with John Rock), or he did not fully realize the implication of his important finding in the rabbit. Chang and Austin, who were working on animals’ fertilization, must had been doing similar experiments. They soon published papers about sperm capacitation within the female genital tract (Austin, 1951; Chang, 1951). Three lessons can be learned from the above: (i) when you have trouble, look at what Mother Nature is doing, (ii) keep thinking what is important and what is not very important and (iii) publish important findings without delay.

SOME ADVICE

(1) Do not mind ‘foolish’ questions. Obviously I am not a genius. I consider myself mediocre, yet in 2003 I was one of 15 persons bestowed with the ‘Hall of Honor’ from the Shriver National Institute of Child Health and Human Development. The only thing I know of myself is that I like asking stupid questions. Nine out of ten questions I made and continue to make were/are stupid or non-sense. Yet, one out of ten proved to be good. The father of modern genetics Thomas (Tom) Hunt Morgan once said: I have made three kinds of experiments in my life. First: stupid experiments. Second: more stupid experiments. Third; worse than the other two. When he first reported a mutation in the fruit fly Drosophila, one in the audience (Morgan’s friend) commented ‘Tom, you are using the wrong species’. In those days guinea pig, chicken etc were standard model animals for genetic studies.

(2) A ‘what’ will blossom in future. The most important assets in your laboratory are not the most expensive equipment in your laboratory but rather your brain. Computers have already surpassed human’s memory power, but they cannot dream. You can. You can dream without spending a penny. Keep dreaming big. The bigger, the better. Keep asking what is of fundamental importance (what is the essence of the problem). You will be surprised to find that the most important thing has not been explored, or people have overlooked or ignored it. There is a saying. ‘When you see a bandwagon, it is too late to ride on’. What is working today stems from the discovery of >20–40 years ago. What will blossom 20–40 years from now is unexplored, overlooked, ignored or under-estimated today.

(3) Be confident. New scientific ventures, reproductive technologies in particular, are destined to face ‘ethical’ and ‘religious’ opposition in one form or another. Fear of the unknown is very natural to laymen. It is the responsibility of scientists to let laymen know about facts and implications of new findings and/or technologies. It may take a long time to get public confidence in new technologies. In the early stage of the development of the cardiac pacemaker, for example, many theologians and religious people opposed the use of this instrument, denouncing it because attempts to revive dead (dying) people from God’s hands is wrong. I (Ryuzo Yanagimachi) am still alive today thanks to this marvellous devise. When gynaecologists induced ovulation in infertile women using gonadotropin from farm animals, many people including some medical professionals opposed it, even saying ‘Do not treat ladies like cattle’. When human IVF was first attempted, it became the subject of moral objection, not only from laymen but also from professionals.
from some scientific colleagues. Many thought, without any concrete evidence, that assisted-fertilization and - reproduction in any form would quickly propagate infertility factors among the general population. Remember that the pioneers were the ones who could withstand criticism and continued what they believed in.

(4) Be the first, not the second. Our paper of mouse cloning in 1998 drew much attention from media perhaps because we, unlike (Wilmut et al., 1997), produced three generations of cloned animals (clone of clone of clone) using adult somatic (cumulus) cells. In the same year, Kato et al. (1998) reported the birth of eight cloned cattle using adult somatic (cumulus and oviductal) cells of a single adult, followed by cloning of animals of many other species (for reviews, see Meissner & Jaenisch, 2006; Niemann & Lucas-Hahn, 2012). It was the late Keith Campbell who lead a team that tirelessly attempted to clone sheep using both embryonic and foetal cells (Campbell et al., 1993, 1996). Campbell was convinced that cloning would be possible by using adult somatic cell nuclei. At that time it was generally thought that adult cells are terminally differentiated and had lost totipotency. In science, the difference between the first and the second is enormous. Remember the lunar landing. We all vividly remember who landed on the moon first, not the second or third ones. The same is true for biological and medical sciences. Be the first, not the second.

(5) Mentor-student relationship and one’s life-time project. Each mentor has his/her own way to work with students and associates. Because I like to make my own experiments, I run small preliminary experiments after reading or learning of something new which might be useful for our studies. Even very light bench work has kept my mind fresh and alert. When students got their heads stuck against a wall, I often could provide them with some constructive advice. Experience was important. It can be used to avoid repeated mistakes. On the other hand, experience often prevented me from thinking or challenging something new. When I said it was impossible, because ….. I was wrong in many cases. Good students carried out the experiments anyway and proved me wrong.

Each of us should keep a life-time project in mind. Instead of one, I had a few projects going side by side. It might be seen unrelated (e.g. in vivo and in vitro studies of fertilization), but each had the same grand goal. When one project struck against a wall, I set it aside for a while. I myself, or more often someone else, cleared the barrier or gave me a hint. Then, I resumed the study. It might be dangerous to use a single approach or have a single project. As long as all have one and the same grand goal, running more than one study simultaneously would be safer and may be more efficient.

(6) Tips in obtaining research grants. When we apply for a research grant with our own initiative (e.g. NIH’s RO1 grants), a key to succeed is asking an important question, not just filling in details. When you write a grant proposal, it is ideal to be 1–2 years ahead of your publication. If you have good preliminary data almost ready to write papers, you can make a very strong proposal. Of course, you should not say that you have performed all or most of the experiments. Research topics are of critical importance. Let reviewers say ‘Oh my heavens! Why did we not think about this’. The funding institution is like a bank. They want to invest in the project for expected return. If it is too risky, they will not give you even a penny. Your bank is competing with other banks. If your research is very likely to raise the bank’s status, it becomes very willing to invest in your project regardless of the amount of money you request.

To obtain a research grant in the USA is very tight these days. Some projects such as stem cell and iPS cell research are fashionable today. It is easy to ride on a bandwagon. Some are happy to be one of a crowd. If I were you, I might get some funds from stem cell or iPS cell research projects (bandwagons) for example. While studying what you promised to do (your bread and butter), collect good preliminary data for the project of your real interest.

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Lessons learned in Andrology: revelations on a road less traveled

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do: 10.1111/andr.12087

INTRODUCTION

Like, I suspect, many of the other contributors to this ‘Lessons in Andrology’ series, I did not start out in life hoping to become an andrologist. Indeed, from a personal perspective, even the notion of becoming a scientist was a relatively late revelation. My journey into science, and ultimately andrology, has been almost half a century in the making, involved a significant amount of meandering across two continents and was more the beneficiary of good fortune than any good judgment on my part. Even within the microcosm of reproductive science, andrology would be considered a road less traveled, despite the major relevance of this topic to infertility, the future of fertility regulation and the efficiency of animal production. Nevertheless, notwithstanding our discipline’s status as a minority sport, I am forever grateful that the vicissitudes of fate and fortune have steered me into this particular corner of the reproductive landscape. In this article, I shall trace some of the milestones along this unexpected journey through the foothills of reproductive science to an andrological mountaintop, and consider whether I have picked up any useful advice on my travels that I can offer those whose journey has only just begun.

THE JOURNEY

Cambridge reproductive biology

After a couple of false career starts, I eventually undertook a BSc degree in Zoology at the University of London for no better reason than this was the swinging 60s and London was in full swing. I enjoyed the reproductive component of this degree and at its conclusion decided that I would undertake a Masters degree in Embryology and Mammalian Reproduction at the University College of North Wales, instigated by one of the pioneers of reproductive science, FW Rogers Brambell (famous for discovering the transfer of passive immunity across the yolk sack placenta of the rabbit and for his Chairmanship of the UK Government’s ‘Brambell Committee’ on intensive systems of...
livestock husbandry). Toward the end of this degree I wrote a speculative letter to another giant in reproductive science, Dr Roger Short who, at the time, was a Reader in the Department of Veterinary Clinical Studies at the University of Cambridge. Amazingly, Roger wrote back and invited me down to Cambridge for an informal discussion on potential research activities. This was the great turning point of my life. Roger applied for a PhD scholarship from the Medical Research Council (MRC) to study embryonic diapause in the roe deer (Capreolus capreolus) and, to my great delight, the application was successful (Aitken, 1974). Suddenly, I found myself catapulted from complete intellectual obscurity to 1970’s Cambridge, which, at the time, was the international nerve center for reproductive research. In the mid 1970’s Cambridge hosted two major research institutes dedicated to reproductive science – the ARC Institute of Reproductive Physiology and Biochemistry directed by Thaddeus Mann and containing people of the caliber of Bob Moore, Dub Adams, Twink Alan, Chris Polge, Hector Dott and Tim Rowson, and the Babraham Institute of Animal Physiology which hosted such luminaries as Brian Heap and Brian Setchell. The major preclinical Departments of the University (Anatomy, Physiology and Biochemistry) also had a strong focus on reproductive science and featured yet more major figures in the field including Bunny Austin, Alan Parkes, Bob Edwards, Martin Johnson, Matt Kaufmann etc. Fellow PhD students were the likes of Gerald Lincoln, Azim Surani and Roger Gosden, all of whom went on to make history in their respective regions of the reproductive landscape. I have very vivid memories of this time, when reproductive science was in its prime and the characters who drove it were larger than life. Roger Short in particular was, and is, the most inspirational mentor that anyone could wish for. He is the most accomplished speaker I have ever heard, has an encyclopedic knowledge of reproductive biology, has a breadth of vision that few can match and, despite the advancing years, continues to provide a constant flourish of new ideas.

Edinburgh reproductive biology

After Cambridge, I secured a position at the University of Edinburgh to conduct research on blastocyst implantation with another colossus of reproductive science, Anne McLaren. Anne had graduated from the University of Oxford and studied under another colossus of reproductive science, Anne McLaren. Edinburgh to conduct research on blastocyst implantation with Anne Edinburgh to provide a constant flourish of new ideas. Developing knowledge of reproductive biology, has a breadth of vision and ensuring that a translational focus was always center stage. Another inspiring presence within the MRC Unit was Rodney Kelly, a biomedical research scientist whose approach was rooted in fundamental chemistry. This niche at the interface of biology and chemistry was a natural one for me to inhabit and has helped create a unique point of differentiation and focus for our group’s research activities down the years. It was this approach that led me to understand that the failures of fertilization we were detecting with the zona-free hamster oocyte penetration test were frequently the result of free radical attack and the induction of peroxidative damage to the sperm plasma membrane (Aitken et al., 1989; Moazamian et al., 2015). This concept is now widely accepted and there are thousands, if not hundreds of thousands, of subfertile males taking antioxidant therapy in the hope that it will improve their chances of conception. One day I hope we shall have secured definitive evidence to support such intervention.

Newcastle reproductive biology

In 1997 I received a random phone call enquiring whether I was interested in a Chair in Biological Sciences at the University Newcastle. Once we had established that this was Newcastle with Mike Harper, I returned to the University of Edinburgh to take up a position in the newly established MRC Reproductive Biology Unit. I had been recruited to the Unit to work on the biochemistry of embryo implantation. However, after spending several months in gynecology wards hoping that someone would drop the odd milligram endometrial tissue into my stainless steel bowl, I finally came to the realization that if I was to make any headway at all in reproductive medicine, I needed to find a cell type that I could access directly, without depending on the largesse of my clinical colleagues. As a direct response to this need for clinical material I took my first faltering steps into andrology with the encouragement of Roger Short and one of the leading figures in this field, David Mortimer.

It was difficult; we had very rudimentary laboratory facilities and I had no real vision about how we could influence this field. However, after a couple of lean years we moved into a brand new building, The Centre for Reproductive Biology in Chalmers Street, and everything changed. I was joined by Edwina Rudak from Pat Jacobs’ laboratory in Hawaii and she introduced me to the zona-free hamster oocyte penetration test, introduced by another scientific hero, Ryuzo Yanagimachi. Yana’s endless energy, powers of observation and spirit of inquiry had discovered this heterologous in vitro fertilization assay and I focused on developing its clinical application; not so much as a diagnostic tool (it was far too complex a procedure to be used in routine clinical practice) but as a bioassay that would allow us to investigate the molecular mechanisms that regulate sperm function (Aitken et al., 1991). I reasoned that if we understood, at a biochemical level, why the spermatozoa generated by infertile males have lost their competence for fertilization, then we could use this information to gain insights into the etiology of this condition and possibly even develop some rational therapeutic strategies. In this venture I was aided by a team of highly talented research assistants and inspired by some brilliant clinicians and scientific colleagues. Stewart Irvine, now Director of Medicine with the NHS, was outstanding as both a student and, later, as an MRC Clinical Consultant, connecting us to the clinic and ensuring that a translational focus was always center stage. Another inspiring presence within the MRC Unit was Rodney Kelly, a biomedical research scientist whose approach was rooted in fundamental chemistry. This niche at the interface of biology and chemistry was a natural one for me to inhabit and has helped create a unique point of differentiation and focus for our group’s research activities down the years. It was this approach that led me to understand that the failures of fertilization we were detecting with the zona-free hamster oocyte penetration test were frequently the result of free radical attack and the induction of peroxidative damage to the sperm plasma membrane (Aitken et al., 1989; Moazamian et al., 2015). This concept is now widely accepted and there are thousands, if not hundreds of thousands, of subfertile males taking antioxidant therapy in the hope that it will improve their chances of conception. One day I hope we shall have secured definitive evidence to support such intervention.

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Australia and not Newcastle-upon-Tyne, I agreed to come out to NSW and site visit the Department, the University and the region. All of these I found so beguiling that uprooting myself from the MRC Unit to take up the Chair of Biological Sciences at the University of Newcastle, NSW, seemed full of exciting possibilities. Although I started out with the ambition of unhitching myself from reproductive science and changing research direction, in the event my new life became an extension of my old life; once again, I returned to andrology and the quest to understand the cell biology of spermatozoa. On this leg of the voyage, I again had the good fortune to work with great colleagues and talented students in one of the most beautiful parts of the world. We established a Priority Research Centre in Reproduction with my colleague Roger Smith and must currently have around 100 people in the group working on a broad spectrum of reproductive issues from conception to parturition. In terms of andrology, I am fortunate to be working with the likes of Brett Nixon, Mark Baker, Zamira Gibb and Geoff De Iuliis. We have a very active program on sperm cell biology in a range of species from horses to duck-billed platypus and Mark, in particular, has been instrumental in pioneering the use of mass spectrometry to understand the fundamental biochemistry of these cells. In addition, we have had a lot of fun recently working on the developmental biology of a range of sub-mammalian species including annelid worms, oysters and fish, just as Yana described in his Lessons-in-Andrology article (Yanagimachi, 2014).

LESSONS LEARNED

I have not consciously plotted a path through life but generally just tried to run as fast as I could in any given situation while retaining a capacity to respond to new opportunities as they arose with as much enthusiasm and energy as I could muster. In addition of a high level of commitment I think, on reflection, there may be a few principles that have kept me in good stead during this journey. For me, the most important have been:

Lesson 1: Resilience

A career in science is clearly not for the faint hearted. It is intellectually challenging, extremely competitive and the road is marked by many a deep pothole of disappointment. You may even have to weather an occasional roadside from the lumbering galleons of mediocrity – and have to exercise restraint. You may also receive accurate fire from the flagships of scientific reason – and have to exercise humility. People who excel in research usually have a deep, almost obsessive commitment to their trade and an inner resilience that allows them to ride out the tides of adversity that invariably punctuate the researchers’ path.

Lesson 2: Humility

I have been struck by how many previous contributors to this series have, in their different ways, cited humility as a key attribute of an effective researcher. I think it goes hand-in-hand with creativity. At the heart of our business is a need to be creative and act as a constant wellspring of new ideas for our students and collaborators. An inevitable element of this process is that many of these ideas will turn out to be wrong. Having the humility to admit defeat with equanimity is critical – as is having colleagues around you who can point out your stupidity without malice or too much enthusiasm.

Lesson 3: Read, read, read and then read some more

Early in life, I learned the importance of reading and assimilating the scientific literature in order to build an internal landscape of how the reproductive system worked. This epiphany was largely the result of reading Arthur Koestler’s ‘Act of Creation’ which pointed out that insight (the force that through the green fuse drives the flower of discovery) is achieved by the juxtaposition of disparate pieces of information to create a new synthesis. Successful scientists are forever reading, assimilating and mentally rearranging information in an internal intellectual kaleidoscope, looking for new patterns to illuminate the path ahead. The capacity that modern technology gives us to chase down an idea by accessing vast databases from our desktop computers is staggering and, dear students, should be exploited at every available moment.

Lesson 4: Be versatile

All over the world the gravitational pull of fiscal austerity means that the tide of federal funding for research is constantly on the ebb. With application success rates falling below 10% in many countries, it is essential that scientists diversify their income streams if they are to retain the capacity to run large successful laboratories. In order to achieve this end, they have to be flexible enough to accommodate the needs of Government Departments, philanthropic organizations and industry. Successful engagement with industry is particularly important and requires a high level of professionalism and a capacity to empathize with the goals of your commercial partners.

Lesson 5: Engage intellectually with the leaders in your field

In this highly competitive world, it is important for young researchers to get their work noticed by opinion leaders in the field. I would encourage any early career academic working in andrology to send pre-prints of their papers to leading researchers and engage with them intellectually over the direction their research is taking. I would also encourage students and Fellows to use every chance they get to present their data to national and international meetings – and polish their presentations to the point that they get invited back.

Lesson 6: Stay optimistic

When the Australian artist Margaret Olley was asked why she kept on painting even though, at the time of being interviewed, she was well into her eighties, she responded that every time she put a brushstroke on a virgin canvas, she thought she was about to produce her best-ever artwork. I think that it is this kind of powerful optimism that keeps andrologists motivated, engaged and excited about the future even though some of us have been researching the complexities of the male reproductive system for a lifetime and still struggle to gain a good understanding of the process.

CODA

There are several other principles that have been helpful to me, but many of these precepts have already been covered by others in this series (have fun, aim high, work hard etc.). At this point, I think I have tried your patience long enough. Ultimately, vision, commitment and humility are for me the hallmarks of good science and effective leadership. I wish all those embarking on similar journeys bon voyage – and bon chance; like me, you might need it.
REFERENCES
Lessons learned in andrology: physicians and animal scientists can learn from each other

R. P. Amann

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Rupert P. Amann sought greater use of superior dairy bulls through artificial insemination; now ~0.4 billion inseminations annually for all species. He completed Ph.D. studies with John Almquist at The Pennsylvania State University, was a postdoctoral fellow in Copenhagen, returned to Penn State where he rose to professor in 1972, was recruited to Colorado State University in 1979, and after ‘retirement’ in 1995 continued university-based research (as emeritus professor) and directed research for two small businesses. His often pioneering research with animals (15 species) and humans emphasized measuring sperm production, maximizing sperm harvest, endocrine regulation of puberty and testis function, effects of environmental agents on a male, sperm maturation, evaluation of sperm quality and efficient use of spermatozoa. His breadth is evident in 229 publications (11 in last 6 years) cited in 4421 articles by others. His interest in both animal and human andrology enabled wide-ranging presentations to animal scientists, biologists and physicians. He was involved in launching the American Society of Andrology, founding the Society for Study of Reproduction, and served both societies in numerous roles including council and program chair, meeting host and for ASA as President (1989-90). He was honoured by ASA as Distinguished Andrologist (1995) and for Distinguished Service by both ASA and the SSR. His research contributions, service activities and awards are detailed elsewhere (Anonymous, 1996; Seidel, 2008).

I entered professional life in the golden age of academic environments when universities fostered unfettered exploration of knowledge with: (a) few bureaucratic dictates; and (b) carefully awarded funds to answer important questions, acceptance of risk, wide sharing of thoughts and observations, judicious rather than intervening concern about intellectual property and recognition of true contributions. Today’s research climate is very different and, perhaps, keeps young non-clinical investigators from thinking how to improve whole-animal reproduction. Investigators would be well advised to identify real problems, and bring in techniques to find solutions.

This paragraph is for young investigators and starts with overarching advice, namely be honest and ‘have fun’. Enjoy seeking out and learning from leaders within and outside your area of interest. In later years, if professional activities become drudgery, abandon them and apply your knowledge in something exciting. Five other messages deserve your consideration. None is new, but the fourth too often is ignored. (1) Do not accept mediocrity, in yourself or others in your field. (2) Formulate your approaches to address societal problems and get practical solutions, rather than identify a seemingly new and ever-smaller fundable unit. (3) Bring or develop new techniques to help in your quest and do not overlook far-distant applications of your new information. (4) Be explicit in phrasing the ‘question’ or hypothesis when planning research and be sure the methods will provide meaningful answers and allow valid conclusions. (5) Seek out and cherish a critical thinking and straight-speaking colleague(s) to provide an independent perspective to sharpen your question and clarify a funding application or publication. The remainder of this article describes how these ‘messages’ evolved or were implemented during my career.

Ideal implementation of (1) probably requires more tact and tolerance than I have demonstrated (Anonymous, 1996; Seidel, 2008).

Applying message (2), my graduate school was selected to enable seeking practical solutions for improving dairy cattle via...
artificial insemination (AI). This quest continued for 55 years, down a winding path facilitated by development/adoption of numerous techniques which, together with broad thinking, also provided answers for far-distant applications with other species (message 3). Addressing thoughts embodied in (2) and (3) was why I sought funding for postdoctoral study in Copenhagen to learn application of radioisotopes in studies of andrology. Principles of quantitative autoradiography of isotope-labelled cells, and validation with other techniques, were drilled in by a world leader (Hilde Levi) and still impact andrology (Amann, 2008). A base in Europe also enabled face-to-face discussions with a diversity of biologists and andrologists at a time when intercontinental communication took weeks.

In Europe I learned the benefit of bringing clinicians and investigators together regardless of species to discuss/dissect critical questions and consider what quantitative approach(es) might provide answers. A decade later, I enthusiastically contributed to the nascent ASA as it fostered interactions among andrologists studying domesticated animals, humans and laboratory animals. Unquestionably, ASA-sponsored interactions facilitated development and validation of CASA (implementation of message 3) by researchers, clinicians and commercial developers (Amann & Katz, 2004); current perspective in Amann & Waberski (2014). Also, a discussion with Stuart Howards (University of Virginia Medical School) at an early ASA meeting resulted in a collaboration (messages 2 and 3) in which he collected and froze testes and epididymides from 25 men dying suddenly, and sent them to me at Penn State where we enumerated testicular spermatids and epididymal spermatozoa using techniques validated with bulls, rabbits and rhesus monkeys (Amann & Howards, 1980). The quantitative data forced conclusions that sperm production in men was much less efficient that in any other mammal studied [still true], sperm maturation in the epididymis typically was accomplished in ≤2 days, and the cauda epididymis might contain 2–4 day’s production of spermatozoa. Amann (2008) provided an update. The concept in message (2) and discussions at an ASA meeting, resulted in provision of data for 20 ejaculates from each of 50 human semen donors by David Karabinus (Genetics & IVF Institute) to enable estimating precision of a single sample for characterizing numbers of subjects and statistical methods are appropriate; case, it is impossible to determine if the analytical methods, these objectives might require a different number of observations. Too many studies (experiments) are designed to be inconclusive for a variety of reasons, including incorrect assumption of ‘experimental units’ resulting in an underpowered study. For example, when co-incubating spermatozoa and oocytes the experimental unit is drop of medium not oocyte.

Implementation of message (5) requires willingness to listen and participate in sometimes painful exchanges, and to thank your straight-speaking colleague. Inevitably, your project or publication will be improved when you address comments from critical thinking colleagues. My demanding graduate mentor taught me to accept such advice, while steering me to research areas and techniques (message 3) he was unfamiliar with. Critique of a project proposal or draft publication requires cutting through the verbiage and examining the essential why, what and how. As a journal reviewer, too often I read an introduction that focuses on ‘why’ and fails to provide an explicit ‘what’. In this case, it is impossible to determine if the analytical methods, numbers of subjects and statistical methods are appropriate; hence, the results can only be unacceptable and the discussion is ‘hot air’.

Andrologists should never lose sight of the end-user of their efforts. Individuals in today’s society are interested in reproduction for two reasons: (i) capability to contribute to production of a daughter or son or prevention thereof; and (ii) necessity for provision of sufficient wholesome and economically priced food to eat. For these reasons the field of andrology will not disappear. However, perceptions of need will change. In the 1960s, the push was for ‘zero population growth’ and increasing food production. Current concerns are insufficient population replacement, population ageing and impact of relocation of temperate-climate zones on production of food for humans and fodder for animals. Linkage of genome and phenotype will enable production of animals or plants appropriate for a climate. Maximizing use of superior males, my research area, will continue to be an important tool in animal agriculture; perhaps a ‘finalized technology’. Today, declining fertility is a major concern for physicians and producers of cattle or pigs and owners of older female horses. Subfertility is a phenotypic problem with myriad causes, some genome based. At least in animals, causative factors centre on the female-microenvironment interaction
exacerbated by poor management. Amelioration of the situation for a given couple or group of animals will require differential diagnosis and individualized therapy, enabled by the explosion of valuable methods. What does this portend for andrology? Each investigator might intentionally change his/her comfort zone to target the evolving needs of society and ever stronger competition for funds. Perhaps the five messages provided above can help you contribute to society and engender their financial support.

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Erma Z. Drobnis began her academic career with a BA degree in mathematics. After a year in the Peace Corps working on a goat meat production project, she continued her work on goats with a master’s project on sperm cryopreservation, thus becoming an andrologist. After completing her MS in Animal Science at Cal Poly Pomona, she began doctoral work at the University of California, Davis, initially continuing to work on goat sperm cryopreservation. There she met David F. Katz and was drawn to his work on the biophysics of sperm motility. She spent 13 years with the Overstreet and Katz group, completing her thesis on the mechanics of sperm penetration of the cumulus matrix and zona pellucida with David Katz; postdoctoral work on sperm cryobiology with James W. Overstreet and John H. Crowe; and research as adjunct faculty. For the last 20 plus years she has been director of the clinical andrology laboratory at the University of Missouri, Columbia, conducting research; teaching in the medical school; and assisting Ob/Gyn faculty and residents with statistics. Notable has been her epidemiology work with Shanna H. Swan and her sperm glycobiology work with Gary F. Clark. She has been a member of the American Society of Andrology and the American Society of Reproductive Medicine (formerly the American Fertility Society) for nearly 30 years and was a charter member of the Society for Male Reproduction and Urology.

My career has involved many switchbacks and pivots, but taken together, has given me a unique vision of sperm biology from basic, applied, and clinical standpoints. I feel deeply honored to be asked to share the lessons I have learned in andrology for this series. A task to which I devote considerable time is reviewing papers for a variety of fertility journals. The lessons I present here address some of the knowledge gaps I see frequently in submitted manuscripts.

I became an andrologist because I wanted to do research on goats; I grew up on a suburban ranch in Los Angeles where we raised dairy goats. After completing my bachelor’s degree in mathematics, I joined the Peace Corps and worked on a Food and Agriculture Organization of the United Nations goat meat production scheme, assisting with applied research. Back in the states, I looked for a school where I could do a master’s degree studying goat production. Edward A. Nelson at Cal Poly Pomona had a USAID Collaborative Research Support Programs grant, looking at reproduction in small ruminants. He needed a graduate student to set up a semen cryobank. I was tasked with this project and figuring out how to freeze goat and sheep spermatozoa. There was no one at Cal Poly freezing spermatozoa at that time, and I had never collected spermatozoa from any species in my life, so I learned by visiting a local bull stud and endless hours in the library reading countless papers. My experience in my master’s program taught me that it was possible to begin work in a scientific area without direct assistance from experts in the field, which brings me to my first lesson:

**THERE IS A RICH LITERATURE ON SPERM BIOLOGY OFTEN OVERLOOKED TODAY**

This literature extends back to the early 20th century. Although modern research instrumentation was not available at the time,
there are outstanding papers with key observations that remain relevant to work being conducted today. Some of the great papers are from cell biology, zoology, or animal science and are not always searchable on MEDLINE and PubMed. Early papers are not as compact as those today; hence, they are rich with observations that are omitted from more modern literature. Because these papers are not always available online, we are often reinventing the wheel in andrology. I have learned that while formulating a research question, it is helpful to find high quality review papers and follow the references back to the classic papers, looking for observations relevant to my research question. In addition to those of my advisors, there were a number of excellent reviews that had great impact on my early career (Mann, 1964; Blandau, 1969; Mazur, 1970; Graham, 1978; Watson, 1981; Yanagimachi, 1981; Saacke, 1982; Bedford, 1983; Moore & Bedford, 1983; Mortimer, 1983, 1994; Quinn, 1985; Hunter, 1988).

From working with goat semen specifically, I learned another important lesson that is often overlooked:

**SEMINAL PLASMA IS TOXIC TO SPERMATOZOA**

While the seminal plasma activates sperm motility and contributes important molecules to the sperm membrane and surface, prolonged incubation in seminal plasma damages spermatozoa in some species. In particular, goat seminal plasma contains high levels of phospholipase A<sub>2</sub> and spermatozoa left in the seminal fluid for more than a few minutes die rapidly. Although human seminal plasma is much less toxic, although toxicity can be significant in some men (Rogers et al., 1983), affecting sperm function rather than changing the motility observed at semen analysis. One observation I made when I first started research with human spermatozoa was that cryosurvival is poor if the spermatozoa remain in whole semen for more than the time required for liquefaction. At UC Davis, we had our research donors collect specimens at home and leave them in a locker where a technician picked them up. These spermatozoa did not survive freezing and thawing; but when I had the donors collect at our facility, the problem resolved. Many seminal plasma constituents act on the female reproductive tract rather than providing a medium supporting the fertilizing spermatozoa (Overstreet, 1983; McGraw et al., 2014).

**SPERM CONCENTRATION IS NOT NORMALLY DISTRIBUTED**

The academic part of my master’s program was a long haul because I was not even a biologist! It required 2 years of undergraduate coursework. Although I had taken probability and statistics as part of my math degree, I had never even done a t-test. A course by Melinda J. Burrill on experimental design got me started in biostatistics and later in my career, Steven J. Samuels taught me more about biostatistics, and I continue to improve my knowledge of experimental design and data analysis by reading texts, papers and courses online. This is one of my current roles in my department, where I give lectures on experimental design and assist faculty and residents with their research. But back to andrology:

I occasionally feel like an army of one reminding authors that it is invalid to describe sperm concentration or total sperm counts from groups of men with the mean and standard deviation (or standard error). Sperm concentration is highly skewed, and must either be transformed to normality, or described and analyzed using non-parametric statistics. For displaying the results, a box plot, the median and inter-quartile range or the median and its 95% confidence interval accurately illustrate these non-normal variables. The difference between means in a study is highly influenced by the outliers having high sperm concentration in each group. When the correct statistical methods are used, they sometimes reveal significant differences that were otherwise obscured.

After completing my master’s degree, I went on to the University of California, Davis, where I initially continued my work with goat semen. While learning objective measures of sperm motility, I met David F. Katz. I was immediately drawn to his work on the biophysics of sperm motility, and that became my doctoral work. I remained in the Overstreet and Katz research group for a total of 13 years, (including 2 more years of undergraduate coursework in systemic physiology and cell biology), completing my PhD with David Katz; conducting postdoctoral work on human spermatozoa cryobiology with James W. Overstreet and with John H. Crowe in the zoology department; and finally becoming an adjunct faculty member. While working on sperm motility I learned that:

**THE SPERM HEAD IS FLAT AND, LIKE A CILIUM, THE FLAGELLUM BEATS PRIMARILY IN A SINGLE DIRECTION WITHIN THE PLANE OF THE HEAD**

Although the flagellum does not beat in both directions, forward motility is achieved by the spermatozoa rolling along the axis of progression. Once motility is hyperactivated, and the sperm head is embedded in the zona pellucida, the large flagellar bends and straightened flagellum cause the sperm head to rock in the zona material, appearing to cut knife-like through to the perivitelline space (Fig. 1).

A major advantage of working in the Overstreet and Katz group was that the ideas of even the youngest member of the group (e.g., the undergraduate hired to wash glassware), were taken seriously, as was information from every scientific discipline, basic and applied. This resulted in new ideas that challenged old assumptions. The lessons I learned there, and attending Stanley Meizel’s weekly journal club, are too numerous to cover here, but the theme is taking a ‘sperm’s eye view’ of sperm function in vivo (Katz et al., 1987). With the advent of the assisted reproductive technologies, the focus has largely shifted away from the rich and complex natural history of the fertilizing spermatozoa on its journey from the testis to the oolemma. Although for basic biology experiments, we must focus on isolated cells and molecules, the most important lesson I learned as an andrologist is always consider the spermatozoa in its biological context:

**THE FERTILIZING SPERMATOZOA SPENDS LITTLE IF ANY TIME IN CONTACT WITH SEMINAL PLASMA**

The population of spermatozoa capable of achieving fertilization migrate quickly into the fluids of the female reproductive tract; meanwhile, the seminal fluids are diluted by female tract secretions. Human semen (as in other primates, ruminants and rabbits) is deposited in the vagina in close apposition to the cervix, from which spermatozoa migrate into the cervical mucus. In other species (e.g., rodents, dogs, pigs, horses) whole semen is deposited in, or is rapidly drawn into the uterus, from which...
spermatozoa migrate through the tight uterotubal junction (UTJ), gaining access to the oviduct. Looking at human semen after liquefaction in a specimen cup is not observing how spermatozoa behave at any time during their natural history in the female.

THE FERTILIZING SPERMATOZOOON IS RARELY SWIMMING FREELY IN VOLUMES OF FLUID

After deposition of semen in the female reproductive tract, fertilization-competent sperm do not remain in the lumina of the tract where sperm are most easily collected for study; rather, the fertilizing population moves in the complex milieu at epithelial surfaces. Although we often use cartoons of the female tract showing fluid-filled tubes, no such structures exist. The lumen of the reproductive tract is minimal, while the epithelia have an enormous surface areas with deep glands, crypts, folds, and ciliated surfaces. The fluid in the small luminal spaces is continually refreshed by secretions, flushing out the spermatozoa less able to maintain refuge in mucins at epithelial surfaces. After deposition in the vagina, spermatozoa with strong motility and appropriate surfaces migrate into the cervical mucus, gaining entry to the uterus by swimming along the surfaces of the cervical epithelial cells. A superb study by Mullins and Saacke (1989) used stereomicroscopic and computer reconstruction on serial sections of the bovine cervix to determine the three dimensional structure of sperm migration. Down in those folds and crypts are where you will find the most motile spermatozoa, migrating to the uterus. Spermatozoa reach the oviduct assisted by adovarian uterine contractions present during the periovulatory phase. At this stage, spermatozoa migrate through the UTJ and form ligand-specific attachments to isthmic epithelial cells. Susan S. Suarez, who was Jim Overstreet’s postdoctoral trainee when I joined the group, has done brilliant work on this association in multiple species (Suarez, 2008; Hung & Suarez, 2010). She has also shown that the UTJ, isthmus and ampulla of the oviduct are mucus filled. In association with the isthmic epithelial cells, sperm motility slows and remains quiescent for up to several days. Once ovulation occurs, some sperm detach from the isthmus, in part due to acquisition of hyperactivated motility, and ascend to the oviductal ampulla.

SPERMATOZOA MUST RELY ON OTHER CELLS FOR SURVIVAL AND FUNCTION

The spermatozoon is small with minimal cytoplasm and most of its DNA packaged compactly on protamines, unavailable for transcription. Thus, the spermatozoon relies on epithelial cells and their secretions in the male excurrent tract, female reproductive tract, and eventually in the ooplasm to enable its functions. When we remove spermatozoa from their normal niches, we can no longer be sure we are observing the behavior they would display in vivo.
IT TAKES VERY FEW GOOD SEMINAL SPERMATOZOA FOR A MAN TO BE FERTILE

A remarkable example showing that very few sperm are required for normal fertility has been reported in some men with hypogonadotropic hypogonadism. When treated appropriately with gonadotropins, spermatogenesis is initiated, and these men can be fertile with much lower total spermatozoa than is considered normal (Burris et al., 1988), as low as 1 million/mL. Clearly these men have a higher proportion of ‘good sperm’. It is important to remember that the few spermatozoa capable of attaining fertilization in vivo are a small fraction of the large, motile population of seminal spermatozoa that we study. Even after careful sperm selection for IVF, many thousands of motile spermatozoa are inseminated per egg, while only a few are believed to be present at the site of fertilization in vivo (Yanagimachi, 2011). In research studies, a measure or treatment effect seen in the evaluated population of spermatozoa may not apply to the spermatozoa competent for fertilization.

THE DIFFERENCES IN SPERM QUALITY ARE SUBTLE

When heterospermic insemination is used to deposit equal numbers of motile spermatozoa from two highly fertile males, one of the males will fertilize the majority of oocytes (e.g., Overstreet & Adams, 1971; Vicente et al., 2004). This method, first used in the 1950’s in mice (Edwards, 1955) has been used extensively in food animal species to compare the fertility of males and spermatozoa treatments. It shows that even in fertile males, there are subtle differences in sperm quality that influence reproductive success.

THE FERTILIZING SPERMATOZOOON IS NOT ALWAYS VIGOROUSLY MOTILE

In fact, vigorous motility is not always a good sign. Under various conditions in vitro, including cooling and warming or freezing and thawing, spermatozoa can display highly active motility and undergo the acrosome reaction due to damage to sperm membranes. Modest increases in intracellular calcium promote both high amplitude flagellar bends and acrosomal exocytosis. While media have millimolar calcium concentrations, intracellular calcium is in the nanomolar range. The spermatozoa remain functional for only minutes after completing the acrosome reaction, so premature acrosome reaction is a bad sign if additional sperm function is required. In contrast, there are times in the sperm’s natural history when motility is quiescent, as during transport in the epididymis and when stored in the oviductal isthmus.

In my reading while writing a review with Jim Overstreet on the natural history of mammalian spermatozoa in the female reproductive tract (Drobnis & Overstreet, 1992), I learned another lesson of which some sperm biologists seem unaware:

THE FEMALE REPRODUCTIVE TRACT DOES NOT ENTIRELY FAVOR SPERM MIGRATION

Rather that providing the ideal environment for each spermatozoon to achieve fertilization, the female reproductive tract impedes most spermatozoa, ensuring that only one spermatozoon reaches and fuses with the oolemma of each oocyte. This is accomplished, in part, by restriction of spermatozoa lacking required surface characteristics, attack by immunocompetent cells, secretion of fluids that flush spermatozoa from the epithelial surfaces, and production of smooth muscle contractions that serve to remove spermatozoa from the female tract. Only a few spermatozoa with appropriate motility and surface characteristics are able to run the gauntlet and reach the oolemma. If the female tract is excessively stringent, or the population of spermatozoa exhibiting the required characteristics is insufficient, fertilization becomes unlikely. Teleologically, it is in the male’s interest to produce many spermatozoa and in the female’s interest to reduce sperm numbers to exactly one at the site of gamete fusion (Parker, 1984). It cannot be assumed that secretions and cells collected from the lumina of the female reproductive tract will produce environments most favorable to spermatozoa.

Just as I was finishing my doctoral work, the AIDS epidemic had become a major focus. Because men could transmit HIV before serum antibodies were detectable, it was apparent that donor spermatozoa must be quarantined, and the donor re-tested for HIV prior to using his specimens. Although human spermatozoa had been cryopreserved for many years with some success, improved methods were desired to increase the feasibility of universal cryopreservation for donor insemination. The NIH released a request for applications on human sperm cryopreservation, and Jim Overstreet and I were awarded one of these grants. When I re-entered the field of sperm cryopreservation after years in basic science, there was renewed appreciation of the membrane lipid composition in cryosurvival:

THE SPERM PLASMA MEMBRANE HAS IMPORTANT SURFACE DOMAINS THAT ARE DISRUPTED DURING CRYOPRESERVATION

We have known for decades that sperm membranes are organized laterally into domains composed of specific membrane lipids and associated proteins (Fawcett, 1975; Quinn, 1985). From the standpoint of cryobiology, the composition of various domains is crucial as different lipids undergo their phase transition from sol to gel at different temperatures. As spermatozoa are cooled, each lipid undergoes its phase transition and separates laterally into a gel phase region. Packing faults between adjacent gel regions increases the permeability to key substances, notable calcium ions. Membrane proteins, excluded from newly formed gel domains, aggregate and can fail to disperse following warming. These membrane changes cause the phenomenon of ‘cold shock’, which occurs when spermatozoa (and many other cells) are cooled rapidly above the freezing point (Watson & Morris, 1987).

Working with John H. Crowe, we used Fourier transform infrared spectroscopy (FTIR) to detect shifts in the –CH₂ absorbance peaks that accompany the phase transition of membrane lipids. We determined that the temperature at which spermatozoa of different species undergo cold shock cryodamage, as measured by potassium leakage and loss of motility, is related to the temperature at which membrane lipids undergo the lipid phase transition (Drobnis et al., 1993). In humans, the critical temperature is at about 20 °C and differs between men.

Also at this time, a seminar by Roy H. Hammerstedt (Hammerstedt et al., 1990) got me thinking about the sperm glycocalyx:
SPERM MEMBRANES HAVE A THICK GLYCOCALYX THAT MEDIATES SPERM INTERACTIONS WITH OTHER CELLS

The glycocalyx, a combination of complex glycans largely attached to membrane glycoproteins, is some 70 nm thick in mammalian spermatozoa, thicker than that of most cells. Glycoproteins are added to and removed from the sperm surface during its natural history, changing how it interacts with epithelial surfaces and the oocyte vestments. Looking at sperm membrane proteins without consideration of their complex glycosylation can be misleading. I realized the importance of the lateral domains and surface glycoconjugates to sperm capacitation, and incorporated this information into a review of that subject (Drobnis, 1992). As I have since learned, working with Gary F. Clark, the important glycosyl residues on the sperm surface are not just the terminal monosaccharides, but are the complex, arboreal structures spermatozoa use to evade immune surveillance and interact with their environment, including the oocyte investments (Clark, 2014).

One of the accomplishments I am most proud of in my career is working with my student, Ted L. Tollner and reproductive pathologist Catherine A. VandeVoort to produce the first offspring from a non-human primate using cryopreserved spermatozoa (Tollner et al., 1990). This was the first species in which I attempted freeze spermatozoa for which cryopreservation techniques had never been developed.

In 1994, I left Davis to become a clinical laboratory andrologist in Obstetrics and Gynecology at the University of Missouri, Columbia. One of the most important lessons I learned in clinical andrology was from a seminar by Rebecca Z. Sokol, and it had a profound impact on how I view care of the infertile couple:

THE MAN IS AN INFERTILITY PATIENT AND WE SHOULD TREAT HIS INFERTILITY

Ideally, the goal in reproductive medicine should be to treat male factor infertility, allowing the male patient to achieve pregnancies by natural intercourse. As a patient, the man should have his own medical advocate to ensure he is getting the treatment he needs for his medical condition. Life-threatening conditions can present as an abnormal semen analysis (Jarow, 1994; Jequier, 2006; Esteves et al., 2011). The male patient may not be best served if he is seen only by a gynecologist and the first therapy considered for his infertility is an assisted reproductive technology.

Due to the financial challenges shared by academic hospitals over the last two decades, I have only intermittently had a laboratory technician. In consequence, I have personally examined countless semen samples during that time, learning in the process:

FAILRE OF SEMEN TO LIQUEFY IS UNRELATED TO SEMEN VISCOSITY

Surprising as it seems, I have reviewed several papers recently in which liquefaction failure was confused with semen viscosity, even when viscosity was the subject of the study. It can be difficult to differentiate these physical properties in the clinical laboratory, particularly because small areas of coagulum can remain once the large gel mass has apparently liquefied. However, there is an easy way to determine if liquefaction is complete: while the molecular mesh causing hyperviscosity is transparent under phase contrast optics, the coagulum is opaque, and the final stages of liquefaction can be readily observed under the microscope.

GEL DROPLETS IN SEMEN CAN LEAD TO OVERESTIMATION OF THE SPERM COUNT

Although the gel fraction is significant in some species (e.g., pigs and horses), this fraction of human semen is rarely discussed in the literature, even in protocols for semen analysis. Though often absent, the gel droplet fraction can account for over a milliliter of the semen volume and is important for at least two reasons, the gel droplets: (i) exclude spermatozoa, thus leading to overestimation when the total sperm count is calculated; and (ii) have high density and will disrupt gradients used for sperm separation. Gel droplets dissolve over time, but not within the time limits required for accurate determination of motility and preparation for cryopreservation or intrauterine insemination. Determination of the gel droplet volume is easily accomplished by centrifuging the whole semen for 1 min at 200 g. The gel volume can then be observed and the supernatant decanted back into the specimen cup for additional processing. For the 187 semen analyses performed in my laboratory in 2014, 37% had gel droplets with a median volume (interquartile range; range) of 0.2 mL (0.1–0.5; 0.1–1.6), and median percentage of gel in the semen volume of 9% (5–14%; 1–35%).

TOTAL SPERM COUNT IS AS IMPORTANT TO EVALUATE AS SPERM CONCENTRATION

In a recent paper, Rupert P. Amann (2009) argued convincingly that the total sperm count and total sperm count per hour of abstinence were better measures of male fertility than sperm concentration. I agree that this is true for men with low to medium semen volume, and the total count should always be included in reports of semen quality. However, in contrast to ruminants, in which the semen volume is low and the sperm concentration is relatively high, in humans, the semen volume varies widely and the concentration of spermatozoa in direct contact with the cervix after coitus is important. In the case of men producing large ejaculates with normal total counts, the fertility may be impaired because much of the semen is not retained near the cervix, and this will be reflected by the low sperm concentration but not by the total sperm count.

It has been a pleasure to write this account of my lifetime journey learning lessons in andrology. This has been a great opportunity as I was forced to revisit my assumptions, shedding a new light on what I have learned in the course of 35 years as an andrologist. I hope that some of these lessons will be useful to younger andrologists following their dreams.

REFERENCES


Lessons in Andrology: many paths to success

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Hello, I’m Donna, and I’m an andrologist. I say this not because we’re in a 12-step recovery programme. I say this not even because of the constant need to define the term. No, I say this to declare my ongoing self-identification as a scientist, specifically, one with a professional interest in the biology and health of the male. The lesson of this article is that there are many paths to success in a career in science.

Since early childhood, I knew I wanted to be a scientist, with an image out of an old horror movie: solo operator, wild-eyed, sparks flying, test tubes bubbling. By the time I reached medical/graduate school, it was chronologically the early seventies yet still politically the sixties, so, of course, I wanted to save the world. With reproductive biology as my chosen route, the cocktail party line was, ‘I want to find the perfect male contraceptive’. Even though I was intent on a research career, every time the choice came up whether to do another year of clinical training, I kept saying yes. The result was 3 years of residency in Internal Medicine. So, part 1 of the lesson is, don’t close any doors. Always keep your options open.

I came to the National Institutes of Health for subspecialty training, allowing me to combine a clinical endocrinology fellowship with a research postdoc. By good fortune, my husband-to-be was also accepted to a fellowship at NIH in the same year. We married the autumn before moving to Bethesda, and went on to have two sons. Thus, part 2 of the lesson, expect your preconceptions about your personal life to change.

At the National Institute of Child Health and Human Development, I trained with Richard Sherins. I saw an astonishing array of patients with infertility and other reproductive disorders, while developing a degree of independence in my research on pituitary gonadotropins.

Time passed. Having become an ageing postdoc, I began to look at mainstream jobs in academic medicine, and quickly realized that I didn’t want to live on a roller coaster. Some people thrive on the ups and downs, but I needed some...
stability. Part 3 of the lesson, then, is pay attention to your personal values – they are important and not to be dismissed. But what to do? There was no such thing as career development. So, I started to talk to people, many of them in the ASA. It was networking, we just weren’t using the word yet. Conversations led to more conversations, and eventually to my first job out of my postdoc. I became the Program Officer for Reproductive Medicine – still in NICHD, but on the extramural (grantmaking) side. I stayed in my field, just working from another perspective. People always asked if I missed the laboratory, and honestly, I didn’t. In Extramural, you have the opportunity to make a much larger impact than you do as a hands-on researcher. I sometimes felt like I had a laboratory with 600 people in it. Of my many jobs, this was the one I’ve had the longest, so far. Part 4, and it’s still true, is, there is no such thing as talking to too many people. If you are an introvert, or otherwise networking-averse, learn the skills, practice them regularly and you will be in a much stronger position to steer your own voyage of career exploration.

Along the way, in addition to my own portfolio of research grants, I was given responsibility for training and career development in my Branch – all the Ts, Fs and Ks. Working with students, fellows and junior faculty, I quickly realized, was the part of the job I enjoyed the most. Around this time, it occurred to many organizations that ‘we have to do something about postdocs’ but nobody seemed to know what that was. After 13 years as a Program Officer, I had the opportunity to be part of that ‘something’ as the first Director of a new office for intramural postdocs in the National Cancer Institute. But I almost didn’t apply for the job. I couldn’t tell from the Vacancy Announcement what they wanted. It turned out, they didn’t know it yet, but they were looking for me. Who better to run your postdoc office than someone who knows a lot about early-career grants?

That makes Part 5 of the lesson, apply to jobs that don’t sound exactly like you, because you might actually be the best candidate.

During several years at NCI, we initiated a number of worthwhile programmes, some of which are still ongoing. I left the federal government in 2005, worked at a foundation briefly, then (again) through pure networking, found my current position. I head the Professional Development Office on the East Baltimore campus of Johns Hopkins, serving students, fellows and junior faculty at the Schools of Medicine, Public Health and Nursing. We offer courses, workshops, other career-related events and individual advising. I am now in what has turned out to be my dream job. And I never saw it coming. If you had asked me 8 or 10 years ago, what is the top priority for your next career move, I would have said ‘an easy commute’. I used to walk to work. Now I have a half-hour walk, then take two trains and a bus.

Part 6 ? Know that your professional priorities can – and likely will – change.

To all of the student, trainee and early-career andrologists reading this, I encourage you to be active in your Society. Yes, you should pay your dues and read your Andrology journal. But do more. Submit manuscripts, be a reviewer, present at the meeting, join a committee, run for office. For over 30 years, I have been active in the ASA. I’ve contributed where able, to help the Society and our field. Despite the fact that I have neither done an experiment nor touched a patient in decades, the ASA saw fit to accord me international visibility and a leadership role. To come full circle: whether by a conventional or an unconventional route, if you stay open to the possibilities and embrace change, you can achieve success in your own career in science.

Editorial Note: After 25 years at the National Institutes of Health and 8 years at Johns Hopkins, the author retired in April. She remains active in ASA, particularly as a career resource for trainees and early career investigators. She continues to identify as a scientist.
Lessons learned in Andrology: Yves Clermont, an interview by Lonnie D. Russell

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INTRODUCTION

Dr. Yves Clermont (Fig. 1) is famous for putting order into the life history of mammalian germ cells as they evolve from spermatogonia to spermatozoa. He accomplished this by defining specific cellular associations in cross-sections of seminiferous tubules referred to as stages of the cycle of the seminiferous epithelium in many species, including humans. He and Dr. C. P. Leblond were credited with the very first description of stem cells (Clermont & Leblond, 1953) and actually coining the term for the first time, cells that are today instrumental in many facets of modern day cell and molecular biology. Dr. Clermont has also touched on many different facets of germ cell differentiation (spermatogenesis), such as the flagellar cytoskeleton and Sertoli cell participation. He is also famous for his description of the germ cell Golgi apparatus in 3-dimensions and that of many other cell types in other organs and coined the term Golgi ribbon. He had an extraordinary love for teaching that reached thousands of undergraduate and medical, dental and graduate students and was awarded the prestigious William Osler Teaching Award. As a skilled artist (Fig. 2), he rendered blackboard drawings during his histology lectures, which were indeed spectacular. His style and passion for his work were complemented by a remarkable sense of good humor.

He was born on August 14, 1926 and passed away on October 10, 2014. Lonnie Russell, who had completed a postdoctoral fellowship under the supervision of Dr. Clermont from 1973 to 1975, interviewed his mentor shortly after a symposium held in his honor at the Spermatology Symposium held in Montréal, Québec, Canada in September of 1998. Dr. Russell passed away unexpectedly in 2001 and the original tape recording was discovered in his office. The following is an edited transcript of this interview. The recorded interview will be made available on the McGill University website.

THE INTERVIEW

Russell: Where were you born?

Clermont: Montréal

Figure 1 Dr. Yves Clermont in 1988, Professor in the Department of Anatomy, McGill University, Montreal, Quebec, Canada.

Russell: What do you remember most about your childhood?

Clermont: I remember many wonderful things. I had a fantastic and pleasant life all through my youth. I was hardworking at school, of course, having all sorts of activities. They were very exciting years – especially my teen years were super.

Russell: On the note of education, would you describe your parents as giving you a push for education? Or, did you feel it inside yourself?

Clermont: My parents didn’t have the opportunity to go to school very long, but both of them felt that it would be good for us, my two brothers, my sister and I, to pursue our studies through the university level. My two brothers
are lawyers. My sister is an artist. I just went to the University. It was my parents’ idea that, to be well-developed, we had to complete our training at universities. They are responsible for this. They didn’t encourage us to follow my father and work in the fur trade.

Russell: Did you enter graduate school shortly after completing your Bachelor’s degree?

Clermont: I was a student at the University of Montreal in biology. I was having a general training in biology and taking courses in a wide range of disciplines such as bacteriology, biochemistry, and zoology. At the time, the number of openings in graduate studies was minimal, and they were in areas that didn’t excite me too much. While I was completing my BSc in biology, I was concerned about what I would do afterward. I was asked by one of the professors in biology at the University of Montreal to go and work on a summer project. It happened that Leblond was involved in that project. The goal of the project was to try to explain whether salmon molting was caused by the influence of the thyroid gland. So, I went to work in the Laurentians (mountains north of Montreal) the year before I graduated. The only job I was doing was to take care of the fish, to clean the basins and to inject the fish with thyroid hormone. So, it was a very mundane type of activity. The person in charge of the project worked directly under the supervision of Leblond. So I didn’t have direct contact with Leblond. But at the end of the summer, the end of August 1948, he said in passing, casually, that ‘if you are interested to do graduate studies in histology you may come to see me.’ That was it. After that it was absolutely evident to me that I had no choice. I had to come to work with him at McGill. That was appealing to me, I had done a little bit of histology at the university and had found it absolutely dull, presumably because the teacher was not stimulating. But, I don’t know why, I liked to look through the microscope at organisms of all kinds, including histological sections. It rang a bell so to speak and I said now I know what I will do next. That was summer 1948. Then, September arrived, I completed my BSc degree in May 1949. Instead of planning on a summer vacation, I decided to go see Dr. Leblond.

At the time, I didn’t know a word of English. I knew how to read English, but had never had an opportunity to speak it. I remember that I came to the Anatomy Department at McGill University and I had to write my introductory sentence. ‘May I see Dr. Leblond, please?’ because the secretaries were only English speaking. He accepted me, but contrary with what he said at the meeting the previous summer, he wasn’t sure of keeping me as a graduate student. So, he took me because I was coming from the University of Montreal and he wasn’t sure of my background. He said, ‘I will take you conditionally.’ I still have the letters from the graduate faculty saying that I was accepted – first, if I had my degree and second, if I was satisfying the requirements of Dr. Leblond. As soon as I graduated in May, I came to work - I didn’t wait until September. He very quickly showed me these slides that he had on periodic acid Schiff stained sections showing carbohydrates. So, I worked during that summer, and it is then that I worked out the classification of steps of spermiogenesis and of the stages of the cycle of spermatogenesis. When Leblond saw that, he felt that I was probably good enough to pursue my graduate studies and changed my status from conditional to permanent. Then, things were moving very well and very quickly. We were accumulating observations of all kinds. He felt that I should not spend time writing a Master’s thesis, which was at the time a requirement. I moved straight to the PhD. In the meantime, instead of writing a thesis, we wrote our first article dated 1952, but we took 2 years to write it. So the time that we spent writing the first manuscript was enormous. But, the final product was there (Leblond & Clermont, 1952a). Because I went straight for the PhD, I finished it in just 4 years, in 1953.

Russell: In speaking with Dr. Leblond, he indicated that the initiative for this project, other than showing you the slides, was yours, and the classification of...
spermatogenesis was derived by you. In those days, it must have been the custom that the Senior professor was the first author.

Clermont: Yes, that’s correct. At the time what sort of experiences did I have in writing a solid scientific article? This was the big part of his training, because he had experience, and he knew how to organize an article for publication, make illustrations, and organize tables. Of course, his input was enormous. I was working on this tissue, with so much excitement and things developed very well. In those days the research director was usually putting his name first. But that was accepted by everyone.

Russell: That has never bothered you, then?

Clermont: Never. Dr. Leblond was very honest about all the publications we had together – very correct, all the time, in my opinion. There is no problem.

Russell: After the first couple of publications with Leblond, you did several others with him as well?

Clermont: Oh yes, before I finished my PhD I had five or six publications (Leblond & Clermont, 1952a,b; Clermont & Leblond, 1953; Clermont, 1954; Clermont & Benoit, 1955; Clermont & Haguenau, 1955; Clermont et al., 1955a,b). One written in French on the hamster (Clermont, 1954). We worked well together all along. He was very demanding, because he was telling us all the time that ‘perfection is the enemy of the good’. But, he was, himself, a real perfectionist in writing these papers. Most of his publications are very well thought through – every line, every word is perfectly in place. This is something that I learned from him. You have to realize that this classification of spermatogenesis that we devised was performed very simply for one reason. It was to find a tool, an instrument to investigate the renewal of the spermatogonial population. I thought of this classification after what, a maximum of 6 months of work or less. This orientation to study the spermatogonial population encouraged me to go in that direction - that was my first objective. It was a very exciting period because I could see data accumulating on the spermatogonial population at various stages of the cycle. An exciting story that was far more precise and accurate than those that had been circulating at the time. We had no idea of the duration of the process at the beginning, but we had some landmarks. From quantitating spermatogonial population we could see, for example, exactly when the spermatogonia were dividing, and whether the divisions were synchronized or at random. We clarified that right from the beginning. Then we injected colchicine to block cells in mitosis and we immediately saw these peaks of mitosis. That was quite exciting. My thesis was directed at understanding the behavior of the spermatogonial population in the rat, in the monkey and in one or two other species. The staging of spermatogenesis was a fallout of something I needed for my thesis; it has been useful for my own work and for the work of others. The idea of the existence of the cycle, was well known by everybody who was working on the tests; it had been well-described by Regaud at the beginning of the century (Regaud, 1901), in particular, and many others. My objective was to find a reproducible method of identifying the stages of the cycle of spermatogenesis - that is all. Interestingly enough, this classification has become better known that the renewal of spermatogonia.

Russell: And would you describe yourself as more driven by Leblond’s drive or self-motivated at this time?

Clermont: I profited tremendously from the presence of Dr. Leblond, of course, but it was not his drive that stimulated me. It was just to see him being passionate about research. Drive and passion are two different things. Drive is hard work – people are working because they have to work. Leblond was always excited, even euphoric! When he was coming over, because I was having an office right next to his, each time I showed him something new or something special, he said, ‘Oh boy, this is so exciting’. But, I was equally excited. He did not have to push me.

Russell: You mentioned the topic of spermatogonial renewal. As you know, there is another theory proposed by Huckins and Oakberg. The data can be translated in two different ways of looking at spermatogonial renewal. Where do you sit now with your own theory and those of others?

Clermont: Having worked on whole-mount of seminiferous tubules with Bustos-Obregon (Clermont & Bustos-Obregon, 1968), having accumulated a mass of quantitative data with Louis Hermo (Clermont & Hermo, 1975), Martin Dym (Dym & Clermont, 1970) and other students, and using radioautography, I developed the conviction that there are two classes of stem cells - and this has not changed. Whether others agree with that, I now couldn’t care less. I still believe that what we have done was well-documented, it was evident, it does not mean that it will not change, but if you ask my opinion now, I am as convinced about the various modalities of cell proliferation and renewal than I was 25 years ago. Now, understand that I have stopped working on these things. You cannot spend all your life on one thing, and I was not trained to use other techniques such as the isolation of spermatogonia. I did not have the tools or the expertise to use these methods. But the evidence I had, indicated to me that I was on the right track. Maybe I am prejudiced, but I was never convinced that my opponents, and I have at least two or three, were right. Because, it was not evident what they were telling me. It never overcame the quality of the mapping and what this mapping was saying in normal or in irradiated animals.

I still have tons of data that I have never published – I
did not have time – on X-irradiation on the spermatogonial population. I still have that at home, and it simply confirms our views, my views and the views of my colleagues. So you see, this is my attitude. Now, if you tell me that in certain conditions, the spermatogonial renewal takes place differently, if they have the facts to support this, I will have to accept it. Don’t forget that my career is practically over and I don’t care if somebody shows something different – on the contrary, I would be happy to see somebody move ahead with some solid facts. For 10 years, I was practically alone working on these topics, so I was not prejudiced one way or the other. And I was alone with my students or colleagues. I had accumulated a mass of facts that was supporting my theory; no, it is not a theory, it is a suggestion. So that is my attitude, even though I was not sure that my ‘suggestion’ was correct, when I was seeing other studies, I wanted to be absolutely convinced that they had the facts to support their view.

Russell: After a period you obtained a faculty position at McGill…

Clermont: Yes, very quickly.

Russell: You have found yourself working more independently with time. But you might want to address the issue of autonomy.

Clermont: Yes, of course. I think this is very interesting. It is very positive too, because as soon as I finished my PhD, I stayed here for a year and wrote a few articles on the renewal of spermatogonia, the very first one on that topic. I started to work on the wave of the seminiferous epithelium. I did all sorts of studies on the development of the testsis, with Bernard Perey, this work I did as a graduate student and published only later. There were so many interesting things. I was doing pretty much all of this by myself. Then I went for a year of post-doctoral training and in those days post-doctoral training was very nice, especially when you were going to Europe. I enjoyed my year tremendously, but I used it to learn the techniques of electron microscopy. That was in 1954–55. The first Porter-Blum microscopes were developed, the first RCA microscopes were being produced, so it was a field that was opening up. I went in the lab at the Cancer Institute in Villejuif (Paris, France), and worked with Wilhelm Bernhard and learned the methodology of electron microscopy. Then I came back to the Department and in my mind, I was not thinking of going anywhere else, because when I left for my post-doc, Dr. Leblond told me ‘if you want to come back, you may come back.’ I said, ‘I am coming back.’ So it is nothing complicated. And this is the interesting thing. I continued to work, more or less in contact with Dr. Leblond. We published a number of articles on the spermatogonial population of the monkey. We worked on the isolation of the carbohydrates from the acrosome of the guinea pig – we did all sorts of things, quite interesting.

There is a point that should be underlined, which is exceptional in a sense. Considering that a man of the caliber of Dr. Leblond, a very strong, dynamic person, there were two possibilities for our relationship. Either he gave me my full independence, or I would go under his thumb and therefore, would not have stayed here very long. Dr. Leblond in the most elegant way, told me ‘now, you are on your own.’ … That was quite interesting, because, as you know in the European style the ‘patron is the patron’ and for life. But, from then on he was always interested in what I was doing; he was always making suggestions and corrections of the manuscripts, but never imposed himself on my research orientation. This is really close to a miracle, when you consider the character of the man. I should like to mention that my relationship with Dr. Leblond is exceptional. … He would have liked to have considered me as a son. But no I said ‘no, I am not your son, I am your friend,’ which is a different story. And we continued, in this manner throughout these 50 years.

Russell: I don’t like to focus on numbers of papers, but about how many do you have?

Clermont: Close to 150.

Russell: If you look back on those papers, which ones make you the most proud?

Clermont: There are, unfortunately, too many. So it is difficult to say. But of course, these first articles on the cycle of seminiferous epithelium of spermiogenesis; I was very happy with those at the time. And then I was very excited by the one on spermatogonia renewal in the rat. Another one was on the spermatogonial population of man; that was a really challenging one. I was the only author on that one. It was a very interesting experience, because I was starting from the work of Branca (Branca, 1926). He had given the description of spermatogenesis, and he asked the right questions, but he couldn’t give the right answers. I enjoyed working on this by myself, mapping spermatogonial population and deriving some conclusions. Even if the conclusions were not 100% solid, at least we moved ahead by one or two steps. This was good; it was very nice. And the cycle of seminiferous epithelium in human I worked a lot on that. The other things I was quite pleased with were the results we obtained on the duration of spermatogenesis, both in the rat and in the human. The radioautography technique developed by Dr. Leblond that I used to calculate the duration of spermatogenesis in the rat was extremely precise, far more precise than any other studies. The human testis is more difficult to study, but we still managed to get the duration of the cycle in the human, and an estimate of duration of spermatogenesis in the human. This was thanks to the collaboration with Carl Heller from Seattle. That article appeared in [43x37]1018 Andrology, 2015, 3, 1015–1021 © 2015 American Society of Andrology and European Academy of Andrology
Clermont: This is where I want to explain to you the view that I had. Russell: You didn’t believe in it at the beginning.

Clermont: Oh well, I always never believe anything at the beginning, but you understand that that was an acute, solid interesting study that you confirmed in other species. When there was something new, I was always excited. What else have I done? We then moved into the study of testis with the electron microscope. There are studies which I found very interesting, not well-recognized by others, such as the formation of the cytoskeleton in the tail of the rat spermatozoa with Margaret Irons (Irons & Clermont, 1982) or the changes in the head components of the spermatozoa with Mike Lalli (Lalli & Clermont, 1981). These studies were quite fascinating because that is when we really developed the notion of a perinuclear theca. I started to work with Dr. Rambourg on 3-dimensional microscopy (Rambourg et al., 1974). All these studies with Rambourg were fascinating. Can you imagine - seeing 3-dimensional images of organelle is always impressive. Don’t forget that I am essentially a morphologist - I love structures, I love to understand and see things in three dimensions. So this is why it was quite exciting. More recently, when Richard Oko came and I sort of indicated to him that one way to go was to analyze the cytoskeletal components of spermatozoa with biochemical techniques and immunocytochemistry (Oko & Clermont, 1991) and now he is moving into the molecular biology aspects of it. This excites me very much.

Russell: Well, moving a little bit to your philosophy. What would you say makes a good paper? What are the qualities that make it good?

Clermont: This is where I want to explain to you the view that I have on research. I don’t want to make generalizations because I am not competent to do that. It is from my experience as a cytologist, histologist and morphologist. I am not trained as a biochemist or as a molecular biologist or geneticist, I think that what I will tell you applies to everybody. I think that what makes a good paper first is the quality of the facts that are presented. The facts, not theory, the facts. So what did this paper demonstrate? Is it a fact or nebulous theory? You know as well as I do that in morphology it is very straightforward. When you discover a new structure like the tubulobulbar complex, you don’t question it, it is there and it is there forever, right? Your job is to present clearly, with proper documentation the existence of what you see –
apparatus or stages. I remember one time he said that there was no such thing as a perforatorium, that the rat was an exception. But now it is obvious that everybody identified a perinuclear theca. I tell you that I always had great consideration and respect for his work. It was sort of complementary. Maybe I had been a pain in his neck on occasion because I was coming with this or that, but my approach was a little different, don't you think?

Russell: Going back to papers and the importance of papers and the impact of papers, there is a group in Philadelphia that is called the ISI and that rates papers with a citation index. You did mention a minute ago that some of your papers have not been picked up, but I think that overall that is not the case. But, is citation index the best we have for looking at contributions?

Clermont: Absolutely not. I don’t think that this is a way of measuring. I have two articles that are citation classics and Leblond had three or something like that, but that does not represent our work.

Russell: One is the kinetics of the development (Clermont, 1972).

Clermont: and the other is on the stages of the cycle (Leblond & Clermont, 1952a), and many others were well-quoted. The Physiological Review article in 1972 on the cycle was very well-quoted. Anyway, I think that to be well-cited may be pleasing to the ego of some people, it happens. Don’t forget the citation index is frequently related to a technique which is extensively utilized by thousands of people. So, what is the value of this? It is a technique. You have some things like the discovery of the DNA helix which are highly cited, but that is normal. So why put a number on that? And to evaluate people first on the frequency of citation and secondly, giving a value to the citation in certain journals and a lower value to other journals, this I find totally ridiculous. This is just a means of providing security to administrators. It means that they don’t have to think, they don’t have to judge, they just take a number in a book and that is it. This is not very healthy.

Russell: So, if you don’t use a citation formula like what is currently being used, what are you left with for evaluation.

Clermont: You are left with your own intuition, not more than that. When you listen to someone, you see if he is interested by what he is doing, if he is competent. And I give a lot of weight to the personality of the person. He has to be able to deal with students, to deal with his colleagues and these things that cannot be measured. There are a lot of factors which have to be considered and evaluation cannot be automated. Do you understand my point? I could see using citation index as one point, but it is as if you were telling me this fellow wrote 1052 articles – but these could be repetitive, it could be this, it could be that, it means nothing to me. But, if you tell me that so and so is a good investigator, that he did something original, that counts. Originality is not evaluated by the citation index. There are all sorts of factors that must be taken into account, and I think that it is very difficult to hire good people and to evaluate them. Sometimes you hire people you think are good and it turns out to be a catastrophe after 3 months; sometimes they work out very well. I have followed the career of many graduates from this Department and very few finally stay in academia. If you want to hire a fellow in a research institute where people just do research – that is another thing, but I was always involved in an academic milieu and therefore, we had to look at other qualifications than just writing articles. So it depends on the situation.

Russell: And your most memorable student?

Clermont: Most memorable student; well I never thought along these lines. There are some who I appreciated because they were very efficient, original, but I appreciated practically everybody that worked with me. There are some who gave me a lot of headaches at times. I had a lot of experiences, imagine, I probably had 30 students and some I had to tell them that they had to leave. So that was difficult. And they had to leave, why? Because, I was convinced that I could not train them properly. They could train themselves, so after their Master’s, I was asking them to leave. In general, I always had good relations with my students. Some of them were not easy, but this is life.

If you were to ask me who was the most interesting collaborator, I would tell you immediately who that is: Dr. Rambourg - and this for his vast variety of qualities. This fellow is exceptional, very peculiar character, but for some reason we worked together in a most efficient manner. This fellow works by himself, in France. He is a person who has a vast spectrum of interests, and not only in science. What a character. He used to come here twice a year for 3 weeks and we would work together. We were fighting each other like dogs at times, but we always managed to work well, very well together, in fact. For a period of 25 years, we published possibly something like 30–35 articles together – always difficult to write. He is a fascinating person. He has interest in languages, he has interest in philosophy, he has interest in music. It has been a very enriching experience each time he came here. You know that I am retired, and he will be retiring soon. We will keep in touch, but it means that the relationship will change. So, I am helping him, he is helping me. He is really a genius, but not easy, you know. I don’t know how, but I manage to work well with him. We were complementary to each other. I was SLOW, he was FAST.

Russell: Is there anything else you would like to add?

Clermont: ...The way I approach things is in pieces that are complementary in order to build up a whole picture. It took all my life, first on the seminiferous epithelium,
then on the Golgi apparatus. ... I need to tell you one more thing. There is a tendency to magnify the value of science and of scientists, to make them like gods, in that modern world of technology. When you think about it, science is something which is not far from a trade, it is not that fantastic. It is like my father who was trying to do a good job with furs. When I say that about Father, there is all the perfectionist approach that he had and the quality of his dedication. I think that when you are an artisan, you are somebody who loves what he is doing. And what he is doing is not necessarily extraordinary. ... So this is my view on science. I don't think that the scientist or even medical people can ever pronounce themselves on all the problems that we meet in our lives. The reason of our existence, where we are going, this and that – that is my view. I am not triumphant about my career as a scientist, I am very close to the ground.

Russell: What about the future?

Clermont: I am not a prophet, so this is very simple. I can't tell you what is the future, I can tell you what was the past, but the future is a mystery. You never know how things will develop. Obviously there are new technologies. Whether it is in research or teaching, obviously the methodologies will change. There will be very extensive use of computers. There will be modification in the approaches taken, because the new generations are changing too. When they come to us they have different backgrounds, so we have to live with that. As to the future of anatomical sciences, that will be modified, evidently. But I think, it has to be modified very carefully, because we may go into the ditch. You understand, that may happen. You know, treating people without knowing their anatomy is a bit of a problem. Now there is something in teaching that will never change. I think, I think education will never be replaced by instruments. The personal contact will always be essential at one point or another in education. Transmission of knowledge is just one aspect of education, of information. There is a lot more than that in education. You know this as a parent, it is the same thing in the academic field. Sometimes I have said something to somebody that helped them tremendously. I never realized that, but it was through a personal contact, and most of all a person-to-person relationship, not between the student and that machine. The computer, right there – it is the poor student who is in front of the computer, this is not human. But I still think, because I know and you know, that my personal experience with Dr. Leblond and others influenced me, always, and we live with that. This is human nature. So these are my views.

REFERENCES


