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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.

Historical Review

A Man, a Syndrome, a Gene: Clouston's Hidrotic Ectodermal Dysplasia (HED)

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This paper presents a biographical sketch of Dr. H. R. Clouston, whose eponym is attached to a type of hidrotic ectodermal dysplasia, and a brief account of the mapping of the gene and its identification as the connexin gene, GJB6. © 2001 Wiley-Liss, Inc.

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WHO WAS CLOUSTON OF THE ECTODERMAL DYSPLASIA, ANYWAY?

Dr. Howard Rae Clouston (Fig. 1) was a physician who grew up in Huntingdon, Québec, a small town about 50 miles from Montréal, and took over his father's practice there. He was a remarkable example of how a general practitioner could make contributions to academic medicine [Clouston, 1929; 1939]. As a boy in Huntingdon, he knew of the families affected with what became known as Clouston's hidrotic ectodermal dysplasia (HED). Later, he saw some of them as his patients, and became aware of related families who lived in other villages along the New York state border and in Montréal. His interest in them developed into a hobby, and he had a three-ring loose-leaf notebook in which he recorded his observations. The notebook was kindly given to F. Clarke Fraser by Dr. Clouston's son, James MacRae Clouston. It is a remarkable document. It was presented by FCF and V.M. Der Kaloustian to the Osler Library of the History of Medicine at McGill University on August 29, 2000. Further information about Dr. Clouston can be found in the book, *Lead Kindly Light*, written and published by Dr. Clouston's daughter, Marjorie Clouston Dale, who generously provided us with a copy.

The notebook contains Dr. Clouston's observations on patients, notes on the articles he read about the



Fig. 1. Portrait of Dr. Howard Rae Clouston.

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ectodermal dysplasias, and on consultations he had with doctors at McGill and elsewhere, as well as insightful accounts of how the affected people were regarded by their unaffected neighbors.

Dr. Clouston had the makings of a syndromologist. His descriptions of patients refer to abnormal hair slopes and vertex whorls, flat noses with upturned nares, protuberant jaws, clubbing of the terminal phalanges, and delayed epiphyseal unions.

He was also an experimentalist. He reports that after treatment of a young man with estrogens, the man's hair turned darker. The patient's ozoena was "relieved at once by Wright-Mortimer-Collip treatment—Progyn beta." (No IRB clearance!).

Dr. Clouston was also something of a sociologist. He relates how the affected persons came to be known as "Zulus." The immediate ancestors of the group came into the English-speaking district of Huntingdon at about the time of the British campaign against the Zulus. "The name 'Zulu' was on everyone's lips—as the enemy—and as 'Hun' is today. The Zulus are related to the 'Fuzzy-wuzzies'—a very aggressive set of tough fighters with lots of kinky black hair. Therefore there was considerable mockery in calling this browbeaten group without hair or nails "Zulus." Therefore it stuck. Ridicule, scorn and contempt are heaped on them at times and ribald jokes." We should add that some affected members of the group were well-educated and respected members of society.

Dr. Clouston gives an example of one "ribald joke," observed when he was a schoolboy. He was in the local shoe repair shop, run by "a small town character who loved to work at everything except his own work. He stuffed squirrels and birds and spent weeks putting a frog in a bottle... One day, after one of the 'Zulu' girls got married, one of the wedding guests came into the shop, well intoxicated, and asked for a wig for a bald headed = (female pudenda). Before he collapsed from laughter, [the shoemaker] cut one from a collie dog hide, and sold it to him for 25 cents." How mortified the bride must have been, and how cruel people can be to others just a little different from themselves.

There are notes on several consultations Dr. Clouston had with McGill professors. A professor of skin diseases attributed the condition to congenital syphilis. Clouston writes "This was a common belief and was another reason that the group was shunned as lepers." Dr. Hebbel Hoff, Professor of Physiology, heard the idea while interviewing family members that prevention of the affliction could be attained by "conception without passion." This apparently never caught on as a eugenic measure—affected individuals did not have smaller families than their unaffected sibs.

Dr. Clouston must have spent considerable time in the McGill Medical Library, and took notes from many textbooks of the day, including Nelson's *Medicine*, Starling's *Physiology*, Cockayne's *Dermatology*, Cushing's *Pituitary Disorders*, Bailey's *Histology*, as well as from a wide variety of medical journals.

Dr. Clouston's breadth of vision and humor are evident in a paper he gave to the local medical society in November 1937. We quote a few of the examples. "In

all medical literature there is the difficulty of accurate observation and precision of presentation, but in dealing with hereditary and disfiguring defects there are opportunities for error not inherent in other forms of medical investigation." An example is given of an affected child whose mother and the master of the house were normal, as were their families. "But a small town has certain advantages (or disadvantages) and it soon became clear that this household was in a state of symbiosis rather than of Holy Matrimony and that while all the laws of Mendel the monk had been completely frustrated, there had been no deviation from the laws of Mendel the scientist by the width of a dystrophic hair."

"One old victim explained that the original ancestor was working in his fields by the sea and flocks of gulls were destroying his crop. He therefore seized a gull and, in exasperation, with his hands and nails and teeth, he tore the feathers from the screaming bird. As a punishment for his cruelty God condemned him and some of his descendants to absence of hair (hair and feathers are related) loss of nails, and rough palms." Dr. Clouston comments: "It is a particularly soul satisfying explanation and I cannot do any better."

Dr. Leonard Huskins, Chair of the newly formed Department of Genetics at McGill, mentioned to FCF, when he was a graduate student there, that Dr. Clouston had been to see him about analysis of his pedigrees. Clouston showed that HED (like Mendel's peas) fitted the rules of autosomal dominant transmission "so accurately that I was almost afraid to give the figures." There were 100 affected to 110 unaffected offspring of affected individuals, and no examples of reduced penetrance. He noted the great variation in intensity of the condition, and developed a scoring system for severity that was "very crude, inaccurate and full of errors, but useful to show the diminishing severity — not diminishing numbers" in successive generations — a sort of negative anticipation. He suggested that this might relate to improved living standards. Later it seemed more likely that the effect was due to increasing severity with age [Williams and Fraser, 1967].

In 1929 Dr. Clouston published his first paper, in the Canadian Medical Association Journal, naming the condition Hereditary Ectodermal Dystrophy [Clouston, 1929]. Ten years later, with additional information and reflection on the condition, he published a second paper, again in the CMAJ, and classified the condition as an "ectodermal dysplasia" [Clouston, 1939].

Some 25 years later, Melodie Williams appeared at FCF's office door along with her father. She was a pretty teenager with large dark eyes, who wanted help with her National Science Fair project. She had heard about some people with unusual hair and nails who, she thought, might be predisposed to cancer, and wanted to investigate this. FCF realized that these people were from the Clouston families. Melodie brought the Clouston pedigrees up to date (Fig. 2), did some analyses, and won a (US) Science Fair prize. She went on to be an academic dermatologist.

In 1986, VDK was obliged to leave Lebanon and the American University of Beirut with his family because

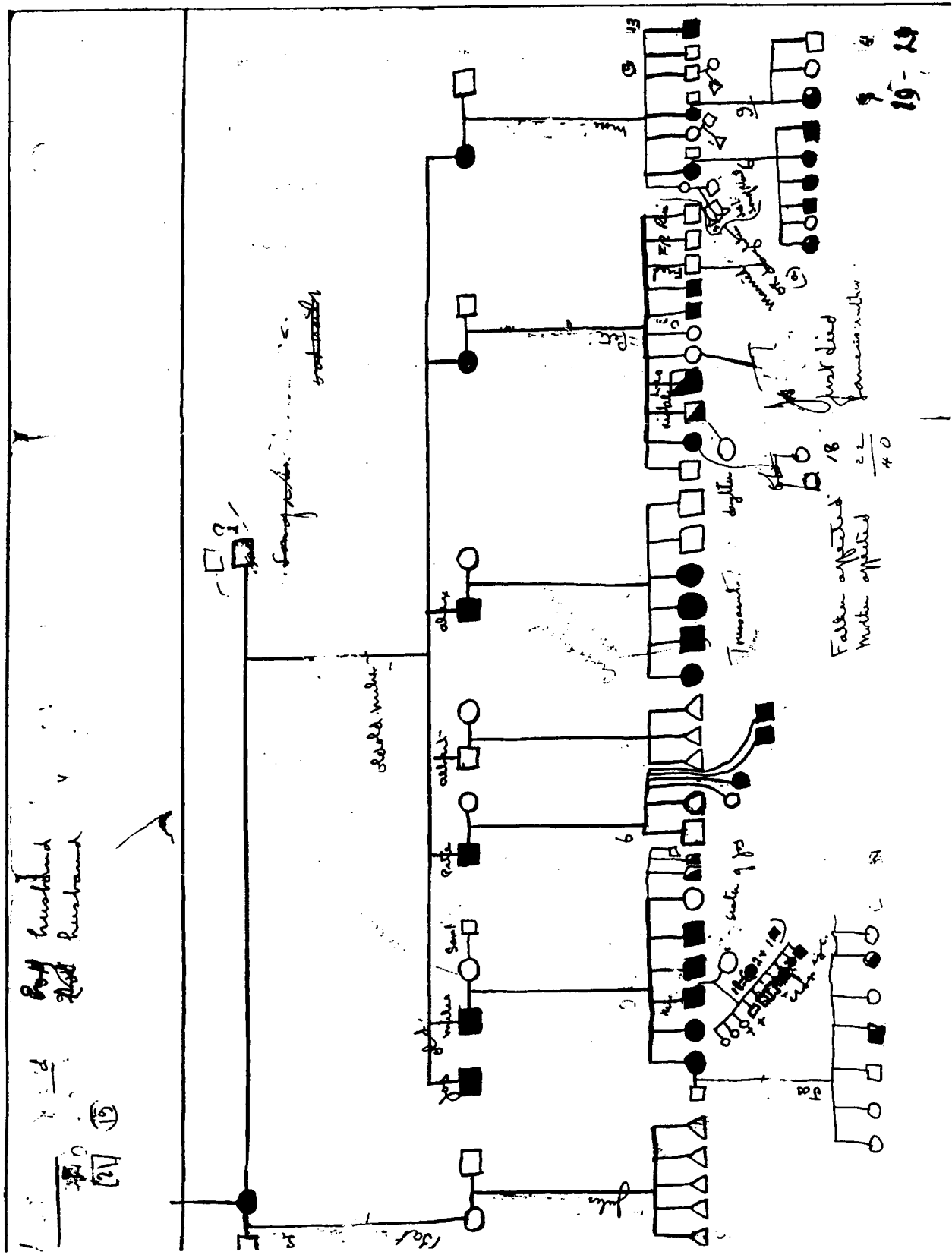


Fig. 2. Example of a pedigree update by Melodie Williams.

of the raging civil war. He obtained a position at McGill and The Montréal Children's Hospital. In 1990, his personal interests in genetic diseases of the skin were kindled when he re-read the paper of Williams and Fraser [1967] and he wanted to continue the study of the condition. FCF put him in touch with the updated pedigrees and addresses of the patients and their families in the files of the Division of Medical Genetics at The Montréal Children's Hospital. At that time, Valerie Hani was a graduate student in genetic counselling, working with VDK. A series of visits started, meeting families, interviewing them, updating pedigrees, and finding new patients.

THANK HEAVEN FOR GRADUATE STUDENTS

However, 1990 was not 1967. To go further in the study, molecular genetics was essential and VDK was a clinical geneticist. By then Guy Rouleau had returned from Harvard and had established a molecular genetics laboratory at the Montreal General Hospital. VDK contacted him about the prospect of mapping and cloning the gene of Clouston's Disease. The idea interested Rouleau, but no potential graduate student could be seen on the horizon. The spirit of Dr. Clouston must have helped since, in 1993, a young graduate student, Zoha Kibar, who had just obtained her M.Sc. degree from the American University of Beirut, contacted VDK to ask if she could study for a Ph.D. at McGill. Soon Rouleau and VDK took her on board. Then came the day treks to Vermont, Albany and Plattsburg (New York) as well as new visits to the families in southwest Québec. By the end of 1996, with Zoha's hard work, Rouleau's guidance, and "wiv a li'l bit o' luck", the gene was mapped to the pericentromeric region of chromosome 13q [Kibar et al., 1996; 1999]. We think Dr. Clouston would be very pleased.

It wasn't long before colleagues from other parts of the world tested their own patients and confirmed the mapping region [Radhakrishna et al., 1997; Taylor et al., 1998; Stevens et al., 1999]. Genetic homogeneity was found to include, besides French-Canadians, families of Indian, Scottish-Irish, African, Spanish, French, and Malaysian origin [Kibar et al., 1996]. The high frequency in the French Canadian population suggested the presence of a founder effect.

THE FRENCH CONNECTION

Zoha Kibar obtained her Ph.D. before the gene was cloned, and the project passed on to Colette Hand. In the meantime, Dr. Gilles Waksman from Evry, near Paris, France, had collaborated with Guy Rouleau's laboratory since the mapping article [Kibar et al., 1996] had come out. In fact, "the French connection" with Rouleau had started in 1990 when Waksman was still a graduate student. They confirmed the map site in their own patients and wanted to continue the collaboration.

The year 2000, like 1997, was a good year for the Clouston syndrome gene. In March, Waksman contacted Rouleau and gave him preliminary results on two candidate genes: GJB2 and GJB6, encoding

connexin-26 and connexin-30. Rouleau responded by sending him, for a double blind study, all the DNA samples he had from patients and their family members. Soon it was confirmed that the GJB6 gene carried mutations in patients, but not in controls. One of the mutations, a transition 31(G -> A), was observed in the coding sequence leading to a missense mutation (G11R). It was present in Scottish-Irish, Indian, Malaysian, African, Spanish, French-Canadian, French, and Welsh patients. Another transition, 263 (C -> T), leading to a missense mutation A88V was detected in patients originating from India, Malaysia, and Wales. A paper was soon sent to Nature Genetics and probably, again with the help of Dr. Clouston's spirit, was accepted on August 19, 2000 [Lamartine et al., 2000].

THE END OF THE BEGINNING

As Francis Collins stated for *Human Genetics* after the completion of the Human Genome sequencing, this work is just "the end of the beginning" for the HED story. The next steps will need more ideas, more graduate students, and more connections; they will involve a study of the structure of the protein, its various functions in different tissues, and the changes that the mutations are responsible for. Perhaps an animal model and even a cellular model will help.

We are grateful for the cooperation of the families that made possible the cloning of the gene. Now they will have to face difficult decisions about prenatal diagnosis until, who knows, a means of treatment or prevention appears.

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