RARE DISEASES AND LESIONS

Their Contributions to Clinical Medicine

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Archives of Internal Medicine, 1962-1966
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With a Foreword by
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Wayne County Medical Society
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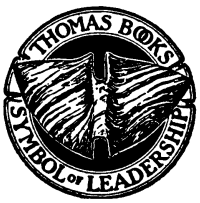

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Dedicated to the Victims of Rare Diseases

I hope that the spirit of this small book reflects my devotion to the victims of rare disease. Their quiet courage is a lesson in patience. Their help in letting us study them adds to our knowledge, with the hope that someday we may control or eradicate the biological troubles they so unhappily exemplify. Thus far our fate is to cure hardly at all, though we help sometimes and try to comfort always.

Foreword

I CAN THINK OF AT LEAST four reasons that rare conditions are, or should be, of interest to physicians. One reason these rare disorders can teach us much about the normal or about more common disorders was better stated in 1657 by William Harvey than I can express it:

> Nature is nowhere accustomed more openly to display her mysteries that in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of Nature by careful investigation of cases of rarer forms of disease. For it has been found, in almost all things, that what they contain of useful or applicable nature is hardly perceived unless we are deprived of them, or they become deranged in some way.

In the second place, these rare manifestations are sometimes valuable clues to the existence of grave internal disease.

In a third place, people have them. It is no consolation to the victim of the disorder that he is one in a million. He still has a right to as thoughtful management as the patient with a run-of-the-mine condition.

Finally, they are fun. They introduce variety into the humdrum of the physician's daily routine. They keep his powers of observation from undergoing atrophy. They stimulate his thinking about mechanisms in clinical problems which may otherwise become stultifyingly commonplace.

William Bennett Bean is one of that now rare species of clinician primarily interested in what his native senses can teach him about disease. This latest sharing of his clinical scholarship is much appreciated.

VICTOR A. MCKUSICK, M.D.

Preface

THE GOVERNORS OF The Beaumont Lectureship have decreed that the lecturer must prepare a book based on, or related to, his lecture. This stipulation saved me for a time from giving the lecture, but at length I relented. Now I am repenting. The obligation did force me to go over a large and motley collection of rare diseases which a wide clinical overview and much reading have helped me to accumulate in my incorrigibly growing files and among my papers. Any thought of making this book all-inclusive is defeated by the rapid discovery of new diseases and the necessity of keeping the survey down to manageable size. I had no such intention, anyhow. Gould and Pyle have usurped the field in *illustrating* the outrages of deformity and freaks. I have resisted the temptation to make this a *gallery* of the unfortunate or ugly. McKusick has brought new insights from his personal experiences with those diseases, for which his writings serve as a complete encyclopedia. My comments will not go much beyond definition. Jonathan Hutchinson and Parkes Weber, omnivalent gentlemen on the clinical scene, and the last of the great generalists, are no more. I follow as a gleaner.

My hope is that this contribution will serve as a range finder, a reference work eclectic and general, but a personal document, perhaps even whimsical in its selections. While designed for those with some experience, it should guide the novice in his further search for the understanding which continual diligence may help ripen into clinical wisdom.

I have used eponyms, though I am against them. One reason for retaining eponyms is to help the reader find what he is looking for. It may be the only clue he has. Where the descriptive name is not too long, it will be used, but even the wrongly-attributed Fabry's syndrome is more simple than *angiokeratoma corporis diffusum universale.* Even *congenital dysplastic angietasis* is

better than the Sturge-Weber-Dimitri-Krabbe-Lannois-Bernoud-Klippel-Trenaunay syndrome. The term "Hurler's syndrome" at least spares the parents from cringing at the horrid label *gargoylism,* which adds the insult of a cruel name to a tragic disease. Osler's disease says in four short syllables what hereditary hemorrhagic telangiectasia manages in more than four times that many. Thus though they often wrongly credit some latecomer, eponyms are not yet finished, despite Ronchese's wise comment that ". . . calling a disease by the name of the author or authors responsible for the first or the best paper is itself a disease afflicting medical writing."

Naming a disease should describe it. For that reason, a glance at some of our ideas of disease and their evolution is timely. "Naming" *per se* will be considered as an epilogue.

About Causes of Disease

Christening or labeling common diseases is a problem of no mean proportions. It is multiplied and magnified when we come to the rarer forms of disease. A study of rare disease encompasses the whole story of medicine — what doctors and people have thought about disease, and how they acted on their doctrines and dogmas. So it is not out of place in an essay on rare disease to consider briefly what we have learned about how man as sufferer, observer and helper, has confronted pain, injury, and the patterned responses to disturbing stimuli which constitute those ever-changing processes which we think of erroneously as states and call diseases. Here are some of the ideas.

Ontological Concept of Disease

Man's original notion of disease still prevails, especially in sophisticated folk confident of the rectitude of their errors, as well as in primitive persons all over the world. It supposes that there is a literal invasion of the victim's body by a demon, an evil spirit, or a magic spell. Treatment is to exorcise the demon, kill it, or atone for some putative sin. Thus, therapy is a mystical exercise in counter magic. It succeeds wherever the mere passage of time lets nature heal. Since this is usual for most hurts, harms, and aches, the usual homeopathy and chiropractic fancies, measur-

ing people's gullibility, abound. They will last as long as a temporal sequence is believed to represent cause and effect.

Platonic Concept

With the Greek discovery of abstract thought, the life and health of a person were assumed to be related to the fabric of the universe. Obviously men and their diseases must be made up of earth, air, fire, and water. Illness was a preponderance of one or another of the humoral counterparts of these four in the body. Sanguine or melancholy, choleric or phlegmatic they were; or if some bad element like lead crept in from outside, it might be saturnine. Such ideas are all very stimulating, but there was no place to hook firmly into reality. Words and ideas were confused with things. It was bewildering rather than illuminating. It is still.

Anthropologic-Biographic Concepts

The Hippocratic reaction to earlier abstraction was to particularize and make the experience of illness descriptive at the level of one person. Though anecdotal, it focused on the patient, the temperament, the place, the diet, and the climate. Without wisely-compared controls, this idea ran aground on *post hoc* reasoning, but it always kept near reality. The method was slowly self-correcting — homeostatic rather than homeokinetic. Finally, this attitude was responsible for gathering the data from which science could at length emerge.

The Ostrich Concept

This dealt with disease by the cheerful approach of denying its existence, vetoing reality, and saying that the external world is void and null. Such attitudes recur in a patient's unwillingness to believe that he could have a serious or fatal disease. He rationalizes it away. It is seen in the physician's general neglect of his own health and medical attention.

The Punitive Concept

This variation on the ontologic view reckons disease as retribution. The greedy man who seeks gratification and satisfaction

lery of connoisseurs of rare disease. Garrod conceived the notion, as well as the title of "inborn errors of metabolism." He recognized that even in well and normal persons different metabolic capacities varied from one to another, depending on each person's hereditary legacy. Gross inborn errors of metabolism are extreme degrees of such variations. He thought that they depended on inadequate or absent enzyme activity of a very specific sort. He identified the precise locus where, in the progression of chemical reaction, stumbling occurs and some compound piles up when a deficient enzyme fails to make the next step. The accretion of natural substances in such abnormal amounts then causes the trouble.

Usually ochronosis is asymptomatic in childhood. Only in adult life does the pigmentation of cartilages cause cosmetic distress at a time when there is a destructive effect on joints. Pigment granules may be deposited in the dermis and the sweat glands, giving a faint bluish or brownish tint to the skin. Deposits accumulate in the sclera, cornea, conjunctiva, tarsal plates, eyelids, ears, and the cartilage of the nose. The discoloration of the cartilage of the joints usually is not seen. The disorganization of cartilage has its most severe clinical manifestation in effusion into joint spaces, and protrusion of the intervertebral discs, causing backache. Spondylosis is apt to occur. As a rule, large joints are more seriously affected than small ones.

Of the more than six hundred reported examples, about 60 percent have been men. This might suggest a lethal effect on females, but there is no evidence to support this idea. Perhaps because men are more likely to have routine examinations in industry and for military service, more men are discovered with the disease.

People living in all parts of the world, and of all varieties of skin color, are susceptible to the disease. It has been suggested that the spondylosis of an Egyptian mummy was of the ochronotic type. Perhaps this qualifies alkaptonuria as the historic grey beard of all inborn disorders of metabolism.

The majority of reported pedigrees suggest that a simple autosomal recessive type of inheritance is responsible, but some dozen pedigrees have been interpreted to indicate that a genetic Men-

This idea is helpful when one understands the kaleidoscopic multiplicity of the intricate interplay of forces and responses, structures and functions. Multiple causality ultimately helps us toward an understanding of the departures from health, which we call disease.

Psychologic Concept

When man had been frustrated regularly in trying to understand his ails and ills by contemplating the attitude of the stars or the workings of spirits, demons and gods, he began to look to his own mind and emotions in an effort to understand disease. It is speculative because it is subjective. How much we can liberate man by moving his destiny from the arena of objective events to conflicts, matters of conscience, and the unconscious forces of our drives? instincts, and adaptations? A little further, but by no means all the way.

Socio-economic Concepts

The diseases of cities, of armies, of sailors, and of miners revealed the need for large-scale protection of populations. Individual adaptations to extreme environmental changes, or ways to engineer the environment, occupy an area of medical study which contributes further to the understanding of disease. The nosographic-biographic concept is partially anecdotal, partially evolutionary, and is based on the anatomic, physiologic, etiologic concepts. These are aided to some extent by psychological, social and economic factors, but the concept rejects the ontologic, platonic, and the metaphysical concepts. This approach has never quite resolved the conflict between overgeneralization and over-individualization.

Ecologic Concept

Each man's genetically unique structure, his predetermined functions, his intellectual and biological memory of racial history and of his own past experience, are under constant pressure to change. A continually varying, but always substantial cluster of external and internal stimuli call for constant homeokinetic ad-

justments. Man's potential for adaptation, reaction, repair, and renewal, vary widely. When they are inadequate or fail, we fall sick. We are ill. We have disease.

Firm belief in any *a priori* system of medicine tends to disqualify the mind for correct observation, since everything is seen through the astigmatic eyes of bias. While the history of medicine is padded with names of persons famous for experiment, for learning, for reasoning, or for speculation, very few physicians are remembered as distinguished *observers,* of either nature or anything else. This review of ideas about disease may help us in a survey of bewildering, irrational and thoroughly inconsistent ways in which disease has been feared, studied, and treated. We can utter the hope that as disease processes come to be understood better, the name will reflect a key element of the disease. Then we can gently bow farewell to eponyms.

I have no thought that anything so rational will ever happen. Even if we omit our historic interest in the names of early describers of disease, eponyms are useful, short, and simple. This is especially true if we do not know enough about the nature of an illness to give it a *denoting* name. But it is of more than passing import to see how often an eponym is chosen with the chauvinistic fervor of the bigot, but with small regard for discovery or priority. Multiple eponyms ligatured together with a dash are as artificial and revolting as the dreary verdure of Latin dermatological jungles in medicine, with which the would-be wise have long gulled the innocent. Happily, we are emerging from those swamps, we hope not just to be stifled in the shops of the chemists who are advancing rapidly in a hectic revolution; or bewildered by the squashed cells and chromosomal paper dolls of the geneticists; or lost in the mass movements of the public health devotees, or drowned in the logarithmic unleashing of the population explosion.

I have tried in each case to find the earliest person with whom to identify the particular diseases I have discussed, as well as a good recent paper or review. But not all the electronic nets of retrieval and recall can keep this book from being a patchwork quilt, put together helter-skelter in time stolen from the variously

somber, exciting and rewarding tasks of not only departmental and editorial duties, but also family duties and delights.

WILLIAM B. BEAN

Acknowledgments

To write a book on rare disease while serving two fulltime sentences, being head of a busy Department of Internal Medicine and the editor-in-chief of the *Archives of Internal Medicine* connotes near madness. I had parried several blows before I succumbed to John Dorsey's pressure and blandishments and delivered the Beaumont Lecture in Detroit in 1965. I realized that I had hung an albatross around my neck — the promise to produce the manuscript for a book. What had seemed mere folly, the exacerbation of a chronic plight of overcommitment would have proved fatal but for the skillful work and steadying hand of my superb secretary, Miss Phyllis Shay. During 1966, the year the manuscript was finished, a concatenation of evil chances had the unholy result of my having five different girls run the mysterious machinery of editing the *Archives of Internal Medicine,* riding herd on over six hundred manuscripts. A series of maddening crises punctuated the vexing musical chairs displacement of editorial secretaries. Frequently Miss Shay had to bail out the foundering Archives boat and run the department at the same time. In the latter gestational stages of the manuscript, I had real help from Miss Peggy Louvar and Miss Carol Schuster, whose diligence and compulsive accuracy, particularly in matters of bibliography, were a marvel to behold.

Mr. Charles Thomas and his son Payne, with their efficient army of assistants, have been helpful. Dr. Hans Zellweger, Dr. John Hoak and many other colleagues have contributed ideas and facts. I thank Dr. John Talbott and Mr. Robert Mayo of the AMA journals for permitting me to use materials which appeared first in the *Archives of Internal Medicine.* I must also thank innumerable friends and thoughtful strangers who have told me of patients, sent me papers, written to me or discussed victims of rare diseases. They have added to my experience and ripened my

knowledge. I take full responsibility for the errors, oversights or misconceptions which unhappily but infallibly get into a survey of this kind. I welcome suggestions for improvement.

I am grateful beyond words for the admirable and undeserved forbearance of my wife and our children. Though they seemed somewhat bewildered when they learned of my project, they were patient and tolerant of any crotchets and peevish reactions to all-encompassing pressures. And finally I must mention my indebtedness to Dr. Victor McKusick for his sustained stimulation and his kind Foreword.

W. B. B.

Contents

RARE DISEASES AND LESIONS

Bleeding from the Gut in Rare Disorders with Diagnostic Lesions of the Skin and Mucous Membranes

Introduction

BLEEDING FROM THE GUT may be flagrant, excessive, and promptly fatal. It may be a slow cryptic seepage of blood indicated by anemia and detected only by refined chemical means. Large quantites of blood may be lost by hematemesis or melena, and large or repeated small amounts may be lost through secret erosion. However it occurs, bleeding from the alimenetary canal is a major problem for physicians and surgeons alike. Perhaps one of the most inauspicious indications for any operation is severe bleeding from an unknown site or sites in the alimentary canal. Every careful report of a large number of patients with bleeding from the alimentary canal contains an unhappy category, "cause unknown." This may range from a small percentage to about a quarter of the total, depending on the nature of the clinical experience, the skill and honesty of the physician and other variables. It is toward the reducing of this group, even by a little, that a consideration of rare diseases which cause such bleeding is emphasized here. This is important, not only because it may give the satisfaction of making a correct diagnosis, but because in certain patients the indications for at least one exploratory operation may be very great. In others, any operation is likely to be foolish or fatal; in a few, the indications for an operation are vague and uncertain. Vascular spiders and palmar erythema suggest cirrhosis. But this is common. In addition to the conditions which I shall discuss in this chapter, and a few others such as Maffucci's syndrome (treated elsewhere) I should mention an occasional patient with Turner's syndrome who has a vermiform transformation of the small intestine into what looks like a bag of worms. The racemose varicose cluster may bleed and exsanguinate the

victim. The bowel may be occupied by angiomas and phlebectasias in Maffucci's syndrome. Angioreticulomatosis, or Kaposi's sarcoma with visceral involvement and diagnostic skin lesions, is another such rare disease.

Each of the entities to be discussed may be the cause of severe or chronic bleeding from the alimentary canal. If such bleeding occurs in a patient in whom the diagnosis of one or another of these conditions is made, the inference is natural that specific lesions related to the particular disease cause the bleeding. But it should be remembered that patients with rare disease may bleed from commonplace lesions. Do not forget the possibility that peptic ulcer, neoplasm or something else may cause the bleeding in a patient with a rare disease. There is no reason to suppose any of the conditions considered in this chapter confers immunity from any of the more common causes of enteric bleeding.

Hereditary Hemorrhagic Telangiectasia (Osler's Disease)

Hereditary hemorrhagic telangiectasia has an interesting history. The eponym "Osler's disease" is convenient and well-deserved. It is the first bleeding disease for which a cause was recognized. It is not a fault in clotting mechanisms, but a flaw in the vascular fabric which normally provides the vital self-sealing vascular element of hemostasis. The disease seems to be increasing in frequency, or interest in it is causing a kind of gravitational flow in my direction. This seems to be true with many rare diseases.

About a hundred years ago, Babington (commenting in a letter to the *Lancet* on Sutton's report of curious examples of increasing nosebleeds) recorded a family with hereditary epistaxis in five generations. He did not refer to skin lesions. Legg in 1876, described "a case of hemophilia complicated by multiple nevi." The assumption is even stronger that it was Osler's disease. Chiari described another probable case in 1887. Then Rendu described briefly the clinical features, especially the lesions of the skin, and called the disease *pseudohemophilia.* Chaufford and Kopp reported early examples.

These physicians had no clear comprehension of the nature of the disease. Some reported only one patient or one kindred. Early in the twentieth century Osler established the true character of the disease. He separated it from the vague but troublesome collection of the then-mysterious hemorrhagic diseases. He recognized that clotting was not at fault; that bleeding resulted from disease of the blood vessels. He reported several kindreds. Parkes Weber elaborated upon these points. He emphasized the lack of sex-linked transmission and the fact that nosebleeds might occur before telangiectases appeared. Hanes made a detailed study of the histopathology, emphasized lesions in the nail beds, the atypical dilated telangiectatic vessels scattered in the skin, fading of the lesions after bleeding and the occurrence of abnormal vessels in the conjunctiva.

As an aside on eponyms there is a series of remarkable papers on Osler's disease by Goldstein. In the early 1930's, he began describing the disease as "heredofamilial angiomatosis with recurring hemorrhages, Rendu-Osler-Weber's disease." In subsequent papers he used the term "hereditary multiple telangiectasia: Goldstein's heredofamilial angiomatosis with familial hemorrhages or Rendu-Osler-Weber's disease." Finally, he simplified matters of nomenclature by sloughing off all antecedent references and simply calling it Goldstein's disease. Later I had much interesting correspondence with Goldstein. Apparently he regretted his earlier egocentric exuberance. He was a capable gadfly and in many letters-to-the-editor informed people about their own omissions in bibliographies and derelictions in assignment of eponyms. This is an interesting reminder of what fascination the sound and printed appearance of one's own name may cause. Goldstein's concern about eponyms reminds us of the present day efforts of Trimble to see that we make proper attributions to establish correct priority and not overlook appropriate references. He must have many hundreds of thousands of references in his all-encompassing files.

Cockayne has reported the melancholy fact that horses may suffer from a similar defect in blood vessels, giving rise to repeated and troublesome epistaxis. In horses, fortunately, the disorder is

inherited as a recessive trait; but where it is not recognized, unwary gamblers have been ruined when bleeding from the nostrils has put a favorite horse out of action.

There is no end of collections of family and case reports. The increasing number suggests this disorder does not deserve inclusion in a treatise on rare diseases. But if a collector of rare disease is permitted to have a favorite, this is mine. I require no further justification.

Bird, Hammarsten, Marshall, and Robinson called attention to a vigorous family with nearly two hundred members, thirty-two of whom had Osler's disease. There was no connection between the disease and ordinary blood groups. This disabling and sometimes demoralizing disorder of bleeding was used by this family as a mark of valor and distinction, symbolizing the capacity of a kindred to endure and overcome hardship. They made their handicap an emblem of pride in their clan. This enabled them to face the threat of repeated bleeding and risk of death with bravery and composure approaching complacency.

The Latin title for Osler's disease implies it is hereditary. I have observed two persons whose parents I examined and found free from any stigma of the disease. One patient has children with nosebleeds, though I have not observed the children. Thus, occasionally we encounter the first person to have the mutation, the patriarch of future trouble, transmitted as the usual dominant trait with the strong penetrance and expressivity. In my experience, new lines of Osler's disease are much rarer than in Marfan's syndrome.

This mutational creation of disease should remind us that medicine has put into the hand of society the capacity to wipe out every disease transmitted by a Mendelian dominant mechanism in one generation. New mutations could be handled as they came. I have no illusion that we will be intelligent enough to use this information for the prevention of human suffering or chronic illness. Any farmer, plant or animal breeder knows how to use the secret.

It was suggested by Snyder and Doan that the homozygous form of Osler's disease is lethal. They described a child dead at

the age of eleven weeks. Both parents had the disease. At autopsy the entire vasculature seemed to have been replaced by telangiectases and hemangioendotheliomas. External and internal hemorrhages hastened death. In discussing a paper by Maier, Himmelstein, Riley, and Bunam, however, Shefts described a family in which the mother, father and all five children had telangiectases and hemangiomas of the skin and mucous membranes. Two members had pulmonary arteriovenous fistula.

Two points emerge. Even if both parents have the disease, a child is not necessarily fatally blighted. Pulmonary arteriovenous fistula may have a familial trend. Another report of its occurrence in a father and son with Osler's disease supports this testimony. A strong genetic "dose" of the disease is likely to result in worse lesions, such as pulmonary arteriovenous fistula. We do not know if either or both of these ideas is corrent. Smith and Leinbeck reported a Negro mother, nine of whose ten children had epistaxis and vascular lesions of the nasopharynx. A father and one son were not found for examination. The genetic potency is remarkable in the frequency and severity of manifestations in offspring.

The tendency to bleed is a major portion of the Latin title as well as of the clinical story. I have seen full-blown telangiectases in skin and mucous membrane in persons where bleeding had not been a serious problem. Some persons who have unequivocal evidence of the disorder may have long periods when bleeding is not a problem. I have also observed families where grown offspring had bled before the parent did. But bleeding may occur before the cutaneous vascular change is recognized. We have tested many patients with Osler's disease with all available coagulation tests and have never found any difficulties. Osler's disease could hardly confer immunity to an associated genetic fault or acquired anomaly of coagulation. Patients may have any clotting abnormality. Thrombocytopenia and thrombocytomegaly occurred in four of nine members of one Negro family with the disease. Two independent anomalies happened to exist in this kindred. Thrombocytopenia may arise in Osler's disease if very large vascular surfaces are available for sequestration of blood and the formation of

clots. This phenomenon may occur when large vascular lakes have a slow ebb and flow of blood through their dilated estuaries and sluggish tributaries. Platelets and perhaps prothrombin may be used up. Bleeding results from a do-it-yourself bleeding anomaly.

The natural history of individual lesions includes acute alterations and secular changes. The cutaneous lesion of Osler's disease (as well as the arterial spider) can fade. It is hard or impossible to identify during the sharp vasoconstriction which follows acute bleeding. Attenuation and fading of the lesions occur in persons who are chronically depleted of blood and stay severely anemic. Soon after transfusion has restored the blood, lesions which had faded are again readily visible. These lesions have not appeared *de novo,* all at once.

One is struck by the commonly echoed tale of a child whose gestation, delivery and early growth were normal. Mild nosebleeds might have plagued childhood, but generally were not very important. The vascular lesions may be detected in early childhood, but they are not any more striking than the rather wraith-like, wispy lesions of ataxia telangiectasia, rarely noticed by mother or child. I do not know at what age one may see the earliest lesions. I have seen them before the child was three. Ehrenborg has reported typical skin lesions in a five-year-old boy who also had bleeding from the stomach.

The individual lesion in Osler's disease is punctiform, a small macular discoloration. Some become slightly papular. Occasionally they are elevated. Usually they are not as red as an arterial spider. Some pulsate; some do not. They rarely have the elegant configuration of the classical arterial spider. At times fine silvery flakes of skin desquamate from the surface of lesions, particularly on the palms. Their distribution in Osler's disease suggests that the disorder affects the terminal nutrient arterioles in the skin. On the palm, the distribution follows the concentration of glomus bodies.

Pressure required to obliterate the spot is of the same order as that required to obliterate an arterial spider — the pressure of small arteries and arterioles. Lesions occur almost anywhere. Just as with arterial spiders, the lesions disappear after death. Autopsy

gives little idea of their distribution unless bleeding has occurred. Almost every organ and tissue of the body has been the site of hemorrhage. The vermilion border and the red portion of the lips, the tongue, particularly the dorsum, the hard and soft palate and the buccal mucous membrane are affected. Ears are a favorite site. As seen by endoscopy, the esophagus, stomach, and rectum all may have lesions. Lesions mark the palmar surface of the more distal portion of the fingers, or anywhere else on the palm or the dorsum of the fingers. Some occur in the nails and look much like splinter hemorrhages. They are distinguished from splinter hemorrhages by gentle compression of the nail which blanches the lesion in Osler's disease. With a splinter hemorrhage, the extravasated blood directly under the nail remains; the splinter appears more sharply outlined when compression blanches the adjacent nail bed. Hemorrhages from or into all portions of the alimentary canal, the meninges, the brain, the retina, the sclera, the lungs, the kidney, the bladder, the liver and the mesenteric vessels attest to the wide dissemination. Martini has described a special variety of cirrhosis of the liver which may occur in Osler's disease.

With the coming of age of thoracic surgery, interest in this disease waxed because of the complicating pulmonary arteriovenous aneurysms. For a great many years, surgeons who wrote about pulmonary arteriovenous fistula did not recognize Osler's disease. Churton came first, immortalized in a few lines. Hedinger (1907) was probably the first to deal with the problem of pulmonary arteriovenous aneurysm as we know it today. Wilkens (1917) observing a woman for seven years, described telangiectases of the lips and tongue, clubbing of the fingers and toes, and a loud continuous murmur with systolic accentuation heard particularly in the region of the left axilla. By x-ray, there was enlargement of the pulmonary artery and calcification in the right hilar region. The patient died of rupture of the largest aneurysm into the pleural cavity. These few words were soon forgotten. Others had reported the lesion at autopsy. Smith and Horton (1939) first made the diagnosis clinically. In 1942, Hepburn and Dauphine reported remarkable improvement of polycythemia in a patient

after such a lesion was removed successfully. This information did not stir anybody until approximately twenty years ago, when Goldman inaugurated the modern era. Papers dealing with operations for pulmonary arteriovenous aneurysm rarely record examination of the skin. My experience with Osler's disease include observations on more than two hundred patients. Only eight had pulmonary arteriovenous fistulas. But nearly all the arteriovenous fistulas I have seen were found in persons with Osler's disease. Impressions derived from both experiences are biased.

The clinical features of pulmonary arteriovenous fistula, with or without Osler's disease, are the same. By-passing the alveoli leads at first to moderate, then increase O_2 unsaturation of the blood. The cardinal symptoms result from anoxia. They vary with the size, progress, and duration of the lesion. Compensatory polycythemia results when the bone marrow is stimulated to manufacture more erythrocytes. The hematocrit increases, the viscosity of the blood increases, cyanosis and clubbing appear and dyspnea occurs. Occasionally, full-fledged osteoarthropathy may develop. Dizziness, unconsciousness, weakness, hemoptysis, pain in the chest, faintness, the "red-out" convulsions, diplopia, hemiparesis or paralysis, palpitation, headaches, nausea, vomiting, and a multitude of other localized symptoms and signs may plague the patient. When the lesion is well established, a continuous murmur with significant systolic accentuation may be heard at a distance from the heart. The electrocardiogram is likely to be normal. Arterial oxygen saturation is severely decreased. Vital capacity may be somewhat reduced. The lesion may be detected readily on x-ray films. The use of the Valsalva and the Müller procedure may enable one to get a very clear picture, especially with angiocardiograms which indicate elegantly the precise location, size, and ramifications of the vascular connections.

Two forms of cerebral complications have been unduly common. One is the occurrence of *brain abscess* caused commonly but not invariably, by organisms which thrive in an anaerobia milieu. Its manifestations may be mistaken for cerebral hemorrhage, since *bleeding* is a traditional part of Osler's disease. An operation may relieve the symptoms dramatically. In patients followed for a long

time after pneumonectomy or lobectomy, the recurrence of polycythemia from new arteriovenous shunts or enlargement of existing lesions causes a return of old trouble.

Today there is no reason to miss the diagnosis. It requires an examination of the patient as well as the x-rays. Every patient with pulmonary arteriovenous fistula should be examined with Osler's disease in mind. The subject is overwritten, with recurring testimony to an inadequate comprehension of the problem.

Giampalmo (1950) published a comprehensive and critical review of arteriovenous angiomatosis of the lung. Brink emphasized that many small shunts rather than one or a few large ones may cause secondary polycythemia. Another problem is infection in the lung. This is not a necessary antecedent of brain abscess. Thrombosis with secondary polycythemia and the commonly associated hemorrhage may cause death.

In two of my patients with Osler's disease and pulmonary arteriovenous fistula, anemia and anoxia produced a double stimulus to the bone marrow. A precarious but balanced pathophysiological battle between anemia and polycythemia often remained a draw. Air embolism to the brain has been reported. This must be a rare and exotic foible of nature.

One patient I discussed at some length (53) (from one of the families observed for two decades) was a young man of twenty-seven who died after localizing symptoms pointed to an expanding lesion in the brain. At operation, an abscess caused by an anaerobic actinomycosis organism was found. Though shunting of infected material around pulmonary capillaries has been blamed, a more likely explanation is that the somewhat anoxic brain provides fertile soil for anaerobic organisms. Anoxia itself may cause impairment of central nervous system function. The patient died after the operation. An injection and clearing study of one of his lungs gave the impression that the arteriovenous aneurysms might be unique. In addition to the pulmonary artery, the bronchial artery seemed to be connected, but this could not be determined with certainty. It is consistent with the severe and occasionally fatal pulmonary hemorrhage. I have found no report of pulmonary AV fistula in children with Osler's disease.

Retinal arteriovenous aneurysm may produce a predictable slash in one visual field, though it may not be noticed by the patient. In the patient Forker and I had under observation, there was no mark in the history to suggest a hemorrhage causing an acquired arteriovenous shunt. Perhaps it was congenital.

Many detailed and painstaking studies of the lesions in Osler's disease imply that physiological weakness in contractility, the failure of muscle and elastic tissue to perform the mechanical part of the self-sealing hemostatic process, is responsible. A reduction in vascular muscle and elastic tissue may be evident. In the skin, many lesions appear as dilated, contorted with variously interdigitating and anastomosing vessels just under the papillary ridges. These vascular structures seen in a single section consist simply of very thin-walled sacs, tubes, or balloons. The only thing separating the blood from adjacent tissue is a single thin film of one or two endothelial cells. Ill-developed connective tissue provides a receptacle for hemorrhage rather than a morphologically identifiable adventitia. The serial sections made by Martini, Nödl, Staubesand and their colleagues suggest that a specific vascular lesion produces the telangiectatic spot. The vessels form a double-spiral pattern with thick bands and cuffs of irregularly placed muscle tissue. Suddenly they change to very thin-walled vascular structures. Some have well-developed valves. Exactly what the dynamic state is, one cannot say. MacFarlane produced minor injury to the cutaneous surface of the nail fold and found that the capillaries did not contract after injury. Blood oozed persistently until pressure stopped it.

Some years ago the suggestion that patients with Osler's disease might well be helped by estrogenic hormones was made by Koch, Escher, and Lewis. They noticed that a woman's nosebleeds usually occurred one to five days before the end of the secretory phase of the menstrual cycle. Shortly after the onset of the menstrual period they disappeared. After castration by roentgen therapy, the hemorrhages lost their cyclical pattern. They increased in severity. Improvement is associated with conversion of ciliated columnar epithelium to squamous epithelium, which protects the telangiectases. The only improvement was a reduction

in nosebleeds. Bleeding from the alimentary canal or elsewhere goes on as usual. The few patients I have tried with a program of estrogen therapy were all postmenopausal women. They stopped estrogen therapy, preferring not to renew defunct menstrual bleeding.

Saunders has tried septal dermoplasty. The fragile mucous membrane of the nasal septum is replaced by a skin graft. Tough epithelium covers an area exposed to much trauma. An effective graft relieves the bleeding. The grafted skin must not have any lesions. It will be interesting to see if any new telangiectatic lesions develop in such transplants.

Subtotal gastrectomy is likely to be done by someone who is not familiar with the ubiquitous manifestations of Osler's disease. It never cures and almost never helps.

Two decades of observations on secular changes in the cutaneous manifestations of Osler's disease indicate a dynamism in the slowly-changing, minute architecture of the small vessels of the skin. This (in conjunction with observations made on the coming and going of arterial spiders in "normal" people) emphasizes the fact that at least as far as the vasculature of the skin is concerned, and probably for other organs and tissues, there may be slow alterations in local blood vessels.

No doubt the larger vessels are well-fixed in structure and position when adult life is reached, and remain so unless occlusion occurs or there is a call for the development of arterial collaterals because of ischemia, or for venous collaterals because of obstruction to large veins. The demand for the development of collaterals is completely different in ischemia caused by impaired arterial flow and in that caused by blocked venous drainage. Curiously, the details of development of such collaterals are not known; nor is it understood why, at least in the rabbit's ear, exposure to warm or hot environmental temperatures brings into action (and probably brings into being) many arteriovenous anastomoses. Although Sir Thomas Lewis emphasized the constancy of vascular patterns in the skin, his observations were matters of only some months. Over a period of more than twenty-five years, I have observed several small areas of the skin of my palm and have

seen slow alterations in the distribution and arrangement of the white spots and the red reticulum which may be called forth by keeping the hand dependent for a few moments. Thus, superimposed on the fixity of large vessel regularity, there are shifting changes in the branches of the vascular tree. Thus, dynamic equilibrium, homeokinesis, the ability to close up and dispose of small vessels and open up new ones, implies a state of considerable activity in small blood vessels in response to readily imagined, but not truly understood, increases and decreases in the needs of tissues locally. When such changes take place in Osler's disease and new vessels are laid down, we may expect to find new lesions occurring when the processes by which the vascular fabric are laid down are disturbed by genetically determined inadequacies in vessel walls.

Congenital Dysplastic Angiopathy

This is one disorder, in particular, where the segregation of papers hidden as isolated property of isolated specialists, combined with the use of a jumbled tangle of eponyms, have kept the disorder from being recognized as a single entity whose manifestations differ according to which tissues are affected. It has been called the *Sturge-Kalischer-Weber Syndrome* and the *Klippel-Trenaunay Syndrome.* Ophthalmologists have separate pigeon holes for their fragments, too. I have called it congenital dysplastic angiopathy of the skin and underlying tissues. I have added my bit to the confusion by reporting, in my first paper on Maffucci's syndrome, an infant I thought had Maffucci's syndrome; but further observation, study, and reflection indicate that the child has a dysplastic angiopathy. The critical point in the differential diagnosis is this. In dysplastic angiopathy, though there may be grotesque localized gigantism and cruel deformity, there is no dyschondroplasia. Though the bone of an extremity may be badly warped or overgrown, it does not have the destructive disorganization characteristic of the dyschondroplasia of Ollier's disease or Maffucci's syndrome. The bone is too big, but it is well formed.

Vollmer of Heidelberg called this to my attention, and I commented on it in my second paper on Maffucci's syndrome in

1958. At least a few cases reported as Maffucci's syndrome are examples of congenital dysplastic angiopathy. This is unfortunate, since the ultimate fate of victims of the two conditions is different. Those with angiopathy of a limb ultimately develop many thrombi in the sluggish circulation of the abnormal vascular swamps. If they become organized, phleboliths form, producing nothing but a dramatic sprinkling of miliary or larger marks on an x-ray film. Often, however, multitudes of thrombi break off a few at a time, but repeatedly. There may or may not be signs and symptoms of pulmonary infarction. Ultimately, patients may die from acquired cor pulmonale. Deaths from cor pulmonale have occurred three times in my experience, which makes me believe strong consideration should be given to venous ligation, or perhaps amputation, in circumstances where repeated pulmonary emboli endanger the life of the patient. Serious intracranial vascular anomalies, or deformity, or destruction of vital organs may cause death.

Congenital dysplastic angiopathies are inborn developmental anomalies in which the skin has lesions which duplicate or resemble an ordinary birthmark or "port-wine" stain. Nearly two decades before 1879, when Sturge reported ". . . a case of partial epilepsy apparently due to a lesion of one of the vasomotor centers of the brain . . ." Shirmer had described an epileptic patient with telangiectasia of the face. He did not speculate on a possible connection. I have discussed at length the sequence of papers dealing with this problem. Sturge, Weber, and Kalischer came on the scene at about Act IV. So did Klippel and Trènauny. In 1900, they described "nevus variqueux osteohypertrophique" associated with an elongation of the affected limb. Cushing reported examples in 1906. Parkes Weber reported a series of cases. His first was published in 1918. A relationship to Lindau's syndrome and phacomas or birthmarks is probable, but it is difficult to determine just where it and the ocular phacomatoses fit.

Because each specialist has been so beset in looking at his own territory, his protective blinders have made him oblivious to the uniformity of process in a wide variety of patterns. Does the Lindau complex fit into the puzzle? Where do we put inborn