

The contributions of Juan Rosai to testicular pathology with personal remembrances

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Summary

The authors summarize their personal interactions with someone for whom they had unbounded admiration, Dr. Juan Rosai. This varied from daily review of cases, to sharing the platform at meetings, being under his tutelage as an author, and co-directing postgraduate courses. These all highlighted the remarkable knowledge of medicine Dr. Rosai had, imparting as he did diagnostic pearls and remarks on the literature including the history of our discipline, often laced with a well-honed sense of humor. The contributions he made to the pathology of the testis are then considered beginning with his role in highlighting a tumor, at the time not particularly well publicized, spermatocytic seminoma. He wrote two major papers on it, one on standard clinical and pathologic aspects, and one on its ultra-structure. The first was associated with his diligent investigation of a prior paper reporting an unusually high number of malignant examples of this tumor but on review that was explained by their representing malignant lymphoma. The organizational skills of Dr. Rosai, and attention to detail, were second to none and shown perhaps most notably with his organizing many courses, but they were also illustrated early in his career when he moderated a symposium on germ cell tumors of the testis which laid the framework for the classification and nomenclature of premalignant lesions. Finally, his almost career-long interest in the entity he codiscovered, Rosai-Dorfman disease, was associated with his reporting testicular involvement by that disorder in his later years. This giant figure in pathology will stand forever in the top tier with other greats who have contributed to the field.

Key words: Juan Rosai, spermatocytic seminoma, germ cell neoplasia, Rosai-Dorfman disease

Received and accepted: September 2, 2021

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Conflict of interest

The Authors declare no conflict of interest.

How to cite this article: Colecchia M, Amin MB, Young RH. The contributions of Juan Rosai to testicular pathology with personal remembrances. *Pathologica* 2021;113:330-338. <https://doi.org/10.32074/1591-951X-353>

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I (MC) had the privilege and good fortune to have the closest personal contact of the three authors of this tribute, working as I did with Dr. Rosai on an essentially daily basis for many years at the National Cancer Institute in Milan. Of course, like all pathologists, I was well aware of this eminent figure before getting to know him personally well and I had indeed attended the 20th and 21st annual courses of the pathology department of Memorial Sloan-Kettering Cancer Center in New York which he organized in 1996 and 1998. For a young Italian pathologist these courses provided new insights about pathology with remarkable lectures. It was a memorable experience to hear lectures by those I knew due to their writings including in textbooks I had read. In September 1999 circumstances began to evolve such that my personal association with Dr. Rosai became particularly close when I suddenly heard his voice in



Figure 1. The senior author with Dr. Rosai looking at slides together in the National Cancer Institute, Milan, early 2000s.

the gross room of the pathology department of the Institute in Milan discussing the preliminary fixation of specimens before sampling. He always emphasized the importance of good fixation, processing, and sampling and much as he also knew a remarkable amount about more modern techniques, he did not forget the basics of our field. To suddenly be in the same room as such a famous person was simply an amazing experience. Soon a wonderful 5 years began when, in January 2000 Dr. Rosai became chief of the department of pathology at the institute where I was already working, and I would sit with him looking at many cases at the multiheaded microscope session he held every day at 1 PM (Fig. 1). His encyclopedic knowledge was evident with regard to almost every case that was shown whether he was evaluating the most unusual cases referred to him or some of the more standard cases in the routine hospital practice. I share with the reader one particular anecdote related to an interchange later which I remember as a lost bet. At the end of 2008 I asked Dr. Rosai for a second opinion in a case of pseudoglandular penile squamous cell carcinoma given the rarity of this neoplasm which as best as I knew had not yet been described at this site. He said, "are you sure"? We wagered the loser would take the winner to the opera, challenging of course my assumption that the entity had not been described. He then showed me the title of a paper on the topic about to be published, which of course he must have reviewed! The happy end was a wonderful evening, with Dr. Rosai and his wife (Fig. 2), at the Regio Teatro in Parma to listen to "I Lombardi alla prima Crociata" a Giuseppe Verdi opera (Verdi was his favorite musician). If only all bets we lost had such a happy result for the loser!! Although writing these words has of course had very sad overtones it has also brought back fond memories of a great pathologist, a remarkable person and I hope in varying ways the reader, like me and my co-authors, will be able to focus on the latter.

The second of us (MBA) first knew Dr. Rosai through his numerous contributions, remarkable lectures, and of course his majestic textbook which I read avidly as a post graduate student in India. I benefited of course from the wisdom of his teachings, and in 1990 as a resident in Pathology applied for a surgical pathology fellowship under Dr. Rosai. I was honored that he responded promptly, but was somewhat initially disappointed that he had discontinued the fellowship for the year for which I was applying as he was moving to Memorial Sloan-Kettering Cancer Center in New York. He stated in his letter that he would prefer not to jeopardize my training experience due to his transition, ensuring my interests and demonstrating the hallmark of a selfless mentor. I soon had significant professional interactions with Dr. Rosai on a more regular basis, particularly in one major way, namely as an author of two of the AFIP fascicles in the third series of those well-known works; he was the series editor. He was most patient with us as we certainly did not meet his initial deadline for completion and he also generously allowed us to split what was initially going to be one fascicle into two, something he was reluctant about but ultimately agreed was a wise decision. Later, I had the special pleasure of sharing the podium with Dr. Rosai at two United States Canadian Academy of Pathology evening slide seminars, one on genitourinary pathology and one in the bone and soft tissue session which focused on visceral involvement by mesenchymal tumors and the diagnostic problems they created. That is an experience I will never forget, and equally memorable were two days I spent as a Grand Rounds speaker when he was chairman of the Department of Pathology at Memorial Sloan-Kettering. He hosted



Figure 2. Dr. Rosai with his wife, Dr. Maria Luisa Carcangui, pictured on Lake Garda having just travelled from their home in Milan, with RHY, prior to the 2009 postgraduate course held at Riva Del Garda.

me for dinner on the evening of the first day of my visit and the next morning he shared some interesting and perplexing kidney tumors with me. His command over the microscope and his encyclopedic recall of even the rarest case reports in the literature and previously diagnosed tumors (including approximate date and name of consultee) during the slide review was mesmerizing to witness and an indelible academic treat. The third author (RHY) had a variety of different opportunities to experience the wisdom and indeed wit of one of the legends of our discipline. I first heard Dr. Rosai speak when I attended a postgraduate course offered by Stanford University School of Medicine in March 1982 when my wife and I took a delayed honeymoon in California. The sparkling nature of that presentation and numerous subsequent ones will forever be an example of mixing both remarkable insights into pathology and medicine with appropriate asides of a somewhat jocular nature which made the talks interesting even for those whose field was not medicine. I became more familiar with him later when my mentor, Dr. Robert E. Scully, worked with Dr. Rosai (Fig. 3) on a variety of academic matters noted below. My mentor was not one to express great admiration for others too readily but very quickly one realized that he thought Dr. Rosai was the proverbial “real deal.” Later, I had frequent contact with him when working on the fascicles just noted and inadvertently, without intending humor, on one occasion told him, as the project was close to finished, that we were “polishing the scrotum chapter!” Dr. Rosai, who had a great sense of humor, did not let that remark go without comment. Perhaps my most remarkable interchanges occurred when we planned three memorable postgraduate courses together in Italy, in Milan in 2003, Florence in 2006 and Riva Del Garda in 2009. His attention to detail and organizational skills were simply out of this world and the great success of the courses was very much due to them. The speakers for those courses were a mix, roughly 50% Massachusetts General Hospital-Harvard Medical School faculty, and the remainder distinguished pathologists from other centers including those in Italy. Working on those courses with Dr. Rosai made many of my colleagues at the Massachusetts General Hospital much more friendly with Dr. Rosai than circumstances would otherwise have enabled and his close association with us was cemented when he was given the title of visiting Professor of Pathology at Harvard Medical School, a rare honor. He was a guest speaker at the 20th anniversary offering of the annual Harvard Medical School course “Current Concepts in Surgical Pathology,” in 1998, given in honor of Dr. Austin L. Vickery, Jr. and Dr. Scully, two of the founding directors of the course. The association of Dr. Rosai with Dr. Scully



Figure 3. Photograph taken in 1980 at “International Symposium on Testicular Germ Cell Cancer” held in Minnesota.

will be clear from these pages. That with Dr. Vickery was also of some note in that they had a shared great interest in the thyroid gland.

I later had the pleasure of codirecting one of the remarkable pilgrimage courses with Dr. Rosai, in Sicily in 2013 (Fig. 4), perhaps the most memorable overall because the site was selected at short notice, because political issues made the site initially selected untenable, and all the organizing done by him, with the able assistance of his wife, at great speed. It was

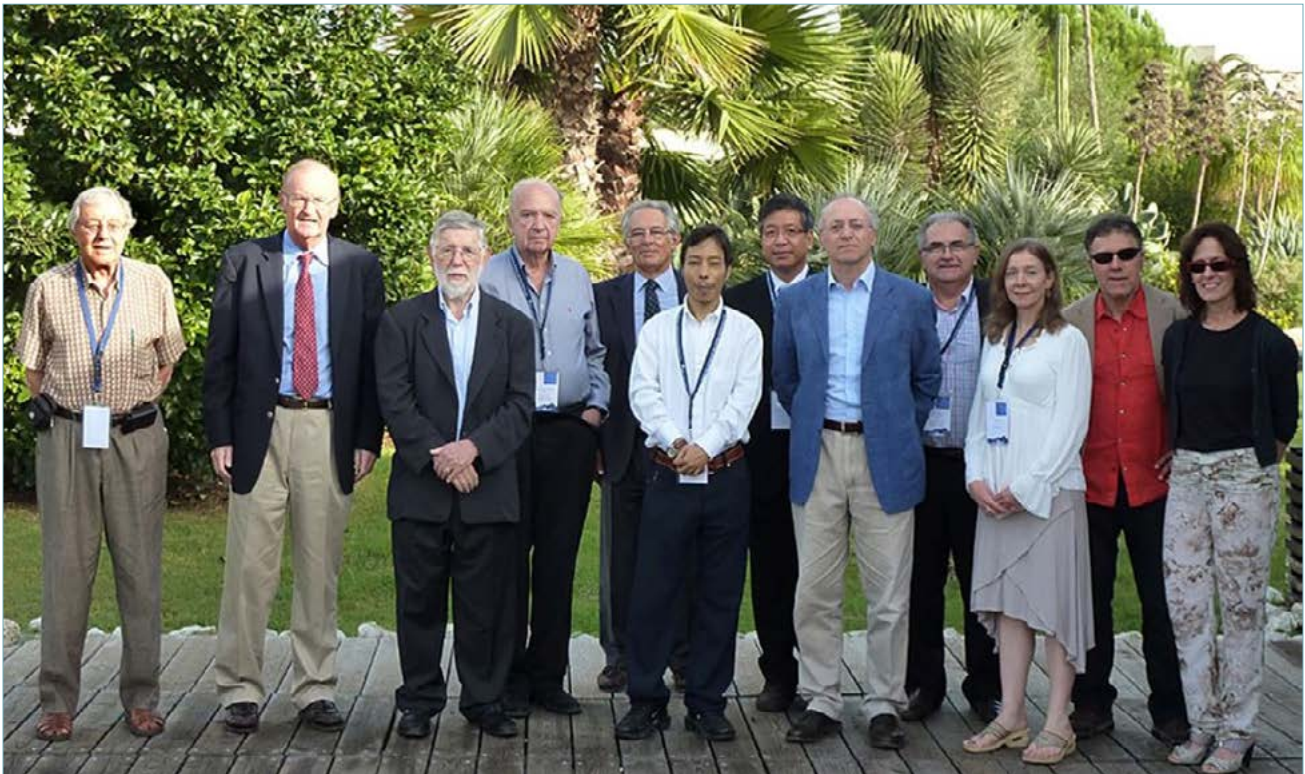


Figure 4. Faculty of the third of the “pilgrimage” courses consisting of walking and bus rides, with a little medicine interspersed. This course was held in Sicily in 2013. From left to right are: Leonard Kahn, Robert Young, Juan Rosai, Jeronimo Forteza Vila, Manuel Sobrinho-Simoes, Claudio Tripodo, John Chan, Fabio Facchetti, José Antunez-Lopez, Judith Ferry, Robert Kurman, Elizabeth Montgomery. Photograph courtesy of Dr. Robin Cooke.

not long until his ill health became known to me and as it was for all who had great affection for him, it was a matter of great sadness. I consider I have had two great privileges in my career, working with him, and the aforementioned Dr. Scully. We truly will not see their like again.

In the second half of the last century when surgical pathology blossomed as a vibrant specialty within pathology, Juan Rosai¹ was the quintessential academic surgical pathologist with possibly the widest breadth and depth of diagnostic acumen across all organs, and with seminal original scholarly contributions in many areas. Although he made several important contributions to Urologic Pathology, including the first description of post-operative spindle cell lesion of the bladder (independently recognized by him and Dr. Robert E. Scully), his major contributions to this area are in testicular pathology. In this review we focus mostly on two important entities, highlighting Dr. Rosai’s erudite microscopic observations and his incredible tenacity in investigating prior observations of relevance. We focus first on the remarkable neoplasm, Spermatocyt-

ic Seminoma, renamed Spermatocytic Tumour in the most recent world Health Organization classification, but respecting tradition, as Dr. Rosai surely did, we refer to it here by the name he knew it. He did not like the name change, commenting to one of us in writing “changing the name to spermatocytic tumor is unwarranted and not necessary.” He went on to comment on some of the many names of entities that could be faulted for diverse reasons. We emphasize how his work has influenced our understanding of the neoplasm and also note how, appropriately, his interest in it links him with two other giants in the field. We then consider his role in a conference which was of great significance concerning the diagnosis and classification of precursor lesions of germ cell tumours of the testis. We conclude, appropriately, with brief comments on testicular involvement by the remarkable disorder Dr. Rosai, with Dr. Ronald Dorfman, characterized, which is known as sinus histiocytosis with massive lymphadenopathy or, by those, such as the writers, who have an affection for eponyms, Rosai-Dorfman disease. We consider the three topics reviewed sequentially, based

on the time Dr. Rosai was working on them, beginning with the one which is perhaps the most fascinating for reasons that will be obvious.

Spermatocytic seminoma

In a recent report of a large series of 85 cases of this tumor², the authors (including one of us – RHY) commented that “*spermatocytic seminoma of the testis is a neoplasm that links 3 giants of surgical pathology: Pierre Masson, Robert E. Scully and Juan Rosai, whose triad of papers made this neoplasm a well-established entity*”³⁻⁶. How appropriate it is that such a fascinating neoplasm (Fig. 5) garnered the attention of three remarkable investigators whose status in the top echelon of anatomic pathologists is secure forever and there is a very special aspect to the career long interest of Dr. Rosai in this tumor.

In 1969 a young 28 years old Juan Rosai, at that time instructor in pathology at Washington University School of Medicine in St. Louis (and in only the fourth year of his decade long time there), authored two original papers regarding spermatocytic seminoma^{5,6}. The introduction in the first of these is a tribute that Rosai offered to Pierre Masson and exhibited his great appreciation for the contributions of those who worked in earlier times and love for the history of our discipline, shown in many ways, perhaps most notably his much later editing a book on the history of surgical pathology in the United States⁷. In his first spermatocytic seminoma paper⁵ he quotes the great French-Canadian investigator as follows, «*Masson compared the*

cytologic characteristics of both tumors and reached the conclusion that while classical seminoma originates from undifferentiated germ cells, spermatocytic seminoma is derived from spermatogonia, and is therefore capable of producing “abortive spermatocytes”»³. The reputation of Pierre Masson was particularly high in the fifties and his friendship with Lauren Ackerman and Arthur Purdy Stout, two of the most prestigious pathologists in the eyes of the young Rosai, was noted thirty years later in Dr. Rosai’s book, noted above, “*Guiding the Surgeon’s Hand: the History of American Surgical Pathology*”⁷. After the first description by Masson in 1946³, as Rosai in his first contribution noted, the tumor was largely ignored, the only other report being of three cases by the third giant who has contributed concerning this tumor, Dr. Robert E. Scully⁴. In his paper Dr. Rosai re-emphasized that this entity was clearly different from the classical seminoma and was, unlike other germ cell tumors, exclusive to the testis, never associated with teratomatous elements, and had a usually favorable prognosis. The second paper he wrote on the tumor⁶, based on two cases studied by electron microscopy, confirmed Masson’s hypothesis, i.e., “*...the finding of nuclei having the appearance of the leptotene stage of the meiotic prophase*”. His skills in supporting the observations of Masson based on ultrastructural findings was further evidence of the talents of someone who was quickly establishing himself as a brilliant young investigator. Before continuing the story of Dr. Rosai’s interest in spermatocytic seminoma, and having just mentioned his paper utilizing electron microscopy, it is worth noting, as that paper illustrates, that from an early age, although he would always emphasize classic aspects of good surgical pathology practice, namely, awareness of the clinical background, gross characteristics, and thorough microscopic examination, he was also someone who explored all available techniques as they came along and he was one of the first broadly skilled surgical pathologists to show special interest in electron microscopy, one he continued throughout his career even when its importance waned because of the advent of other techniques particularly immunohistochemistry and, as his career was coming to a close, molecular pathology. Given his inquisitive mind it is no surprise that both the latter techniques were utilized by him in many of his later papers. Furthermore, when reviewing his curriculum vitae while preparing this paper we were struck that he must have been one of the first to explore immunohistochemistry in germ cell tumors of the testis as he wrote a comprehensive review of the topic⁸ with the late Dr. Lucien Nochomovitz in 1978, a time when that technique was very new on the scene from the perspective of surgi-

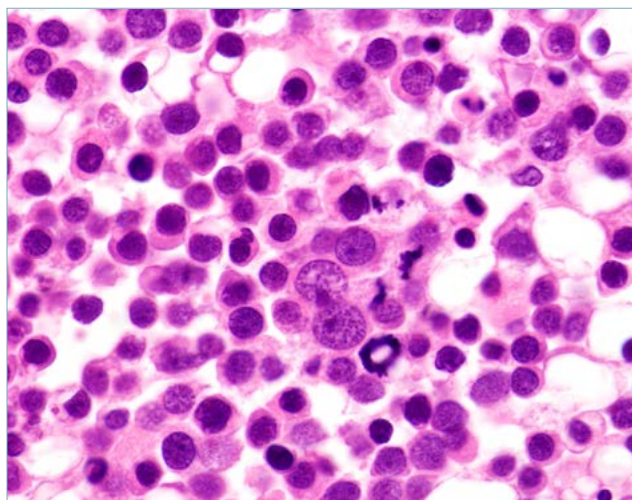


Figure 5. Spermatocytic seminoma. Typical histologic features. Case four of series referred to in text.

cal pathology practice. He authored other articles on germ cell neoplasia we will not discuss here but they attest to his major interest in the topic, his curriculum vitae containing no less than eight on germ cell neoplasia, usually of the testis, in addition to those specifically cited by us here. Two, not surprisingly, given his long-term interest in mediastinal neoplasia, concerned germ cell tumors of that site.

We now recount a story which shows his remarkable energy and by its nature is perhaps unique in investigative surgical pathology. Four years before his 1969 paper on the clinicopathologic features of six cases of spermatocytic seminoma, a paper had appeared documenting a malignant behavior of four of five of these tumors. In his paper Dr. Rosai deftly considered them and he and his coauthors state *“We wondered if this fact could be explained based on some morphologic peculiarities of those tumors. We have been able to review the microscopic sections from those 5 cases. It is our opinion that their case 4 is a typical example of spermatocytic seminoma. On the contrary, the other 4 appeared to be highly anaplastic tumors spreading between the seminiferous tubules, separating and encompassing them.”* He and his coauthors then note that the tumors were shared with Drs. Lauren V. Ackerman and Robert E. Scully and that it was the opinion of the latter that they were tumors of the hematopoietic system, an interpretation Dr. Rosai agreed with. Many years later when one of us (RHY) had the good fortune to spend some time with Dr. Rosai he told the story of how he had obtained the slides, shared them with Dr. Scully, and the former gave the latter credit for interpreting the malignant neoplasms

as malignant lymphomas (Fig. 6). Many years later RHY asked for the story to be summarized in writing and an email from Dr. Rosai of August 6, 2016, slightly modified, reads in part (the portion of interest to us here) as follows: *“I was driving through Ottawa on a visit to Eastern Canada and was reminded of a paper from the Canadian Tumor Registry, based in that city, reporting 5 cases of spermatocytic seminoma, four of which followed an aggressive course. I visited the registry, and they were kind enough to let me take slides of the cases back to St. Louis. When back in the office I looked at the cases and concluded that only the tumor from the one patient with a benign course qualified as spermatocytic seminoma. I sent the slides to Dr. Scully who thought the other four cases were all lymphomas”.* Later when reviewing some old cases in Dr. Scully’s collection, RHY came across representative slides of the cases in question (Figs. 5, 6 a-b) Dr. Scully had been allowed to keep and it was fascinating reading the accompanying correspondence between Drs. Rosai and Scully who at that time had not met but subsequently did and formed a warm friendship. It became well-known to RHY that each greatly admired the other, not a surprise, and Dr. Rosai wrote a typically original tribute to Dr. Scully on the occasion of the 80th birthday of the latter⁹.

The two giants (Fig. 3) who are part of the interesting story just recounted had a later further connection because of this remarkable testicular tumor. Sometime in the early 1980s each became aware that the other had seen malignant examples of spermatocytic seminoma with a clinical course that was related to a sarcoma developing within the neoplasm and they com-

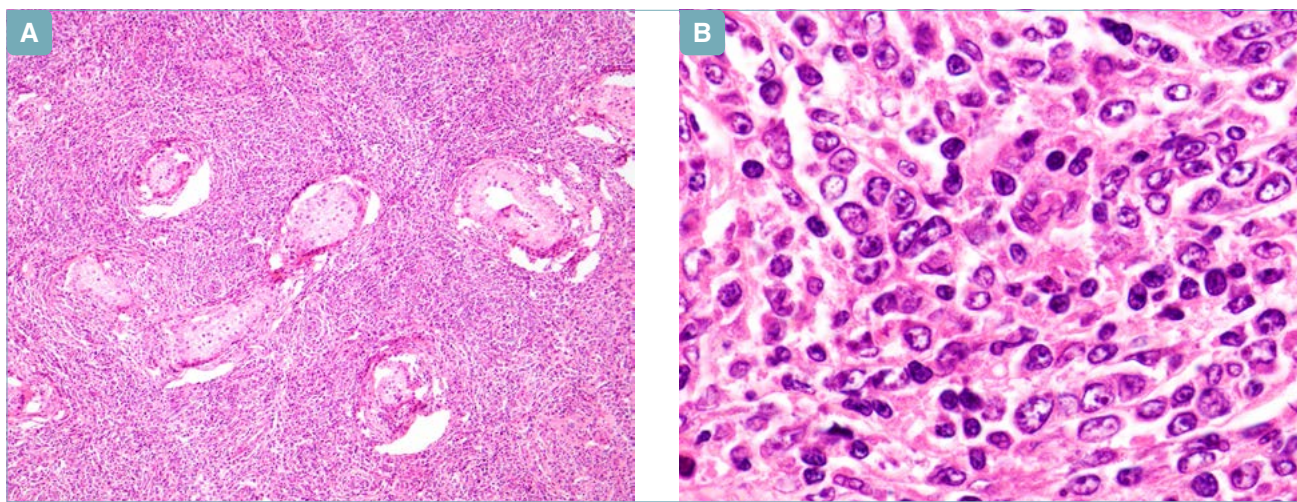


Figure 6. (A) Malignant lymphoma of testis. Typical intertubular growth is seen in the low power illustration. (B) Typical cytomorphology of large cell lymphoma is seen in the high-power view.

bined their cases for a report in the literature of five examples¹⁰. There was an essentially synchronous report of two other examples of that phenomenon the same year¹¹. Towards the end of his career a final contribution on the neoplasm by Dr. Rosai and others appeared in the form of a case report of an example that had a morphology that has been characterized by some as “anaplastic”¹². In conclusion with regards to spermatocytic seminoma, it is surely appropriate that it garnered the attention of not one but three legendary figures in our field and until the end of time Dr. Rosai’s role will be unique.

Precursor lesions of testicular germ cell neoplasia

The sixth edition of Ackerman’s Surgical Pathology textbook has a paragraph on the entity intratubular germ neoplasia (IGCN). “... *A pathology panel that met in*

*Minnesota in 1980, as part of an International Symposium on Testicular Germ Cell Cancer accepted with slight modification the following classification of intratubular germ cell neoplasia (IGCN) as proposed by Dr. R. E. Scully”*¹³. In the book, Dr. Rosai lists four different subtypes of intratubular germ cell neoplasia (IGCN): a) unclassified type (IGCNU), the prototypical lesion; b) IGCN with extratubular extension; c) intratubular seminoma; d) IGCN, other forms, based on the “Scully classification” as reported in detail elsewhere¹⁴.

This nomenclature for testicular precursor lesion resulted from a three-day meeting in 1980 on various aspects of testicular tumours organized by Dr. Elwin Fraley, the chief of the Urology Service at the University of Minnesota. The morning session on the first day was moderated and organized in significant part by Dr. Rosai. A portion of the program listing the first seven presentations is reproduced here (Fig. 7) and includes figures well-known for their contributions to

The figure consists of two parts. The top part is a title card for the 'International Symposium on Human Testis Cancer, Mouse Teratocarcinoma & Oncofetal Proteins' held from June 26-28, 1980. The card features a logo on the left and the University of Minnesota logo on the right, along with the text 'ABSTRACT' and 'Department of Urologic Surgery Continuing Medical Education Medical School Continuing Education and Extension UNIVERSITY OF MINNESOTA'. The bottom part is a program for the 'MORNING SESSION' moderated by Juan Rosai, listing seven presentations with their times and speakers.

MORNING SESSION		
Moderator: Juan Rosai		
8:40	Development of the Seminiferous Tubule.	David W. Hamilton
9:00	Cancer <i>In Situ</i> of Testis.	Robert E. Scully
9:15	Cryptorchidism and Testis Cancer.	Clyde Blackard
9:25	Seminoma of the Testis.	Lucien E. Nochomovitz
9:45	Comparison of Existing Classification Systems for Germ-Cell Cancers of the Testis.	F. K. Mostofi
10:05	REFRESHMENT BREAK	
10:20	Immunocytochemistry of Testicular Cancer.	Eadie Heyderman and Robert J. Kurman
10:50	Tissue Immunoelectrophoretal Detection of Tumor Markers.	Bent Nørgaard-Pedersen

Figure 7. Title of symposium held in Minneapolis late June 19, 1980, taken from cover of meeting syllabus (top), with program for first portion of morning session on day 1, moderated by Dr. Rosai (bottom).



Figure 8. Group of pathologists who spoke at the 1980 symposium, see figure 7, and formulated a classification of precursors of malignant germ cell neoplasia of the testis. Standing, right to left, R.E. Scully, R. Kurman, L. Nochomovitz, sitting, right to left, F.K. Mostofi, E. Heyderman, J. Rosai.

the field (Fig. 8). Some changes have recently been made in the terminology adopted at that time, but it still very much is the framework for the current approach to this challenging area. This is but one example of many one could use to highlight Dr. Rosai's organizational skills and attempts to bring order to the approach and classification of tumors and tumor-like lesions of different organs over the years, such as a later one concerning breast pathology.

Rosai-Dorfman disease involving the testis

As all readers will well know one of the most remarkable contributions of Dr. Rosai is his description of this entity and it is worth pointing out that it was done when he was still relatively early in his career, yet he still recognized a very particular pathologic entity, in conjunction with Dr. Dorfman. His original paper ¹⁵ was published in the same year as his two papers on

spermatocytic seminoma. His interest in this remarkable disorder which can involve numerous organs was lifelong and is at the very top of the list of his many significant contributions. His experience with the disease was published as an issue of *Seminars in Diagnostic Pathology* ¹⁶ relatively late in his career. A table in that contribution lists all the cases known at that time in which there was involvement of the genitourinary system and a small number of cases with testicular involvement were recorded. Some years later one of us encountered an example of this disease, shared it with Dr. Rosai and it was published along with another case in his collection ¹⁷. On a sad note, this was published very near the end of Dr. Rosai's career when ill health was beginning to take its toll, but he still contributed significant papers, particularly on thyroid disease, for some years. The journal in which Rosai-Dorfman disease was covered in great detail also printed a *Festschrift* for Dr. Rosai in 2016 ¹⁸, edited by one of his trainees Dr. Mark R. Wick, who with 14 others presented reviews related to some of

Dr. Rosai's numerous areas of interest. Eight years earlier Dr. Rosai had, with one of us, edited the 25th anniversary addition of the same journal¹⁹. In the latter he wrote two essays one entitled "The benign versus malignant paradigm in oncologic pathology" and the other "Lauren V. Ackerman: a wit, a rogue, a giant: selected anecdotes".

In conclusion, it has been a privilege, albeit tinged with sadness, to record the above reflections on the contributions of a great scholar to just one organ of the body. He must be close to unique when one considers the countless organ systems to which he made significant contributions. We were honored to know him and to have experienced his wit and wisdom personally by attending many of his presentations over the years. His position in the pantheon of pathology is secure.

Acknowledgments

Dr. Judith A. Ferry, Director of Hematopathology at the Massachusetts General Hospital and Professor of Pathology at Harvard Medical School kindly took the images depicted in figures 5 and 6. Slides from which images obtained are in the collection of Dr. Robert E. Scully at the Massachusetts General Hospital. Dr. ML Carcangiu authorized the publication of Figure 2.

Author's contributions

M.C. and R.T. wrote the manuscript and reviewed the scientific literature. M.A. contributed to the design and all approved the final manuscript.

Ethical consideration

No ethical issue was raised by this work.

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