

Good morning everybody. I'm Juan Rosai, or better the digital image of Juan Rosai whose body is many miles away from here. I wish I was here with my friends, but circumstances beyond my control prevent me from doing this. You will have to do with my image and the images that you will see in a minute in this screen. Let me first thank Dr. Rachel Factor the director of the course for the kind invitation and Dr. Mary Bronner the chief of surgical pathology.

The task that they gave me for the meeting was that of discussing the intraductal proliferative lesions of the breast, and that is what I'm going to do. But a disclaimer first. If you expect me to show you to go over the minute criteria that I use to distinguish one proliferative type of breast tissue from the other, you will be disappointed. Those you can find in many textbooks and monographs, some of which I will show. I'm going to discuss instead this field from a holistic point of view, from a historic point of view, describing how the changes and the constant change over the years, who are the main players, what influence they have in these changes, where we are now, and what can we expect in the future.

Well these lesions have been around for a long time and the various names that have been given to them is a good reflection on how difficult, how mysterious, how challenging they were to the pathologists who examined them. Here are some of the terms that have been used over the years: precancerous, premalignant, precursor, preinvasive, atypical hyperplasia, intraepithelial carcinoma, and carcinoma in situ. Some of them indicated by the prefix pre, pre, pre, pre to find that they are thought to be the lesions that can evolve or that will evolve into invasive carcinoma, or in the case of the last two, they are carcinomas already despite the fact that they do not invade.

Just as an example of how difficult and abstruse the terms could be and the significance would be, let me quote you from Dr. Fred Stewart, at the time the chief of pathology at Memorial Sloan Kettering Cancer Center and regarded at the time as the best surgical pathologist of his generation. In the fascicle that he authored on tumors of the breast as part of the first series of the famous AFIP fascicles published in 1950, on the section dealing with precancerous lesions he had this to say: (quoted on slide)

And just to be sure that you didn't miss the point, he says: (quoted on slide)

The fact is that these conditions do exist and the question is how to name them, trying to give them a user terminology that would reflect their nature and potential, so we call them precancerous, premalignant, and precursor, etc.

In this memoire written by the great pathologist, Leopold Koss, who by the way died a few months ago in his loved New York City, his reminiscences, among them some related to cytology and the nomenclature in cytology. He says: (quote on slide)

And this is the paper that Koss was referring to, it's entitled "Histologic study on atypical epithelium in the portio that is the exocervix and the Innerflache (inner surface), the endocervical canal of the cervix," published in 1908.

Again, on the basis of Dr. Koss' information, we learn that the first one to use a third carcinoma in situ was this team, by two pathologists from Vienna, Schottlaender and Kermauner. But the

person who really put carcinoma in situ on the map and made it a household word, especially for American pathologists, was the man you see here, Albert Broders, from the Mayo Clinic. He wrote a paper that should be considered a classic in the field entitled "carcinoma in situ contrasted with benign penetrating epithelium". He was published in 1932 in the journal of the American Medical Association and he did it with the identification of carcinoma in situ in a particular site, the lip, but later on he applied the same system and the same criteria to lesions in several other organs. The definition he had for what he considered in situ was very good, very clear, very concise. He said: (quoted on slide) Just perfect.

Not everybody among gynecologists and among pathologists liked this term; carcinoma for lesions that were not invasive, to the point that in 1952 a debate was organized, almost a contest, between the early champions of the carcinoma theory or the carcinoma terminology, and the champion of the benign or non-carcinomatous nomenclature. This debate took place in Minnesota and the two adversaries were Arthur Hertig and John McKelvey.

Here is Arthur Hertig, at the time the chief of pathology at Harvard Medical School doing his favorite thing, studying a human embryo; that was his main field of interest, but he also knew a few things about carcinoma of the female genital tract. And in the discussion of his paper, he concludes that carcinoma in situ is the preinvasive phase of invasive carcinoma. Why? Because he says carcinoma in situ is coexistent with invasive carcinoma, it precedes invasive carcinoma, it is followed by invasive carcinoma, and it resembles invasive carcinoma. You know it is like saying it looks like a dog, it barks like a dog, it runs like a dog, it must be a dog! His conclusion was carcinoma in situ is the preinvasive stage of squamous cell carcinoma of the cervix, period.

Dr. McKelvey who was the chairman of gynecology at the University of Minnesota Medical School felt otherwise. He said: (quoted on slide)

He added, on conclusion (quoted on slide)

What happened after this article was written, to use a political type of analogy, what can be lost? A healthy one. A healthy one maybe because he used or employed scientific objective criteria to decide on the relationship between CIS and invasive carcinoma, whereas McKelvey as a clinician was more interested in the effect that those words would have on the patient. Whatever the reason may have been, from there on the term carcinoma in situ entered in the pathology lexicon, and it became known to everybody in pathology, and gynecology, and in cytopathology, either as carcinoma in situ or as its abbreviation CIS.

The next episode or the next link in this chain was provided by George Papanicolau, the legendary cytologist at the New York Hospital Cornell University who used the carcinoma in situ for lesions having the cytologic features of cancer as you see here, and then he asked the question, 'if we call these carcinoma in situ, how shall we call lesions or preparation that show atypical cells, which are atypical alright, but not enough to be called carcinoma?' Again, to quote him: (quoted on slide)

He commented that: (quoted on slide)

And the person who came up with that term, dysplasia, apparently was this doctor, William Ober, a pathologist from New Jersey who attended the meetings run by Papanicolau, and suggested that dysplasia may be a good term to indicate the morphology and the potential of these intermediate lesions. Dr. Ober was an interesting fellow. Apparently he was a good pathologist, and wrote some very good papers on mesenchymal tumors of the uterus, including a very nice classification of mixed Mullerian tumors.

But he was also interested in more, how shall I say, other interesting subjects of different kinds, always with a comic sort of undertone and a light prurient taste, for instance, some of his papers were the ones you see here:

(quoted on slide) You will remember the complex of Ghon of tuberculosis.

(quoted on slide) I'm sure you remember the striae of Zhan in thrombi.

This is a good one: (quoted on slide)...

And one more on Leydig, Sertoli, and Reinke: Three Anatomists Who Were On The Ball. Written by him and by an imaginary co-author; this person did not exist, Che Sciagura, means in Italian, what a calamity. And that was one of the many jokes that Ober played on pathology. He then founded a society called the Meconium Society that will give a Gold Medal to the most important representatives.

Well the fact is that with the contribution of the pathologists and gynecologists from Europe and from the States, the term dysplasia was added to that of carcinoma in situ and later on the term dysplasia was further subdivided into mild, moderate, and severe depending on the degree of atypia. And this is the scheme that many of us, including myself, learned and used when entering pathology in the 60s.

But then Ralph Richart came, a gynecologist/pathologist at Cornell Weill University in New York City, who after studying the problem, he made a series of very important conclusions. He said (quoted on slide)

And so CIN was born, cervical intraepithelial neoplasia, CIN as the abbreviation, three grades of increasing atypia.

Some people liked these very much and that included Buckley, Butler, and Fox, three British pathologists and gynecologists who wrote a paper in 1992 which pushes even better the concepts of CIN that the original purported. They liked it for the following reason, because (quoted on slide)

II. Because (quoted on slide)

III. (quoted on slide)

So what do we have now? We have at least three different systems for naming and for grading these various type of lesions. The traditional one as used for the cervix as we have shown, that of dysplasia, mild, moderate, and severe, to carcinoma in situ. That which is applied to the mucosa immediately above the cervix, that is endometrium, in which the terminology is still that of hyperplasia, atypical hyperplasia, carcinoma in situ. And finally, the system in which the generic term of intraepithelial neoplasia is used and has been applied somewhat successfully in several sites. Okay?

Now what about a breast? Which here you see a very nice example of an intraductal proliferative lesion. What system should we apply to this?

When talking about breast we can certainly not ignore a man who has been one of the most astute observers of this organ, and that is Dr. John Azzopardi, a pathologist originally from Malta, who spent most of his professional life at the Hammersmith Hospital in London, having a nice dinner with Vincenzo Eusebi, an Italian pathologist also well known for his studies in breast disease, his wife, and myself.

Dr. Azzopardi was an outstanding pathologist, who wrote about tumors in many organs, in many sites, but his fame is actually derived from this monograph that he wrote as part of the series on Major Problems in Pathology. The book was entitled "Problems in Breast Pathology".

In this work, he maintained that there is not a progressive worsening of the condition from hyperplasia to carcinoma in situ, but rather that one is dealing with two different diseases that do not relate to each other; one benign hyperplasia and the other malignant carcinoma in situ.

He stated (quoted on slide)

And he concluded by stating that (quoted on slide)

So how did the other breast pathologists react to this proposal? They didn't seem to like it very well in the sense that if you look at the standard textbooks written these days, such as Rosen's Breast Pathology and David Page "Diagnostic Histopathology of the Breast" and many articles, you see that this scheme is the one that prevailed, basically the belief that we are dealing with a group of diseases that are not related to each other, going all the way from mild hyperplasia to moderate or florid to atypical hyperplasia and eventually progress into carcinoma in situ.

So this is the system or nomenclature that would have prevailed, at least in the United States, and the one that I learned when I started in my pathology training in the 60s. Three categories of proliferative ductal disease of the breast: (quoted on slide)

Naturally, the most important aspect of these classifications or systems is their ability to indicate if there is an increased risk for the development of carcinoma in the patients harboring them, and if so, what is the risk?

Several papers were written on the subject, the most important, and the most widely quoted are the ones that came from Vanderbilt, having David Page as the senior pathologist and William

Dupont as the senior epidemiologist. 'Atypical Hyperplastic Lesions of the Female Breast, A Long-Term Follow-Up Study', and the risk factors that derive from an aberration of that group of patients.

What both papers say is that there is an increased risk for the development of carcinoma, depending on the nature of the preliminary lesion. This increased risk is about two for usual ductal hyperplasia, 4.5 to 5 for atypical ductal hyperplasia, and 10 times the risk for ductal carcinoma in situ. A very sharp and progressive separation, very good, maybe too good to be true.

In 1990, the Stout Society of Surgical Pathology decided to have, as a companion meeting of USCAP, a half day meeting on breast cancer, which was moderated by my good colleague and friend, Louis Dehner, who asked me to begin the proceedings by giving a sort of introduction on borderline epithelial lesions of the breast, tenet speakers being David Page, Peter Rosen, Bob McDivitt, and Dr. Haagensen.

When I was given this task and I started preparing for it, I became concerned because I had very little to say that was either original or not already known by the pathologist community. And then I had an idea. I wanted to see what kind of relation these lesions had with each other as judged by the diagnosis made by the pathologist; in other words, a concordance study.

Dr. John Chan from Hong Kong was visiting the department at the time and I asked him to go to the files, the Yale files, and to get for me as many cases as he could find of lesions belonging to this general category. He did it very quickly and very efficiently, and what I did was select one slide from each case and one area which I circled from each slide, and I then called five pathologists, noted authorities of breast pathology; Darryl Carter from Yale, Bob Fechner from the University of Virginia, Richard Kempson from Stanford, David Page from Vanderbilt, and Peter Rosen from Memorial and asked them 'you look at these slides and you make a diagnosis on the lesion that is here within the circle of the single slide, and you tell me whether you think the diagnosis is hyperplasia, atypical hyperplasia, or carcinoma in situ.' I am very, very grateful to them because they are all agreed to do it and this is the result.

A B C D and E are the five pathologists who remain unnamed. In the column you have ten different types of cases of ductal proliferative lesion and from L1 to L7 lesions of the lobular type, which we will not discuss on this occasion. H in green is hyperplasia, AH in yellow is atypical hyperplasia, CIS in red is carcinoma in situ. What did we find? We found #1 that there was not a single case, not one, in which all five pathologists agreed on the diagnosis. We found that there were only three cases in which four of the five pathologists agreed to the diagnosis. We also found that the diagnosis given to the specimen ranged all the way from hyperplasia without atypia all the way to carcinoma in situ depending on who was the pathologist who saw it. Finally, we discovered as we had suspected for a long time that there are some pathologists who are more malignant than others. Take for instance, pathologist A, for whom 9 cases were carcinoma in situ; all the others were atypical hyperplasia, to where not a single case was called usual hyperplasia. The other extreme is presented by pathologist E, who did not have a single case of carcinoma in situ, and only three cases of atypical hyperplasia. All the other cases he thought were usual hyperplasia. So obviously there was a problem here.

But there were reflections on the fact that a similar problem existed in other organs and then a proposal had been made, to begin with the cervix, which I have shown to you, of changing the diagnostic terminology to one that would reflect the natural history of these lesions, and that is intraepithelial neoplasia and abbreviated as IEN of which the example of what I described in the cervix, in the oral cavity, or in the prostate PIN, in the vulva VIN, in the pancreas PanIn, and in many others.

So we ask, if this has been proposed and seems to be working very well in so many organs, why not in the breast in which the problem also exists? So I ask, what about calling these lesions generically mammary intraepithelial neoplasia or MIN? I have to acknowledge the fact that this proposal did not go very well among pathologists, with one outstanding exception, Fattaneh Tavassoli, a pathologist who at the time was working at the AFIP, who brought the concept with the right terminologic distinction, where as I had put together all the lobular and ductal lesions into the category MIN, she divided them into ductal type or DIN and the lobular type LIN. We will be discussing again only the ductal ones.

She was asked at the time as a result of the seminal papers that she had written on the condition, and very good papers they were, to be the main volume editor of the series from the WHO on the pathology of tumors. And what she did was combine data with tumors of the breast and female genital organs in which she pushed for her classification, the declassification, and compared them with the terms used in the traditional classification and for the reasons that were already given, she obviously preferred this one.

Again, the proposal was not accepted very easily. Regarding my concordance study, Stuart Schnitt decided to do a similar study, which he published in the American Journal of Surgical Pathology, a series of ductal proliferative lesions and he asked a bunch of breast pathologists to divide them into hyperplasia, atypical hyperplasia, and carcinoma in situ as I had done.

Now, if you look at the pathologists that I used for the study and those that Schnitt used for his, some interesting things become apparent. Fechner, Kempson, and Page stayed. Carter and Rosen disappeared for some reason, and three new players were added, Schnitt himself, Connolly, his associate, and Tavassoli. What were the results of the study?

Six of the six agreed in 58%, 5 or more agreed in 71% of the cases, 4 or more in 92% of the cases. Good results, certainly better than those from my study, but perhaps not good enough.

So again a call was made to keep studying these ductal lesions to see whether the combination of morphologic, immunohistochemical, genetic, and molecular studies could define them better. Papers appeared on the subject from England, Sarah Pinder, and Ian Ellis of the Elston and Ellis classification of breast cancer.

Whole monographs were devoted to the subject, such as this one, edited by Ellis, Eusebi, and Schnitt.

Atypical hyperplasia of the breast from the New England Journal of Medicine, as late as January 1, 2015; as you can see I keep up with the literature.

And during this time, Tavassoli kept writing articles trying to convince people about ductal intraepithelial neoplasia. She wrote in pathology journals, in breast critical journals, and in monographs.

So what happened with her continuing proposal? Ten years after this book had been written on the WHO having her as the main editor, it was decided by the WHO organizer to have again another edition, 10 years later, this time devoted only to the breast and being edited by Lakhani, Ellis, Schnitt, Hoon, and van de Vijver.

This is the 2003 edition and this is the 2012 edition, and they are very different from each other regarding the DIN concept; with here as you saw was heavily discussed and illustrated; whereas here it was essentially dismissed.

In the chapter on intraductal proliferative lesions, which you see after introduction and overview, terms that correspond to the traditional terminology; usual ductal hyperplasia, atypical ductal hyperplasia, ductal carcinoma in situ.

And criteria are provided how to tell apart these three terms, again in the traditional classification. What about the Tavassoli DIN proposal? This is what was stated in the 2012 edition of the WHO book. (quoted on slide)

And why, why was that? What did they have against the DIN terminology? They thought that no new diagnostic criteria were used. They felt that this new classification would not improve an inter-observer variability, and more important that they have different molecular profiles, although there were cases with added molecular analysis should help to improve upon the traditional classification, not changing it to the DIN classification, but improving the traditional one.

And there was in this fascicle a rather new view of the significance of usual ductal hyperplasia in the sense that from a molecular standpoint, it was found that the characteristic genetic alterations seen in ADH and low-grade CIS are not found in UDH. Additionally, they found that there are no consistent genetic alterations associated with UDH. It looked like UDH was something different from ADH and CIS.

And a relatively new term appeared entitled the columnar cell lesions. It had been decided, long categorized again by Azzopardi, but only now acquired a popularity which it still maintains.

What are they within this genetic term? I am sure you have seen them, this terminology being increasingly used. Columnar cell change, columnar cell hyperplasia, and flat epithelial atypia. How do these relate to each other? This was the proposal: Columnar cell change and columnar cell hyperplasia depending on whether you have one row or a stratified epithelium, and each one of them should be divided into those with atypia and without it. And it will say those that have

atypia, we will call that flat epithelial atypia; those that don't have atypia, we have the columnar cell change or hyperplasia.

Which is slightly different from what Ellis proposed in 2010. He said (quoted on slide) So no atypia, columnar; atypia, flat epithelial.

Schematically this is what they are proposing. Traditionally it was felt that UDH could progress to ADH which could progress to CIS and they were all linked to each other from a biologic standpoint, whereas columnar cell change and flat epithelial atypia was either ignored or regarded as a dead end type of lesion, which never progressed to cancer.

In the current view, UDH has been declassified. It is now the one regarded as a dead end lesion, whereas in the columnar cell lesions, flat epithelial atypia are the ones that are thought to progress to ADH and from there to CIS.

What else I had found of interest from a genetic molecular standpoint in this year's, one, the genetic alterations have been found in normal breast tissue away from the carcinoma, and the genetic alterations have been seen in the mammary stroma in patients with malignancy.

So here is just a statement but paying homage to Dr. Fred Stewart who said in 1950 (quoted on slide) and that seems to be indeed the case.

Now in 2003, you will remember it was stated (quoted on slide) Most of this can be said today, so there is still lots of work to do.

Let me finish now by showing you some representative examples of the lesions we have been talking about, after all I am a pathologist, this is a pathology audience, so I think we should show some pathology.

What do you think this lesion represents, hyperplasia, atypical ductal hyperplasia, or carcinoma in situ? Those who think that this is benign ductal hyperplasia, raise your hand. Okay. Those who think that this is atypical ductal hyperplasia, raise your hand. Okay. Those who think that this is cancer, raise your hand. Very few. The majority is right. This is usual or florid ductal hyperplasia.

What about this lesion? Usual hyperplasia, your hands? Atypical ductal hyperplasia? Carcinoma in situ? Very good. It is difficult, but I think that most people, including Azzopardi and the others who have called this carcinoma in situ because it has what he called trabecular bars, rather rigid columns in which the cells are arranged perpendicular to the major axis of those columns.

What about this? Hyperplasia, atypical hyperplasia, carcinoma in situ? I find this very difficult. I am debating or struggling between atypical hyperplasia and carcinoma in situ, but I am slightly on the side of carcinoma in situ because of the regular shape of the spaces and the presence of a substance that looks like necrotic tissue, interlobar, something that again was first pointed out by Azzopardi.



Here is what is being called flat epithelial atypia and columnar hyperplasia.

And this is what people who now regard as flat epithelial atypia which Dr. Azzopardi coined the term clinging carcinoma low grade. And here is a valid observation by him, the presence of calcification in these lesions is of importance, not only the presence but the location. If they are in the stroma or within the lumen, they are of no great importance. When they are, like in this instance, between the epithelium and the underlying stroma, you better look at this lesion carefully, because it is likely to be either a columnar/flat epithelial atypia, or a low-grade carcinoma in situ.

So this is the end of my presentation. Thank you very much for your attention.