Ovarian Tumors and Those who Wrote About Them:

Brief Notes

Robert H. Young, M.D.

James Homer Wright Pathology Laboratories, Massachusetts General Hospital,

Harvard Medical School, Boston, Massachusetts

In this brief summary I endeavor to give some sense of the time-line and major individuals who have brought our knowledge of ovarian tumors to its current state. Comments of a biographical nature on the various individuals who have contributed are kept to a minimum but the reader is referred to cited tributes which cover this aspect and appropriate comments of a biographical nature will be given in the spoken version. I am well aware that what follows is incomplete and, in particular, as of this time I have not had time to review the older foreign language literature to the degree I would wish and would be appropriate. Nonetheless, I believe most of those who have contributed significantly are noted below. As is generally customary in matters of this nature I do not consider those of very recent times, whose story is for another day.
Ovarian tumors have of course been a human affliction since the dawn of time but for practical purposes knowledge in this area only began to evolve with the work of the great Morgagni (1). He is credited for the first significant mention of ovarian tumors in the earliest book I have been able to find with the words ovarian (or ovary) and pathology in the title, Dr. Charles G. Ritchie's publication of 1865 (2). Ritchie's work is indispensable in providing information about contributions made before 1865, many of those mentioned by him not being easily available for review. He notes the 1762 English translation of a book by Astruc (3), consulting physician to the King of France, entitled "A treatise on the diseases of women". In it ovarian diseases are considered under six headings, but it did not advance knowledge much although Ritchie's concluding generous remark reads "such as it was, Astruc's treatise seems to have been for some time the best guide to ovarian pathology in the English language".

At around this same time Morgagni's work appeared with description in it of dermoid cysts. He referred to ovaries having "vesicles filled with grumous material" and a tumor that was "evidently bony." Another giant of anatomic pathology, Matthew Baillie, also recognized dermoid cysts, mentioning in his ‘Morbid Anatomy of the Human Body”, published in 1793, “the ovaria changed into a fatty substance with hair and teeth”(4).
The 19th century saw a significant increase in exposure of surgeons and ultimately pathologists to ovarian tumors because of the advent of surgical exploration of the abdomen and what we now know as oophorectomy, known at that time as ovariotomy. Dr. Ephraim McDowell (5) performed the first ovariotomy on Christmas Day in 1809, in Danville, Kentucky. That was over 30 years before anesthesia was introduced so the skill of Dr. McDowell and courage of the patient need no elaboration. The story of the slow acceptance of operative removal of the ovary and the pioneering surgeons who blazed the trail is the domain of surgery more than pathology so is not considered here. I will note in this essay only those such as the British stalwarts Spencer Wells (6) and Lawson Tait (7) who had a major interest in pathology.

The third and fourth decades of the 19th century saw two giants best known for other contributions enter our story. In 1829, Dr. Thomas Hodgkin (8) read a paper before the Medico-Chirurgical Society entitled "Upon some adventitious structures". In his comments on serous cysts he notes that they may be solitary or can "reproduce themselves ad infinitum". Some of the second group which he refers to as "proliferous" were noted by him to be found in great abundance in the ovary. 1838 saw the publication of a report on abdominal tumors by Dr. Richard Bright (9), whose greater fame is for his contributions to renal disease. Two of his four categories of pelvic tumors he attributed to ovarian abnormalities. He noted
as follows: "by far the most frequent form of ovarian tumor, is essentially a specific disease assuming all the varieties of structure which result in the numerous modifications of that morbid action called malignant". That comment is one of the first to herald the now well-known great diversity of morphology seen in ovarian tumors.

A little later (1854) Sir James Paget (10) made his contributions to the area in his lectures on surgical pathology. In his 23rd lecture he gives ovarian tumors detailed consideration. He generously acknowledges the prior contributions of Hodgkin by the following comment, "the principle varieties of the complex ovarian cysts have been described to the very life by Dr. Hodgkin, to whom we are indebted for the first knowledge of their true pathology". He goes on to say that "I will more briefly say that according to his arrangement, we may find in the proliferous ovarian cysts two principal or extreme forms of endogeneous cysts". According to the descriptions and illustrations that follow, he appears, and Hodgkin likewise, to be categorizing the tumors into what we would not recognize as mucinous and serous groups. Mixed forms are referred to and he notes "but a lecture would not suffice to describe, even briefly, the variety of forms into which these ovarian proliferatous cysts may deviate." Paget comments on what were probably Krukenberg tumors (11).
In 1870 Heinrich Waldeyer (12) (of eponymous fame for other reasons) wrote a lengthy paper on epithelial ovarian tumors, being one of the first to suggest a histogenesis similar to that now widely accepted for the most common form of ovarian cancer. The early 1870's also saw the publication of two major books on the ovary. The first was E. Randolph Peaslee's "Ovarian Tumors: Their pathology, diagnosis, and treatment, especially by ovariotomy" (13). It begins with a helpful time-line listing prior contributions, including many of those already referred to here and present in Ritchie's summary. This book is divided into two parts, the first deals largely with clinical aspects but the second is entitled "Ovarian Tumors - Their Classification and Pathological Anatomy". A particularly striking illustration (his Figure 21) is a drawing of what may well have been a serous cystadenoma and surface papilloma of borderline malignancy. The "polycystic lesions" appear for the most part to have been mucinous cystic tumors. He concludes with relatively detailed consideration of dermoid cysts, knowledge of which was better developed at the time than was that of other ovarian neoplasms.

One of the giants of ovarian surgery, Spencer Wells, contributed a work on the ovary almost synchronously with Peaslee, the edition of his book “Diseases of the Ovaries: Their Diagnosis and Treatment” available to me (the American one) being published one year after Peaslee's (14). Two of the 20 chapters concern pathology, the second entitled “Morbid Anatomy and Pathology of the Ovaries”
and the third, on dermoid cysts. The latter stands the test of time particularly well. He considered other ovarian tumors in three groups: adenoid, fibrous, and malignant with the first category being further subdivided into simple cysts, multiple cysts, and proliferous cysts. His description of proliferatous cysts and use of the word “budding” suggests that at least some would now be considered serous papillary tumors of borderline malignancy. The discussion of fibrous tumors appears to refer largely to tumors that today would be considered in the fibroma group but he also makes perhaps the earliest reference to a smooth muscle tumor of the ovary and compares their rarity in the ovary to their frequency in the uterus. He notes having seen two ovarian examples and that in both there was a large quantity of fluid in the peritoneal cavity. In his discussion of malignant tumors, Wells states “every kind of cancer infesting other organs is in turn reproduced in the ovary”. Most of the cases summarized in the section on cancer of the ovary read as if they were probably cases of serous carcinoma. One case of “encephaloid cancer” from a 14-year-old girl cannot be confidently classified but it is suspect for dysgerminoma. The attention he gave to extraovarian tumors mimicking ovarian tumors on clinical, and even sometimes pathologic evaluation is noteworthy. There is detailed consideration of tuboovarian cysts and mention of cysts of Wolffian derivation.
1873 also saw the publication of a book containing consideration of ovarian tumors by someone whose name is, for various reasons, linked with that of Spencer Wells, Lawson Tait, another giant of 19th century surgery (15). The two men initially were on good terms but subsequently had a bitter row and sadly can fairly be said to have been "sworn enemies" but we shall not dwell on that unfortunate situation. One of the six chapters in Tait's book is entitled: Ovarian Tumors and Conditions Which Simulate Them. It is the longest chapter, 101 pages, and accounts for close to one third of the book. However, it is even more difficult than in the case of Wells' book judging how lesions described by Tait would be classified today, problems being compounded by the limited illustrations and charming, but at the same time, sometimes confusing, wording. He may have been referring to the common problem of invagination of epithelium into stroma that often complicates the interpretation of serous borderline tumors when he remarks “by the growth of subsequent cysts, these papillary remains are often forced into irregular and very complex folds, the apparent complexity of which may be greatly increased by the accidents of the section”. The association of ovarian tumors with a number of interesting clinical manifestations, notably amenorrhea is referred to.

Two additional influential British surgeons of the late 19th century who had considerable interest in pathology were Alban Doran and John Bland Sutton (16). Each wrote books on the ovary. Doran's book, published in 1884, had 12 chapters
accounting for 175 pages and 32 illustrations (17). Two of the major chapters were on dermoid cysts and "solid tumors" of the ovary. Bland Sutton’s “Surgical Diseases of the Ovaries and Fallopian Tubes” published in 1891 (18), runs to 488 pages divided into 42 chapters with 119 black and white illustrations and five color plates. Bland Sutton is critical of previous writers for recording largely their own personal experiences in his firmly worked preface and indicates his own intent that “full justice is done to the original work of other surgeons”. Aspects which struck me as of interest are as follows. There are some comments which I took to refer to the imprecise line between inclusion cysts and neoplastic cysts, as well as a few pages concerning the association of dermoid cysts and mucinous cystic tumors. The chapter on dermoids reflects amongst other things Bland Sutton’s interest in the teeth of dermoids, a matter he had studied in great detail and indeed made a presentation about to the Odontological Society of Great Britain in 1890. The chapter on “solid tumors” considers them under four headings: fibromata, myomata, sarcomata, carcinomata. When dealing with sarcomas it is stated that “both ovaries are frequently affected primarily” but a few pages later when discussing secondary tumors of the ovary the following remark appears “it is quite possible that in some cases described as primary sarcoma or carcinoma of the ovary, the growth in the ovary was really secondary to cancer of some other organ”. Other comments in the section on secondary tumors that stood out were
mention of the frequency of bilaterality and the striking lobulation of metastatic breast cancer which, along with uterine cancer and melanoma, are the three secondary tumors considered. One chapter pertains to ovarian tumors in infancy and childhood. It begins with the discussion of neonatal cysts, presents a case of a tumor of uncertain type in a 7 month fetus, has a table of cases in the literature of tumors in girls under 15 years of age (most of them dermoids), mention some dermoid cysts with associated malignant components (? Yolk sac tumor, ? dysgerminoma) and concludes with a two page long discussion of “oophoromata” and based on an illustration they are suspicious for dysgerminoma. The next chapter is noteworthy because the discussion and illustrations under the heading of “warty ovarian cysts”, almost certainly refer to serous papillary tumors including the borderline forms. Bland Sutton's work is advanced for its time.

It is around this time that the famous “Krukenberg tumor", arrived on the scene resulting from Friedrich Krukenberg’s description in 1896 of six cases (19). The work was carried out in the laboratory of Felix Marchand, eminent amongst other things for his work on trophoblastic disease (20), in Marburg. Krukenberg believed the tumors he described were primary in the ovary and his description of the gross characteristics as translated by Speert (21) “Unevenly knobby, firm areas alternate with rather myxomatous ones – larger, smooth-walled cysts may develop as a result of progressive softening of the myxomatous tissue” will resonate with
all who have had experience with this tumor. The familiar stromal proliferation of this tumor tricked Krukenberg into considering it a fibrosarcoma, albeit one with prominent mucin, despite the fact that it appears some had been correctly interpreted when initially examined as “fibrocacinoma”. He appears to have concluded as he did because of the lack of an apparent epithelial origin despite noting that the tumor cells appeared epithelial. Only six years later Schlagenhaufer firmly established the secondary nature of the Krukenberg tumor (22).

In the last decade of the 19th century major contributions were made by the German investigator Herman Johannes Pfannensteil. Writing in the famous German book “Veit’s Handbook of Gynecology” in 1898, he segregated, more clearly than Waldeyer had, the tumors arising from the surface epithelium (23). He was probably the first to introduce the general concept of neoplasms intermediate between those that are unequivocally benign and those that are overtly malignant in his comment on papillary tumors that “are not really malignant but they have clinical features that stand on the border of malignancy.” He was also likely the first to clearly distinguish between serous and mucinous tumors and wrote on pseudomyxoma peritonei amongst other topics within the field of ovarian neoplasia. In 1929 Dr. Howard C. Taylor of New York expanded on Pfannensteil’s concept of tumors intermediate in behavior between benign and malignant (24). Three years later he authored another important paper on
spontaneous regression of the peritoneal implants of serous ovarian tumors (25),
and a career-long interest in “borderline” ovarian tumors is exemplified by the fact
that 30 years later he wrote another significant contribution on the topic (26).

The waning years of the nineteenth century saw the emergence of a second
famous eponymous ovarian tumor, the Brenner tumor (27). Dr. William B. Ober’s
masterful telling of the story of the Brenner tumor (28) is recommended reading as
is Dr. Harold Speert's consideration of it (29). Despite the priority of other
workers it was Fritz Brenner who became immortalized because of his 1907 paper
and the fact that when Robert Meyer (see below) clearly distinguished the Brenner
tumor from the granulosa cell tumor in 1932 (30) he perpetuated the association of
Brenner's name with the tumor Brenner had described 25 years earlier. Brenner’s
paper “Das oophoroma Folliculare” concerned three cases, two of them autopsy
findings, and the descriptions and illustrations leave no doubt as to the nature of
the tumors (27). Brenner had thought his tumor arose from the Graafian follicle,
the same explanation for the granulosa cell tumor (folliculoma) described by von
Kahlden in 1895 (31). In Germany this led to the two folliculomas (of Brenner and
von Kahlden) being qualified as “Al Typhus Brenner” and “Al Typhus von
Kahlden” until Meyer’s classic paper of 1932. The eminent British pathologists
Drs. Harold Fox and Fred Langley (33) in their book (one of many strengths of
which is good consideration of the historical background to the entities they
discuss) credit the great Rokitansky with perhaps first describing what we now know as the granulosa cell tumor. It was not until 1895, however, that von Kahlden (31) described the histologic features of this tumor in detail and the designation “granulosa cell tumor” was only introduced in 1914 by von Werdt (34). In addition to being the subject of many papers, this tumor has been the subject of two monographs, one by Schiller in 1934 (35) and another by Varangot in 1937 (36).

This brings us to Dr. Robert Meyer truly one of the titans of ovarian pathology (32). Apart from his clearly delineating the Brenner tumor as a distinctive neoplasm separate from other tumors with an insular pattern such as the granulosa cell tumor he elaborated on the various morphologic features of the granulosa cell tumor to a degree greater than before. Meyer also introduced the term “arrhenoblastoma” (37) for the often masculinizing tumor known most widely now as Sertoli-Leydig cell tumor. Although tumors that can retrospectively be recognized as Sertoli-Leydig cell tumors are present in the older literature, Meyer’s work on these neoplasms brought knowledge of them to a new level. His subclassification of them into well differentiated, intermediate, and poorly differentiated forms remains the major subcategorization of these tumors that is of practical importance.
One can discern examples of dysgerminoma in the older literature under the designation "medullary carcinoma", but they had been first referred to in appreciable detail by Chevassu in his famous thesis describing the seminoma and described in detail as an ovarian neoplasm by another French investigator, Marcel Chenot, in 1911 (38) and by Pierre Masson (39) a year later, although both the latter authors used the seminoma designation. It was Meyer who coined the term "disgerminoma", the change to dysgerminoma being made soon after.

In 1925 Dr. John Sampson, referred to as "the Father of Endometriosis", described the association of ovarian endometriosis with carcinoma resembling the common endometrial carcinoma and delineated the nature of ovarian endometriotic cysts. His career has been elegantly reviewed elsewhere quite recently (40).

The Danish pathologist Dr. Gunnar Teilum contributed significantly to knowledge concerning both sex cord tumors and germ cell tumors but it is for his work on one tumor in the latter family that he will be most remembered. His observations elucidating the germ cell nature of the yolk sac tumor of the ovary (and elsewhere) represents one of the most astute in the study of human neoplasia. In 1944 he wrote the first of many English language papers on this neoplasm (41) and over the ensuing years (42), culminating in his book published in 1971 (43), established the yolk sac tumor (which he referred to as “endodermal sinus tumor”) as a distinctive variant of primitive germ cell tumor and described most of its now
well known patterns. In 1939, Dr. Walter Schiller, an Austrian pathologist who had immigrated to the United States (44), had reported a series of ovarian tumors under the designation “mesonephroma ovarii (45).” It became slowly apparent that within it were cases we now recognize as clear cell carcinoma (see below) and yolk sac tumor. In the last decade of his life Teilum wrote papers on the localization of alpha-fetoprotein in the tumor cells (46) and relating the morphology of the tumor to alpha-fetoprotein production (47). In one of the most striking examples of the benefit of comparative morphology, Teilum had noted that the papillary structures of the yolk sac tumor morphologically resembled the endodermal sinuses of the rat placenta. This was the result of a visit to an embryologist in Paris who showed him slides of the rat placenta. The placental structures in the rat had been designated “endodermal sinuses” by M. Duval in the 19th century and were known to be of yolk sac origin, resulting in Teilum's application of the now famous eponym “Schiller-Duval bodies” for these structures in yolk sac tumors. Tributes to Dr. Teilum, one of which lists all his papers, are available (48,49).

A neoplasm related to the yolk sac tumor is the polyembryoma, containing as it does yolk sac epithelium as a component of the embryoid bodies, myriads of which constitute the polyembryoma. In 1939 a French histologist, Albert Peyron (50), described these enigmatic and picturesque structures within a testicular
teratoma and polyembryomas were subsequently described in the ovary and even at extragonadal sites. They arguably are the most photogenic of all gonadal tumors.

Dr. Lars Santesson of Sweden (51) was a major figure in the International Federation of Gynecology and Obstetrics (FIGO) and in conjunction with the pioneering gynecologic oncologist Professor Hans L. Kottmeier, had a major influence in the development of the modern classification of ovarian tumors. Santesson, with Kottmeier, was responsible for the organization of a meeting at the Radiumhemmet in Stockholm in August 1961, which produced the first classification of the surface epithelial stromal tumors which closely approaches that used today. Others participating were: Dr. Lauren V. Ackerman, Dr. Georg Gricouroff, Dr. H. Hamperl, Dr. Arthur T. Hertig, Dr. J.H. Muller, Dr. Claud W. Taylor, Dr. Herbert C. Taylor, and Dr. Teilum. Dr. Santesson reported on 660 primary ovarian cancers that had been treated at the Radiumhemmet through 1940 and divided them into the serous, mucinous, and endometrioid groups, this being the first large series in which endometrioid carcinomas were separately categorized (52). His observations provided the framework for the proposal of that conference that endometrioid tumors be considered a separate entity and that an association with endometriosis, although common, was not required for the diagnosis as it had generally been until then. Endometrioid carcinomas quickly became established as
a separate entity (53). Santesson and Kottmeier introduced the low malignant potential terminology (a well-known synonym for the borderline tumor group). In the words of Dr. Robert E. Scully “he (Santesson) can be truly called the father of the modern classification of the epithelial tumors of the ovary” (Scully RE, personal communication, January 2004). Santesson also contributed excellent papers on dysgerminoma (54) and yolk sac tumor (55).

Santesson was one of those to first appreciate that clear cell carcinoma, (or as it was still being called at that time, mesonephroma), was related to the endometrioid carcinoma, his belief being clearly stated by Kottmeier in a review of ovarian tumors (56). The occurrence of clear cells in ovarian adenocarcinomas began to receive attention (57) soon after Schiller’s paper on "mesonephroma" and although the histogenesis was debated, a mesonephric origin was still favored until the late 1950s when De Santo and colleagues (58) indicated a probable origin from mullerian epithelium. Subsequently Dr. Laman A. Gray (59) put forth a similar opinion. The matter was put firmly to rest in 1967 when Scully and Barlow (60) unequivocally demonstrated a mullerian origin. The existence of true mesonephric ovarian neoplasms (wolffian tumors) was sporadically acknowledged by various earlier workers, and by the time this writer began working with Dr. Scully in July 1979 it was clear that Dr. Scully had a clear opinion on their morphology based, in part, on earlier work on broad ligament examples and diagnosed ovarian examples
of wolffian tumors sporadically as these rare tumors were submitted in consultation. Dr. Peter Hughesdon reported the first series in 1982 (61) and Dr. Scully’s experience was reported a year later (62).

A major development in ovarian tumor pathology was the publication of the World Health Organization (WHO) classification of ovarian tumors in 1973 (63). This was the culmination of work carried out over more than a decade by numerous major figures in the field of gonadal tumor pathology. That undertaking began when the FIGO Ovarian Cancer Committee subdivided the surface epithelial tumors of the ovary into five major categories based on cell type, subdividing each category into three groups, benign, malignant, and an intermediate group designated “atypical proliferating tumors of low-malignant potential.” In 1956-1957 the WHO requested that its cancer committee classify tumors of various sites including the ovary. Dr. Humberto Torloni, editor of the series of WHO tumor classifications, was contacted by FIGO, which requested a joint meeting of representatives of its committee and the ovarian WHO group. At that meeting, held in Geneva in 1963, Dr. H. Hamperl of Germany was Chairman of the FIGO group; Dr. Santesson of Sweden, Dr. Teilum of Denmark, and Dr. Gricouroff of France were additional members of both committees and Dr. Fred Langley, Dr. Antonio Luisi, and Dr. Robert Scully were members of the WHO group. Dr.
Hamperl and his associates urged the members of the WHO committee to accept with no more than minor modifications the FIGO classification of surface epithelial tumors to avoid the chaos that might result if it were to be substantially altered. Dr. Scully subsequently served as co-chairman of the further meetings of the WHO group along with Professor S.F. Serov of Russia. Dr. Mikhail Glazunov, a Russian pathologist, who had written a book on ovarian tumors, had been appointed chairman of the WHO group, but died suddenly before the first meeting and was succeeded by his younger associate, Professor Serov, whose primary interest had been bone and soft tissue tumors. The subsequent meeting of the WHO ovarian group was held in St. Petersburg (at the time Leningrad) in 1965. Slides were circulated amongst the various participants and discussed at a series of meetings that took place between 1967 and 1971. Finally the classification (and selected cases) were reviewed by a second small group of pathologists, and the final classification was adopted and published in 1973 as one of the familiar “blue books” of the International Histologic Classification of tumor publications. Major differences between the FIGO and the WHO dedications were that the latter preferred by a very close vote "tumors of borderline malignancy" over "tumors of low malignant potential", and also classified all other ovarian tumors and tumor-
like lesions. The classification was used in the second series fascicle "Tumors of the Ovary and Maldeveloped Gonads" authored by Dr. Scully (64) and the excellent British contribution of Drs. Harold Fox and Fred A. Langley, "Tumours of the Ovary" published in 1976 (33).

Dr. Robert Scully's work in the WHO meeting having just been considered it is now appropriate to conclude these notes with comments on other contributions of this remarkable investigator, who with Dr. Meyer, in my opinion is one of the two above all others who dominate the history of ovarian tumors.

A lifelong interest in functioning tumors of the ovary was stimulated by Dr. Scully's collaboration with a gynecologist, Dr. John McLean Morris, on the book “Endocrine Pathology of the Ovary,” published in 1958 (65). A year before Drs. Scully and Morris had drawn attention to the phenomenon whereby tumors that are not normally associated with endocrine manifestations sometimes have such features because of the development of lutein cells in their stroma (66). They introduced the term “ovarian tumors with functioning stroma”, a now familiar term. Dr. Scully rapidly became known as a consultant for unusual cases in ovarian pathology and developed a remarkable collection which lent itself to many important investigations by him and various fortunate collaborators over the years. Although others share the stage with Dr. Scully in the author listing of these many papers, all will acknowledge that he was the individual who recognized the various
entities, including such now well-known neoplasms as the sclerosing stromal
tumor, sex cord tumor with annular tubules, juvenile granulosa cell tumor, strumal
carcinoid, small cell carcinoma of hypercalcemic type, and retiform Sertoli-Leydig
cell tumor. Dr. Scully's contributions are legion and the reader is referred to a
detailed appreciation of him for more detailed comments than space allows here
(67). One need only review his classic 1970 paper on gonadoblastoma (68) to get
some sense of the remarkable diligence and painstaking care that he took with his
academic contributions, just as he did with his review of individual cases. To have
worked with him on some of these, and on his second ovary fascicle (69) (also co-
authored by Dr. Philip B. Clement of Vancouver, Canada, one of Dr. Scully's most
illustrious and distinguished trainees), has been a treat of the highest order and
those who have had the good fortune to spend any significant amount of time
working closely with Dr. Scully will feel firm that he is truly a giant not just of
gynecologic pathology but of pathology in general given his remarkable
constellation of talents.

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