A review of hereditary hemorrhagic telangiectasia

GENE E. GRAFF, D.O., MAJ., MC., U.S. ARMY
Frankfurt, West Germany

Hereditary hemorrhagic telangiectasia (HHT) is a disease of worldwide distribution. Its variable clinical manifestations include both mucocutaneous and systemic telangiectasias, with or without hemorrhage. The involvement of visceral organs and systems suggests that HHT is a generalized vascular dysplasia. Principal associated conditions can include pulmonary arteriovenous fistulas and central nervous system arteriovenous malformations with accompanying neurologic symptoms. Disseminated intravascular coagulopathy (DIC) may develop more frequently than heretofore suspected, and associated von Willebrand's disease has been described. Life usually is not shortened by HHT; nevertheless, epistaxis, the hallmark of HHT, must be treated since life can be difficult for these patients and unchecked bleeding can lead to fatalities. Various treatments employed include chemical and electrocauterization, electrocoagulation, laser therapy, radiotherapy, surgery, and grafting to cover stripped bleeding sites. The use of estrogen is probably not of significant clinical benefit.

Hereditary hemorrhagic telangiectasis (HHT) is an autosomal dominant, clinically variable disease consisting of mucocutaneous and systemic telangiectasias, visceral and central nervous system vascular anomalies, and possibly clotting defects. Clinical manifestations include mucocutaneous telangiectasias, which are often hemorrhagic, congestive heart failure with its protean presentations, and a myriad of neurologic symptoms, some of which can be profound.

History

The historical evolution of HHT as a disease entity began in the mid 1800s. Sutton, in 1864, gave the first account of hereditary epistaxis.[1] One year later, Babington also described a family with recurrent hereditary epistaxis.[1-4] Eleven years later, Legg described familial telangiectasias.[2,4] The association of multiple telangiectasias with epistaxis was described by Rendu in 1896.[1-4]

Osler, in 1901, and Weber, in 1907, were instrumental in establishing HHT as a syndrome apart from other hemorrhagic disorders,[1,2,4] although it was not until 1909 when Hanes proposed the term "hereditary hemorrhagic telangiectasia" that this disorder actually received its name.[3,4] Because of their contributions to our knowledge of this disease, synonyms bearing their names were coined, including Osler's disease, Rendu-Osler-Weber disease, and Sutton-Babington-Rendu-Osler-Weber disease.

Evidence was mounting that HHT affected not only mucocutaneous surfaces, but other organs as well. In 1917, Wilkens described a patient with epistaxis, telangiectasias, clubbing of fingers, cyanosis, and dyspnea.[4] Goldstein, in 1921, reported the case of a young patient with HHT who suffered a stroke.[3] In 1932, Reading described the triad of cyanosis, polycythemia, and clubbing of fingers associated with pulmonary arteriovenous fistula (PAVF).[4] The association of HHT with PAVF was stressed by Rodes in 1938, thus establishing PAVF as a common finding in the disease complex of HHT.[2,4] One year later, in 1939, Smith and Horton emphasized the value of arteriography in the diagnosis of HHT with PAVF.[4]

In more recent years, new associations have been found. In 1964, Graham described a patient with HHT, hepatic artery aneurysm, and portal vein fistula.[6] Later, in 1978, Radtke and coauthors[6] reported two cases of congestive heart failure which were found to be secondary to HHT with hepatic arteriovenous (A-V) fistula. In 1976, Waller and coworkers[2] reviewed the 14 cases of cerebrovascular malformation associated with

HHT in the literature, and added 3 of their own.

Quick, in 1967, first suggested the relationship between von Willebrand's disease and HHT.[5] In 1978, Pandolfi and Ehinger[7] described a patient with HHT and an associated platelet dysfunction, and Conlon and associates[5] reported on two families with von Willebrand's disease and HHT. Román and coauthors[3] reviewed the neurologic manifestations of HHT.

Bourdette and Greenberg,[8] in 1979, described a patient with gastrointestinal bleeding, aortic stenosis, and HHT. This association was also noted by Weaver and associates,[9] who described two similar patients, in addition to others with gastrointestinal and cardiac abnormalities as the only manifestations of the disease. They preferred to call these vascular changes "angiodysplasia."

Incidence and genetics

HHT is inherited in an autosomal dominant fashion with wide clinical variability.[10] The homozygous state for HHT is lethal.[11,12] Atavism, if it occurs at all, is quite rare.[3,10] Although it was previously held that one tenth of those with the trait showed telangiectasias and A-V fistulas, that estimate is now much higher.[1] It has been suggested that the gene responsible for HHT may be linked to blood group O.[11,12] The mutation rate in HHT is estimated to be about $2\text{-}3 \times 10^{-6}$.[3]

The incidence of HHT is 1-2 per 100,000 (European figures).[1,3] HHT has a worldwide distribution and affects all races,[3,10,13,14] although those most commonly affected are the Anglo-Saxon, Latin, Scandinavian, and Jewish.[13,14] Until 1978, only fourteen blacks (nine in one family and three in another) and one Chinese family had been reported with HHT.[14]

Clinical manifestations

The cutaneous telangiectasias in HHT most commonly involve the upper trunk, face, ears, hands, nailbeds, and palms.[2,10,15] The forearms, soles, toes,[15] and, indeed, any site may be involved. Usually, the telangiectasias appear in adolescence or in the third decade.[2,10] They can, however, appear in childhood at around 8-10 years of age.[10] Most lesions are 1-4 mm. in size, and are punctate, marginate, flat[2] and bright red to purple.[10] They have been described as tightly woven mats of telangiectatic vessels,[10] which appear initially as red dots, and can be elevated.[2] Diascopy may[10] or may not[2] cause blanching. Older lesions tend to remain as new ones arise, occasionally forming a linear distribution.[15,16] The clinical variability of the lesions is moderate; pinpoint, spider, and papular lesions have been described.[13] The spiderlike lesions are not reported to pulsate,[15,16] and most often occur in the elderly.[13]

Telangiectasias of the mucous membranes can affect the lips, tongue, palate, buccal mucosa, gingiva, nasal mucosa, nasopharynx, pharynx, larynx, conjunctiva, and vagina.[7,10,13,15] Typical lesions of the tongue include expanded fungiform papillae containing a dilated vessel.[15] Lesions of the oral cavity also have been described as nodules, papules, ulcers, and hemorrhagic vesicles.[17] Epistaxis, often triggered by coughing and sneezing, is the clinical hallmark of HHT[10,11] and is the most common presenting complaint.[13]

Although the majority of patients present with only mucocutaneous lesions, systemic involvement in HHT may include any one or any combination of the following organs or systems: brain, spinal cord, retina, thyroid gland, lungs, liver, spleen, pancreas, prostate, cervix, bladder, urethra, diaphragm, vertebrae, major arteries including aorta, kidneys,[1,3] heart,[6] meninges,[10] esophagus, stomach, intestine, uterus,[13] and joints.[11]

From this exhaustive list, one can readily surmise that HHT is a generalized vascular dysplasia, as suggested by Weaver and associates.[9] Hemorrhage is usually manifested by epistaxis, followed by oral, gastrointestinal, genitourinary, and pulmonary bleeding, in descending order of frequency.

PAVF are found in approximately 7-10 percent of families with HHT[3] and affect the sexes equally. Younger patients are usually not affected with PAVF.[10] Conversely, 49 percent of patients with PAVF have a family history of HHT,[3] and 66 percent of patients with PAVF have mucocutaneous telangiectasias.[3] Thus, HHT is the most common cause of PAVF.[15] In patients with PAVF, increasing age is associated with a higher frequency and greater number of mucocutaneous telangiectasias, so that over 90 percent of those over the age of 60 years demonstrate such telangiectasias.[3]

The symptoms of PAVF are quite variable, although they classically include dyspnea, cyanosis, clubbing of fingers, and polycythemia.[4,10,15] Polycythemia may lead to thrombosis and central nervous system symptoms, and occurs in over 50 percent of cases.[4]

A pulmonary-artery-to-pulmonary-vein fistula leads to cyanosis, polycythemia, and finger clubbing if greater than 25-30 percent of the blood is being shunted.[4] Systemic circulation to pulmonary vessel fistulas cause less shunting and fewer symptoms. In decreasing frequency, shunting involves the right lower lobe, left lower lobe, right middle lobe, left upper lobe, and right upper lobe.[4]

Neurologic symptoms in HHT most commonly

are secondary to PAVF.[3] In a review of 392 cases, Román and coworkers[3] found that one third of those with PAVF had neurologic symptoms, and 65 percent of these had features fulfilling the criteria for HHT.[3] These authors[3] cited Gomez's observations that in patients with PAVF and HHT, the frequency of multiple PAVF is higher, symptoms progress more rapidly, and the rate of complications is greater. Neurologic symptoms secondary to PAVF are usually secondary to the right-to-left shunt with resulting decreased cerebral blood flow. Continuous murmurs over the fistulas can be heard in approximately 50 percent of cases.[4] One case of central nervous system involvement secondary to air embolism from the PAVF to the brain has been reported.[3] Transient ischemic attacks and paradoxical embolism can occur when peripheral venous emboli pass through the PAVF and proceed to the brain.[3] Brain abscess occurs in about 5 percent of cases with PAVF and can be the initial manifestation of such fistulas.[3] Septic emboli, most commonly of anaerobic bacteria, can lead to abscess formation, bacterial encephalitis, or meningitis.[3] Román and associates[3] described a resulting cerebellar abscess. They also cited Davidson and Robertson's case in which Aspergillus caused a basilar artery aneurysm.[3]

Neurologic symptoms secondary to PAVF include diplopia, dysarthria, focal and generalized seizures, paresthesias, pareses, recurrent syncope, vertigo, and visual and auditory disturbances.[3,4] Symptoms tend to be transient and recurrent; however, deficits may become permanent.[3] A concise summary of the causes of central nervous system involvement in HHT was published by Román and coworkers,[3] and is shown in Table 1.

Hepatic involvement in HHT may include vascular lesions, cirrhosis, or both.[6] Vascular lesions include cavernous hemangiomas, hepatic artery aneurysm, hepatoportal and hepatohepatic arteriovenous fistulae, and smaller telangiectasias.[1] Abnormal bruits may be audible.[6] An atypical, coarse, nodular type of cirrhosis is found in HHT,[1] which has been termed "Osler's atypical cirrhosis," or "cirrhosis telangiectasia hepatis."[3] Prominent hepatomegaly may be appreciated, often extending up to 18 cm. below the costal margin.[3] Fifty percent of cases with hepatic involvement have pain in the right, upper abdominal quadrant and 50 percent have associated splenomegaly.[3] Hepatoma,[11] portal hypertension, and portacaval encephalopathy have been reported. In cases with liver involvement, histologic study may show a thickened capsule with increased subcapsular vascularity.[1] Broad bands of fibrosis with varying sized telangiectasias and irregular septa formation are noted. In some areas, connective tissue is infiltrated by lymphocytes, histiocytes, and plasma cells. The extending fibrosis seems to carve out parenchymal lobules of varied size, a feature similar to the pseudo-lobule formation seen in the Laennec type of ordinary cirrhosis.[1]

TABLE 1. SUMMARY OF CENTRAL NERVOUS SYSTEM INVOLVEMENT IN 392 PUBLISHED CASES OF HHT.*

Kind of lesion	Percent	
Complications of PAVF (excluding brain abscess)	48.4	
Brain abscess	13.0	
Vascular malformation of the brain	27.9	
Cerebral telangiectasias and angiomas		16.7
Cerebral A-V malformations		7.9
Aneurysms		2.8
Carotid-cavernous fistula		0.5
Spinal cord A-V malformations	7.9	
Portal-systemic encephalopathy	2.8	

*Reproduced in modified form, with permission, from Román and coworkers.[3]

Cardiac failure secondary to profound left-to-right hepatic shunt can occur, with its resulting pulmonary and central nervous system manifestations. Elderly patients seem particularly prone to this,[1] as do postmenopausal women. As reported by Radtke and associates,[6] two patients who underwent cardiotomy for repair of an assumed atrial-septal defect (ASD), actually had hepatic A-V fistulas with secondary congestive heart failure. Hepatic artery ligation corrected their malady. Liver function is usually well preserved in patients with hepatic involvement, although a slight increase in alkaline phosphatase and bilirubinemia is fairly common.[3]

The gastrointestinal tract may be involved in HHT. Gastric, duodenal, and intestinal telangiectasias may lead to nausea, hematemesis, and melena. In 1958, Heyde first reported several cases associated with severe calcific aortic stenosis, in whom an associated gastrointestinal hemorrhage originated in the right colon. A patient with gastric and duodenal bleeding was reported by Bourdette and Greenberg.[8]

The genitourinary tract may be involved in HHT, and hematuria may originate at any point from the kidney to the urethra.[4,7,11,12]

Retinal as well as conjunctival hemorrhage has been noted in HHT. An associated platelet dysfunction (a qualitative aggregation defect), which contributed to the hemorrhage, was reported in one patient.[7]

Anemia secondary to bleeding, often with evolving iron deficiency, occurs in HHT.[11,18] Polycythemia may occur via the mechanism previously dis-

cussed. Von Willebrand's disease has occasionally been found to be associated with HHT,[5,12,25] and results from a qualitative or quantitative defect of the FVIII-vWF portion of factor VIII, which is synthesized by endothelial cells.[5,12] It induces platelet agglutination in the presence of ristocetin (a glycopeptide antibiotic). The association of factor XI deficiency and HHT has also been noted.[12] Hopefully, further delineation of these associations will be made in the future.

A fibrinolytic system defect has also been described.[11] Disseminated intravascular coagulopathy (DIC) may occur in HHT. A recent study by Bick has shown that the acute, rather than chronic, form of DIC is more common than had been previously realized.[12] If sought carefully, DIC can be found in about 40-50 percent of patients with HHT. Thus, a Kasabach-Merritt-like syndrome may exist.[11,12]

The histologic and pathophysiologic alterations in HHT involve small arteries, arterioles, capillaries, and venules.[1] The arteriolar changes include intimal proliferation with some thrombus formation, whereas the capillary changes consist of a network of aneurysmal communications. The most conspicuous findings occur in the venules,[1,3] which have longitudinal muscle bundles and an outer ring of muscle. They appear to have the chief role in the pathogenesis of "Osler's vessels" by contracting to cause stasis and the resultant distended capillary network.[1] Defective overlapping of terminal villi in intraendothelial junctions occurs in such vessels.[1] It is difficult to determine from the literature the role of degenerated perivascular connective tissue and elastic fibers.[1,3]

Differential diagnosis

The differential diagnosis of HHT includes other bleeding diastheses, especially von Willebrand's disease.[10] Other telangiectatic diseases, such as calcinosis-Raynaud-scleroderma-telangiectasia (CRST) syndrome[16] and multiple phlebectasias of the scrotum, oral cavity, and jejunum must be considered. However, calcinosis, Raynaud's phenomenon, and sclerodactyly are absent in HHT, and multiple phlebectasias are not familial.[16] Fabry's disease and Degos' disease must also be considered. Rook and coworkers' *Textbook of dermatology*[15] tabulates all those disorders that also may be considered in the differential diagnosis.

Prognosis

HHT does not usually lead to a shorter lifespan.[10,15] Demis[10] cites a 4 percent death rate from HHT and its complications, and Rook[15] states that the mortality is less than 10 percent.

Treatment

The treatment of epistaxis must be pursued in nearly every case. Septal mucous membranes are the usual sites of hemorrhage. Fatalities have resulted from unchecked bleeding from these locations.[19] Treatment modalities include tamponade[10] and vasoconstrictive nasal sprays, which often eventually prove inadequate. Adrenosem, 5-10 mg. by mouth every 3-4 hours, has been recommended for mild gingival, oral, or nasal bleeding.[11] Chemical or electrocauterization may be employed.[10,19] Excellent results have been obtained using the carbon dioxide laser,[19,20] and in a recent study, photocoagulation of nasal hemorrhage sites with the argon and Nd:YAG lasers provided excellent results.[20] Estrogen[1,10,11,21] or estrogen and progesterone combined[18] have been used to induce squamous metaplasia or keratinization of involved mucosa; however, there has been much controversy regarding the efficacy of this treatment.[22] Indeed, Vase, in a recent study, found oral estrogen to be of no practical value in reducing nasal hemorrhage in patients with HHT.[22] Small doses, as provided in oral contraceptives, may worsen the bleeding.[15]

Various kinds of grafting procedures and materials are now being used to cover stripped bleeding sites. Cutaneous grafts seem inadequate, since the grafts are not self cleansing and therefore tend to be malodorous.[22,23] They often shrink and tear away from the site. Mucosal grafts have been employed with some success, but the most exciting results with graft material include the use of chorion and/or amnion.[23] Amnion has powerful hemostatic properties, and trophoblasts are immunologically privileged, thus rejection is negated. Such grafts are not malodorous. Arterial embolization of nasal vasculature under arteriographic control has been attempted; however, permanent facial discoloration and pain may result.[22]

Visceral hemorrhage may be treated with endoscopic laser,[1] electrocautery,[14] electrocoagulation,[9,14] radiotherapy,[25] or surgery.[10] Brown and coworkers described a case in which staged bilateral thoracotomies were successfully performed to remove multiple A-V malformations in a 19-year-old man.

Supportive measures may include transfusion,[7,14] ferrous sulfate if iron deficiency has evolved,[14,15] and the avoidance of trauma or of strong Valsalva's maneuver. Acute DIC in HHT has been noted to respond to mini-dose heparin therapy or antiplatelet therapy.[12] If an associated platelet defect is suspected, antiplatelet drugs such as indomethacin, aspirin, dextran, or banked blood should be avoided.

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From the Dermatology Service, Fitzsimons Army Medical Center, Aurora, Colorado. Major Graff is now with the Dermatology Service, 97th General Hospital, Frankfurt, West Germany.

Dr. Graff, Dermatology Service, 97th General Hospital, Frankfurt-APO, New York, New York 09757.

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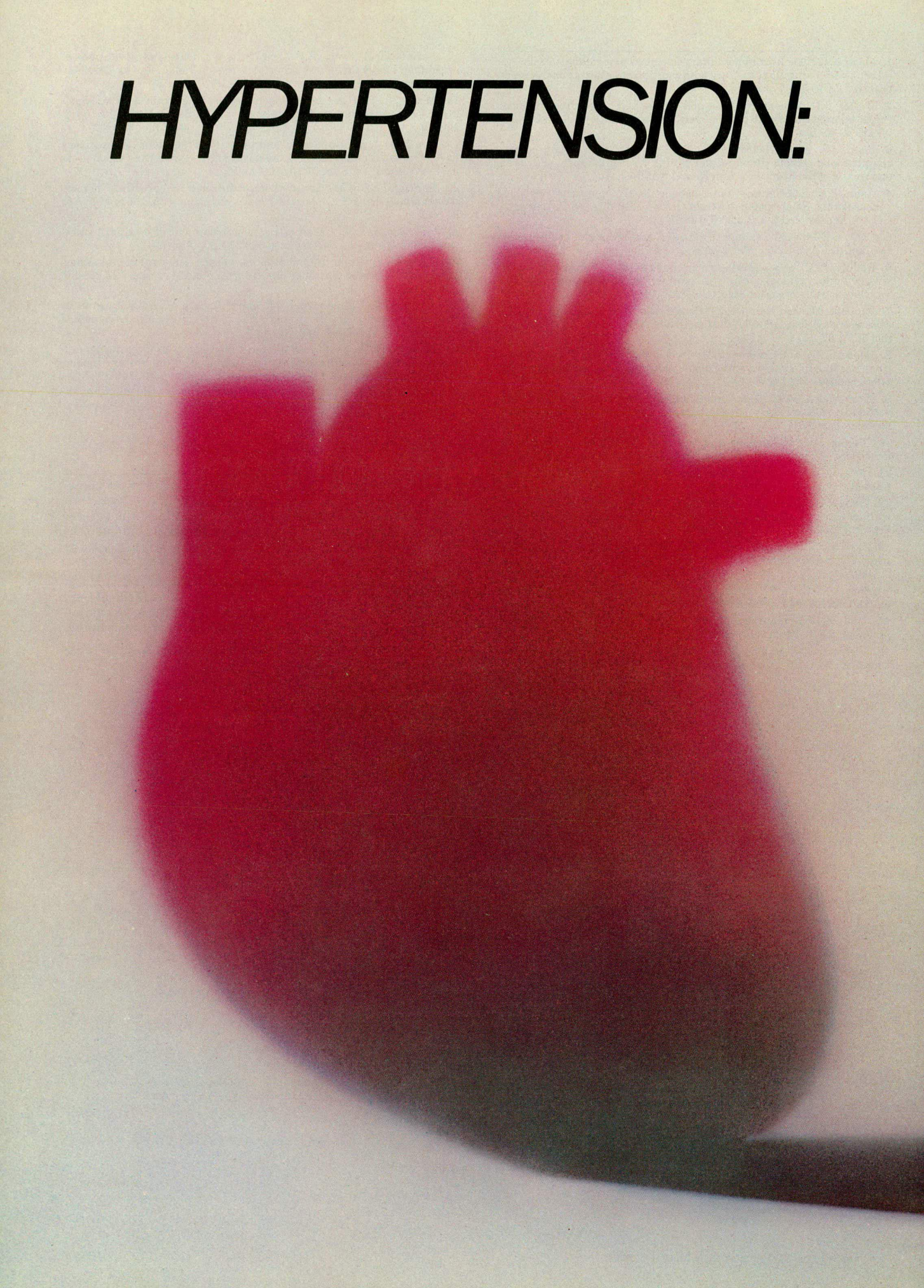

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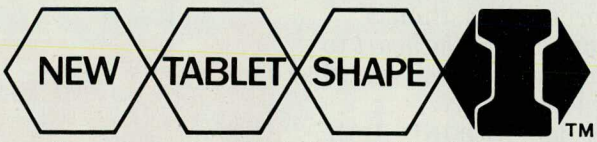

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IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Give special consideration to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol should be withdrawn slowly, since abrupt withdrawal may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

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Observe laboratory parameters at regular intervals. Use with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura. *Central Nervous System:* lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. *Gastrointestinal:* nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis. *Allergic:* pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress. *Respiratory:* bronchospasm. *Hematologic:* agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. *Miscellaneous:* reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta-blocker (practolol) have not been conclusively associated with propranolol. *Clinical Laboratory Test Findings:* Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

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TABLETS

—Each hexagonal-shaped, orange, scored tablet is embossed with an "I" and imprinted with "INDERAL 10," contains 10 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0421-81) and 1,000 (NDC 0046-0421-91). Also in unit dose package of 100 (NDC 0046-0421-99).

—Each hexagonal-shaped, blue, scored tablet is embossed with an "I" and imprinted with "INDERAL 20," contains 20 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0422-81) and 1,000 (NDC 0046-0422-91). Also in unit dose package of 100 (NDC 0046-0422-99).

—Each hexagonal-shaped, green, scored tablet is embossed with an "I" and imprinted with "INDERAL 40," contains 40 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0424-81) and 1,000 (NDC 0046-0424-91). Also in unit dose package of 100 (NDC 0046-0424-99).

—Each hexagonal-shaped, yellow, scored tablet is embossed with an "I" and imprinted with "INDERAL 80," contains 80 mg propranolol hydrochloride, in bottles of 100 (NDC 0046-0428-81) and 1,000 (NDC 0046-0428-91). Also in unit dose package of 100 (NDC 0046-0428-99).

The appearance of these tablets is a trademark of Ayerst Laboratories.

Store at room temperature (approximately 25° C).

INJECTABLE

—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as 1 ml ampuls in boxes of 10 (NDC 0046-3265-10).

Store at room temperature (approximately 25° C).

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Reference: 1. Freis, E.D.: Hypertension (Suppl. II) *3*:230 (Nov.-Dec.) 1981.

Ayerst AYERST LABORATORIES
New York, N.Y. 10017