William Osler on telangiectatic syndromes

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Osler's description of recurrent mucous membrane bleeding from multiple cutaneous telangiectases was initially published in 1901. He credited Rendu's 1896 report of a 52-year-old man with telangiectases of the lips, nose, soft palate, and tongue who had recurrent epistaxis. Other physicians earlier had noted vascular nevi in familial epistaxis and had suggested a variant of hemophilia as the etiology. Osler clearly stated in his 1901 report that this disease was unrelated to hemophilia. Rendu noted the widespread nature of these telangiectases, and Osler observed that visceral telangiectases may be present with diverse hemorrhagic manifestations. In 1909, Hanes called the disease “hereditary hemorrhagic telangiectasias,” but it is often referred to as Osler-Weber-Rendu disease, recognizing the contributions of these 3 physicians in presenting clinical examples of this disorder. Osler's contribution to telangiectatic syndromes is explored, emphasizing his remarkable observational skills and his ability to correlate clinical findings. Current concepts of pathogenesis and treatment are discussed in a historical context.

Osler's initial description of a familial form of recurrent mucous membrane bleeding from telangiectases was published in 1901 in the *Johns Hopkins Hospital Bulletin* (1). In his report, Osler described 3 patients. Two were brothers in a family where 7 members had epistaxis. Both men were sailors and alcoholics, had recurrent nosebleeds since age 10, and had not bled from cuts. They had dilated venules and capillaries on their ears, noses, cheeks, tongues, and mucosal surfaces of their lips and nostrils. Both had normal coagulation times in contrast to hemophilia. One brother subsequently died of gastric cancer and was autopsied. The third case in Osler's initial paper was a man who did not have a positive family history of epistaxis but clearly had telangiectases of various sizes on his cheeks, lips, ears, tongue, gums, and hands. He had bled frequently and profusely from his nose since childhood, to the degree that not a week would pass without some bleeding from the nostrils. He was hospitalized for epistaxis and bled 1400 mL during a 24-hour period even
though his coagulation time was only 2 minutes. Years later he saw Osler while using his own treatment device—a tamponade of the nasal bleeding site with a lubricated finger cot tied to a catheter inflated in the nostril.

Prior to Osler's publication, hereditary forms of epistaxis had been noted by Sutton in 1864 and by Babbington 1 year later (2, 3). Babbington noted epistaxis in 5 generations of 1 family. Although neither of these descriptions included the presence of telangiectases, in retrospect it is likely these are the first examples of telangiectatic syndromes noted in the literature. However, these families could have had a more common autosomal dominant disorder associated with mucous membrane bleeding, such as von Willebrand's disease.

Vascular abnormalities were first associated with familial epistaxis by Legg in 1876 (4). Yet, Legg's patient had “nevi scattered over the face, forehead, and trunk that did not develop until age 41 and had painful swelling in the joints,” all atypical features for this syndrome. In 1887, Chiari described 2 families with recurrent epistaxis associated with multiple telangiectases (5). Yet he concluded, “I am constrained to designate the spots blood extravasation, a thing that is not uncommon in hemophilia.” In reading Chiari's text, these individuals were unquestionably classic examples of telangiectatic hemorrhage, and the diagnosis of hemophilia was incorrect. Chauffard in 1896 coined the term cutaneous hemophilia to describe a 50-year-old woman with recurrent bleeding from telangiectases without a family history of a bleeding disorder (6).

Yet, at least 1 physician, Rendu, clearly published a classic description of telangiectases in 1896, 5 years before Osler's article (7). A 52-year-old man had recurrent epistaxis, as did his mother and brother, yet he did not bleed from cuts or from tooth extractions. Cutaneous angiomas on his nose, cheek, and upper lip blanched on pressure but did not disappear. After Rendu's case, the stigma of hemophilia and, worse still, of a hemorrhagic diathesis was removed from this disease. Osler recognized Rendu's contribution in his 1901 article but elaborated that visceral involvement could occur, as noted in the autopsy on the man who died of gastric cancer. Scattered telangiectases were present in his stomach along with the gastric malignancy.

Over the ensuing 10 years, multiple reports described additional families with telangiectases. Brown Kelly, in 1906, described a 41-year-old woman with numerous telangiectases on her cheeks, ear lobes, nasal mucosa, lips, palate, and dorsum of her tongue (8). Lesions were described as “bright red dots, short lines, and spider like formations” (Figure 1). The patient died of intractable epistaxis, as did her father. Her brother, sister, and daughter had similar vascular abnormalities. In 1907, Parks Weber published a report about a typical family association, again emphasizing transmission by both sexes, with mucous membrane bleeding from telangiectases, especially the nares, and absence of any hemophiliac tendency (9). Osler's final article on this syndrome was published in 1907 in the Quarterly Journal of Medicine shortly after his arrival at Oxford (10). He added an additional family with at least 4 members affected and classified telangiectasia into 7 types, the last being the “multiple hereditary form with recurrent hemorrhage,” characteristic of this syndrome.
Two years later, a review of the 13 families described with this syndrome was published by
Hanes in the *Johns Hopkins Hospital Bulletin* (11). Dr. Hanes was a pathology resident at
the time and had been a first-year medical student at Johns Hopkins University Medical
School during Osler's last year there. Hanes described 4 generations of 1 family with
telangiectatic syndrome. One patient was a 32-year-old stonecutter with over 100
telangiectases scattered over his cheeks, ears, lips, and tongue. The lesions blanched on
pressure and regained color when pressure was removed. A diagram of his skin biopsy
showed enormous dilatation of blood vessels, seen as wide spaces lined by a single layer of
endothelium (*Figure 2*). These vessels could be traced into the subcutaneous fatty tissue. On
sections stained by various methods, no muscular or elastic tissue was noted in the walls of
the dilated superficial vessels. In this report, Hanes coined the most common name for this
syndrome, *hereditary hemorrhagic telangiectasia*, incorporating its 3 major clinical
features.

Little has been added to the diagnostic criteria of telangiectatic syndromes in the past 90
years. These disorders have a prevalence of 1:50,000, with complete penetrance by age 40.
They are autosomal dominant with a 20% spontaneous mutation rate. Epistaxis is noted in
90% of cases, and visceral lesions are common in the stomach, respiratory tract, bladder,
and liver. Pulmonary arteriovenous (AV) malformations are noted in 5% to 30% of cases,
with 30% to 60% of patients with pulmonary AV fistulae having these syndromes. Finally,
recurrent cerebral embolism and abscesses have been noted secondary to paradoxical
emboli.

Treatment options for hereditary hemorrhagic telangiectasia are limited (*Table*). Osler made
no mention of therapy in his 1901 article, except for the nasal tamponade for epistaxis
described by his third patient (1). Osler was often referred to as a therapeutic nihilist, given
his insistence on reviewing the proven benefits of drugs before recommending their use. In
his second article, he noted that calcium lactate had been prescribed by another physician,
with improvement of the patient's symptoms and a decrease in coagulation time (10). This
observation seemed irrelevant since coagulation times were normal in these nonhemophiliac
patients. Osler further stated that he used calcium chloride in his first patient without
success. No mention was made of iron supplements, as many of these patients almost
certainly were severely iron deficient from blood loss anemia. Ferrous sulfate in the form of
Blaud's pills was available at that time, as Osler noted in *Principles and Practice of
Medicine* (12). Blood transfusions were not an option, being popularized only after 1910.

<table>
<thead>
<tr>
<th>Table. Treatment of hereditary hemorrhagic telangiectasia</th>
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<td>1. Local therapy: tamponades, topical hemostatic agents,</td>
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<tr>
<td>laser coagulation, cautery</td>
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<td>2. e-Aminocaproic acid</td>
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<td>3. Hormones (estrogen, danazol)</td>
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<td>4. Surgery (septal dermoplasty, AV resections)</td>
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<td>5. Transcatheter embololtherapy for pulmonary AV fistulae</td>
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Local treatment is often applied for epistaxis, including tamponade, topical hemostatic
agents, laser therapy, or cautery. e-Aminocaproic acid, a fibrinolytic inhibitor, may be
effective in some cases of acute mucous membrane bleeding, especially from the mouth or
nose (13). Various hormones, especially estrogens and the attenuated androgen danazol, have been recommended. One of the additional patients in the family described by Hanes in 1909 was a 53-year-old woman whose bleeding had worsened over 2 years (11). Although Hanes did not make the clinical correlation, his medical history noted that her bleeding became excessive after menopause, at age 51. Since estrogens enhance vascular integrity, postmenopausal hormone replacement can be effective in this situation. Surgery has been used in limited cases, including septal dermoplasty for intractable epistaxis and resection of AV malformations. Finally, transcatheter embolectomy for pulmonary AV fistulae has been successful (14).

Some recent studies have provided new information on the etiology of hereditary hemorrhagic telangiectasia. Linkage studies have established in some families a locus to chromosome 9q33-34 at the endoglin gene, designated OWR1 (15). Endoglin is an integral membrane glycoprotein expressed on endothelial cells in arterioles, venules, and capillaries and serves as a binding protein or receptor for transforming growth factor b. This specific chromosomal mutation is associated with pulmonary AV malformations. Another locus, OWR2, has been linked to chromosome 12q and probably codes another receptor for transforming growth factor b (16). The earliest identifiable morphologic abnormality is postcapillary venule dilation, which ultimately results in direct arteriolar venular communication without intervening capillaries. Bleeding appears primarily secondary to inherent mechanical fragility of these vessels.

In addition to his contribution to hereditary hemorrhagic telangiectasia, in October 1907 Osler described a patient with a different purpuric lesion (17). This patient was a 39-year-old man with a 10-year history of purpuric mottling with resolving lesions that left a brownish stain. On examination Osler noted splenomegaly and patches of urticaria with marked dermatographia. No individual blood vessels were seen. Osler called this syndrome telangiectasia circumscripta universalis. Although no biopsy was ever obtained, Weber in 1930 assumed this was one of the earliest reports of adult urticaria pigmentosa or mastocytosis (18).

In conclusion, there remains the thorny issue of the most appropriate eponym for hereditary hemorrhagic telangiectasia. The syndrome is often called Osler-Weber-Rendu disease but has been termed Rendu-Osler, Osler-Rendu-Weber, Rendu-Weber-Osler, or just Osler's syndrome. Hanes readily admitted that Osler's 1901 paper accounted for the "growing knowledge of recurring hemorrhage of telangiectatic origin" (11). Yet Rendu clearly had the first complete published description of this disease, noting its heredity, its association with bleeding secondary to telangiectases, and its being an entity separate from hemophilia. There is little reason to include Weber, as his report in 1907 only added the 10th family described with this disease (9). Hence, the most historically correct eponym is probably Rendu-Osler disease.

Acknowledgment

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References


5. Chiari O. *Enfahrungen auf dem Gebiete der Hals und Nasenkrankheiten*. Wien, 1887;60 et seq.


Figure 1

Figure 2

B. V. = Blood Vessels.
C. B. = Closed Blood Vessels.
Epl. = Epidermis.
H. = Sheath of Hair Root.
Gl. = Gland of Hair Follicle.