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Chapter 7

Historical note

Jan Peutz, Harold Jeghers and a remarkable combination of polyposis and pigmentation of the skin and mucous membranes

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In the 1920s and 1940s, respectively, Dr. Peutz [1] and Dr. Jeghers [2] described a gastrointestinal polyposis syndrome characterized by specific melanin pigmentation of the skin and mucous membranes, now called the Peutz-Jeghers syndrome.

Two doctors from two continents

Johannes Laurentius Augustinus Peutz (called Jan) (Figure 1) was born in the village of Uithuizen in northern Holland on March 24th 1886. He was the first of nine children of the principal of an elementary school. After completing high school at the Catholic Seminary Rolduc, Jan Peutz studied medicine at the Universities of Groningen and Utrecht. He received his Medical Degree in 1914 and took his training in Internal Medicine in Rotterdam. In 1917 Peutz started to work at the Johannes de Deo Hospital (Westeinde Hospital) in The Hague; later he became Chairman of the Department of Internal Medicine there until his retirement in 1951. In 1921, he completed his thesis on pancreatic disorders and diabetes in order to obtain his PhD degree. Soon afterwards, he published a case report on a family with gastrointestinal polyposis and distinctive pigmentation of the skin and mucous membranes. Peutz was a dedicated and beloved teacher with broad scientific interests. He inspired his pupil van Wijk to write his thesis, subtitled 'Peutz Disease', about the original family with this disease [3]. Peutz was married and had one son. He died in The Hague, in 1957, at the age of 71 years. During his life, Peutz received numerous honors and awards in recognition of both his social and medical achievements.

When Peutz published his observations on 'a very remarkable form of familial polyposis', Harold Joseph Jeghers (Figure 2), who was born on September 26th, 1904, in Jersey City, New Jersey, USA, was 16 years old [4]. He was fascinated by electricity, and ran his own radio station before he was admitted to Rensselaer Polytechnic Institute to study electrical engineering. As a freshmen, he became interested in medicine and changed his major to biology. He graduated from the Western Reserve University Medical School in Cleveland and went to Boston for his internship and further training in Internal Medicine at Boston City Hospital. Jeghers held his first faculty position as instructor of the Department of Medicine at Boston University. Later he was a faculty member of many institutions throughout the US. Early in his career, Jeghers developed the habit of collecting and systematically filing articles from medical journals. His collection, formally known as the Medical Index, is nowadays still accessible as Jeghers Medical Index (www.jeghers.com). During his Boston years, Jeghers saw several patients with intestinal polyposis and abnormal pigmentation of the skin. The detailed description of these patients, published in the New England Journal of Medicine in 1949 [2], led to the identification of the syndrome, now named after him. Jeghers was married and had four sons. He died in 1990. He was a respected medical educator, honoured with numerous awards during his life.

Peutz-Jeghers syndrome

It appears likely that the identical twin sisters with dark pigment spots on their lips and oral mucosa, reported by Connor in 1895 [5], were the first patients with Peutz-Jeghers syndrome to be described in the literature. The association of these sisters with the Peutz-Jeghers syndrome was the work of Jeghers and his colleagues, reported in the 1949 publication [2]. It illustrates Jeghers' remarkable knowledge of the literature. An illustration published by Hutchinson in 1896 [6] was reproduced in the papers from Jeghers et al. [2] and McGarrity et al. [7]. One of the sisters died from intestinal obstruction [8], the other from breast cancer [2]. However, the presence of polyposis was never confirmed.

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The initial report by Peutz [1]

On December 6th, 1920, a 15-year-old boy was admitted to the Johannes de Deo Hospital in The Hague and was seen by Dr. Peutz for anorexia, nausea, abdominal pain and weight loss. The boy also had numerous distinctive pigment spots on his face (Figure 3). In his publication in the ‘Nederlandsch Maandschrift voor Geneeskunde’ (Netherlands Monthly Journal of Medicine) in 1921, Peutz wrote: ‘When I saw the boy for the first time, I thought that I saw someone I already knew, such was his resemblance to an eleven-year-old boy whom I had examined that summer and was referred to me by colleague Kuynder because of the highly remarkable pigmentation on the face and the buccal mucosa, with the remark that other family members apparently had the same spots. Proof was now indeed established, since the two boys turned out to be brothers’. The patient developed an ileus due to intussusception of a small bowel polyp and underwent abdominal surgery. Pathological examination of the resection specimen (Figure 3) by Professor Landsteiner showed malignant degeneration of the polyp [1, 3]. Evaluation of the family revealed a similar pattern of pigmentation in four of the patient’s siblings. For three of the children, including the above-mentioned patient, intestinal polyps were confirmed. In addition, two of the children with pigmentation had nasal polyposis (Figure 4). In his concluding paragraphs, Peutz attributed the intestinal polyps with malignant potential, the nasal polyps and the distinctive pigmentation to one congenital and familial syndrome, which he considered to be a severe disorder.

A detailed description of the syndrome by Jeghers and his colleagues [2]

In March and October, 1939, two female patients with intestinal polyposis and ‘distinctive melanin pigmentation’ on the face, fingers, toes and oral mucosa visited Boston City Hospital, where Jeghers was Associate Professor of Medicine. Jeghers mentioned these cases briefly in his extensive publication ‘Pigmentation of the skin’ in the New England Journal of Medicine in 1944 [9]. Several other cases of intestinal polyposis and pigmentation had also been reported, some of which were reviewed in a French publication by Tournaire & Couder in 1945, entitled ‘Syndrome de Peutz’ [10]. However, the combination of polyposis and pigmentation of the skin and mucous membranes was not established as a distinct entity until 1949, when the syndrome was described in detail by Jeghers, then Head of the Department of Medicine at Georgetown University, together with Dr. Victor McKusick from the Department of Medicine at Johns Hopkins University, and Dr. Kermit Katz of the Boston City Hospital [2]. During his Boston years, Jeghers had collected information about several patients with the syndrome in collaboration with Katz. McKusick, who had also collected several patients with the stigma during his residency at Johns Hopkins,
visited Jeghers at his home in Washington DC where they prepared the manuscript. Their paper, published in two consecutive issues of the New England Journal of Medicine in 1949, described 10 patients with polyposis and pigmentation and included a review of the literature. Follow-up of previously reported cases, collected by means of personal communication with various authors, was also presented. One of these authors was Peutz, who 'has very kindly supplied us with further information on this family, permitting the construction of the fabulous family tree', which was included in the manuscript of Jeghers et al. They mention the paper of Peutz as 'the first specific reference in the medical literature concerning this disorder', an article which was already listed in the Index Medicus at that time. Regarding the genetic interpretation of the syndrome, Jeghers and colleagues (correctly) predicted that the explanation 'must be the presence of a single pleiotropic gene responsible for both characteristics, the polyps and the spots'.

**Peutz-Jeghers syndrome**

In 1954, Bruwer introduced the eponym Peutz-Jeghers syndrome [11]. The polyps are now classified as hamartomas. As predicted by Jeghers et al. in 1949, the hamartomatous polyps and the pigment spots are indeed caused by mutations in a single gene. In 1998, two
groups independently reported germline mutations in the tumor suppressor gene STK11 in patients with Peutz-Jeghers syndrome [12, 13]. Such mutations have subsequently been identified in most patients with Peutz-Jeghers syndrome [7, 14], although there may also be a second unidentified Peutz-Jeghers gene [15]. Germline mutations in STK11 were also found for the family described by Peutz [16] and the 'Harrisburg family' [17], one of the families reported by Jeghers et al. Both 'original families' have been followed over time. In 1950, van Wijk described the original family observed by Peutz in his thesis [3] and recently a 78-year follow up was published [16]. The latest follow-up of the 'Harrisburg family' was reported by Foley et al. in 1988 [18]. The clinical observations in the two original Peutz-Jeghers pedigrees reflect the main clinical problems of the syndrome: abdominal pain, rectal blood loss, anemia, intussusception of polyps leading to a high laparotomy rate, and a very high cancer risk. Of note, Peutz considered nasal polyposis to be a clinical feature of the syndrome (Figure 4). Although the association between nasal polyposis and Peutz-Jeghers syndrome has been mentioned occasionally by others [19, 20], it is generally not considered an established extra-intestinal manifestation of the syndrome. Recently, we found loss of the wild type STK11 allele in nasal polyps of Peutz-Jeghers patients, similar to that in hamartomatous Peutz-Jeghers polyps and carcinomas [17, 21], providing molecular-genetic support for the original observation made by Peutz [22].

Peutz-Jeghers syndrome is now considered to be one of the hereditary colorectal cancer syndromes, with a very high risk for intestinal and extra-intestinal cancer [23]. The need for surveillance has been recognized and guidelines have been proposed [7, 14]. Still, many questions regarding Peutz-Jeghers syndrome remain unanswered. Detailed clinical descriptions and reports on large cohorts of patients with this rare syndrome are needed to further define the extra-intestinal phenotype. Furthermore, the wide intrafamily and interfamily phenotypic variation may point to yet unidentified (genetic) modifiers of expression and genotype-phenotype correlations, respectively. Finally, molecular genetic studies are needed to further unravel the process of Peutz-Jeghers syndrome-related carcinogenesis. Eventually, such investigations may improve risk assessment, surveillance guidelines and future therapeutic modalities for patients with this remarkable syndrome.

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Notes

1. Dr. V.A. McKusick still works at Johns Hopkins University Hospital. His contribution to the genetic interpretation of the syndrome, as described in the original Peutz-Jeghers paper, was the starting point of his renowned career in Clinical Genetics. He is the author of 'Mendelian Inheritance in Man' and the online version OMIM (http://www.ncbi.nlm.nih.gov/omim/), including the #175200 Peutz-Jeghers site.
2. The authors sought advice of Bentley Glass, at that time Professor of Genetics at Johns Hopkins University, for help with the genetic interpretations.

References


