Review Article

Cancer-associated genodermatoses: a personal history


Abstract: Cancer-associated genodermatoses are a group of genetic disorders inherited in an autosomal-dominant fashion in which unique cutaneous findings are a reliable marker for the risk of developing internal malignancies. The historical, clinical and dermatopathological aspects of basal cell nevus syndrome, Muir–Torre syndrome, Cowden syndrome, Carney complex and Birt–Hogg–Dubé syndrome are reviewed in a personal and informal fashion. The latest advances in the molecular genetics of the disorders are also summarized.

Introduction

David Bickers and I are of roughly the same age and our paths have crossed many times over the years. Our special interest is nourishing German–American interactions in dermatology. As our scientific interests have never overlapped, I instead offer, for David’s 65th birthday, a personal recollection of the progress which has been made in bringing cancer-associated genodermatoses from early warning signs for systemic malignancies to extensively researched genetic disorders, whose responsible genes have given important insights into the molecular biology of cancer. My two special interests have been genodermatoses and dermatopathology – not two subjects one instinctively links – but I will also try to show how in this group of disorders they fit together nicely.

Another link, which David and I have, is Columbia University. I certainly would not be here today but for the fact that a red-headed Alabamian grade school teacher and a young German law student both lived at International House 1 year in the 1930s while pursuing advanced degrees at Columbia. The two met, got married, and I am their only child. My other Columbia link is through the man who stimulated my interest in clinical genetics, Bob Gorlin. He in turn was introduced to clinical genetics by a dermatologist, Helen Ollendorff Curth, a long-time clinical faculty member at Columbia, who was an international expert on acanthosis nigricans.

Why bother?

As I have lectured across the USA and Europe about cancer-associated genodermatoses over the past 30 years, the almost invariable question is ‘Why bother with such rare diseases?’. One of the great attractions of dermatology for me was the possibility to walk into a room, glance at a patient and make a pronouncement such as ‘You ought to have your thyroid checked; you have an increased risk of a medullary thyroid carcinoma.’ In many instances, cutaneous findings precede systemic tumors by many years and the possibility for either careful monitoring, prophylactic treatment or genetic counselling of relatives at risk is available. In addition, it has been clear since the days of Warthin (1) a century ago that familial cancer has the potential to offer insights into sporadic cancer. In no field has this played out to be more true than in
cancer-associated genodermatoses. As a dermatopathologist, one fascinating aspect is that multiple cutaneous tumors, usually adnexal neoplasms, often indicate a genodermatosis, while a solitary but microscopically identical lesion is of little significance (2).

**Basal cell nevus syndrome**

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<tr>
<th>Abbreviation</th>
<th>BCNS</th>
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<td>OMIM</td>
<td>109400</td>
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<tr>
<td>Gene</td>
<td>PTCH at 9q22.3</td>
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<tr>
<td>Cutaneous findings</td>
<td>Multiple basal cell carcinomas, palmo-plantar pits</td>
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<tr>
<td>Systemic malignancies</td>
<td>Medulloblastoma, ovarian fibrosarcoma</td>
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<tr>
<td>Other clinical findings</td>
<td>Macrocephaly, odontogenic keratocyst, cardiac fibroma, ovarian fibroma, fetal rhabdomyoma, calcification of falx cerebri</td>
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<tr>
<td>Synonyms</td>
<td>Gorlin syndrome, Gorlin–Goltz syndrome, nevoid basal cell carcinoma syndrome</td>
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My first introduction to basal cell nevus syndrome (BCNS) happened in 1974 as a first year dermatology resident at the University of Minnesota. A delightful lady, M.S. (Fig. 1), was a regular patient of my chairman, Bob Goltz. She was the first patient Bob Gorlin and he had described in their classic paper on BCNS in the *New England Journal of Medicine* in 1960 (3). M.S. has had hundreds of basal cell carcinomas (BCC) removed, most superficial, and was very fussy about allowing residents to work on her. She, for unclear reasons, accepted me, and for the next few years, I had the honour of curetting or excising many of her lesions. She taught me to always listen to the patient, as she could find a new BCC better than any physician. The second patient with BCNS was L.P., who presented in an extraordinary way. Working in a pet shop, he was bitten by a poisonous snake, which had been given to Owen Wangensteen, the revered Chairman of the Department of Surgery at Minnesota. A friend in the store took L.P. to the hospital on his motorcycle and they were involved in an accident. When Bob Gorlin first met L.P., the latter not only had a fractured femur but also a funny-shaped head and lots of skin cancers.

The next lesson I learned was as a junior faculty member in Oklahoma. The residents showed me a 7-year-old boy with a few tiny telangiectatic papules on his fingers. They were disturbingly confident and I was totally confused, offering ‘treated warts’ as a diagnosis. The answer was BCNS – tiny papules in a child with palmar pits and fairly obvious frontal bossing. The residents were so sure because they had been treating the child’s mother, grandmother and great-grandfather for years. In this family, ‘little skin cancers’ were nothing extraordinary, and surely no indication for getting excited.

The relevant dermatopathology question here is – can one see anything microscopically to indicate which BCC are taken from patients with BCNS? The answer was long ‘Yes, lesions from syndrome patients are more likely to calcify.’ This surely has not been my experience and in any case, looking at a patient is a much quicker way to ascertain association. Once the gene had been identified, then this question became more interesting and we will return to it.

A dermatologist was part of the research team that helped identify the *PTCH* gene, a homologue of the *patched* gene in *Drosophila*. Erwin Epstein Jr from UC-SF, a close personal friend of David’s, moved from clinical practice back into the laboratory to associate with a worldwide group of researchers and produce a classic paper in 1996 (4). Since then, the world of *PTCH* has become incredibly complex and linguistically challenging. In a simplified form, *PTCH* encodes a transmembrane protein Ptc, which interacts with Smo protein (from *SMO* or *smoothened* gene) to serve as receptor for the sonic hedgehog signalling molecule Shh (5). When Shh is missing, Ptc suppresses Smo; when Shh binds, Smo is freed from

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*Figure 1. M.S. Gorlin and Goltz's first patient with basal cell nevus syndrome with scars where hundreds of basal cell carcinomas had been removed over the years.*
inhibition with increased signal transduction and activation of target genes. Thus, \textit{PTCH} is, in one sense, a tumor-suppressor gene and \textit{SMOH} is a proto-oncogene. Mutations in both are important in the development of sporadic BCC (6); thus, understanding this rare syndrome has done what I and many others suggested would be possible – given us an insight into the most common human malignancy (7,8).

Returning to the microscopic appearance of the tumors, it became clear in the 1990s that BCC were derived from hair germ in most cases, not from ordinary basal layer keratinocytes. The UC-SF group with Erv Epstein and Phil LeBoit noted that PTCH +/− mice develop follicular neoplasms which resemble trichoblastomas, but when they are exposed to UV or ionizing radiation, the tumors evolve in BCC (9). The human equivalent may well be the infundibulocystic BCC described by Tozawa and Ackerman in 1987 (10), and expanded upon by Walsh and Ackerman a few years later (Fig. 2) (11). They emphasized that any type of BCC could be found in BCNS patients with nodular being most common, but pointed out that when a biopsy was encountered where virtually every infundibulum was associated with a small infundibulocystic BCC, the diagnosis was BCNS – or perhaps in rare cases multiple hereditary infundibulocystic BCC without other features of BCNS (12). A most important parallel clinical point is that 10% of patients with BCNS have absolutely no BCC (13).

A picture is still worth 1000 words. One afternoon a few years ago, I was moonlighting in a dermatology practice in Munich when a bus driver came in. He had BCNS, known in Germany as Gorlin–Goltz-Syndrom and was very impressed that I actually knew Gorlin and Goltz; he soon demanded to see only me, the temporary help. I brought in a picture (Fig. 3) of the three of us together with Mark Allen Everett and after that he was in awe of my knowledge, which had not radically changed. Then, I decided to ask both Bob Goltz and Bob Gorlin how they preferred to have their syndrome named. Bob Gorlin in a modest way said he identified more with BCNS than with any other of his syndromes; in the fourth edition of \textit{Syndromes of the Head and Neck} (14), he used the title Gorlin (nevoid BCC) syndrome. Bob Goltz said he was happy to be associated in any way.

Finally, in contrast to the other syndromes mentioned below, systemic malignancies are not a great problem in BCNS. The main risk is childhood medulloblastomas. The exact risk is hard to determine because medulloblastoma is the most common childhood brain tumor, accounting for about 25% of such lesions (15). Only 3% of all medulloblastomas occur in patients with BCNS, while about 5% of BCNS patients develop medulloblastoma. Returning to the laboratory, the activation of the Shh pathway predisposes neural progenitor cells to develop into medulloblastomas by inactivating the retinoblastoma tumor-suppressor gene (\textit{Rb}) and inducing the proto-oncogene \textit{N-myc} (16). The main clinical factor is that radiation therapy is the treatment of choice for medulloblastoma; often children are irradiated before the diagnosis of BCNS has been made. As the skin of BCNS patients is exquisitely radio-sensitive, such unfortunate individuals often develop thousands of BCC in the radiation fields.

\textit{Figure 2.} Infundibulocystic basal cell carcinoma (photomicrograph courtesy of Peter Soyer, MD, Graz, Austria).

\textit{Figure 3.} Mark Allen Everett, Robert J. Gorlin, Walter Burgdorf, Robert W. Goltz; Albuquerque NM, 1993.
Muir–Torre syndrome

Abbreviation  MTS  
OMIM  158320  
Genes  Mismatch repair genes  
MSH2 at 2p22–p21  
MLH1 at 3p21.3  
Cutaneous findings  Multiple sebaceous tumors (especially cystic sebaceous tumors), multiple keratoacanthomas  
Systemic malignancies  Carcinomas of colon, endometrium, ovary and many other organs  
Synonyms  Hereditary non-polyposis colorectal cancer, Lynch syndrome, cancer family syndrome  

In 1979, Aly Fahmy, a general pathologist at the Oklahoma City Veterans Administration Hospital, asked me to come by and look at some slides which he and his colleague Jan Pitha found interesting. They were from a patient whom I already had seen in clinic; R.S. had had lots of funny cutaneous tumors (Fig. 4), but I knew little else about him. Aly and Jan were way ahead of me. In those days, before computers, they had little index cards containing all the previous pathological diagnoses on each patient and R.S.’s card was most interesting. In addition to keratoacanthomas and sebaceous tumors, he had already multiple primary gastrointestinal carcinomas at a relatively early age. Dr Elson B. Helwig at the Armed Forces Institute of Pathology had agreed that they were all primary tumors. R.S. died several years later from radiation-induced pneumonia, but was tumor-free after having nine primary systemic malignancies over more than a decade.

I was still in the dark, but Aly and Jan knew the answer – Muir–Torre syndrome (MTS). Douglas Torre, one of the pioneers in dermatological cryotherapy and a private practitioner in Manhattan, had presented a patient at the New York Dermatologic Society with several gastrointestinal tumors, prolonged survival and a collection of peculiar cutaneous tumors including an ‘epidermoid cyst with squamous cell carcinoma’ and multiple poorly defined sebaceous tumors (17). In the interval between Torre’s presentation and the publication of the meeting proceedings in the Archives of Dermatology, E. G. Muir, a surgeon, and his colleagues from London described a Maltese patient with multiple keratoacanthomas, sebaceous neoplasms and gastrointestinal tumors (18). Dr Helwig and his fellow Dave Rulon, a dermatopathologist, had also recently written about the association of sebaceous neoplasms and visceral tumors but had lacked sufficient information to diagnose our case (19).

About this time, two exogenous factors forced me to become further interested in MTS. First, my chairman, Mark Allen Everett (also shown in Fig. 3), had agreed to arrange a dermatopathology meeting in New Orleans and simply told me I would be presenting ‘something’ there. I asked Aly if he would help me and he did. We identified two other veterans with multiple malignancies, and I then had a ‘moment of understanding’, recalling a patient I had presented to Hermann Pinkus a few months before. J.M. was a young lady with a personal history of thyroid cancer, a family history of gastrointestinal cancer and a single red papule on her thigh. The lesion was a small basaloid tumor with a few sebaceous cells scattered throughout; Pinkus had been stumped but identified the sebocytes. She became our fourth MTS patient. All fit the pattern – multiple systemic tumors, early onset and relatively long survival. After our paper on R.S. written by Bob Schosser, our dermatopathology fellow, had been accepted by Cancer (20), Wolf-Ingo Worret, a young German visiting dermatopathologist, helped us write up all four patients in the German literature. Because of the vagaries of publishing schedules, the paper in Hautarzt appeared first with the initial German-language mention of MTS (21).

Next, Henry Lynch asked me to write a chapter in a book, he and Ramon Fusaro were editing, entitled Cancer-associated Genodermatoses. My assignment was ‘Dermatopathologic aspects of cancer-associated genodermatoses’ (22). This chapter in 1982 convinced me that I was not wasting my time trying to combine dermatopathology and clinical genetics. I had the opportunity to learn from another master

Figure 4. R.S. My first patient with Muir–Torre syndrome; notice the sebaceous carcinoma of the chin, as well as the typical paranasal lesions and scars.
clinician-geneticist, Henry T. Lynch of Omaha. Henry shared his insights into MTS with me and convinced me that MTS was simply part of the cancer family syndrome (CFS), today known as hereditary non-polyposis colorectal cancer 1 and 2 (HNPPC1 and HNPPC2) (Lynch syndrome 1 and 2) (23–25). He had several large pedigrees of CFS, some of which he had inherited from Warthin’s files at the University of Michigan (26). In this collective, Henry had already identified a few patients with sebaceous neoplasms (27,28), whom we would now identify as either MTS or HNPPC2 with colonic and extracolonic tumors. HNPPC is caused by mutations in a variety of DNA mismatch repair (MMR) genes; MSH2 (29) is almost always responsible for HNPPC2 (MTS), while MLH1 (30) is equally important in HNPPC1. The revised Bethesda guidelines incorporate much of the carefully acquired clinical and genetic data from Lynch and his colleagues (31).

Our first patient nicely summarizes the entire HNPPC story; he developed multiple tumors, primarily gastrointestinal, but also involving other organs, at a relatively early age but survived far longer than age-matched controls with similar sporadic tumors (32). Another distinguishing feature is that the colon carcinomas are far more likely to be on the right side, as in our case, than in familial adenomatous polyposis (FAP) with its cutaneous marker, Gardner syndrome. By then, I had numerous biopsies from our four patients with MTS and had received cases in consultation from around the country. So, I had a burgeoning collection. I was becoming more and more convinced that the cutaneous lesions in MTS frequently defied classification, often showed overlaps between sebaceous tumors and keratoacanthomas and on occasion were most distinctive. All this information I published with Jan and Aly in an article in American Journal of Dermatopathology in 1986 (33).

Some 15 years later, Roland Kruse, a young German dermatologist at that time working in the genetics department in Bonn, called me to discuss MTS. His group made many new discoveries about MTS, showing they had the same spectrum of MMR gene mutations as HNPPC (34), although MSH2 was more likely to be involved (35). They also showed the presence of microsatellite instability in skin tumors (36) and demonstrated that the loss of heterozygosity (LOH) was not the preferred mode of tumor development in MTS (37). Roland placed me in contact with Arno Rütten, a dermatopathologist in Friedrichshafen, Germany, who had a long interest in MTS and had provided much of the pathological material for Roland’s studies.

I agreed to bring my collection of biopsies to Friedrichshafen, where Arno and I spent a day looking at funny sebaceous lesions. We decided that the most distinctive tumor was what we then designated a cystic sebaceous tumor (CST), a deep cystic sebaceous proliferation (Fig. 5) (38). I had identified such lesions in passing a decade earlier, but now Arno found at least one in half the patients in his much larger collective. Prospectively, we identified several patients who had only a CST, but investigation revealed a personal or family history that strongly suggested MTS and then germline DNA repair gene mutations were found (39).

Mathiak, Rütten and others refined the process even further. Their group employed commercial monoclonal antibody stains with which the presence of MSH2 or MLH1 protein had been identified in gastrointestinal biopsy sections (40). In CST and other tumors with microsatellite instability, in most instances, there was no staining for the appropriate gene products in the cutaneous tumors. Thus, it was possible to exactly identify the gene harbouring the germline mutation responsible for a whole spectrum of problems simply by staining the right skin biopsy in the right way. This is truly an elegant combination of dermatopathology and genetics.
I first learned about Cowden syndrome (CS) under the wrong name – multiple hamartoma syndrome. Peyton Weary, Bob Gorlin, Bill Gentry (my favourite clinical teacher at Minnesota) and several of Peyton’s colleagues from Virginia published a paper on this disorder in 1972 (41). As it was a Minnesota-Virginia paper, I accepted it as the whole answer. I saw several of Bill Gentry’s patients and many biopsies but never grasped the essence of the disease. In 1976, Bob Goltz took me with him to the Michigan Dermatologic Society meeting held one spring weekend in Dearborn Village near Detroit. My most vivid memory of the meeting is a case discussed by Amir Mehregan in which the patient had a baffling array of cutaneous tumors – lipomas, hair follicle tumors, warts and peculiar fibrous lesions – and was introduced under a complex new name which I have forgotten. Bob Goltz was one of the guest discussants and in his inimitable way praised the clinicians, praised Amir, indicated this was just about the most puzzling thing he had ever seen, but asked if he could pose a possible alternative diagnosis – multiple hamartoma syndrome. The minute he said it, everyone in the audience simultaneously clapped their foreheads in the ‘Oh, why didn’t I think of that?’ routine, and I became a fan of this disorder.

I went to the library immediately on the following Monday to read about my new interest and as always bumped into Bob Gorlin, the most conspicuous user of Diehl Hall (the medical library) at the University of Minnesota. He reminded me that Ken Lloyd in Youngstown, OH, had first described the syndrome and told me of his personal first encounter with CS. He was visiting the Armed Forces Institute of Pathology and was shown a tray of slides by Dr Southern Hooker, a descendent of General Fighting Joe Hooker of Civil War fame. I later asked Bob to write down these events and now I quote…

It was the case of a woman who had lots of bumps on her lips, gingiva and skin, who had huge breasts and breast cancer. About six months later Lauren Ackerman contacted me and said, ‘Bob I have a patient with this, this, this and this.’ I said, ‘My goodness, Lauren, I just (saw slides) of a gal with almost the identical findings.’

The doctors caring for the first case were two young internal medicine residents in Youngstown, OH, Kenneth Lloyd and Macey Dennis. They published their case in *Annals of Internal Medicine* in 1963 (42), choosing the name Cowden syndrome to honour their patient Rachel Cowden, who later died of metastatic cancer. Ken Lloyd went on to become a dermatologist and still practices today in Youngstown.

Carcinoma of the breast remains the major risk for CS patients. About 75% of female patients have fibrocystic disease or other breast changes and fully a quarter develop carcinoma. Prophylactic mastectomy is often recommended (43). In addition, recent evidence shows that male individuals with CS are also at risk for breast cancer (44). Around 50% of patients have hamartomatous polyps of the gastrointestinal tract, but the risk of malignant degeneration is very small. Similarly, about two-thirds have thyroid disease, but once again, malignant change is rare. Theo Starink, a dermatologist in Amsterdam, accumulated considerable data from several large Dutch pedigrees (45).

Cowden syndrome evolved into an even more interesting dermatopathological issue. The facial lesions were identified as trichilemmomas (46,47), and the dermal lesions occasionally showed a peculiar cut-onion layered pattern which was designated as sclerosing fibroma (48). Although multiple sclerotic fibromas were first described, soon solitary sporadic ones were identified (49). Two giants of dermatopathology, Marty Brownstein and Bernie Ackerman, argued for years whether the trichilemmomas were warts or not. Bernie was sure all trichilemmomas were warts (50), and Marty was just as sure they were not (51).

While at the University of New Mexico, I saw a college freshman, who had presented as an infant with an enlarged head but did not have hydrocephalus and now in college, was having trouble concentrating and developing lots of warts. The referring physician had already thought of CS, so I could only agree,
but I learned that many patients are originally evaluated by paediatricians for increased head circumference. I also found out that Lhermitte–Duclos syndrome (52), a form of cerebellar hypertrophy, was closely associated with CS (53).

The next major jump in our knowledge of CS occurred at Columbia University. The group of Ramon Parson in the Institute for Cancer Genetics reported, in early 1997 in Science, on the finding that the PTEN gene, a member of the protein tyrosine phosphatase family, is mutated in human brain, breast and prostate cancers (54). Parson’s group had already joined efforts with the group of Monica Peacocke in David Bicker’s dermatology department. Together, these researchers found out that mutations in the PTEN gene are also responsible for CS (55). Subsequently, diagnostic criteria were established for CS and everything seemed clear (56). The diagnostic criteria included mucocutaneous lesions:

1. six or more facial papules are present, of which three or more must be trichilemmomas;
2. cutaneous facial papules and oral mucosal papillomatosus are present;
3. oral mucosal papillomatosus and acral keratoses are present;
4. six or more palmoplantar keratoses are present.

Mutations in PTEN are responsible for a befuddling list of syndromes, which are sometimes given the group name Bannayan–Riley–Ruvalcaba (57) and at other times further subdivided into Bannayan–Zonana syndrome (58), Riley–Smith syndrome and Ruvalcaba–Myhre–Smith syndrome. Even the names are confusing – two different Smiths were involved; Harris ‘Pete’ Riley was a long-time Chairman of Pediatrics at Oklahoma and kind to me when I ran paediatric dermatology clinics at Oklahoma Children’s Hospital. Today, we know all these alphabet soup syndromes are caused by PTEN mutations (59) and can be viewed as ‘PTENosis’ or paediatric variants of CS, featuring haemangiomas, lipomas, juvenile polyps, macrocephaly and the classic pigmented macules of the penis (speckled pecker sign). In addition, mutations in PTEN also cause Lhermitte–Duclos syndrome. The association with juvenile polyposis syndrome has been more confusing; latest information suggests that PTEN mutations should exclude this diagnosis (60), while two other causative genes for JPS have been identified. The diagnostic criteria are now more comprehensive and address the PTEN spectrum (61).
PTEN mutations can somehow lead to an epidermal growth pattern which resembles that induced by HPV; I have asked lots of PTEN experts and never received an answer. Any suggestions?

**Carney complex**

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<tr>
<td>Genes</td>
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<td>CNC2: CNC2 at 2p16</td>
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<td>Cutaneous findings</td>
<td>Myxomas, multiple freckles or lentigines, blue nevi</td>
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<td>Systemic malignancies</td>
<td>Large-cell calcifying Sertoli cell tumor, psammomatosus melanotic schwannoma</td>
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<td>Other clinical findings</td>
<td>Cardiac myxoma, pigmented nodular adrenocortical disease with Cushing syndrome, myxoid mammary fibroadenoma</td>
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<td>Synonyms</td>
<td>NAME syndrome, LAMB syndrome</td>
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For many years, I read about Carney complex (CNC) and saw cases at meetings, but never personally diagnosed or followed a patient. I had written to J. Aidan Carney, a pathologist at the Mayo Clinic, a number of times requesting information for lectures or review papers. The minute I read his classic paper (64), I realized that he was correct to lump together both NAME (65) and LAMB (66) syndromes which were clearly describing the same patients with slightly different choice of words and emphasis. I was sure that when I saw a patient, I would immediately recognize the admixture of freckles and blue nevi and promptly make a brilliant diagnosis. It turned out differently.

In the midst of a busy clinic, a resident called me in to look at some molluscum before he cur- etted them. J.H. was a tall teenage boy, accompanied by his mother, a hospital employee whom I knew in passing. The resident said, ‘J. has a few molluscum. I’m going to curette them and not get pathology, as there is no need of wasting the family’s money.’ (In defense of the resident, we rarely submitted molluscum for pathology). But…J. had two little glassy papules on his eyelids (Fig. 8). I knew they were not molluscum but was totally stumped. I briefly looked at the rest of his skin; he had nothing else. Then his mom asked ‘Could this have anything to do with his bilateral large-cell calcifying Sertoli cell tumor of the testes?’ I said, ‘Just that these are myxomas in Carney complex.’ Histological examination of the tangentially excised papules proved me correct (Fig. 9). I examined J. again; he had absolutely no pigmented lesions. I ran back to my office and called Dr Carney. He excitedly told me that he was doing a paper on myxomas of the eyelids and external ear as almost dead-certain markers for CNC. Soon thereafter, Ferreiro and he published their findings in this area (67).

The extraordinary finding in my first cases was the lack of pigmented lesions. Seventy per cent of patients have either freckles or lentigines; the matter has never been resolved.

For many years, I read about Carney complex (CNC) and saw cases at meetings, but never personally diagnosed or followed a patient. I had written to J. Aidan Carney, a pathologist at the Mayo Clinic, a number of times request-
The ‘E’ in NAME refers to ephelides, while the ‘L’ in LAMB indicates lentigines; in my experience there are both. The most striking cutaneous findings are the myxomas (68), nodules with lacy epithelial strands and lakes of mucin. They are almost pathognomonic of CNC. Another unusual feature is epithelioid blue nevi which should suggest CNC (69) but may be sporadic (70).

I stayed in touch with Dr Carney and learned much from him. First of all, one must say Carney complex, because Carney triad refers to gastric (epithelioid) leiomyosarcoma, functioning extra-adrenal paraganglioma and pulmonary chondroma (71). In CNC, the prevalence of cardiac myxomas is 70% and that of Cushing syndrome is 30%. Carney spent a great deal of time trying to track down Harvey Cushing’s first patient, Minnie G., with what is now known as Cushing syndrome; it appears likely that Minnie G. actually had CNC (72). Similarly, William Young re-evaluated the first patient with primary pigmented nodular adrenocortical disease 50 years later and she too had CNC (73).

The main problem in CNC is the cardiac myxomas, which are histologically benign, but potentially life-threatening. In a familial patient, the myxomas tend to occur at earlier age than in a sporadic case, more often are multiple, involve any chamber and tend to recur. They may cause emboli or cardiac failure and the surgery itself is risky, so that perhaps 25% of CNC patients die from their myxomas. Psammomatous melanotic schwannomas usually involve the gastrointestinal tract (74) but have been reported in the skin (75); they metastasize in about 10% of cases. The breast tumors are benign (76).

Carney complex was one of the first diseases to turn out to be caused by mutations in at least two different genes, without discernible differences in clinical appearance. Mutations in \textit{PRKAR1A} (77), a protein kinase, at 17q23–q24 and a not characterized gene at 2p16 (78) cause exactly the same problems. Who would have thought 30 years ago that two different genes could cause exactly the same autosomal-dominant disorder? The possibility never crossed my mind. Recently, I was lucky enough to be able to join Dr Carney in writing the section on CNC in the latest World Health Organization book on skin tumors (79).

### Birt–Hogg–Dubé syndrome

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<tr>
<td>Gene</td>
<td>\textit{FLCN} (folliculin) at 17p11.2</td>
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<td>Cutaneous findings</td>
<td>Multiple perifollicular fibromas and trichodiscomas</td>
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<td>Systemic malignancies</td>
<td>Renal cell carcinomas (unusual histological types)</td>
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<tr>
<td>Other clinical findings</td>
<td>Spontaneous pneumothoraces</td>
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<td>Synonyms</td>
<td>Hornstein–Knickenberg syndrome</td>
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I go back a very long way with Birt–Hogg–Dubé syndrome (BHDS). Arthur Birt was a dermatologist in Winnipeg, Canada, who frequently visited the University of Minnesota for state dermatology meetings or occasionally just Friday afternoon grand rounds. He was often accompanied by his colleague Arthur Anhalt, father of Grant Anhalt (who needs no further introduction to readers of this journal). This trip alone shows the devotion of Dr Birt to dermatological education; the two cities are 450 miles (720 km) apart. Dr Birt was Winnipeg through and through. His father and grandfather had been mayors of the city. He completed his entire medical training there and then practised in the same office for over 50 years. The syndrome which made Winnipeg famous was initially identified by Jim Dubé, an endocrinologist originally from Trinidad who discovered a family with multiple thyroid cancers and funny skin lesions. He referred the family to Arthur Birt who biopsied the lesions and sent the specimens to Georgina Hogg, a pathologist. She identified them as follicular tumors but sought help from Herman Pinkus who was able to provide an almost-correct diagnosis, as discussed below. She also sent
slides to Bob Goltz and I still have some of the original slides which she shared with me. The Canadians then published their description of the syndrome in 1977 (80).

My first encounter with a patient with BHDS was at the University of Oklahoma. I was sitting in my office at Oklahoma Children’s Hospital reading a paper by Otto Hornstein and Monika Knickenberg on a new syndrome (81). The phone rang and Dennis Weigand was calling from the Veterans Administration Hospital across the street. He said ‘I have a patient who has been boarded out of the service with the diagnosis of acne scars, but he has something else. Could you take a look?’ I walked over, entered the room and saw a man who looked identical to the pictures I had been glancing at a few minutes before. I confidently said, ‘He’s got Hornstein–Knickenberg syndrome.’ This tour de force convinced Dennis and the residents that perhaps the new faculty member was not so bad. There are still divided opinions, but to me it is clear that Hornstein and Knickenberg were describing the same syndrome as Birt, Hogg and Dubé; they clearly published first – 2 years earlier.

C.P. had hundreds of small white dome-shaped perifollicular papules most prominent on face and chest, clearly not acne scars (Fig. 10). I biopsied 10 lesions; five showed perifollicular fibrosis with lacy epithelial strands (fibrofolliculoma) (Fig. 11) and five showed a disc-shaped subepidermal proliferation of spindle cells (trichodiscoma) (Fig. 12). We referred the patient for internal medicine work-up because Hornstein and Knickenberg had mentioned a risk of gastrointestinal carcinoma, while Birt and colleagues had suggested a possible association with thyroid cancer. Nothing was found, but he died a few years later of metastatic colon carcinoma.

I saw several more patients clinically, but the most interesting question was the nature of the lesions under the microscope. The hair disc is a well-established sensory structure, prominent on cat and rabbit lips, and especially well seen in gloves made from the hide of the peccary, a pig-like mammal of the Southwestern Desert of the USA locally known as javelina. Felix Pinkus first described the ‘Haarscheibe’ (German for hair disc) in 1902 (82) and even identified it in peccaries (83). It consists of an acanthotic epidermis overlying a spindle-shaped proliferation; the epidermis is rich in Merkel cells and the dermal elements are neural, as the hair disc is a highly specialized neuroreceptor. Felix’s son, Hermann Pinkus, identified cutaneous tumors resembling hair discs which he named trichodiscomas (84). Initially Burnier and Rejsek (85) and later Zackheim and Pinkus (86) had described perifolliculomas. With this background, it had...
been relatively easy for Hermann Pinkus to suggest a diagnosis for the slides sent to him by Hogg. Because of the presence of perifollicular fibrosis interlaced with thin epithelial strands or fingers, the Winnipeg group as well as Weintraub and Pinkus (87) proposed the name fibrofolliculoma.

Unfortunately, the issue was more complex and Pinkus was not 100% correct. I met one of my best friends over this issue. Gerd Plewig, when he was Chairman of the Department of Dermatology in Düsseldorf, Germany, became interested in the trichodiscomas; he and his co-workers clearly showed that they were fibrous proliferations, not neural, in a poster presented at the American Academy of Dermatology in 1987 (88). I visited Gerd in Düsseldorf on one of my German trips just to see these slides and we became close friends. Even though clinical professors are almost non-existent in Germany, I have one enabling me to work closely with Gerd in the Department of Dermatology at the Ludwig Maximilian University in Munich since 1993, editing and translating several books, as well as taking numerous hikes and bike trips.

The next step in understanding these lesions was made by Bernie Ackerman who often lectured about what I call ‘Ackerman’s rule of multiple adnexal neoplasms’. I paraphrase, but he stated, ‘If a patient has multiple lesions which are interpreted with two different histopathological diagnoses, but a good clinician cannot tell them apart, then the lesions are probably variants on a single process.’ This is surely the case in MTS where the sebaceous lesions and keratoacanthomas overlap and in CS where trichilemmomas and fibromas merge together; it is also true in BHDS where the best name is probably that proposed by Charlie Steffen – mantleoma (89). The sebaceous mantle consists of strands of epithelial cells that emanate from the infundibulum of a hair follicle and drop down aside the follicle in the form of a mantle or skirt; sebocytes appear at the tips of these chords and evolve into sebaceous lobules and glands. Later, the mantle and sebaceous glands involute with fibrosis. Thus, perifollicular fibrosis, lacy strands and finally pure fibrosis occur. The connection between this normal process and the microscopic appearance of fibrofolliculomas and trichodiscomas is obvious. Two German workers, Tilman Schulz and Wolfgang Hartschuh, took things a step further and showed that if one sectioned carefully, features of both the epithelial proliferation and fibrosis could be found in the same specimens (90).

My most fascinating contact with BHDS – even though I contributed nothing – was a phone call from Burton Zbar at the National Institutes of Health perhaps 10 years ago. Paul Duray, one of my oldest (better said, longest serving) friends, with whom I worked at Hennepin County Hospital in the spring of 1975, had told Burt I was an expert on BHDS. The story had evolved as follows: the NIH had become interested in families with multiple, often bilateral, renal cell carcinoma, often with unusual histological types (usually chromophobe, oncocytic or overlap, with the common sporadic clear cell carcinoma found in only 10%). Maria Turner and other clinicians at the NIH noticed immediately that many of these patients had cutaneous findings – multiple perifollicular papules which on biopsy were mantleomas, so they knew that BHDS was the answer (91).

In 2002, Zbar’s group was successful in identifying mutations in the folliculin (FLCN) gene underlying BHDS (92). Folliculin is a cytoplasmic protein with a predicted size of 64 kDa. Alternative splicing of the FLCN gene results in two isoforms, a full-length form and one that uses an initiation codon in intron 6. Although the precise function of folliculin and its alternate splice variant is not clear, it is thought to be a tumor suppressor with LOH initiating tumor formation. All germline mutations in patients suffering from BHDS described so far are splice-site mutations or insertions/deletions that result in putative protein truncation and haplo-insufficiency.

Today, it appears that Birt’s suggestions of associated thyroid carcinoma and Hornstein’s of gastrointestinal carcinoma were incorrect; the major tumor risk is that of renal cell carcinoma, as well as of spontaneous pneumothorax and pulmonary cysts (93). The picture may be more complex. My last contact with BHDS was just a few weeks ago. One of the junior faculties in Gerd Plewig’s department called to tell me she and colleagues in Nuremberg were following twin sisters with BHDS and dysplastic nevus syndrome, whose mother had similar skin lesions but had died of melanoma. One of the patients has an endometrial carcinoma. Who knows where this trail will lead?

**My big question**

One thing fascinates me about these disorders – the unexplained paradox about why they cause malignant systemic tumors and very often benign cutaneous tumors. Of course, in BCNS,
the skin tumors are malignant, but generations of dermatologists have argued about the terms ‘basal cell carcinoma’ and ‘basal cell epithelioma’ because of the almost 0% lifetime risk of metastasis. In MTS, only a very rare sebaceous tumor is malignant. Our first patient had a small-cell sebaceous carcinoma of the soft tissue of the chin, mimicking a Merkel cell tumor under the microscope. When I presented the case, Richard Winkelmann, a superb dermatopathologist among his other considerable talents, doubted it was a carcinoma. Several months later, the patient had jaw metastases. In CS, CNC and BHDS, the cutaneous lesions are completely benign. I have no explanation. Once again, maybe, a young experimentally oriented reader of this journal can solve this puzzle for me.

My purpose in writing this highly anecdotal account has not been to highlight my own achievements. They have been minimal and of interest to no one, not even to my mother. Instead, I present them just to show how if one remains alert, communicates with everyone possible and always tries to learn something new, there are many interesting adventures to be had in the field of cancer-associated genodermatoses. Over the 30 some years, David and I have been active in dermatology. These five syndromes have advanced from being odd diseases set aside for the ‘stamp collectors’ to fascinating diseases, giving us new insights into cutaneous and systemic tumor development.

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