Fifty Years of the Spermatology Symposium

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The foundation of the International Symposium on Spermatology (ISS) was made by Baccio Baccetti (1931–2010) of the University of Siena, Italy, and its first meeting was held in Siena and Rome in 1969. The term, spermatology, was used the first time for this meeting. In other words, Baccetti invented this term. He gathered eminent electron microscopists working with spermatozoa of various kinds of animals all over the world. Among them, from Japan, there were Jean Clark Dan who was the discoverer of the acrosome reaction and Gonpachiro Yasuzumi who worked with bird and snail spermatozoa and the superviser of Osamu Tezuka, a famous mangaka or animation creator. Tezuka was also a medical doctor. Almost 100% of the presentations at this meeting were morphological ones, revealed under the electron microscope. Charles Brokaw was the only one person working with sperm motility among the attendants of the first meeting which the author could not attend. The exact name of the symposium was the International Symposium of Comparative Spermatology. Thus the title of the proceedings book published from Academic Press was "Comparative Spermatology." Some articles were written in French. Since then this international symposium has been held every 4 years just like the Olympic Games (Figs. 1, 2, and 3).

Incidentally, in 1965, 4 years earlier, the author, together with veterinarians, gynecologists, and anatomists, etc., founded a similar symposium on spermatozoa in our country. This Japanese symposium has also continued until now repeating annual meetings. Baccio Baccetti was a good electron microscopist, but sometimes worked with biochemists in sperm motility or metabolism, and was even interested in AIDS. He, together with Björn Afzelius, published "The Biology of the Sperm Cell," a classic in spermatology, or more exactly in comparative spermatology.

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Fig. 1 Baccio Baccetti, the founder of the ISS and the organizer of first and sixth meetings

Fig. 2 Upper left to lower right: Björn Afzelius, the organizer of second meeting; Don Fawcett and Michael Bedford, the organizers of third meeting; J. André, the organizer of fourth meeting; Hideo Mohri, the organizer of fifth meeting and Jim Cummins, the organizer of seventh meeting

The second meeting was held in Stockholm in 1973, organized by Björn Afzelius (1925–2008). The author first met him at the Misaki Marine Biological Station, the University of Tokyo in 1958. He was famous in discovery of the details of so-called 9 + 2 structure of flagella and cilia in 1959, describing arms, now dynein arms, and spokes in the axoneme of sea urchin spermatozoa and also numbering the outer doublet microtubules. Furthermore, he had already suggested that sliding between the adjacent doublet microtubules is the fundamental mechanism of flagellar and ciliary movement, based on his morphological observation with the electron microscope. Later in 1975, he described the immotile cilia syndrome.

Fig. 3 Upper left to lower right: Claude Gagnon, the organizer of 8th meeting; Gerhard van der Horst, the organizer of 9th meeting; Eduardo Roldan, the organizer of 10th meeting; Masaaki Morisawa, the organizer of 11th meeting; John Aitken, the organizer of 12th meeting; and Lars Björndahl, the organizer of 13th meeting

As indicated by the title of the proceedings book, "The Functional Anatomy of the Spermatozoon," Pergamon Press, the functional aspects of spermatozoa was taken up together with morphological ones in this meeting, although the name of the symposium was again the International Symposium on Comparative Spermatology. Thus fertilization, sperm motility, etc. were added as the main subjects. The author, together with Ian Gibbons, the discoverer of dynein, attended as a motility person and talked about the comparison of the newly discovered tubulin and dynein with actin and myosin in muscle.

Among the attendants, there were Laura and Arther Colwin, who first described the fusion of egg and sperm membranes at fertilization, and Gerald Edelman, a Nobel laureate with his work on the chemical structure of antibody, who was interested in mammalian fertilization around that time. As a matter of fact another Nobel laureate, Yoshinori Ohsumi, who elucidated the mechanism of autophagy, was in Edelman's laboratory and once worked with mammalian fertilization. Both Colin Austin and Min Chua Chang who discovered independently the phenomenon called capacitation in 1951 were also present in this meeting.

The third meeting was held in Boston and Marine Biological Laboratory, Woods Hole, in the United States in 1978. The organizers were Don Fawcett (1917–2009) and J. Michael Bedford (1932–2018). Fawcett, as an eminent anatomist, made various excellent electron microscopical works as summarized in his book, "The

Mammalian Spermatozoon" and after retirement from Harvard, he devoted himself to studies on parasitic diseases in Africa. Bedford was the first postdoctoral fellow of M.C. Chang and has much contributed to maturation, capacitation, and fertilization of mammalian spermatozoa.

The name of this symposium was the International Symposium on the Spermatozoon. As the subtitle of the proceedings book, "The Spermatozoon," Urban & Schwarzenberg, also indicates, the scope of the symposium was further extended to Maturation, Motility, Surface Properties, and Comparative Aspects. Comparative and evolutionary aspects became the backbone of the ISS from the first meeting through this 13th meeting. As there were many motility people including Ian Gibbons and his wife Barbara, a very skillful biochemist, in the United States, the hot discussion was made on the then-current topics concerning the mechanism of sperm motility. Also, quantitative assessment of sperm motility was taken up as a workshop organized by Robert Rikmenspoel. Surface properties of spermatozoa in connection with fertilization, capacitation, and spermiogenesis were one of the main subjects. Human spermatozoa were also one of the targets in this meeting. Thus there was a tendency to include also applied fields from this meeting. The author revealed that the arms in the sperm flagella are really dynein molecules with peroxidase-conjugated anti-dynein antibody prepared by Kazuo Ogawa, who later determined the whole sequence of dynein heavy chain in 1991.

In this meeting, Ryuzo Yanagimachi, Yana, attended for the first time together with Claudio Barros of Chile. Yana succeeded in in vitro capacitation, and thus in successful in vitro fertilization of mammalian sperm. He also discovered hyperactivation and succeeded in ICSI and ROSI, etc. and reared many excellent reproductive biologists. He is 2 years elder than the author, i.e., 90, but is still actively working. Both Gibbons and Yana received the International Prize for Biology, which was established to commemorate the contributions that the late Emperor Showa (Hirohito) and the present Emperor, Akihito, of Japan have over long years made to biological sciences by themselves.

The fourth meeting was held in Seillac of the Loir district in France in 1982, organized by Jean André (1922–2017), who observed the genesis of sperm mitochondria under the electron microscope. "The International Symposium on Spermatology" was used the first time as the name of the symposium. The subtitle of the proceedings book, "The Sperm Cell," Martinus Nijhoff Publishers, was Fertilizing Power, Surface Properties, Motility, Nucleus and Acrosome, and Evolutionary Aspects. Together with the development of in vitro fertilization (IVF) and embryo transfer, we had to evaluate not only motility but also the fertilizing power of human and domestic and experimental animals' sperm. Changes in nucleus and acrosome were specifically discussed. Monoclonal antibody and evaluation of sperm motility using light scattering were introduced. It was impressive that many French colleagues spoke in French with the English summary on the slides. We took the pleasant outdoor lunch.

We can find the names of Jim Cummins, Claude Gagnon, Masaaki Morisawa, and David Mortimer who have been or will be the organizer of the ISS among the attendants of this meeting. David Phillips who published excellent electron

micrographs of spermatozoa in many kinds of animals was also included. In the Loir district, there are many old castles, so that we enjoyed the sightseeing very much. At that time, the members of international organizing committee were Jean André, Björn Afzelius, Baccio Baccetti, Michael Bedford, Don Fawcett, Gunther Meyer, and Hideo Mohri. After this meeting, Meyer's name disappeared from this list and new names of the organizers of succeeding meetings were added one by one, losing the names of persons who passed away.

The fifth meeting was held in Fujiyoshida, a small town in the foot of Mt. Fuji, in 1986, organized by the author. The reason why this town was selected as the venue of the meeting was that Bedford insisted that in the big city like Tokyo with many attractive places it would be difficult to keep all the attendants together for discussion. Of course, beautiful scenery of Mt. Fuji was another reason. The author planned this meeting for Jean Dan and Gonpachiro Yasuzumi, but unfortunately both of them had passed away before the meeting was held. In this meeting, sperm metabolism, male contraception, and separation of X- and Y-sperm were added as main subjects. The last was realized later by Laurence Johnson based on DNA difference, using cell sorting and flow cytometry. Unfortunately, the difference between X- and Y-sperm is quite small in humans, and furthermore now sexing of early embryo is available after in vitro fertilization, but its practical application has been made to cattles, etc.

Ties and scarfs with the cross sections of mammalian sperm flagellum were prepared for the attendants. At the beginning of banquet, Austin and the author broke the top of the container of sake with wooden hammers, the ceremony called kagamiwari in Japanese. Several attendants climbed up to the summit of Mt. Fuji. We can find young John Aitken, Claude Gagnon, and Eduardo R.S. Roldan who also organized the ISS meetings later among the attendants. The proceedings book, "New Horizons in Sperm Cell Research," Japan Scientific Societies Press, was published.

Incidentally, this year, 2018 is also the 50th anniversary of the naming of tubulin by the author. The paper proposing the name tubulin for the main constituent of microtubule appeared in a March issue of Nature in 1968. To tell the truth, the author asked Thaddeus Man of the UK, the author of "Biochemistry of Semen," for recommendation of his manuscript to Nature, and Jean Dan was the recommender of this name. Now about 1500 tubulin papers have been published every year, and the author is very happy as the godfather.

The sixth meeting was again held in Siena, organized by Baccetti in 1990. Celebrating the 20th year of spermatology, he used the name, International Congress on Spermatology, but this was only for that time, because spermatologists did not like a big name. Baccetti tried to summarize all the results obtained so far in the field of spermatology. Indeed, at the beginning of the meeting and of the proceedings book, "Comparative Spermatology 20 Years After," Raven Press, "History of Spermatology" was presented by Afzelius and Baccetti, and the book was quite voluminous, including all the about 200 presentations. In applied field, the number of gynecologists, andrologists or pathologist, etc., increased. Reactive oxygen species (ROS) and gene expression were among the topics. An award was given to Don Fawcett for his great contributions to spermatology.

Thaddeus Mann attended this meeting and talked about octopus sperm. As described above, he wrote "Biochemistry of Semen" and later its revised book "Biochemistry of Semen and of the Male Reproductive Tract" summarizing enormous data concerning sperm metabolism and related subjects. Since the author started his academic carrier with studies on respiration and lipid metabolism of spermatozoa, these books were bibles for him. Owing to his wife's health conditions, Mann could not attend the preceding meetings and unfortunately his attendance was limited only this one. Every night we enjoyed good Italian wine.

The seventh meeting was held for the first time in the Southern Hemisphere, in Cairns of Australia in 1994, organized by Jim Cummins. He spent several years in Yana's laboratory in Hawaii as a postdoc. Cummins made several experiments concerning maturation, capacitation, and fertilization and then greatly contributed to the development of reproductive biology and medicine in Australia. The proceedings book "Advances in Spermatozoal Phylogeny and Taxonomy," Museum national d'Histoire natureelle, summarized only the contributions in the field of phylogeny and taxonomy of spermatozoa, together with some articles of nonparticipants. Editors were Barrie G.M. Jamieson, a comparative spermatologist and one of the co-organizers of this meeting, Juan Ausio of Canada, and Jean-Lou Justine of France.

In this meeting, applied spermatology sections both in human and in animal science occupied great portions. SRY, sperm competition, and CASA were found among the topics. Technology of molecular biology was gradually and more and more used also in sperm researches. We presented some phylogenetic results concerning the number of subunits of outer arm dynein. The outer arm dynein in all the animal spermatozoa and cilia, both Protostomia and Deuterostomia, consists of two heavy chains and the outer arm looks like a hook, while that of other organisms such as *Chlamydomonas* and *Paramecium* consists of three heavy chains and their outer arm looks like a pistol. As reported at the preceding meeting in Newcastle, recently Kazuo Inaba showed that a flagellar protein regulating sperm motility, caraxin, has the same distribution, namely in uniconta, as two-headed outer arm dynein has among all the living organisms. This group, uniconta, would be keeping some ancient genes and characters, because three heavy chains were caused by duplication of a certain heavy chain.

We can find the name of Gerhard van der Horst among the attendants. We loved the Nature of Australia including the Great Barrier Reef very much. Fortunately, we could see many wild platypuses as well as kangaroos or wallabies and nests of termite on the way of excursion.

The eighth meeting was held in Montreal, Canada, in 1998 after a competition with the Worcester Foundation in the United States where the pill was developed By Gregory Pincus and M.C. Chang. Organization was made by Claude Gagnon (1950–2012). He was the head of urology laboratory and had spent several months in the author's laboratory in Tokyo. He studied the effects of ROS on spermatozoa and obtained sperm motility inhibitor, semenogelin, from the seminal plasma. This meeting was characterized by the title of the proceedings book, "The Male Gamete, from Basic Science to Clinical Applications," Cache River Press. Various topics

were discussed in relation to assisted reproduction. Male infertility was becoming a main problem.

At the beginning of the proceedings book, a tribute to Yves W. Clermont of Canada was presented for his long-term contributions to studies on seminiferous epithelium. Thus spermatogenesis was a main theme. Interactions with egg and egg coat, transmembrane and intracellular signaling, HIV, etc., were among the topics. One session was devoted to fish spermatozoa. To this meeting, the big three pioneers in reproductive biology and spermatology, namely Austin, Chang, and Yana attended.

The ninth meeting, the first in twenty-first century and also in African continent, was held in Cape Town of South Africa in 2002, organized by Gerhard van der Horst. He has examined the semen of more than 100 species of animals including endangered wild animals ultrastructurally and with CASA and has thus contributed to human and animal reproduction. The conservation of endangered wild animals is an urgent problem in Africa and was one of the main themes of this meeting. Criteria of semen quality were discussed in relation to assisted reproduction in addition to other main subjects.

At the banquet, we enjoyed the meat of crocodile, ostrich, a kind of antelope, etc., which we could not taste in other places. Of course, these are not the species going extinct. The venue was not far from the table mountain. We also visited the Cape of Good Hope and watched whales and cape penguins.

The tenth meeting was held in Madrid, Spain, more exactly at El Escorial in the suburb of Madrid, in 2006, organized by Eduardo Roldan. He has contributed sperm biology in general, including bioenergetics and signal transduction, and is much interested in sperm competition in relation to sperm evolution. Relief of endangered wild species is also his research subject. Thus, these themes were reflected in the sessions of this meeting. Various manipulations of sperm cells were discussed. There was one report on male contraception.

The proceedings book of this meeting, "Spermatology," Nottingham University Press, was also quite voluminous. For Afzelius, this became the last meeting to attend. Tim R. Birkhead, a debater of sperm competition, attended this meeting.

The 11th meeting was held in Okinawa, again in Japan, but with somewhat different atmosphere from that of the main islands of Japan, in 2010. The organizer was Masaaki Morisawa, who was the director of the Misaki Marine Biological Station and elucidated the signal transduction mechanism at motility initiation and in chemotaxis of spermatozoa. In this meeting, Björn Afzelius memorial symposium concerning motor proteins and sperm motility and Jean Clark Dan memorial symposium concerning molecular biology of the acrosome reaction were held together with the tributes to them. Sperm genomics, environmental impacts, male sterility were among the main themes. Several luncheon seminars and workshops were also provided.

The proceedings book, "Sperm Cell Research in the 21st Century: Historical Discoveries to New Horizons," Adthree Publishing, was published, including the obituary of Baccio Baccetti. Among the attendants, there was Gen Hoshi, the former president of the International Union of Biological Sciences (IUBS), who identified

the factors inducing the acrosome reaction in starfish. The presentation ceremony of the awards for the excellent posters took place at the end of this meeting. The sunset viewed from the venue where once held the so-called summit was very beautiful.

The 12th meeting was held in Newcastle, again in Australia, in 2014, organized by R. John Aitken. This was a joint meeting with AAAA, the Association for Applied Animal Andrology. He is also an eminent reproductive biologist and concerned with the effects of ROS and other factors on sperm functions from a long time ago. The meeting started with sperm biology in domestic animals. Paternal impacts on development were also discussed. As a new technology CRISPR/CAS system was introduced. There were lunch workshops concerning CASA and DNA damage, etc.

The proceedings book was not published after this meeting. Masaru Okabe, who made excellent work in molecular biology of spermatozoa concerning fertilization, gave us Thaddeus Mann Memorial Lecture. The awards for excellent talks were presented at the banquet. We enjoyed the excursion visiting some winery in the suburb.

In 2018, we had the 13th meeting in Stockholm, organized by Lars Björndahl and his colleagues. He worked with chromatin stabilization of human sperm with zinc and standardization of semen analysis. The presentations at this meeting are described in this proceedings book. At this meeting, Hagai Levine and his group reported a significant (50–60%) decline in human sperm counts in Western countries for these four decades, reconfirming the report by Skakkebaek's group in 1992. Based on this presentation, "Stockholm Male Reproductive Health Statement 2018" was compiled to call on governments, organizations, the scientific and medical communities, and individuals in the world.

In all the preceding meetings, we have enjoyed their friendly atmosphere. We have much learned and have been inspired from each other and have got new ideas for future researches through the mutual exchange, sometimes resulting in cooperative works. The next meeting in Canada organized by David Mortimer will be no exception.

In future, it is needless to say that molecular biology and information biology together with further improvement of image analysis would elucidate the basic problems concerning various facets of spermatozoa from primordial germ cells to fertilization or the onset of development. Male infertility and decline of sperm counts are serious problems not only for individuals suffering from it but also for the survival of human being as described above and of endangered wild animals in future. Induction of a single gene necessary for a certain step of sperm formation has already been tried in a special case lacking such a gene. Although asthenozoospermia could be overcome by ICSI, and even some of azoospermia by TESE, in vitro spermiogenesis, spermatogenesis in other animal's body or production of egg and sperm from the somatic cells such as iPS cells, etc., would be further improved or carried out. As the rapid increase in human population is also serious big problem, so we should pay more attention to male contraception. It was not often that this theme was taken up in the ISS. In fact, the author made some experiments on alpha-chlorohydrin and gossypol, once the candidates of the male pill, but

never talked about them in the ISS. Evolution of spermatozoa is always a fascinating problem. We need more evidences concerning sperm competition and other hypotheses.

Even living, in other word reproduction, in the space and the revival of once extinct animals like in the film "The Jurassic Park" would not merely dreams. Teruhiko Wakayama who first succeeded in cloned mice in Yana's laboratory told us the other day that freeze-dried semen samples of mice are now going around the earth in the space laboratory and that the injection of sperm nuclear DNA from the testis of the mouse frozen under the ground with mammoth gave offsprings or something. Finally, the author would like to recommend to include some researchers of male gametes of the organisms other than animals, for instance, plants and seaweeds, in this symposium. Recently, we had a research group on sexual reproduction in animals and plants in Japan, and have found that there are common phenomena and common genes among them concerning gamete recognition and fusion. Viva spermatozoa!