A HISTORY OF DIABETIC RETINOPATHY: AN OBSCURE ENTITY BECOMES AN INTERNATIONAL PUBLIC HEALTH DILEMMA

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Abstract

Diabetic retinopathy is a disorder that was unknown until the late 19th century and that did not become important until at least the 1940's. This study describes the disorder's history and provides support for the thesis that most of the world's health care systems have responded inadequately to the subsequent epidemics of diabetic retinopathy and its cause, diabetes mellitus, particularly in view of the well documented availability of evidence-based management strategies that have been developed over decades. The global distribution of health care systems to combat these disorders is exceptionally limited, and although contemporary exemplary plans are available in most corners of the world, they are limited in the percentages of populations that can be appropriately managed. In general, optimal systems are available only in environments containing sophisticated equipment and personnel in which only patients with appropriate medical insurance or funding are managed. Many caregivers remain unable to provide exemplary support because of inadequate access to patients, funding, or education, and few patients are genuinely compliant in managing their diabetes. Each of these factors is amplified in regions of relative poverty and poor hygiene. It currently appears that most of the world's diabetic patients with retinopathy will remain underserved.

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Chapter 1.

Introduction

Diabetic retinopathy (DR), a major and growing cause of impaired vision worldwide, was largely unknown to eye specialists until well into the 20th century because identification and subsequent awareness of the disorder required its appearance as a clinical entity, the development of relevant diagnostic equipment, and the training of appropriate caregivers. Prior to insulin's introduction into clinical practice in the 1920's, diabetic patients almost never lived sufficiently long to lose vision from DR, so there was no need to identify it as a significant disorder or to develop relevant teaching institutions, specialist clinicians, and therapeutic strategies to combat it. But as patients with diabetes lived longer, and their numbers grew precipitously, microvascular complications of this systemic disease (retinopathy, nephropathy, and neuropathy) assumed epidemic proportions in all parts of the world.

In this thesis, I concentrate upon a history of DR and its becoming recognized as an important entity, and upon the medical and societal responses that followed. I emphasize that the disorder was generally unappreciated as a potential public health problem until at least the mid-1930's and that reactions to its becoming so have been significantly delayed for additional decades in most parts of the world by failures of national and international health care systems in developing optimal measures to prevent or retard both the systemic disease and this ocular

complication.[1] As a trainee in the late 1960's and then a practitioner in the retina subspecialty of ophthalmology, I witnessed heated debates about DR therapy. Blindness was genuinely unpreventable in many cases,[2] and the situation was sufficiently dismal that along with contemporary therapeutic strategies mentioned below, abortions for newly pregnant diabetic patients with retinopathy were sometimes recommended to prevent its progression to blindness.[3] Hypophysectomies with surgery or irradiation were also widely accepted therapeutic alternatives. A thorough accurate narrative regarding both the early history of DR and the steps that lead to current management strategies is needed to explore both the adequate and insufficient states of care that exist in most countries today. This history is intended to provide readers with information that they need to know about the past.[4] This story of diabetic retinopathy can serve as a metaphor for a variety of additional diabetes-related chronic diseases that impact millions of patients around the world.

Historian Keith Wailoo has stated "one can think of twentieth-century specialties as being organized around one of four primary features - tools, patients, organs, or diseases."[5] The contemporary specialty of DR-related ophthalmology

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[1] Di Iorio DT, CarincI F, Benedetti MM. The diabetes challenge: From human and social rights to the

[2] A famous ophthalmic historian, Sir Stewart Duke-Elder, wrote in 1967 "Diabetic retinopathy is one of the major tragedies of ophthalmology in our present generation; always common and rapidly becoming still more common, affecting the young as well as the aged, predictable but not preventable and relatively untreatable, chronic and progressive in its course and leading to blindness in a distressing percentage of cases." (Duke-Elder S, Dobree JH. *System of Ophthalmology: Volume 10. Diseases of the Retina.* 1967, St. Louis, C.V. Mosby, p. 410)

[3] Report by B.M.A. Committee on therapeutic abortion. Indications for termination of pregnancy. Brit Med J 1968;1:171-5.

[4] Maza SC. *Thinking About History.* 2017, Chicago, University of Chicago Press, p. 6.

[5] Wailoo K. Notes to pages 9-12, in Wailoo K. *Drawing Blood. Technology and Disease Identity in Twentieth-Century America.* Baltimore, The Johns Hopkins University Press, 1997, p. 204.

encompasses all four of these variables: the evolution of diagnostic and therapeutic *tools* have been critical in the management of *patients* with the *diseases*, diabetes mellitus (DM) and DR; although DR, diabetic nephropathy, diabetic neuropathy, and various cardiac problems are all complications of DM, I concentrate on the *organ* as the eye.[6]

Prior to the development of those critical tools, the pre-20th century specialty of ophthalmology was relatively primitive.[7] Although ocular therapy including oculoplastic and cataract surgery had existed for millennia, treatment was primarily confined to disorders of the outer eye; and non-physicians treated most ocular problems in a variety of ways in evolving fashions.[8,9] The birth of a more specific specialty was initially sparked by the reappearance of *Chlamydia trachomatis,* an organism subsequently designated as "trachoma". This was known as a source of external eye infection in ancient societies of China, Egypt, and Greece, and it stimulated the establishment of ophthalmology in the western world.[10,11] (Still, and consistent with "retrospective diagnoses",[12] it should be noted that some cases of "Egyptian

[6] The *disease*, DM dates to antiquity, but the *organ* became involved with DR only after affected *patients* lived for many years, whereas *tools* to detect DR developed later.
[7] Ophthalmoscope (1851), slit lamp (1911), diagnostic 3-morror contact lens (1948)
[8] Cataract surgery was literally intraocular and performed ("couched") with a single needle stab incision into the eye posterior to the iris.
[9] Hubbell AA. *The Development of Ophthalmology in America, 1800-1870.* Chicago, AMA Press 1908: 18-27.
[10] Davidson L. Identities ascertained: British ophthalmology in the first half of the 19th century. Soc Hist Med 1996;9(3):313-33.
[11] Feibel L. John Vetch and the Egyptian ophthalmia. Surv Ophthalmol 1983; 28(2):128-34.
[12] Mitchell PD. Retrospective diagnosis and the use of historical texts for investigating disease in the past. Int J of Paleopath 2011;1: 81– 8.

ophthalmia" were apparently due to *Hemophilus aegypticus*, *Neisseria gonorrheae, and adenoviruses.*[13])

The Egyptian campaign of the Napoleonic war ended temporarily in 1802, and by then a substantial percentage of returning soldiers had developed trachoma, a disorder characterized by acute inflammation of the external eye and eyelids followed by eyelid malfunction and secondary corneal scarring leading to permanent losses of vision. Although military hospitals had been established specifically for infected patients as well as for eye trauma, the incidence of the former contagious problem grew profoundly, magnified by the crowding of the ever-enlarging immigrant populations that had moved into living conditions devoid of adequate hygiene. The need for additional study of ocular disorders stimulated the establishment of academic centers devoted to eye care. Previously, ophthalmology had been regarded as "an uncoordinated offshoot of surgery, largely peddled by illegitimate practitioners and quacks, and it was for the first time given the dignity of an academic specialty and science with the Austrian royalty's establishment of the world's first Chair in Ophthalmology in Vienna in 1812".[14,15] Working independently but influenced by the epidemic of "ophthalmia", John Saunders established and opened an eye department as the London Dispensary for

[12] Wagemans M, Van Bijsterveld OP. The French Egyptian campaign and its effects upon ophthalmology. Doc Ophthalmologica 1988;68:135-44.
[14] Duke-Elder S. Moorfields and British ophthalmology. Lang Lecture. Proc Roy Soc Med 1965;58(7):541-5.
[15] This first Chair was established after Georg Joseph Beer, the "father of the Vienna Ophthalmological school", who had by 1806 demonstrated that ophthalmology should be considered as a legitimate specialty within the house of medicine (Lesky E. *The Vienna Medical School of the 19th Century* Baltimore, The Johns Hopkins Press, 1976, 60-1.

Curing Diseases of the Eye (later named Moorfields Eye Hospital) in 1805.[16] American physicians studying at the latter institution in efforts to improve their self-described minimal knowledge of ocular disorders returned in 1820 to establish the first charity eye hospital in the U.S. to become a lasting institution,[17] the New York Eye and Ear Infirmary (NEEI). Other early and enduring ophthalmology centers included the Massachusetts Eye and Ear Infirmary in Boston, also founded by London alumni and founded in1824; and Philadelphia's Wills eye Hospital, established in 1834.[18,19] These Vienna, London, and American eye institutes were all initially founded as charity clinics funded by philanthropic individuals in the respective cities to treat indigent patients, although their ophthalmologists were also able to establish private practices with hopes of significant remunerations. Globally, London-trained physicians established the Regional Institute of Ophthalmology and Government Ophthalmic Hospital in Madras (now Chennai), India, in 1819.[20] The first American ophthalmology textbook was published in 1823 and authored by Baltimorean George Frick, who received specialty training in Vienna after graduating from medical school in Philadelphia in 1815.[21] It of course contained no references to DR.

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[16] Collins ET. *The History and Traditions of the Moorfields Eye Hospital.* London, H K Lewis and Co, 1929, 1-226.
[17] The literal first eye infirmary was the established as the New London (Connecticut) Eye Infirmary by Elisha North in 1817, but it remained in place only a few years; similarly, two short-lasting institutions in Philadelphia were founded in 1821 and 1822 (Hubbell AA. *The Development of Ophthalmology in America, 1800-1870.* Chicago, AMA Press, 1908,16-27.
[18] Ibid.
[19] Snyder C. *Massachusetts Eye and Ear Infirmary. Studies on its History.* Boston, Massachusetts Eye and Ear Infirmary, 1986, 19.
[20] Collins, Op cit., 36-7.
[21] Hubbell, Op. cit., 96-8.

Rosen[22], Rosenberg[23] and others have stressed that medical specialties develop in response to scientific and technical improvements coupled with contemporary social influences and human needs. The impact of trachoma upon a substantial number of veterans returning to civilian life was a critical factor in the establishment of ophthalmology as a specialty, as noted, and the establishment of eye hospitals expanded the number of students and physicians interested in the profession. But importantly, management of trachoma and additional ocular disorders during the first half of the 19th century could not include evaluations of the eyes' interiors, and it was not until the introduction of the invaluable tool the ophthalmoscope in the mid-19th century that a genuinely distinct and novel comprehensive eye specialty was established.[24] And in the years that followed, a great number of "new" ocular disorders such as retinal detachments and retinal venous obstructive disorders were identified, although DR was not among the earliest of specific diagnoses, due to the reality that its common appearance required years of patients living with the systemic disease, and this became of practical importance only after the introduction of insulin.

The growth of DR-related vision loss worldwide has been fueled by the systemic disease DM, the rise of which has been the result of complex social and cultural factors. Clearly, DR represents "…an occasion and agenda for an ongoing discourse concerning the relationship among state policy, medical responsibility,

[22] Rosen G. *The Specialization of Medicine with Particular Reference to Ophthalmology.* New York, 1944, Froben Press, 30-49.
[23] Rosenberg CE. *The Cholera Years: The United States in 1832, 1849 and 1866*. Chicago: The University of Chicago Press, 1962. Reprinted in paperback, University of Chicago, Phoenix Books, 1968; second ed. with a new afterword.
[24] Rosen, op. cit., 23-4.

and personal culpability".[25] It is an example of the multifactorial criteria for "disease" articulated by Rosenberg and Golden in their classic book, *Framing Disease*.[26]

In the next Chapter, I provide a description of the pathophysiology of DR followed by a brief history of the diabetes mellitus, including the introduction of insulin and recognition of the importance of serum glucose control. In Chapter 3, I discuss the epidemiology of DM and DR and in Chapter 4, the evolution of techniques to diagnose DR, early therapeutic efforts, and development of the evidence base for its contemporary management. In Chapter 5 I report more recent international recognition of DR as a growing healthcare issue and subsequent attempts to establish management goals and also recounts efforts of specific eye care programs to combat DR-related vision loss in India and the U.S., comparing them to more advanced strategies available in England.[27] The Conclusion emphasizes the importance of the contemporary evidence base regarding measures to prevent vision loss from DR and the steps that should be taken internationally to improve future care for this important disorder.

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[25] Rosenberg CE. *Explaining Epidemics and Other Studies in the History of Medicine.* Cambridge, Cambridge University Press 1992, p. 317.

[26] "Disease is at once a biological event, a generation-specific repertoire of verbal constructs reflecting medicine's intellectual and institutional history, an occasion of and potential legitimization for public policy, an aspect of social role and individual – intrapsychic- identity, a sanction for cultural values, and a structuring element in doctor and patient interactions" (Rosenberg CE, Golden J (eds) *Framing Disease. Studies in Cultural History.* 1992, New Brunswick, NJ, Rutgers University Press p xiii).

[27] England was selected as an example of a country with an advanced DR management system; the U.S. as a country in which most research on DR care has been conducted but one with a fragmented healthcare network; and India was chosen as an example of a huge lower income country comparable to China (both of which have even more disconnected healthcare structures) in which English is the primary language. Appropriate research data are available for all three English-speaking countries.

Chapter 2.

A description of diabetic retinopathy and a review of its cause.

A scientific description of retinopathy and its responsible cause, diabetes mellitus, is necessary for a thorough understanding of this thesis.

Diabetic retinopathy in a nutshell

DR is a microvascular complication of diabetes, occurring in the eyes (with similar alterations in kidneys and several peripheral nerves). The precise mechanisms leading to retinopathy are unclear and apparently multifactorial, but there is agreement that small (25 – 100 μm) round red spots observed with an ophthalmoscope and termed "micro-aneurysms" are usually the first clinical sign of the disorder; they are small outpouchings of the capillary walls in the posterior retinal vasculature. As they increase in number, alterations in the permeability of the capillaries lead to leakage of serum into the interstitial spaces and thickening of the retina, and the focal areas of leakage are easily detectable with the photographic techniques of optical coherence tomography (OCT) and fluorescein angiography (the latter involves an intravenous injection of dye and subsequent photography employing appropriate filters). This localized or more diffuse thickening due to leakage in the back of the eye is termed "diabetic macular edema" (DME), and patients do usually not recognize its symptoms until the swelling involves the

central retina or “macula”. The retinal thickening is frequently associated with “hard exudates” which are localized deposits of extracellular lipid and protein materials due to vascular leakage. DME is today responsible for most vision loss in diabetic patients, but it is typically not catastrophic and rarely in itself leads to genuine blindness. As DR progresses, many involved capillaries cease to carry blood, a process known as “capillary drop-out” or “vascular non-perfusion”. This causes focal areas of retinal ischemia and significant vision loss if occlusions involve the macula.

More importantly, retinal ischemia causes production of “vascular endothelial growth factors (VEGF)” and additional alterations in the retinal vasculature; these in turn are associated with both increased permeability of retinal capillaries and the development of “neovascularization”, the growth of abnormal vessels upon the inner surface of the retina and on the optic nerve. Once these become visible, “proliferative DR” is present, and the situation becomes quite ominous. DR prior to the appearance of neovascularization is termed “non-proliferative DR”; once new vessels are identified, “proliferative DR” becomes the proper diagnosis, and it frequently is accompanied by DME affecting the macula. Signs of non-proliferative disease always precede the proliferative form.

The vitreous gel filling the eye space between the retina and the lens is of fundamental importance as DR progresses. In locations in which neovascularization develops, adhesions between these vessels and the posterior surface of the vitreous gel become manifest, and when the vitreous gel subsequently “contracts” (shrinks, moving anteriorly), proliferative DR enters a more serious 3-dimentional phase in which traction upon the vessels causes bleeding into the vitreous cavity; and similar

traction forces upon the retina lead to retinal detachment. Intravitreal hemorrhages and retinal detachments are responsible for most cases of literal blindness due to DR. As the retinopathy progresses, collagen is laid down in areas of vitreoretinal adhesions, making them much more visible as "fibrotic" areas, and this stage was recognized by early observers who termed the entity "retinitis proliferans". Both non-proliferative and proliferative DR have been categorized with evidence-based standardized classification schemes that allow comparisons of natural history with various therapeutic efforts, and these are discussed later.

The best method of preventing DR remains optimal control of DM, as noted in multicenter collaborative trials to be discussed later in this chapter. Once DR develops, proven therapies to prevent vision loss from DR have included attempts at prevention and reduction or elimination of DME and neovascularization. Blindness from DR can currently be prevented in as many as 98% of cases if detected in a timely fashion.[28]

Diabetes mellitus (DM)

The fundamental cause of DR is of course DM. Individual as well as generalized social factors have played major roles as determinants of the systemic disease's course. In this section, I describe a brief history of diabetes, including pre- and post-insulin eras and studies regarding the importance of glucose control. The epidemiology of the systemic disease among various ethnic and societal groups, and

[28] Ferris FL. How effective are treatments for diabetic retinopathy? JAMA 1993;269(10):1290-1.

the importance of social realities as influential factors regarding the appearance and progression of disease will also be discussed.

Symptoms of DM were known for millennia, but the pathophysiology of the disease and successful forms of management required studies that extended over centuries. One of medicine's most important triumphs was the identification and production of insulin, an agent that converted an affected patient's anticipated brief life span into the possibility of a long existence with a meaningful quality-of-life. But prior to that achievement, the systemic disease was well known as a significant problem for both those afflicted and their caregivers.

The pre-insulin era

Unlike DR, DM has a long history that has been thoroughly described by many authors. Nwaneri,[29] Poulson,[30] and others, noted that the disease DM may have been documented by the year 1550 BC, as revealed in Ebers' ancient Egyptian papyrus. Later, the Indian physician Sushruta described the sweet urine of glycosuria, and in the second century AD a more thorough description of the problem was introduced by the Greek physician Aretaeus, who emphasized the excessive thirst, urine volume, and frequency associated with the systemic disorder and who employed the term "diabetes" to describe the phenomenon of ingested fluids simply passing through the body on their way to the bladder. (Interestingly,

[29] Nwaneri C. Diabetes mellitus: a complete ancient and modern historical perspective. Webmed Central Diabetes 2015;6(2):WMC004831
[30] Poulson JE. *Features of the History of Diabetology.* Philadelphia 1982, Lee & Fibiger, 11.

the former described DM as associated with obesity, whereas the latter mentioned it as a "wasting disease".)

Aretaeus' writings were not recognized in the West at the time they were written, but Galen (c. 130 – 210 AD) briefly described DM as a disease of the kidneys, a belief that persisted beyond 1800. In 1674, Willis "re-discovered" the sweet urine associated with the "pissing evil" but didn't associate the sweetness with glucose, and more than 100 years passed before Dobson identified the presence of sugar in both the urine and blood of affected patients.[31] In 1798, Rollo coined the term "mellitus", meaning "honey", in noting the sweetness of diabetic glycosuria. His additional efforts included the introduction of radical diets to improve the longevity of the inflicted.[32]

The first screening test to detect the presence of glucose in the urine was published by Trommer in 1841,[33] but this was quite cumbersome, and a more practical method was later developed and presented by Roberts in 1862, although this was apparently employed only rarely. [34] Still, it stimulated further studies of dietary manipulations, one of which was described in Osler's 1909 textbook[35] aimed at eliminating glycosuria. Although, as noted above, DM had been previously recognized in obese patients with diabetes, French physicians were credited with

[31] Ibid, 14.
[32] Ibid, 34.
[33] Tattersall, Op. Cit., 19.
[34] Ibid, 19-20.
[35] Osler W. *The Principles and Practice of Medicine* 7th Edition. New York, Appleton, 1909, 421.

distinguishing *diabetes maigre* (thin) from *diabetes gros* (big) in the early 20th century.[36]

And for hundreds of years, dietary manipulations were the primary forms of therapy for diabetes.[37,38] Notably, Bouchardat has been credited with the observation that severe restrictions of food intake, such as occurred during a siege of Paris in 1870, caused a marked reduction of glycosuria in some diabetic patients, and he also claimed that physical exercise was beneficial.[39] In the early 20th century, the so-called "starvation diet" (high-fat and low-carbohydrate) became favored by leading experts of the time including Frederic Allen and Eliot Joslin in the U.S.;[40] all diet strategies shared the goal of lowering serum glucose levels by limiting caloric input. Each of these programs was superseded by the introduction of insulin in1922, even though diet continued (and continues) to be a critical variable in the management of the systemic disease.

The introduction of insulin

The work of Von Mering and Minkowski proved conclusively the importance of the pancreas in the pathophysiology of DM. Serendipitously, these investigators had discovered that complete removal of the pancreas produced clinical diabetes

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[36] Lancereaux E. Note et reflexions à proposde 2 cas de diabète sucré avec altération du pancréas. Bull Acad Med Paris. 1887;2(Sér 6)1215-1240. Cited in Nwaneri.
[37] See Poulson, Nwarni.
[38] Feudtner C. Ideas, ideas, and innovation in the history of diabetes. Arch Pediat Adoles Med 2011;165(3):195-6.
[39] Bouchardat A. *De La glycosuric ou Diabete Sucre.* é, *son traetement hygienique*,. Germer-Baillière.Paris, 1875. cited in Nwaneri.
[40] Westman AC, Yancy WS Jr., Humphreys M. Dietary treatment of diabetes mellitus in the pre-insulin era (1914-1922). Persp Biol Med 2006; 49(1):77-83.

mellitus in the canine model,[41] and subsequent histopathological evaluations of specimens from both laboratory canines and diabetic patients identified abnormalities in the pancreatic islet cells that had been initially described by Langerhans in the later 19th century.[42,43] Tattersall reported that between 1900 and 1921, at least five investigators almost discovered a hypothetical substance, termed "insulin" by de Meyer in 1909, but it was the Montreal group of Banting, Best, Mcloud, and Collip that successfully succeeded in extracting an effective pancreatic extract to treat DM in 1922.[44] That path towards the discovery of insulin profoundly transformed the reconfiguration and management of DM, and it has been well described by many authors.[45,46,47]

Glucose control and the problem of medical complications

The use of insulin resulted in recognition that the relatively good health enjoyed by insulin-dependent diabetic patients was being altered by the later onset of microvascular complications of retinopathy, nephropathy, and neuropathy. Controversy regarding the value of glucose control in retarding these disorders as

[41] von Mering J & Minkowski O. Diabetes mellitus nach pancreas exstirpation. Arch Exp Path Pharmacol 1890; 26 371-87.
[42] Medvei VC. *History of clinical endocrinology: A comprehensive account of endocrinology from earliest times to the present day.* 1993, London, Taylor and Francis, 1-538.
[43] Langerhans P. Uber die nerven der menschlichen haut. Archives of Pathological Anatomy 1868;44:325–37.
[44] Tattersall, Op. cit., 42.
[45] Poulson, Op. cit, 44.
[46] Bliss M. *The Discovery of Insulin. 25th Anniversary Edition*. Chicago, 2007, Chicago University Press, 1-304.
[47] Best HBM. Margaret and Charley: *The Personal Story of the Co-Discoverer of Insulin.* Ontario, 2003, H. D. M. Best, 1-542.

well as in the overall health of the patients raged for over 60 years.[48] Joslin pioneered strict glucose control in the prevention of microvascular complications,[49] while Jackson, a pediatrician at the University of Iowa School of Medicine, provided substantial evidence of the value of glucose control in preventing DR in 1956.[50]

However, it was not until the Prospective Diabetes Study (UKPDS) trial[51] in the United Kingdom regarding Type 2 DM and the Diabetes Complications and Control Trial (DCCT)[52] concerning Type-1 DM that the value of glucose control was firmly established. These will be more thoroughly described later. (And it should be noted that a study that preceded both the DCCT and UKPDS, the University Group Diabetes Programme (UGDP), suggested *macro*vascular harm from glucose reduction treatment with tolbutamide;[53] this was a highly debated study that never satisfactorily resolved the questions regarding glucose control.) Additional evidence of the value of strict glucose control came with the 2010 ACCORD study.[54]

The Diabetes Complications and Control Trial (DCCT)[55] evaluated the outcomes of intensive glucose control upon the development of retinopathy,

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[48] Guthie RA. Controversies of the sweet urine disease. Diab Spec 2003;16(3):133-4.
[49] Joslin EP. Status of living diabetics with onset under forty years of age. JAMA 1951;147(3):209-13.
[50] Hardin RC, Jackson RL, Jackson TL, et al. The development of diabetic retinopathy: effects of duration and control of diabetes. Diabetes 1956;5(5):397-405.
[51] UK Prospective Diabetes Study (UPDS) Group. Intensive blood glucose control with sulphonyureas or insulin compared with conventional treatment and risks of complications in patients with type 2 diabetes. Lancet 1988;352:837-53.
[52] The DCCT Research Group: The effect of intensive treatment of diabetes on development and progression of long-term complications in insulin dependent diabetes mellitus. N Engl J Med 1993; 329:977–86, 1993.
[53] University Group Diabetes Programme. A study on the effects of hyperglycaemic agents on vascular complications in patients with adult-onset diabetes. I: Design, methods, and baseline characteristics. Diabetes 1970; 93 (suppl 2): 747-83.
[54] The ACCORD study group and ACCORD eye study group. Effects of medical therapies on retinopathy progression in Type-2 diabetes. NEJM 2010;363(3):233-44,
[55] The DCCT Research Group. Op. cit.

nephropathy, and neuropathy in patients with insulin-dependent DM. Patients were randomly assigned to intensive therapy with three or more daily insulin injections or with insulin pumps or to conventional management with one or two daily insulin injections. The study cohort included 1,441 patients, 726 with no DR at baseline and 715 with mild retinopathy. Over a mean follow-up period of 6.5 years, intensive therapy reduced the risk of developing DR by 76%; and importantly, in those that already had retinopathy, significant progression was reduced by 54%, and the chance of developing severe non-proliferative or proliferative DR was reduced by 47%. The major complication of intensive treatment was a significant increase in the likelihood of hypoglycemic episodes. Additional studies provided substantiation of the value of glucose control.

Another important trial, the UK Prospective Diabetes Study (UKPDS)[56] studied the effects of intense glucose control upon the subsequent development of complications of diabetes in newly diagnosed patients with type 2 DM. Between 1977 and 1991, 5,102 patients from 23 centers were recruited and followed for an average of 10 years. A blood pressure arm was added in the course of the study and compared rigorous vs. less intense blood pressure control in hypertensive people with diabetes and also the relative benefits of an ACE inhibitor (captopril) or β-blocker (atenolol) in achieving hypertension control. Median HbA1c was 7.9% with conventional treatment and 7.0% with intensified therapy, and this was associated with a 25% reduction in the rates of retinopathy, nephropathy and (possibly) neuropathy. There was a non-significant 16% reduction in myocardial infarction or

[56] UK Prospective Diabetes Study (UPDS) Group. Op. cit.

sudden death with intensified therapy, and a 25% reduction in the risk of death for every 1% drop in HbA1c. Antihypertensive therapy markedly reduced all end-points, macro- as well as microvascular complications. A 10-year follow-up study of the original UKPDS demonstrated a continued benefit of reduced risk with improved glucose control.[57] And an additional study, ACCORD[58], provided additional documentation of the value of reducing hyperglycemia.

The ACCORD study recruited 10, 251 diabetic patients at 77 clinical centers in an effort to evaluate the value of intensive glucose, anti-dyslipidemia, and blood pressure control in reducing the rate of progression of retinopathy. A subgroup of 2,856 patients with baseline and 4-year follow-up protocol retinal photographs was included in this project, and intensive glucose control and anti-dyslipidemia therapy significantly reduced the rate of progression of DR, whereas the value of intensive anti-hypertensive treatment was of no apparent benefit.

Clearly, the DCCT, UKPDRS, and ACCORD studies highlighted the importance of glucose control in the management of both DM and DR. The latter disorder can literally be prevented or its progression significantly reduced with optimal therapy. Thus all strategies to reduce the impact of vision loss due to DR must include recognition of the critical variable of chronic hyperglycemia. However, in spite of the overwhelming evidence regarding the value of glucose control, the increase of DR, due both to the growth in numbers of patients with the systemic disease and their poor but life-sustaining control, has reached epidemic proportions, clearly an

[57] Holman RR, Paul SK, Bethel AA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. NEJM 2008;359:1577-89.
[58] The ACCORD study group and ACCORD eye study group. Op. cit.

example of the limitations of the body to adapt to changes in social circumstances such as diet.[59] The global perspective has changed as noted in a 2017 address by the Director-General of the WHO, who stated "in just a few decades the world has moved from a nutritional profile in which the prevalence of those underweight was more than double that of obesity to the current situation in which in which more people worldwide are obese than underweight".[60] The strain that such changes have caused is explored in the following chapter.

[59] Rosenberg CE. Pathologies of progress. The idea of civilization at risk. Bull Hist Med 1998;72:714-730.
[60] Chan M. Obesity and diabetes: the slow-motion disaster. Keynote address at the 47th meeting of the National Academy of Medicine, Washington, D.C., October 17, 2017.

Chapter 3.

The epidemiological burden of diabetes and retinopathy

DR due to DM has become a major cause of visual disability in all corners of the world due to the profound increase in the incidence and survival rate of the systemic disease responsible for DR's development.[61] I provide a condensed literature review of society's "post-insulin" responses to the growing prevalence of the systemic disease and its complications by examining historical comparisons of figures in the U.S., India, and England.[62]

The World Health Organization (WHO) did not issue its first report on DM until 1965, over 40 years after insulin's introduction, and this publication stressed the alarming worldwide increase in the disease's prevalence but only briefly mentioned the appearance of microvascular complications (and not mentioning DR by name) "after some years [of the disorder]".[63] Still, the report was prescient in noting that many new cases of DM could be prevented through "education and practical public health measures"; that the percentage of undetected patients with DM was large; and that the disorder would cause an increasing burden on healthcare resources around the world. Fifteen years later in 1980, a second WHO

[61] The issue regarding the "shifting diagnostic criteria" of DM associated with the introduction of oral hypoglycemic agents (Green JA. *Prescribing by Numbers: Drugs and the Definition of Disease.* Baltimore 2007, Johns Hopkins University Press, pp. 82-148.) will not be discussed in this manuscript.

[62] As noted earlier, England was selected as an example with an advanced DR management system; the U.S. as a country in which most research on DR care has been conducted but one with a fragmented healthcare network; and India as an example of a huge lower income country in which English is the primary language. Appropriate research data are available for all three of these English-speaking countries.

[63] Diabetes Mellitus. Report of a WHO expert committee. Wld Hlth Org tech Rep Ser, 1965, 310.

report was published,[64] and this stated that at least 30 million patients were affected with DM worldwide and that prevalence was growing precipitously.[65] Sure enough, in 2006, the WHO reported that in 1980 there were 108 million diabetic patients in the world but that the number would grow to 422 million by the year 2014;[66] (this in spite of the fact that this same organization had two years earlier predicted that there would be "only" 366 million such patients by the year 2030).[67] In a 2016 WHO Report[68], the 422 million figure was reaffirmed along with the observation that the prevalence of DM had increased from 4.7% to 8.5% among the world's adult population.

The International Diabetes Federation (IDF), an organization of more than 230 national diabetes associations in 170 countries and territories, published a periodic Diabetes Atlas, and in the 2015 seventh edition[69] their estimate of the worldwide prevalence of diabetes had grown to 415 million with an expected increase to 642 million by 2040. Clearly, the disorder assumed epidemic proportions over a relatively brief period of time.

Regarding retinopathy, the 1980 WHO report cited above noted that "retinopathy is the commonest single cause of blindness registration in the middle-

[64] WHO Expert Committee on diabetes mellitus. Second report. Wld Hlth Org tech Rep Ser, 1980, pp.1-64.
[65] Ibid. This report mentioned DR by name and noted that photocoagulation therapy had been proven as an effective treatment. It also suggested that "diabetic outpatient clinics" might be established. No specific screening strategies were recommended, although it suggested "diagnostic and therapeutic facilities should be made available wherever possible".
[66] Matthers CD, Luncor D. projections of global morbidity and burden of disease from 2002 to 2030. Pl0S Medicine 2006;3(11):2011-30.
[67] Wild G, Roglic G, Green A, et al. Global prevalence of diabetes. Estimates for the year 2000 and projections for 2030. Diab care 2004;27(5); 1047-53.
[68] WHO Global Report on Diabetes. 2016, Geneva Switzerland, World Health Organization, pp. 1-87.
[69] International Diabetes Federation (IDF). *Diabetes Atlas, Seventh Edition.* Brussels 2015, International Diabetes Federation, pp.1-144.

aged in most economically advanced communities", and a published meta-analysis of visual disability due to DR from 1990-2010 revealed that over 800,000 adults worldwide were totally blind and an additional 3.7 million visually disabled; these figures represented increases over those two decades of 27% and 69%, respectfully.[70] A variety of racial, genetic, environmental, and social factors have been instrumental in the epidemic of DM. These are briefly discussed below, but it is clear that the increased prevalence of DM and associated retinopathy, nephropathy, and neuropathy have occurred more frequently among indigenous peoples in low and middle-income countries. Poverty, poor hygiene, inadequate diet, substandard housing, and lack of education are all social determinants of both DM and DR.[71]

Society's healthcare structures represent systemic attempts to combat diseases as contemporary health workers understand them at that time. Awareness of the number of living patients became apparent virtually immediately following insulin's introduction although the subsequent global impact of DM remained underappreciated. For the importance of localized vascular diseases retinopathy, nephropathy, and neuropathy, the "diabetic triad of complications"[72] required more time to become appreciated.[73] Patients who previously might have worried about

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[70] Leasher JL, Bourne RRA, Flaxman SR, et al. Global estimate of the number of people blind and visually impaired by diabetic retinopathy: A meta-analysis from 1990-2010. Diab Care 39 (9):1643-7.
[71] Hill, J, Nielsen M, Fox MH. Understanding the social factors that contribute to diabetes: A means of informing health care and social practices for the chronically ill. Perm J 2013;17(2):67-72.
[72] Root HF, Pote Jr WH, Frehner H. Triopathy of diabetes. Sequence of neuropathy, retinopathy, and nephropathy in 150 patients. AMA Arch Int Med 1954;94(6):931-41.
[73] A somewhat similar story to that regarding insulin emerged following the introduction of respirators in lower income countries with limited access to optimal practices for management of premature babies. Thus, those who would have died without at least oxygen are now living, and a major increase in rates of retinopathy of prematurity (ROP) is being observed. (Khalid AM, Haider AA, Fatima T, et al. Retinopathy of prematurity: an experience in a tertiary care hospital. Pakistan Ped J 2018; 42(2):97-102; and personal communication with Anthony Capone, M.D. July 20, 2018.

surviving with DM therefore had to become aware of the complications that would be expected if they continued to live.[74,75]

Responses to the epidemics of both DM and DR have featured a broad variety of therapeutic recommendations and countermeasures of different types and in various locations, but effective public health strategies to combat both disorders were and continue to be unfortunately slow in most areas of the world. The importance of detecting affected patients has been repeatedly stressed, although optimal screening methods for each problem continue to be debated. Still, the impact of both disorders upon the world stage over a brief time period has been remarkable, as is the fact that an adequate public health response to them remains delayed in most regions.

The increase in obesity (a "plague of plenty"[76], "a pathology of clinical progress"[77]) has been a major driver influencing the growth of both DM and DR. Their altered prevalence is most clearly due to changes in the environments as reflected in selected populations, and subsets of affected cohorts provide excellent examples of the phenomena among various somewhat genetically dissimilar groups. I include brief descriptions of native-Americans of the U.S., citizens of the Pacific and Indian oceans, and inhabitants of India, the U.K., and the U.S. in an effort to document epidemiological variations among social groups. In all of these, the prevalence of DR closely follows that of DM, which is influenced by societal

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[74] Feudtner C. B*ittersweet. Diabetes and the Transformation of Illness.* Chapel Hill, NC, University of North Carolina Press 2004, pp. 1-320.
[75] Tattersall R. *Diabetes. The Biography.* Oxford, NY. Oxford University Press, 2009, pp. 1-231.
[76] Phrase from Baily J. *The End of Healing.* Memphis TN 2017, The Healthy City, Kindle p. 997.
[77] Rosenberg 1998, Op. cit.

evolutions to "western diets" containing excessive fats and sugar-sweetened beverages and to physical inactivity.[78]

Indigenous Native-Americans serve as excellent examples of the roles of both genetic and social factors in promoting the development of DM and its complications. An underlying theme of this history is that the spike in obesity and therefore DM and DR levels among Native American tribes following World War II was due to evolution from a hunter-gatherer environment toward an adoption of a Western style diet and lifestyle.[79] There is increasing evidence that these factors began to occur earlier - in the mid- and late 19th century.[80] For instance, the Pima Indians have been studied for decades, and their DM is almost exclusively Type 2 (as is true of all the tribes); this group has the highest recorded prevalence and incidence of diabetes in the world – 19 times that of citizens of Rochester, Minnesota.[81] In 1940, only 21 cases of diabetes were identified among the Pima living in the Sonoran Desert in Arizona,[82] whereas in 2006, 38% of adults in the tribe aged ≥20 years had acquired the disease.[83] Although there clearly are genetic predispositions to the disorder as evidenced in the finding of a genetic marker

[78] Hu FB. Globalization of diabetes. The role of diet, lifestyle, and genes. Diabetes Care 2011;34(6):1249-1257.
[79] Mihesuah DA, Diabetes in Indian Territory: revising Kelly M. West's theory of 1940. Am Ind Cult Res J 2016;40(4): 1-21.
[80] Ibid.
[81] Narayan KMV. Diabetes mellitus in North Americans: The problem and its implications. In Sandefur GD, Rindfuss RR, Cohen B (eds.). *National Research Council (US) Committee on Population.* Washington, D.C. 1996. National Academics Press, 262-88.
[82] Joslin EP. The universality of diabetes: a survey of diabetic mortality in Arizona. Diabetes 1940;115:2033-8.
[83] Schulz LO, Bennett PH, Ravussin E, et al. Effects of traditional and western environments on prevalence of type 2 diabetes in Pima Indians in Mexico and the U.S. Diabetes care 2006;29:1866-71.

linked to insulin resistance,[84] obesity is the major determinant of DM in this group, and the interaction of this variable with genetic susceptibility is striking: individuals with affected parents are profoundly more likely to develop DM at relatively early ages.[85] The incidence of DR is directly related to degrees of obesity and levels of glucose control,[86] as is generally true for all patients with diabetes.

Plains Indians appear to be less likely to develop DM than the Pima. Although incidence figures among various North American tribes vary considerably, the figures for plains Indians are only approximately a third those of the Pima.[87] Still, the clear association between environmental factors and the odds of developing DM are strikingly apparent in all groups. West[88] and others have documented that the apparent low prevalence of DM in plains Indians prior to WWII was followed by a dramatic increase thereafter, even though the precise incidence of DR in diabetic patients varied among different Oklahoma tribes.

Internationally, similar patterns are apparent. Studies regarding the primarily Polynesian population of Nauru in the Pacific Ocean, the island of Mauritius in the Indian Ocean, and Australia provide additional evidence of the epidemic of DM around the world. On Nauru, the prevalence of DM among the primarily Polynesian citizens is almost 35%, with evidence that the figure increased

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[84] Prochazka M, Lilloya S, Taiet JE, et al. Linkage of chromosomal markers on 4q with a putative gene determining maximal insulin action in Pima Indians. Diabetes 1993;42:514-9.
[85] Gohdes D. Diabetes in North American Indians and Alaska natives. In Harris MI, Cowie CC, Stern MP, et al (eds.). *Diabetes in America. 2nd Edition.* Washington D.C. 1995;DHHS publication no. (NIH)95-1468.
[86] Pettit DJ, Knowler WC, Bennett PH. Development of retinopathy and proteinuria in relation to plasma-glucose control in Pima Indians. Lancet 1980;15;2(8203):1050-2.
[87] Ghodes, Op. cit.
[88] West K. Diabetes in American Indians and other native populations of the new world. Diabetes 1974;23:841-55.

significantly over the past decade.[89] On Mauritius, with a relatively small population of approximately 1.2 million people that includes three major ethnic groups, Asian Indians from India, Creole-South African Blacks, and Chinese, the prevalence of diabetes grew from 14.6% to 23.6% from 1997-2009, a 62% increase, that was similar in each ethnic group.[90] In Australia, the DM prevalence has also grown precipitously, and the Indigenous populations there were disproportionately affected by diabetes and its complications, with a 4-fold higher prevalence compared to the general Australian, mainly European population.[91] In the first Australian national survey to determine the major causes of visual impairment and blindness, DR was recognized as the culprit in 5.5% of Indigenous Australians but in only 1.5% in the non-Indigenous population.[92] In all of these regions, a modified life style featuring western diets and low physical activity played a major role in the DM epidemic, but additional differences are due to genetic variability; and social factors including poverty and poor nutrition have also been important.

And in India there was an increase of diabetes prevalence of nearly 5% between the years 2000 and 2006, more notably in cities than in rural villages.[93] An additional study documented similar growth with additional information that improved socioeconomic status with its greater exposure to Western diets was an

[89] Zimmet PZ. Diabetes and its drivers: the largest epidemic in human history? Clin Diab and Epidemiol 2017; 3:1
[90] Ibid.
[91] Guest CS, O'Dea K. Diabetes in Aborigines and other Australian populations. Aust J Public Health. 1992;16:340–9.
[92] Centre for Eye Research Australia and Vision 2020 Australia. The National ye health Survey 2016.Melbourne, 2016, Vision 2020 Australia, 1-32.
[93] Ramachandran A, Mary S, Yamuna A, et al. High prevalence of diabetes and cardiovascular risk factors associated with urbanization in India. Diabetes Care. 2008;31:893–8.

important variable impacting prevalence rates, especially in urban areas.[94] In the latter study, the prevalence rate of DM in relatively affluent patients inhabiting cities of more economically developed states was higher than in those individuals of relatively low socioeconomic class, whereas the opposite was true in urban regions that had experienced less development, suggesting a recurring theme that increasing access to more western diets may increase the rate of diabetes. Regardless, the prevalence rate of diabetes in India, currently second only to China, now includes 80–90 million people living with the systemic disorder, representing over 10% in the adult population;[95] and India is projected to outnumber China in number of affected patients by 2030.[96] The India DR market size is currently valued at eight billion US dollars and is expected to grow by almost seven percent annually to 12 billion by 2025.[97] Factors responsible for the prevalence include (as noted previously) the genetic influences coupled with environmental variables such as the obesity associated with rising living standards, steady urban migration, and lifestyle changes.[98]

Retinopathy rates among Indian patients with DM appear to be consistent with other regions of the world mentioned above. A 2014 nationwide survey of over 5,000 diabetic individuals revealed a DR prevalence of almost 22%, and the typical

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[94] Anjana RM, Deepa M, Pradeepa R, et al. Prevalence of diabetes and pre-diabetes in 15 states of India: results from the ICMR-INDIAB population-based cross sectional study. The Lancet. Diabetes and Endocrinology. 2017;5(8):585-96.
[95] International Diabetes Federation 2015 Disease Atlas Op. cit.
[96] Nadarajan B, Saya GK, Krishna RB, et al. Prevalence of diabetic retinopathy in rural area of Villupuram district of Tamil Nadu, India. J Clin Diag Res 2017;11(7);LC23-6.
[97] Sankritayan R. Diabetic retinopathy market 2019share, trends, and forecast, 2019-2025. www.express-journal.com/july 26, 2019. Accessed August 9. 2019.
[98] Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. Aus Med J 2004;7(1):45-8.

variables of duration of systemic disease, age, and glucose control quality were significantly associated with the likelihood of developing these retinal vascular changes.[99] Specific prevalence figures vary somewhat from region to region and study to study, but it is quite clear that increasing numbers of patients with DM leads to more cases of DR, and that both disorders will increase the healthcare burden of the country.[100]

In the United Kingdom, the overall prevalence of DM among citizens is approximately 6.2%, representing a doubling of the number of affected individuals between 1996 and 2014, and an estimated 50% additional increase is expected by 2025.[101] Once again, the increased rate of obesity in the population is a major determinant. Rates of DR are consistent with those in other countries in being associated with age, duration of disease, and poor control of serum glucose. However, the UK is in the forefront of those taking measures to identify and manage this disorder, as described later.

In the United States, the prevalence of DM varies among different ethnic groups. Native Americans were mentioned above due to their representation as a relatively distinct group, and compared to the Caucasian American patients, DM is almost two and 1.6 times as common in Latino-American and African-Americans, respectively.[102] In addition to these racial/genetic variables, additional major social

[99] Gadkari SS, Maskati QB, Nayak BK. Prevalence of diabetic retinopathy in India: The all-India Ophthalmological Society diabetic retinopathy screening study 2014. Ind J Ophthalmol 2016;64(1):38-44.
[100] Nadarajan 2017, Op. cit., 25.
[101] Diabetes UK (formerly the British Diabetic Association). *Facts and Stats, Version 4, 2015,* p. 1.
[102] Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. Diab Care 1998;21:518-24.

determinants of the systemic disease (described below) are similar around the globe: obesity and reduced physical activities associated with contemporary life styles. Similarly, rates of DR are strongly related to the control of serum glucose levels and duration of disease. And there are additional factors of importance.

The impact of social determinants of health upon diabetes mellitus

In addition to the ethnic and genetic variables mentioned above, the influences of poverty, education, and additional socioeconomic factors upon the incidence and course of DM has been clearly and extensively articulated in the literature, and any variable correlated with the prevalence of DM as well as inadequate care of this systemic disorder is reflected in an increased presence and severity of DR. Lacks of income and education (the two most common dimensions of poverty[103]) are two predictive variables for life expectancy,[104] but considerations of these factors alone may miss data regarding the extremes of poverty and squalor that exist, especially in many lower income countries with growing populations of diabetic patients. As noted earlier, patients of low economic status in high-income countries are much more likely to have a higher chronic disease burden than individuals of a higher economic status, and obesity among other variables increases among the relatively poor as exposure to western dietary increases (another example of Sigerist's 1933 statement "Each change of cultural conditions

[103] The *Lancet* taskforce on NCDs and economics 2. Tackling socioeconomic inequalities and non-communicable diseases in low-income and middle-income countries under the Sustainable Development agenda. Published online April 4, 2018, http://dx.doi.org/10.1016/S0140-6736(18)30482-3.

[104] Knickman JR, Kovner AR. (eds). *Jonas and Kovnar's Healthcare Delivery in the United States, 11th Edition.* New York, 2015, Springer Publishing, 86.

has a definite repercussion on the diseases of the time".[105]) Major dietary changes that have occurred in Asia in the last several decades have included a shift from consumption of coarse grains to polished rice and refined wheat; reduced diets of cereals particularly among urban populations and higher-income groups; increased consumption of dairy products and added sugar; and higher energy intake among the poor, lower energy intake among the rich, and greater consumption of fat in all income groups.[106] And of course the ability to access and pay for contemporary care including patient education may be quite impossible for impoverished individuals.

One contemporary study of the influence of socioeconomic status upon DM prevalence revealed that regional areas of relative deprivation may contribute to the effects upon individuals, even after controlling for the latter's personal characteristics.[107] Lower income dictated a reduced access to optimal foods and increased insecurity regarding their availability;[108] and also the quality of diets available to patients in differing regions.[109] Higher educational attainment would be expected to be associated with increased competence in managing health issues, including the understanding of instructions regarding optimal dietary habits and the necessity of periodic evaluations.

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[105] Sigerist HE. Problems of historical-geographical pathology. Bull Inst Hist Med 1933;1(1):10-18.
[106] Hu FB. Globalization of diabetes. The role of diet, lifestyle, and genes. Diab Care 2011;34(6):1249-1257.
[107] Maier W, Holle R, Hunger M, et al. The impact of regional deprivation and individual socioeconomic status of the prevalence of type-2 diabetes in Germany. A pooled analysis of five population-based studies. Diab Med 2013;30(3):e78-e86.
[108] Seligman HK, Lavatia BA, Kushel MB. Food insecurity in association with chronic disease among low-income NHANES participants. J Nutr 2010;140:304-10.
[109] Darman N, Drewnowski A. Does social class predict diet quality? Am J Clin Nutr 2008;1109-17.

In this chapter I set out to describe a brief history of DM during post-insulin eras. The impact of studies regarding the importance of glucose control that was emphasized in the last chapter were explored. In addition, the epidemiology of the systemic disease among various ethnic and societal groups and the importance of social determinants as influential variables were described. Most patients that have acquired the systemic disease ultimately develop signs of DR. Effective clinical practices that reduce the incidence of both the systemic and ocular disorders have been developed, but they remain poorly instituted in most parts of the world. In the following chapter I discuss retinopathy in more detail.

Chapter 4.

Diabetic Retinopathy: recognition and management

In this chapter I review historical and contemporary methods for the detection and treatment of DR, including the development of the ophthalmoscope, early therapeutic attempts, and descriptions of trials that established the evidence base for contemporary therapeutic strategies. This information is important for an understanding of the steps that that have occurred as evidence-based treatment maneuvers have been developed.

As noted previously, it took some time for concepts of localized vascular diseases due to DM to emerge.[110] Any variable associated with an increased prevalence of DM and inadequate management of the systemic disorder will be reflected in an increased presence and severity of DR; thus the data regarding development of the systemic disease are consistent with studies regarding the prevalence of retinopathy.

The diagnosis of diabetic retinopathy

The story of DR did not begin until it could be detected clinically with an ophthalmoscope – a literal "knowledge-producing tool"[111]. The clinical diagnosis is purely morphologic, constructed upon its appearance: someone has to observe it (or

[110] Rosen, Op. Cit., 16.
[111] Wailoo, Op. cit.. 13.

an image of it) before a diagnosis can be made, and this became possible only after the introduction of the ophthalmoscope, which hastened the evolution of specialties in medicine in addition to providing the first means of visually assessing human pathophysiology *in vivo.* The device was initially very difficult to employ, thereby adding to the authority of those who mastered its use.

A number of textbooks have described the development of the ophthalmoscope and its role in the establishment of subspecialties.[112,113,114] All that was ultimately required for an ophthalmoscope was for the proper lenses to be placed in front of the luminous pupil, the observer to be appropriately positioned, and a means of separating the light entering the eye from that emerging from it. The development of the ophthalmoscope was almost accomplished by several scientists, but Hermann Helmholtz has been rightfully credited as the originator.

The invention of the ophthalmoscope was announced to the Berlin Physical Society in 1850, and descriptions of the instrument were published the following year. His device employed three plates of glass that simultaneously acted as a mirror to reflect light into the eye while allowing the observer to see an image through them; to this was attached a lens to focus the emerging light rays (Figure 1).[115] The early devices were cumbersome and difficult to use, and a couple of decades passed before more practical models were developed. Even then, only a few investigators used them, prompting an 1871 quote "the number of physicians who are working

[112] Rosen, Op. Cit.
[113] Rucker WC. A history of the ophthalmoscope. Rochester, Minnesota: Whiting Printers and Stationers, 1977; 127.
[114] Sherman SE. The invention of the ophthalmoscope. Doc Ophthalmologica 1989;71:221-8.
[115] Ibid.

with the ophthalmoscope in England may… be counted on the fingers of one hand".[116] But this situation did not persist as instruments improved.

For more than a decade, illumination for reflecting ophthalmoscopy employed candles, oil lamps, and (later) gaslights. Electric bulbs for illumination were adapted in the later 19th century, but reflected light continued to be used well into the 20th. By 1913, over 200 different reflecting ophthalmoscopes had been developed. The availability of electricity prompted a need for small light bulbs, and although the first electric ophthalmoscope with self-contained illumination was demonstrated in 1885, more practical devices did not reach the marketplace until the second decade of the 20th century.

Retinal changes associated with diabetes were observed soon after the ophthalmoscope was invented. Jaeger in 1856 described the retinal vascular anomalies that he had observed and provided a drawing, which although not pathognomonic of DR, was unequivocally the first publication describing retinal vascular lesions in the eye of a patient with DM.[117] Twenty years later, Manz published an illustration and paper that described advanced proliferative DR as "retinitis proliferans".[118] However, the concept of the disease entity "diabetic retinopathy" remained elusive for many more decades. Blurry vision associated with DM had been recognized for centuries, but it was usually due to variable serum glucose levels or cataracts. When these variables became ruled out and

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[116] Ibid.
[117] Jaegar E. *Beiträge zur Pathologie des Auges. 2. Lieferung, S. 33, Tafel XII. K. K. Hof-und Staatsdruckerei,* Wien 1855.
[118] Manz W. Retinitis proliferans. Graefes Arch Clin Exp Ophthalmol. 1876;22:229.

ophthalmoscopes were available, visible lesions in the retina became suspected as the cause of vision loss. Although some authors have stated that Hirshberg first claimed that DR was a distinct entity,[119] debates regarding the specificity of the findings versus those of "albuminuric retinopathy" associated with renal failure continued for decades because the two conditions so frequently coexisted, and both featured intraretinal hemorrhages and swelling in the posterior retina.[120] Bouchut[121] (1866) and Desmarres[122] (1864) reported that signs of "glycosuric" (diabetic) retinopathy were identical to those of "albuminuric retinopathy"; Galezowski[123] (1875) regarded the former to be only rarely distinguished from the latter; whereas Noyes[124] (1868) and Nettleship[125] (1872) described cases of DR *unassociated* with albuminuria. Still, the relative roles of hyperglycemia, arteriosclerosis, and renal failure in the pathogenesis of retinal vascular changes long delayed acceptance of DR as a specific entity, and well into the 20th century it was incorrectly framed as a complication of renal failure and/or hypertension.

This diagnostic dilemma was clearly demonstrated in sequential papers from the Mayo Clinic that were published 13 years apart by the same group of

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[119] Pouslon, Op. cit. ,120.
[120] Contrary to DR, albuminuric retinopathy has become an exceedingly unusual diagnostic entity in the western world primarily because of the availability of dialysis. The author last observed a case in 1972 in a non-diabetic teenager with renal failure secondary to chronic pyelonephritis.
[121] Bouchut E. *Du Diagnostic des Maladies du System Nerveux Pars L-Ophthalmoscopic.* 1866, Paris, Germer Bailliere, pp. 442-6.
[122] Desmarres LA. *Traite Theoriquebet Practique des Maladies Des Yeux, 3rd Edition.* 1864, Paris, Germer Bailliere, pp. 642-6.
[123] Galezowski X.*Traite des Maladies Des Yeux ,2nd Edition.* Paris, Germer Bailliere, pp. 642-6.
[124] Noyes HD. Retinitis in glycosuria. Trans Am Ophthalmol Soc. 1869;4:71–75.
[125] Nettleship G. On oedema or cystic disease of the retina. Roy Ophth Lond Hosp Rep. 1872;7(3):343–51.

investigators. In the first, published in 1921, 44 cases of "diabetic retinitis"[126] were identified in a cohort of 300 patients (15%), and the retinal alterations were considered to be due to systemic arteriosclerosis or to renal disease.[127] The authors stated "…retinitis characteristic or diagnostic of diabetes, comparable to the retinitis of nephritis, must still be regarded as unproven".[128] Subsequently in 1934, 1052 diabetic patients were evaluated (evidence of the growing prevalence of both DM and DR), and retinal changes were identified in 187 (17.7%). Fifteen percent of diabetic patients were under age 40 years, but DR was evident in only 4,3%, whereas it was present in over 20% of patients older than that, and it occurred exclusively in those with mild, easy-to-control DM (i.e., those who continued to live with DM). In this publication, the authors stated that DR featured a distinct picture that was solely due to the systemic disease,[129] and this view came to be accepted worldwide.

Early treatment of diabetic retinopathy

> *In the spring of 1967, Janet was a 27 year-old Caucasian female with a 17- year history of type-1 diabetes mellitus*[130]*; she had been pregnant for ten weeks. In the preceding days, she had experienced blurred vision associated with dark*

[126] The term "retinitis" was initially employed to describe retinal vascular changes due to DM even though an inflammatory basis was not (and has not been) established. It gradually was replaced by the term "retinopathy", stimulated by a publication describing the histopathology of the disorder (Ballantyne A J, Loewenstein A. Diseases of retina: pathology of diabetic retinopathy. *Tr. Ophth. Soc. U K* 1943:63: 95.)
[127] Wagener HP, Wilder RM. The retinitis of diabetes mellitus. JAMA 1921;75:515-17.
[128] Ibid, 515.
[129] Wagener HP, Dry, TJS, Wilder RM. Retinitis in diabetes. NEJM 1934;211(25):113-17.
[130] "Janet" is a pseudonym, but the true history was witnessed by the author.

floating images in her visual fields and was subsequently diagnosed with intraocular hemorrhages and localized retinal detachments due to diabetic retinopathy. For these problems, which were not amenable to recently available photocoagulation therapy, she was offered accepted alternative treatments of either abortion or brain surgery to remove her pituitary gland; but she rejected these options. Over the following five months, Janet lost all vision including light perception in both eyes.

The case cited above demonstrates the frustration level that patients and their caregivers faced with untreatable retinopathy. Early attempts to manage DR were initially topics of clinical research on local levels. Such therapies included dietary restrictions, x-irradiation of the retina, systemic administration of vitamins C and B12, clofibrate (Atromid), para-aminosalicyclic acid, anticoagulants, testosterone, and later, induction of glaucoma with topical use of topical corticosteroids.[131] The importance of a rapidly increasing prevalence of DR appeared (to the author) to be of more importance to the eye care community than to broad based healthcare systems. Responses to many epidemics are slow to develop in communities of affected patients,[132] and time is required for widely accepted recognition of a disease entity; so it was with DR, a problem that implicated both personal behavior of affected patients and management strategies

[131] Goldberg MF, Jampol LM. Knowledge of diabetic retinopathy before and eighteen years after the Airlie House Symposium on treatment of diabetic retinopathy. Ophthalmology 1987;94:741-6.
[132] Rosenberg CE. *Explaining Epidemics and Other Studies in the History of Medicine.* Cambridge, Cambridge University Press 1992, p. 281.

accepted by the medical community. The former variable remains a formidable goal, and the latter was a source of major controversy that preceded the establishment of evidence-based therapies.

The most important historical techniques—pituitary ablation and photocoagulation—both became viable options via serendipitous routes, and their relative values were hotly debated among physicians in the retina community. Very importantly, until they were properly evaluated, there were virtually no evidence-proven therapies to prevent blindness from proliferative DR. Minkowski and co-workers demonstrated the relationship between the pancreas and DM before the end of the 19th century: removal of the canine pancreas caused diabetes mellitus to develop, and this stimulated a flurry of subsequent research. (Interestingly, Minkowski's initial pancreatectomy had been performed for the physician von Mering in an effort to study lipid absorption, and the subsequent polyuria of diabetes was unexpected.[133])

In 1930 Houssay[134], employing a diabetic canine (following pancreatectomy) model, described a remarkable increase in insulin sensitivity following removal of the dog's pituitary gland, and additional case reports in the mid-30's described improvement of DM control in human diabetic patients following loss of pituitary function.[135] Later, in 1953, Poulson reported a serendipitous case in which spontaneous necrosis of the anterior pituitary gland (Sheehan's syndrome) had

[133] Editor's Note. *Diabetes. A Medical Odyssey*. USV pharmaceutical corporation 1971, Tuckahoe, NY, p.111.
[134] Houssay, BA, Biasotti, AA: Diabetes pancreatica de los perros hipofisoprivos, Rev Soc Argent Biol 1930; 6:251-69.
[135] Hernberg C A, af Bjorkesten G, Vannass S. Hypophysectomy in the treatment of diabetic retinopathy and nephropathy in severe juvenile diabetes. Diabetologica 1959;3:241-60.

occurred in a postpartum patient with established DR, following which the retinopathy resolved over a lengthy follow-up period.[136] However, even prior to this publication, Oliveron (a neurosurgeon) and Luft (a physician friend of Poulson who knew about his case) began studying the value of hypophysectomy for proliferative DR. In 1955 they reported 20 such cases; some had poorly defined improvements in retinopathy, but the mortality rates were disappointingly high.[137] Nevertheless, with no hopes for vision in patients with severe DR, it was widely proposed that studies of pituitary ablation should be initiated in spite of the fact that the disease of hypopituitarism would be superimposed upon that of DM.

Pituitary ablation was accomplished with a variety of surgical and irradiation maneuvers, and by 1967 over 1,200 patients in the western world had undergone the therapy.[138] And contrary to opinions in some contemporary publications regarding DM,[139,140] these techniques were clearly of value in some patients with certain stages of severe DR. Results from a large and diverse group of participating investigators were reported along with those regarding photocoagulation at a pivotal meeting at Airlie House, Virginia, in 1967 and published in 1968[141] (the meeting is more thoroughly discussed below). Data regarding ablations at 11 centers involving 599 eyes were reported, and of these, 63% exhibited an "arrest" of

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[136] Poulson JE: Houssay phenomenon in man: Recovery from retinopathy in a case of diabetes with Simmonds' disease. Diabetes 1953: 2:7-12.
[137] Luft R, Olivercrona H, Ikkos D, et al. Hypophysectomy in man. Further experiences in severe diabetes mellitus. Br Med J 1955;2:752-6.
[138] Davis M in: Fine SL, Goldberg MF (Eds). *Symposium:Treatment of Diabetic Retinopathy.* Washington, D.C. 1969, U.S. Dept of Health, Education, and Welfare, pp. 1-913.
[139] Feudtner, *Bittersweet,* op cit, 192.
[140] Tattersall, op cit, 99-100.
[141] Fine SL, Goldberg MF. (Eds) *Symposium:Treatment of Diabetic Retinopathy.* Washington, D.C. 1969, U.S. Dept of Health, Education, and Welfare, pp. 1-913.

retinopathy, whereas the remaining 37% progressed. There was unanimous agreement that the "angiopathic aspect of retinopathy responded well to pituitary ablation".[142] Compellingly, one report documented a direct relationship between the degree of pituitary ablation and the likelihood of retinopathy regression.[143] Still, concerns regarding the expected complications of secondary hypopituitarism were recognized as negative outcomes,[144] and the success rates of photocoagulation described below resulted in a generalized abandonment of pituitary ablation with rare exceptions.[145]

Photocoagulation was a result of an additional serendipitous observation and subsequent publications by a single German investigator, Gerhard Meyer-Schwickerath . Solar burns of the retina had been recognized since antiquity, and such a case was reported soon after the development of the ophthalmoscope; and in the later 19th century Czerny and others described effects of retinal burns from the sun on the eyes of experimental animals after focusing sunlight upon their retinas.[146,147] The first report of the effects of focused sunlight on the human retina (in eyes with tumors that were scheduled for enucleation) was published in the

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[142] McMeel JW. Summary of papers on ocular aspects of pituitary ablation. In: Fine SL, Goldberg MF (Eds). *Symposium:Treatment of Diabetic Retinopathy.* Washington, D.C. 1969, U.S. Dept of Health, Education, and Welfare, pp. 375-379.
[143] Joplin GF, Oakley NW, Hill DW, et al. Diabetic retinopathy II. Comparison of disease remission induced by various degrees of pituitary ablation by Y90. Diabetelogica 1967;3:406-412.
[144] Physicians managing these patients were burdened with many acute metabolic problems as well as the long-term future issues. "The psychosocial dimensions {in these patients} are the missing link in these reports. I became burdened with offering the operation {pituitary ablation} to a less-than-40-years age group who would be made old overnight." (Personal communication, Burnett D (an endocrinology fellow at the Joslin Institute from 1960-62), April 2, 2017)
[145] Kohner EM, Hamilton AM, Jopkin GF, et al. Florid diabetic retinopathy and its response to treatment by photocoagulation or pituitary ablation. Diabetes 1976;25:104-10.
[146] Czerny V. Uber blendung der netzhaut durch sonnenlicht. Ber Wien Acad Wiss 1867, 56:II.
[147] Deutschmann R. Klinisch-ophthalmologische miscellen. Graefes Arch f Ophthalmol 1882;28:241.

Italian literature in 1927, and it was not until 1949 that Meyer-Schwickerath published his initial experiences.[148] He had been stimulated by his observation of a scar in the retina of a patient who had witnessed an eclipse, and he initiated experiments to establish a means of therapeutic photocoagulation of the human retina. He initially developed a "heliostat" to focus the sun's rays but then began experiments with a high-intensity carbon lamp. Subsequently, a xenon arc device was developed in 1956, and this was employed as a photocoagulation device worldwide until laser therapy was introduced a decade later.

The physics surrounding the development of the laser will not be discussed, but research on ruby laser photocoagulation was initiated in experimental animals in 1961 and two years later in human eyes.[149] But red light was not generally effective for red retinal vascular lesions, and searches for alternative wavelengths were continued, and the argon green laser quickly became the instrument of choice for many, particularly after the development of a binocular stereoscopic observation systems in the late '60s.[150] Commercially available argon lasers became widely distributed globally beginning in 1970.

Photocoagulation therapy was initially directed at visible retinal vascular lesions, other sites of apparent leakage of serum (unusual), or areas of neovascularization (common). A major problem was that new vessels arising on the optic nerve could not be treated for fear of damaging this vital structure. As data

[148] Meyer-Schwickerath G. Koagulation der netzhaut mit sonnenlicht. Ber Dtsch Ophthalmol Ges 1949;55:256.
[149] Kapeny NS, Peppers NA, Zweng HC, et al. Retinal photocoagulation by laser. Nature 1963; 199:146-149.
[150] Little HL, Zweng HC, Peabody RR. Argon laser slitlamp retinal photocoagulation. Trans Am Acad Ophthalmol Otolaryngol 1970;74:85-NEED PAGE.

accumulated regarding photocoagulation, an ironic outcome became apparent: eyes in which a large number of burns (initially with xenon light) had been placed seemed to have better outcomes than those with fewer spots of therapy because of less severe proliferative DR. Regardless of treatment technique, eyes in which a genuine "involution" occurred were characterized by widespread narrowing of retinal vessels, mild optic atrophy, and (of course) a large number of pigmented burn scars. Coincidentally, Beetham is credited with recognizing that such cases were similar to those with widespread chorioretinits or optic atrophy due to vascular accidents;[151] it was widely accepted but poorly documented that such cases provided apparent protection from retinopathy progression when they occurred in a single eye of a patient with diabetes in which the "unaffected" eye with DR continued to progress.[152] This in turn lead to the development of a second photocoagulation technique, "scatter therapy", in which large numbers of burns were placed randomly in the posterior retina, avoiding the macula, and disregarding the locations of neovascularization. The originators of this technique initially employed a ruby laser, but both xenon arc and argon green therapies were later employed in collaborative studies discussed below. Results of photocoagulation were collected in advance of the Airlie House Symposium mentioned both above and below. A total of 1,635 eyes had been treated, and there was general agreement

[151] Aiello LM, Beetham WF, Balodimos MC, et al. Ruby laser photocoagulation in treatment of diabetic proliferating retinopathy: preliminary report. In: Fine SL, Goldberg MF (Eds). *Symposium: Treatment of Diabetic Retinopathy.* Washington, D.C. 1969, U.S. Dept of Health, Education, and Welfare, p.438.
[152] This appearance was also recognized in rare cases in which extensive retinal burns had been created for retinal detachment in one eye of a diabetic patient, and severe proliferative disease developed only in the other eye. Okun E. Discussion of visual and anatomic results. In: Fine SL, Goldberg MF (Eds). *Symposium: Treatment of Diabetic Retinopathy.* Washington, D.C. 1969, U.S. Dept of Health, Education, and Welfare, pp. 619.

that the treatment was significantly better than no therapy. Still, the need for better studies comparing treated and control eyes with similar stages of DR was also expressed.[153]

The profound increase in DR as a major cause of visual disability stimulated the U. S. Public Health Service to sponsor a symposium at Airlie House, Virginia in the autumn of 1968.[154] In advance of the meeting in June, 1968 a small group of seven experts met in Chicago near the O'Hare airport in an effort to establish a novel DR grading system based upon a handful of prior reports[155]; this was necessary to establish a standard classification of disease so that clinically equivalent cases could be compared following treatments of various types and after lengths of time with no therapy.[156] A select group of approximately 55 experienced ophthalmologists and a similar cohort of neurosurgeons, epidemiologists, and endocrinologists were invited to the symposium and asked to prepare reports of their successes and failures utilizing their preferred techniques and employing the O'Hare classification. The outcome data in attendees' manuscripts were then distributed to all in advance of the meeting so that meaningful discussions would occur when the symposium took place. This International Symposium on Treatment of Diabetic Retinopathy was held

[153] Davis MD. Summary of personal impressions of Airlie House symposium on diabetic retinopathy. In: Fine SL, Goldberg MF (Eds). *Symposium: Treatment of Diabetic Retinopathy.* Washington, D.C. 1969, U.S. Dept of Health, Education, and Welfare, pp. 718-719.

[154] Personal communication, Stuart Fine, MD, September 2017.

[155] Historian Henry Marks stated "…clinical research is intrinsically a social process". (Marks HM. *The Progress of Experiment. Science and Therapeutic Reform in the United States, 1900-1990.* 1997, Cambridge, Cambridge Medical Press, p. 240), in which "endless negotiations took place". Still, the academic retina community was very small in 1968, and the members of this group, lead my Mathew D. Davis, was recognized as composed of the leading legitimate experts on DR. Similarly, those invited to the Airlie Symposium were acknowledged experts in their respective fields.

[156] Davis MD, Norton EWD, Myers FL. The Airlie classification of diabetic retinopathy. In: Fine SL, Goldberg MF (Eds). *Symposium: Treatment of Diabetic Retinopathy.* Washington, D.C. 1969, U.S. Dept of Health, Education, and Welfare, pp.

at Airlie House September 29- October 1, 1968. Six sessions included: classification of DR; natural history and visual prognosis; relationship of DR to glucose control; pituitary ablation; photocoagulation; and miscellaneous topics. This meeting was *the* critical event in the path toward more scientific evaluations regarding treatment for DR because the presented data had demonstrated that photocoagulation was more effective than hypophysectomy, and (more importantly) it stimulated the development of several randomized trials of the former therapy.

The methods described in the Airlie House publication had been difficult to interpret because of an insufficiency of data regarding the predictability of any given case. Both hypophysectomy and photocoagulation produced a variety of outcomes that made comparisons of the two modalities and also of the natural courses of untreated eyes quite untenable. Clearly, experienced physicians of high integrity had recorded successes with both photocoagulation and pituitary ablation, but failures also had occurred. The situation was perhaps best exemplified by a leading expert on the subject who, when asked to discuss photocoagulation at a symposium, stated that of course he would be pleased to comment but that he would need to know if he should plan to deliver the speech on the success of the modality or how dangerous it appeared to be;[157] for photocoagulation had well-known severe complications, especially when applied to eyes with advanced DR, and it was not always successful, even in non-advanced cases.

Thus, in spite of the many case series reports regarding photocoagulation and pituitary ablation, it was clear that by 1968 there was no unequivocal answer to

[157] Fine 2017 Op cit.

the question "what is the best way to treat advanced DR?" in spite of the fact that over 1,200 reported pituitary ablations and 1,600 recorded photocoagulation procedures had been performed in the decade 1958-1968.[158] But the implications of the Airlie House Symposium had stimulated an acceptance of photocoagulation as preferable to pituitary ablation even though questions remained about the genuine efficacy of the former alternative, and this stimulated interest by both practitioners and the government to move away from the personal experiences and opinions of experts and initiate the development of a randomized trial (RCT) to provide conclusive evidence regarding the benefits or lack of efficacy of photocoagulation therapy.

Development of the evidence base for treatment of diabetic retinopathy

There is a rich literature on the history of RCT's.[159,160,161,162] According to Lilienfeld,[163] the first trial featuring randomization began in 1931 in regard to the use of sanocrysin for tuberculosis, and this study was also the first to employ a double-blind strategy.[164] Still, it appears to be widely accepted that traditional randomization of large numbers of patients began in England in the 1940's with the

[158] Fine SL, Goldberg MF, Tasman W. Historical perspectives on the management of macular degeneration, diabetic retinopathy, and retinal detachment. Personal reminiscences. Ophthalmology 2016;123:S64-S77.
[159] Marks HM. *The progress of Experiment. Science and Therapeutic Reform in the U.S, 1900-1990.* New York, 1997, Cambridge University Press.
[160] Bothwell LE, Greene JA, Podolsky SH, et al. Assessing the gold standard-lessons from the history of RCT's. NEJM 2006;374(22):2175-81.
[161] Chalmers TC. Randomization of the first patient. Milbank Mem Fnd Quart 1981;59(3):.324-9.
[162] Chalmers TC. The clinical trial. Med Clin N Amer 1975;59(4):1035-8.
[163] Lilienfeld AM. Ceteris paribus. The evolution of the controlled trial. Bull Hist Med 1982;56(1):1-18.
[164] Amerson JB, McMahan BT, Pinner M, Amerson JB. A clinical trial of sanocrysin in pulmonary tuberculosis. Am Rev Tuberculosis 1931;24:401-35.

work of A. B. Hill and the Medical Research Council in regard to Streptomycin for tuberculosis[165], although an analysis of attempts to demonstrate therapeutic efficacy, forerunners of RCT's, revealed that less sophisticated methods were initiated much earlier.[166,167] The early RCT's were employed in the evaluations of medical rather than surgical therapy, and some authorities stated that there existed a "double standard", with surgical procedures not having to meet the rigid criteria for efficacy demanded by agencies such as the FDA.[168] However, this opinion contrasted with an alternative explanation that the manual skills, experiences, and intraoperative variables demanded of surgeons made a comparison of surgical and medical therapeutic outcomes quite unrealistic.[169] Still, surgical RCT's became important, in spite of their inherent potential difficulties regarding surgeon experience and expertise,[170,171] although the majority of these followed the studies mentioned below.

In his text on the development of clinical trials in medicine, Marks noted "new therapeutics was a product of two institutions: the laboratory and the

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[165] Streptomycin in tuberculosis trails committee. Streptomycin treatment of pulmonary tuberculosis. Br J Med 1948;2:769-782.
[166] Bothwell LE, Podolsky SH. The emergence of the randomized, controlled, trial. NEJM 2006;375(6):501-4.
[167] Greene JA. Therapeutic proofs and medical truths: the enduring legacy of medical drug trials. Bull Hist Med 2017;91(2): 420-9.
[168] Spodick DH. Numerators and denominators. There is no FDA for the surgeon. JAMA 1975;232(1):35-6.
[169] Love JW. Drugs and operations. Some important differences. JAMA 1975;232(1):37-8.
[170] Roman H, Mocrpeau L, Hulsey TC. Surgeons' experience and interaction effect in randomized controlled trials regarding new surgical techniques. Am J Obst and Gynec 2008;199(2):108.e1-108.e6.
[171] Tang CL, Schlich T. Surgical innovation and the multiple meanings of randomized controlled trials: the first randomized controlled trial on minimally invasive cholecystectomy. J Hist Med Allied Sci 2017(72(2):117-41.

market".[172] Although there clearly was a "market" for effective therapy for DR, I believe that the former variable (the laboratory) was not relevant at the time RMT's were being formulated, for although numerous preclinical laboratory research studies regarding photocoagulation had been performed by the time that clinical trials of the treatment modalities (Xenon and Argon) were being considered, the devices had become standards of therapy for both DR and several non-diabetic retinal vascular and retinal detachment disorders, and the physical skills necessary for treatment were not extraordinary - expertise was acquired in residency programs. Prior to establishment of randomized trials, a variety of therapeutic photocoagulation strategies were routinely practiced on the above conditions worldwide as physicians acquired the devices in the latter 1960's. The studies to be described below were funded by the National Eye Institute (NEI) of the NIH, and the randomization process in the Diabetic Retinopathy Study was simply a matter of selecting one of a pair of eyes with similar stages of retinopathy for treatment and the other as a control. The establishment of appropriate trials required extensive preparation.

The Diabetic Retinopathy Study (DRS)[173] was the first formal randomized and controlled study in ophthalmology, although a prior trial of the effects of oxygen upon premature babies had featured comparisons between groups of similar

[172] Marks , Op. Cit.
[173] The Diabetic Retinopathy Study Research Group: Preliminary report on effects of photocoagulation therapy. Am J Ophthalmol 1976; 81:383-396.

patients.[174] The DRS required a group effort that included the country's leading authorities, and this was particularly important in the establishing of a more sophisticated DR classification system regarding the severity of retinopathy.

The Hammersmith group in the UK had established a scheme for grading DR severity in 1966, and this served as a stimulus for later classifications.[175] In June, 1968, as noted above, a small group of experts met near the O'Hare airport and produced a scheme for the meeting at Airlie House in Virginia also mentioned above.[176] Publications of the papers and discussions appeared soon thereafter, and minor modifications of the O'Hare classification resulted in the "Airlie House DR classification" that was employed during the subsequent DRS.[177]

The NIH-funded DRS was begun in 1971; patients were recruited from 15 clinical centers; initial outcomes were published in 1976.[178] The study included patients with relatively advanced DR and vision 20/100 or better in both eyes; thus one eye could serve as a control. The study's primary end-point was the "severe loss of vision" (less than 5/200 and well less than the definition of legal blindness as 20/200) on two consecutive 4-month follow-up visits. Therapeutic strategies included either Xenon or Argon treatment with photocoagulation burns applied

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[174] Patz A, Hoeck LE, De La Cruz E. Studies on the effect of high oxygen administration in retrolental fibroplasia. 1, Nursery observations.Am J Ophthalmol 1952;35(9):1248-53.

[175] Oakley N, Hill DW, Joplin GF, et al. Diabetic retinopathy. I. The assessment of severity and progress by comparison with a set of standard fundus photographs. Diabetalogia 1967;3(4):402-5.

[176] Even though I was a retina fellow at the time, i personally knew or had met each of these individuals through their contacts with my Chairman in Miami, and I was familiar with the state of classifications. These ophthalmologists were indeed the leading authorities at the time. Although I was not present at any of these meeting, it was my impression that debates about "fine points" were managed in an equitable and amicable fashion.

[177] Fine, Goldberg, Tasman 2016, op. cit.

[178] The Diabetic Retinopathy Study Research Group, 1996, Op. Cit.

directly to flat areas of neovascularization and also to the retina periphery in a "scatter" (random) pattern.

In the initial report regarding 1,727 patients, 869 eyes had received Xenon therapy and 858, Argon. After two years, 16.3% of untreated eyes had experienced severe visual loss, but this occurred in only 6.4% of treated cases, a reduction of 61% (Fig. 2). These significant differences resulted in treatment for the fellow eyes to be offered, and photocoagulation became accepted worldwide as the treatment of choice for proliferative retinopathy.

The significance of the DRS should not be underestimated. Up until the time of its publication, practitioners had no evidence-based data regarding how to treat an increasing number of eyes with advancing proliferative DR. For example, in 1972 as a young retina specialist in an academic center but not participating in the DRS, I adapted the premise of the protocol since the value of photocoagulation remained undocumented. I recall a 38-year old woman with a 21-year history of type 1 DM with severe but symmetrical proliferative disease in each eye. She and I literally flipped a coin and decided to treat her right eye with the laser and follow the left. She did well with photocoagulation therapy but became blind in her left eye due to a series of vitreous hemorrhages over the following 15 months. Ultimately, the blood was removed with a vitrectomy (see below) and useful vision was restored. Fortunately, further guidelines for management were developed in additional trials.

A second DRS report was published in 1978 and described a change in study protocol to require the consideration of untreated cases of PDR with selected

features that were termed "high risk characteristics".[179] The major conclusions in this publication were that photocoagulation treatment continued to demonstrate significant efficacy for high risk cases and that the xenon-treated eyes were more likely to suffer complications of treatment, including losses of both central vision and peripheral visual acuity, than were those treated with argon laser. A third DRS report corroborated these finding and described the cumulative effects of four risk factors: the presence of vitreous or preretinal hemorrhage; the presence of new vessels; a location of new vessels on or near the optic disc; and the severity of the new vessels.[180] As the number of these factors increased in an eye, so did the chances of it's suffering a severe loss of vision without treatment.

Additional trials further contributed guidelines for management of DR. The Early Treatment Diabetic Retinopathy Study (ETDRS)[181] was the second prospective randomized controlled multi-center clinical study regarding DR, initiated in 1980 and funded by the National Eye Institute (NEI) of the NIH. The original intent of the effort was three-fold: to learn the optimal time to begin scatter photocoagulation for "less than severe" DR; to discover if aspirin therapy was helpful or harmful regarding DR; and to establish the value of photocoagulation for diabetic macular edema (DME). The first published report in 1985 was in regard to only this third issue. Several prior studies had claimed a benefit from this treatment, but they were

[179] The Diabetic retinopathy research group. Photocoagulation treatment of proliferative diabetic retinopathy: The second report of diabetic retinopathy study findings. Ophthalmology 1978(1):82-106.
[180] The Diabetic retinopathy research group. Severe visual loss in diabetic retinopathy. The third report from the diabetic retinopathy study. Arch Ophthalmol 1979;97(4);654-5.
[181] Early Treatment Diabetic Retinopathy Research Group. Early treatment diabetic retinopathy report number 1. Arch Ophthalmol 1985;103(12):1796-1806.

inconclusive due to deficiencies such as non-randomization, small cohort size, incomplete descriptions of techniques, and a variety of methodological issues. For the purposes of the ETDRS, “clinically significant DME” was defined, but no visual acuity levels were included in these definitions.

From April, 1980 through August, 1985, 3,928 patients at 23 clinical centers were recruited for the ETDRS. At follow-up, eyes assigned to immediate focal laser treatment for DME were approximately half as likely to lose visual acuity as those assigned to deferral, and the differences between groups increased with time (5% vs. 8% at one year of follow-up and 12% vs. 24% at three years). The recommendations of the study were that focal laser photocoagulation therapy should be recommended for all eyes with clinically significant DME. Patients were usually advised that therapy was more effective in preventing further loss of vision than in improving visual acuity.

In regard to the first of three goals for the ETDRS, the 2,052 patients with no DME had eyes randomized 50:50 to laser therapy or observation. These eyes had moderate to severe non-proliferative or early proliferative retinopathy, and laser treatment included either "full" or "mild" scatter laser treatment.[182] Ultimately, data demonstrated increasing value of photocoagulation as the stage of non-proliferative DR approached the “severe” stage, with early therapy appearing to be of particular value in type-2 patients.[183] Regarding the second goal of the ETDRS, the value of aspirin treatment, the study demonstrated that aspirin use did not alter the course

[182] Ferris FL. Early photocoagulation in eyes with either type I or type II diabetes. Trans Am Ophthalmol Soc 1996;94:5065-537.
[183] Ibid.

of DR.[184] An additional and very important contribution of the ETDRS was the production of a DR severity scale that ranged from "no retinopathy" to "very severe" disease.[185] This scale was subsequently employed in numerous studies and trials regarding the appearance and progression of DR.

Vitreous surgery was developed in the early 1970's, and it became the first intraocular method to manage DR, and subsequent studies were performed to assess its value. It was considered for diabetic eyes in which no other form of therapy was available; laser burns could not penetrate vitreous blood and were ineffective for detached retinas. The Diabetic Retinopathy Vitrectomy Study (DRVS)[186,187,188] was a NEI-supported randomized trial of vitrectomy for advanced DR with either massive vitreous hemorrhage or retinal detachment. The goals of this DR surgery included the removal of all blood and the posterior cortical surface of the vitreous gel, thus eliminating traction forces upon both the new vessels and the retina. Additionally, improved technology allowed intraocular laser treatment near the end of the procedure. This randomized trial demonstrated a benefit of surgery: vitrectomy improved the prognosis for good postoperative vision without

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[184] Early Treatment Diabetic Retinopathy Research Group. Effects of aspirin treatment on diabetic retinopathy. ETDRS report number 8. Ophthalmology 1991;98:757-65

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[185] ETDRS study group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. Ophthalmology 1991;98:823-33.

[186] The Diabetic retinopathy vitrectomy study research group. Two-year course of visual acuity in severe proliferative diabetic retinopathy. Diabetic retinopathy vitrectomy study (DRVS) report number 1. Ophthalmology 1985;92:492-502.

[187] The Diabetic retinopathy vitrectomy study research group. Hemorrhage in diabetic retinopathy. Two-year results of randomized trial. Diabetic retinopathy vitrectomy study report number two. Arch Ophthalmol 1985;103(11):1644-52.

[188] The Diabetic retinopathy vitrectomy study research group. Early vitrectomy for severe proliferative diabetic retinopathy in eyes with useful vision. Results of a randomized trial. Diabetic vitrectomy study report number 3. Ophthalmology 1988;95(10):1307-20.

increasing odds of reducing visual acuity. Many subsequent trials regarding DR continue to be published.

The DRCR Network (DRCR.net) was and is a collaborative NEI-supported network that was founded in 2002 to facilitate and expedite results of multicenter clinical research regarding DR and a variety of additional retinal disorders. Although only four study sites are located outside of the U.S. and Canada, the program has produced results that have profoundly altered DR care around the world. By early 2018, the Network included over 400 investigators at 115 clinical centers, both academic center-based and community practice-based. The DRCR.net supports the identification, design, and implementation of multicenter clinical research initiatives with established protocols that allow a pooling of data in randomized trials from the separate clinical centers; various clinics are involved in separate trials, and the protocols are readily accessible to ophthalmologists uninvolved in the program. Since its inception, and as of January 2018, the DRCR.net group has completed 18 study protocols and continues to recruit for several others.

Over 80 DRCR.net manuscripts have been published in peer-reviewed journals, and several other papers have been accepted for publication. In regard to DR, the most important reports have demonstrated that anti-vascular endothelial growth factor (anti-VEGF) agents (ranabizumab, bevacizumab, aflibercept) were more efficacious than laser therapy in the treatment of DME, and the more recent trials have indicated that these drugs are as effective as PRP for selected forms of PDR. At the present time, both ranabizumab and aflibercept injections have been

approved by the FDA for treatment of all forms of retinopathy.[189] However, they require intravitreal injections on a 4-6 week schedule for varying lengths of time and they are expensive, so their roles in the international markets, especially in lower income societies, remain unknown. Ongoing research regarding devices for sustained release of effective compounds over many months will hopefully improve the situation.

This chapter has discussed the early development of instruments to detect DR and most importantly reviewed a condensed history of research trials that established the evidence base for its contemporary management. Clearly, the development of an evidence-based algorithm for recognition and treatment of DR has occurred; strong evidence exists regarding both the identification of stages of retinopathy in need of therapy and the optimal therapeutic strategies that should be employed[190]. The development of an internationally accepted sequence of "what to do" steps for various stages of DR has been demonstrated.

However, it does not necessarily follow that knowledge regarding the most appropriate treatment modalities will be followed by the adoption of optimal practices globally. Indeed, despite the convincing data for DR photocoagulation treatment, efforts by national and international health care systems to combat the disorder have proved successful only in patchy regions. The next chapter explores this dilemma in more detail.

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[189] Diabetic Retinopathy Clinical Research Network. Intravitreous anti-VEGF treatment for prevention of vision threatening diabetic retinopathy in eyes at high risk. Jaeb Center for Health Research website. https://public.jaeb.org/drcrnet/stdy/340. Accessed June 27, 2019.

[190] Still, research efforts continue to evolve. In particular, the appropriate roles of anti-VEGF injections for all forms of DR compared to previously developed evidence based laser therapies continue to be explored, especially for lower income countries.

Chapter 5.

Development of healthcare systems for management of retinopathy

In the prior chapter, DR was described along with the research leading to an algorithm for its effective treatment. And in Chapter 2, the importance of glucose control upon the complications of DM was documented. In the present chapter, I describe the development of subsequent efforts to reduce the global impact of DR-related vision loss, including the introduction of telemedical technology.

The trials and subsequent publications described in the previous chapter demonstrated that evidence-based treatment for diabetic retinopathy could reduce the risks of DR blindness in over 90% of cases, and if treatment were initiated at relatively early stages, this figure could rise to 98%.[191,192] Although such success rates were recognized by at least 1985, biomedical advances regarding *diagnosis* and *treatment* were not reflected by the ability to *manage* affected patients, as the prevalence of visual disability due to DR continued (and continues) to grow worldwide.

Investigators in most parts of the world have become more aware of the epidemic of DM and its many complications, including DR, as attested to by huge numbers of both scientific and lay articles. Contemporary management

[191] World Health Organization. Report of a WHO Consultation in Geneva Switzerland 9-11 November 2005. Geneva 2006, WHO, pp. 1-39.
[192] Ferris FL. How effective are treatments for diabetic retinopathy. JAMA 1993;269(10):1290-1.

(identification and treatment) has reaped rewards in preventing vision loss in some selected regions, especially those with universal health care, but rates of vision loss have continued to increase in lower income countries, in which identification of patients with diabetes, let alone retinopathy, is difficult, and treatment facilities are sparsely distributed if located away from of medical centers.

The important St. Vincent Declaration of October, 1989 (13 and four years, respectively, following publications of the DRS and ETDRS) was an effort to stimulate European programs to combat DM and DR.[193] The Declaration was the product of a meeting of government health departments, concerned patient organizations, and diabetes experts in St. Vincent, Italy under the aegis of the WHO and IDF. There was a consensus that DM represented an increasing major health problem in all countries and that a reduction in the burdens of the disease should be a major goal, as it would reduce human misery and result in massive savings of both human and material resources. There was a unanimous resolution that included as a major goal the reduction of blindness due to DR by one-third in the following ten years.[194] This goal proved to be overly optimistic and was not achieved in most areas of the world: as of 2009, only 13 of the EU's then 28 member states had developed and implemented a national framework or plan to help reduce DR-related vision loss.[195]

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[193] St Vincent Declaration. Diabetes care and research in Europe. Acta Diabetelogia 1989;10 (suppl):143-4.
[194] The St Vincent Declaration. Diabetes in Europe: a problem of all ages in all countries. Acta Ophthalmol Scand 1997;75 (suppl):223.
[195] Felton A-H, Hall MS. Diabetes — from St Vincent to Glasgow. Have we progressed in 20 years? Brit J Diab Vasc Dis 2009;9(4):142-144.

Additionally, the WHO in 2006 (approximately 30 years after results of the DRS were published) issued its very first report aimed specifically at DR, "Prevention of Blindness from Diabetes".[196] It was developed by a panel of widely distributed international experts in Geneva in November, 2005, and section titles included "Global presence of diabetes and its complications", "Evidence base for prevention and treatment of DR", "Principles in eye care for people with diabetes", and "Principles for organizing an eye health care system for the care of DR". These recommendations were consistent with the evidence-based management documented in the "DR Preferred Practice Patterns" published and updated regularly by the American Academy of Ophthalmology, but they included recognition that realities of situational differences among countries would limit abilities to achieve all goals.

As noted earlier, optimal contemporary management strategies for both DM and DR are based upon evidence-based trials. However, the ability to implement good practices has been hampered in most regions of the world by a combination of variables, including availabilities of physicians, equipment, and pharmaceutical resources; financing of care; and compliance of patients managing their systemic disease and DR in prescribed fashions[197]. These variables in turn are profoundly affected by the respective states of healthcare systems in given countries or territories, and these vary considerably, as noted below.

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[196] WHO. *Prevention of Blindness from Diabetic Retinopathy*. Geneva 2006, WHO, pp1-40.
[197] Holtz, *Glodal Healthcare*, Op cit.

The WHO periodically rates the overall performances of international healthcare systems, and a 2017 publication ranked the countries discussed here as 18th (UK), 37th (U.S.), and 112th (India).[198] Similarly, in an earlier Commonwealth Fund analysis of the comparative performance in highly developed countries[199], the U.S. underperformed the others, failing to achieve better health outcomes in spite of its being the most expensive health care system[200]. In another report, the U.S. was ranked as the "worst health care system in the industrialized world" with the most privatized compensation schemes[201]. Thus, although the vast majority of studies that documented the value of DR management were performed in the U.S., and although patients with appropriate health insurance are generally well treated there, the absence of an institutionalized social welfare medical care insurance system similar to those in other industrialized countries results in many diabetic patients not receiving optimal care.

In a lower income country such as India, the maldistribution of patients, caregivers, and resources has compromised management in regions unassociated with contemporary facilities. Still, in all regions of the world, the introduction of telemedical technology to facilitate the identification and grading of DR in diabetic patients represents a potential major improvement in the healthcare process, although this is currently available in only a few regions.

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[198] Tandon A, Murray CJL, Lauer JA, et al. Measuring overall health care system performance for 191 countries. Geneva Switzerland 2017, World Health Organization.
[199] The countries included Austria, Canada, France, Germany, the Netherlands, New Zealand, Norway, Sweden, the UK, and the U.S.
[200] Davis K, Stremikis K, Squires D, et al. *How the performance of the U.S. health care system compares internationally*. New York 2004, The Commonwealth fund, pp. 1-31.
[201] Sanchez-Serrano I. *The Global Healthcare Crisis. From the Laboratory Bench to the Patient Bedside.* Elsevier, London 2011.

To date, the English Diabetic Screening Program (and similar programs in a few nearby European countries) represents the gold standard regarding the identification and management of DR. Admittedly, this was facilitated by the existence of an established "universal" national health care program. In the U.S., healthcare plans are erratically and incompletely distributed, as no universal health care is available; and in India, all programs are in a developmental stage in most regions. The contemporary evidence for DR care is well recognized by retina specialists around the world, and the major dilemma in the therapeutic process is an inability of patients to physically interact with appropriate caregivers.

The relatively recent development of telemedical technology that facilitates connectivity between patient and caregiver, thus reducing the inability to link patients with optimal diagnostic and therapeutic entities, has improved the potential for effective care. Early efforts in telemedicine were improved exponentially by the introduction and implementation of Internet capabilities.

The earliest documented telemedical applications date to the early 20th century[202 -203], and a multitude of subsequent research efforts have resulted in progressively more sophisticated means of combining medical information with communication technology[204]. Since the clinical morphology of DR can be categorized at various levels of risk for visual loss, stages of the disorder can be captured photographically from any clinical care facility with effective resources

[202] Strehle EM, Shabde N. One-hundred year of telemedicine: does this new technology have a place in paediatrics? Arch Dis Child 2008;91(12):956-9.
[203] Einthoven W. Le telecardiogramme. Arch Int de Physiol 1906;4:132-64 (translated into English *Am Heart J* 1957;53:602–15).
[204] Strehle, Op. Cit., 8.

and transmitted to remote grading centers from which appropriate treatment strategies can be relayed back to physicians at treatment facilities. Theoretically, this telemedical scheme may appear to be straight forward and easily performed, but its accomplishment has required major efforts on a variety of levels.

The establishment of severity scales of DR and diabetic macular edema required progressive modifications of schemes beginning with the O'Hare classification and evolving into the ETDRS severity scale, both of which were mentioned previously. The images employed in those gradings were captured on film and then employed to create the analysis of DR image stage versus risk. These pictures required a standardized protocol that ultimately consisted of seven standard color stereo 30° fields, developed as 35-mm slides. The transfer and analyses of the film images was quite cumbersome, so the process was profoundly improved with the introduction of digital fundus photography in 1987; and a subsequent study comparing film and digital processing of protocol fields through dilated pupils demonstrated equivalence of the two techniques[205].

The technology advances that progressed to the reality of modern contemporary digital cameras and telemedical systems are not described, but two significant variables are: first, the necessity of dilating the pupils for more optimal pictures and second, the number and location of fields of the retina that should be photographed to obtain a reliable picture of the status of DR. Compromises have been required: the use of vastly improved non-mydriatic cameras would result in

[191] Fransen SR, Leonard-Martin, TC, Feuer WJ, et al. Clinical evaluation of patients with diabetic retinopathy. Accuracy of the Inoveon diabetic retinopathy-3DT system. Ophthalmology 2002;109(3):595–601.

more non-gradable images (but with a simplified process that was more patient-friendly)[206]; and alternative field choices to the 7-field 30° standards of the DRS could miss sites of significant disease. Still, non-mydriatic cameras that employed three 45° fields became the standard for the Joslin Vision Network employed in the Indian Health Service and Veterans' Administration[207] and mentioned below, whereas the English National Health Service utilized mydriatic cameras that document two 45° retinal fields[208]. A number of additional telemedical programs have been developed for screening of diabetic patients, and the American Telemedical Association (ATA) published a review of these, including various levels of validation, in 2015[209]. The essential point regarding these telemedical screening programs is that they offered the potential to detect large numbers of patients with significant DR who would otherwise remain undiagnosed.

The introduction of artificial intelligence (AI) into screening algorithms has constituted a potentially major advance in remote telemedical screening for DR, and in April, 2018, the U.S. Food and Drug Administration approved marketing of the first medical device that employed AI; approval was based upon a clinical study of retinal images from 900 diabetic patients at 10 primary care sites. The AI device, termed "IDX-DR" was able to identify the presence of more than mild diabetic

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[192] Scanlon PH, Malhotra R, Thomas G, et al. The effectiveness of screening for diabetic retinopath by digital imaging photography and technician ophthalmoscopy. Diabetic Medicine 2003; 20: 467–74.
[207] Bursell,S, Cavallero JD, Cavellaro AA, et al. Stereo non-mydriatic digital-video color retinal imaging compared to Early Treatment Diabetic Retinopathy Study seven standard field 35-mm standard color photos for determining level of diabetic retinopathy. Ophthalmology 2001;108(3):572-85.
[208] Harding S, Greenwood R, Aldington S, et al. Grading and disease management in national screening for diabetic retinopathy in England and Wales. Diabetic medicine. 2003;20(12):965-71.
[209] Tozer K, Woodward MA, Newman-Casey PA. Telemedicine and diabetic retinopathy: Review of published screening programs. J Endocrinol Diab 2015; 2(4): 1-10. DOI: http://dx.doi.org/10.15226/2374-6890/2/4/00131.

retinopathy 87.4 percent of the time and to correctly identify patients who did not have more than mild diabetic retinopathy 89.5 percent of the time[210]. Connecting such diagnostic capabilities with patients in the offices of primary diabetes caregivers that contain these cameras would significantly increase the percentages of patients with DM who are screened for DR, although costs could be excessive for small "captured" populations, as noted below. A second critical step in the care process, linking those in need of treatment with therapeutic facilities and personnel remains a problematic variable in many locations of the world. I will now present descriptions of the comparative histories of pertinent health care systems in England, India, and the U.S.

Retinopathy care in England

The English national screening program for diabetic retinopathy was initiated in 2003 in an effort to reduce the burden of retinopathy on both affected individual patients and the nation[211]. Inspired by the St. Vincent Declaration mentioned earlier and the existence of the National Health Service (NHS), the program extended coverage over all of England by 2008, and by 2016, over 80% of patients with diabetes had agreed to be screened with annual photographs, thereby ultimately displacing DR as the number one cause of certifiable blindness among England's working age group.

[210] U.S. Food and Drug Administration, FDA News Release, April 11, 2018.
[211] Scanlon PH. The English national screening programme for diabetic retinopathy 2003-2016. Acta Diabetologica 2017;54: 515-25.

Initially, a UK National Screening Committee considered WHO screening principles in appraising the viability, effectiveness and appropriateness of a proposed screening program[212,213]. These principles included: first, screening is a public health program, not a diagnostic test; second, large numbers of apparently healthy individuals are invited for retinopathy screening, and, if their test is positive, they are offered further diagnostic investigation; third, some people may be harmed by the process, or falsely reassured; fourth, there is an ethical and moral responsibility to ensure that the programs are of high quality; and finally, quality assurance of screening programs is essential to ensure that the program achieves the highest possible standards and minimizes harm[214]. Subsequently, digital photography through dilated pupils was demonstrated to achieve an approximate 85% sensitivity and 95% specificity, and the UK's National Institute for Clinical Excellence (NICE) initially approved the basics of such a program in 2002, and it has provided periodic annual updates as treatment options grow in number[215].

Very importantly, the NHS in England provided major advantages over non-"socialized" health care systems, especially regarding patients with diabetes. A National Diabetes Audit (NDA) provided a comprehensive overview of diabetes care in United Kingdom and Wales. This audit collected information from both primary and secondary care from approximately 4,700 general practitioners (GP) offices and

[212] Wilson J, Jungner G (1968) The principles and practice of screening for disease. Public Health Papers 34. Public Health Papers, WHO, Geneva, GPE discussion paper number 30.
[213] Scanlon PH (2008) The English national screening programme for sight-threatening diabetic retinopathy. J Med Screen 15:1–4.
[214] Scanlon 2017, Op. cit.
[215] National Institute for Clinical Excellence (2002) Management of type 2 diabetes, retinopathy - screening and early management. *NICE Inherited Clinical Guideline* E. London: National Institute for Clinical Excellence. Available from www.nice.org.uk

100 specialist services; and in the 2014–2015 NDA report, data were acquired on roughly 1.9 million people with diabetes.

NICE has recommended annual studies for all diabetic patients aged 12 years and older to include blood tests (glycated hemoglobin (HbA1c), serum creatinine, and cholesterol), blood pressure, urine albumin, foot surveillance, body mass index, and smoking history. Scheduling and collating results of these studies are the responsibility of Diabetes Care Providers. Finally, annual digital photography retinal screening is recommended by NICE, and this is conducted under an NHS Diabetic Eye Screening program on an annual basis[216].

The algorithm of the management strategy is as follows: people newly diagnosed with diabetes are invited annually for digital retinal photography screening (usually in the caregivers' offices), and images are graded using a scale quite similar to that developed by an international committee of retinopathy experts that in turn was based upon the ETDRS data mentioned previously[217]. Patients found to have potentially sight-threatening retinopathy are referred to ophthalmology surveillance clinics or to the NHS Hospital Eye Service. Patients without signs of DR or with only non-severe retinal changes are scheduled for annual rescreening photographic evaluations. As noted, the national screening program has progressively evolved to cover more than 80% of the diabetic population. In 2014–2015, there were 83 screening entities including both NHS and private providers in United Kingdom, and in that year, 2.5 million people with

[216] Scanlon, 2017, op. cit.
[217] Wilkinson CP, Ferris FL III, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1679-xx

known diabetes were offered screening appointments, and 2.1 million (84%) were screened[218]. As a result, DR no longer was the leading cause of severe visual impairment among working age adults. Still, it has been noted that a number of diabetic patients do not appear for their retinal photographs, and absences have been due to a variety of issues, as discussed below.

The overall success of the English screening program in identifying and managing diabetic patients with DR has been possible only because of the reality of the NHS and its associated programs. The abilities to identify those with DM, regardless of age, and to enter their medical records and retinal photographs locally (usually in the respective GP office) for grading and indicated treatment are impossible in other healthcare systems that do not provide means of placing patients of all ages in a national database and strongly encouraging the management of identified complications of the systemic disease. The successes of this program, a product of a national universal health care system, could serve as a model for all countries, but its adaptation has been accomplished only in selected European counties in the UK, Scandinavia, and Iceland, all of which have contemporary DR screening services as portions of centralized national healthcare systems.

Retinopathy care in the United States

As the only industrialized country in the world to not provide universal health care, the diagnosis and management of DM and DR in the U.S. is quite fragmented; the Medicare program can provide a database of patients over age 65

[218] Scanlon, 2017, op. cit.

with diabetes, and so can a variety of additional insurance programs. But a major "disconnect" in the U.S. is the inability for optimal periodic eye examinations to be performed, even though they are required as a HEDIS measurement of quality performance. Although such evaluations are routinely suggested by physicians managing patients with diabetes, an unfortunately significant percentage of the latter do not follow through for those eye visits, especially if they are uninsured, destitute and members of minority groups, all of which are more likely to be associated with greater likelihoods of DM and DR prevalence[219]. But even in a "best case" situation in which patients have adequate insurance, patient adherence is frequently poor. In one 2019 study of over 298,000 patients with type-2 diabetes and continuous 5-year commercial or employee-sponsored health insurance, only 15% met American Diabetic Association guidelines for annual or biannual eye screening.[220]

Individual healthcare programs that that provide "universal care" to all of its members, such as those (mentioned below) within the Indian Health Service (IHS), the Veterans' Administration (VA), and isolated private insurance programs, have provided strong evidence that improved systems for management of DM and associated DR could be made possible for all.

The prevalence of DM and DR in American Indians and Alaskan Natives, who represent 1.5% of the population of the U.S. was discussed earlier, and

[219] Barsegian A, Kotlyar B, Lee J, et al. Diabetic retinopathy: focus on minority populations. Int J Clin Endocrinol Metab 2017;3(1):34-45.
[220] Benoit SR, Swenor B, Geiss LS, et al. Eye care utilization among insured people with diabetes in the U.S., 2010-2014. Diab Care 2019;42(3):427-433.

approximately 60% of them rely on the IHS[221]. This is a division of Health and Human Services (HHS) that is responsible for providing health care to federally recognized tribes and Alaskan Natives through its 33 hospitals, 59 health centers, and 50 health stations[222]. A substantial percentage of these entities are located rurally, making the delivery of services relatively problematic. As mentioned earlier, there is considerable diversity in precise prevalence rates of DM and DR among the tribal communities, but all share an increased likelihood of the systemic disease and its microvascular complications. In spite of the general poor health in this population, selected IHS hospitals have developed state-of-the–art programs to diagnose and treat DR that can serve as examples of optimal care rivaling that of the English Screening program mentioned earlier.

As a good example, the Phoenix Indian Medical Center (PIMC) was the site of a pilot study conducted in their primary care medicine clinic at which diabetic patients were seen at no personal expense. In 2000, the PIMC added a retinal digital surveillance modality orchestrated by the Joslin Vision Network (JVN)[223] to evaluate DR status in patients at this clinic, so that referrals to eye care professionals were not necessarily required; only patients with ungradable images or worrisome DR would need such appointments. The JVN includes a stereoscopic, non-mydriatic, digital color retinal imaging acquisition system. Digital images of the retina and

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[221] Center for Disease Control and Prevention 2014. *Healthy People 2020.* Retrieved from http://www.cdc.gov/nchs/healthy_people/hp2020.htm.
[222] Holtz C. *Global Health Care. Issues and Policies. Third Edition. Burlington MA* 2017, Jones and Bartlett Learning, p. 40.
[223] Aiello LM, Cavallerano JD, Cavallerano AA, et al: Preserving human vision: the Joslin Vision Network (JVN) innovative telemedicine care for diabetes. Ophthalmol Clin North Am 2000; 13:213–23.

pertinent patient health data are forwarded to a centralized image reading center, where a diagnosis and treatment plan tailored to the patient's level of DR, determined by an expert photographic analyzer, can be made, and patients with significant stages of DR can be promptly referred for treatment. In the year that PIMC added the JVN program, DR annual retinopathy surveillance rates among diabetic patients were approximately 50%, a figure comparable to many health care systems in the U.S.; but it had increased to approximately 75% by 2003, a 50% increase; and evidence-based treatment of DR also grew by 50% even though the rate of therapy per patient screened remained stable, thus demonstrating that improved screening lead to greater numbers that received needed therapy.

An IHS-JVN Teleophthalmology Program was subsequently formally established, and by 2005, it was deployed in 97 health care facilities in 25 states, where approximately 18,000 patients were screened annually[224]. In 2014, a modification in the screening cameras was evaluated, and ultra wide field retinal imaging with scanning laser ophthalmoscopy was compared to the standard nonmydriatic technique. The ultra-wide screening cut the rate of ungradable images by 81%, thus reducing the number of patients that would have to be referred for eye examinations by an estimated 4,000 cases per year[225]. In addition, the identification of the presence of both DR and DR needing referrals were increased significantly.

[224] Silva PS, Horton MB, Clary D, et al. Identification of diabetic retinopathy and ungradable image rate with ultra wide field imaging in a national teleophthalmology program. Ophthalmology 2016; 123(6):1360-7.
[225] Ibid.

This HIS-JVN Program is practically almost identical to the English screening program described above, a significant difference being that the English patients have their pupils dilated prior to photography, a measure that reduces the percentage of ungradable images. The essential feature of both strategies is that diabetic patients visiting their respective "diabetes caregivers", which they do relatively reliably, are also able to have their retinal status captured by expert graders at this same site of care, thus avoiding the issues associated with additional referral appointments for eye evaluations, which are notoriously inadequate for a variety of reasons.

The U.S. Veterans Health Administration (VHA, VA) is an additional example of the value of DR screening in a primary care setting. The VA has become one of the largest health care systems in the world, growing from 54 hospitals in 1930, to include 152 hospitals, 800 community-based outpatient clinics, and 126 nursing home care units. Approximately a quarter of its patients have DM[226]. In 2014, over 9,100,000 veterans were enrolled in the program, and more than 6,000,000 used its services[227].

The same Joslin Vision Network (JVN) associated with the IHS was instrumental in developing a telemedical DR screening program in the VA. In 1999, the Veterans Health Administration (VHA) collaborated with the Joslin Diabetes Center to implement a pilot teleretinal imaging program. It included the same nonmydriatic digital retinal imaging platform employed in the IHS, and cameras

[226] Https://www.va.gov
[227] Bagalman E. The number of veterans that use VA health care services. Washington, D.C., 2014, Congressional research service, pp. 1-3.

were installed at VA medical centers and community-based outpatient clinics in New England and the Pacific Northwest. Images captured at these remote imaging stations were transmitted to reading centers at the JVN and the VA Puget Sound Healthcare System in Seattle. This pilot program was quite successful in identifying patients in need of timely further care for DR while at the same time recommending eye care at appropriate intervals for those with little or no risk factors for retinopathy progression[228].

In 2001, the VHA convened an expert panel to address issues of clinical application, quality and training, information technology, and healthcare infrastructure needs regarding the imaging program, and it was subsequently deployed on a system wide basis in 2006[229]. Cost effectiveness of the program was reported in 2013: a model was employed in an evaluation of 900 patient records to estimate the progression of DR and determine average quality-adjusted life years (QALYs) saved and the average additional cost incurred by the telemedicine screening program. The study results indicated that the program was quite cost-effective for DR, but only in patient populations of 3500 or more and in patients less than 80 years of age. Telemedicine lowered the average age of those screened, increased the number of known diabetic patients, and reduced the average number of miles travelled by patients for screening. Participation in the program was observed to be increasing. Thus the VA screening program is an additional example

[228] Conlin PR, Fisch BM, Orcutt JC, et al. Framework for a national teleretinal imaging program to screen for diabetic retinopathy in Veterans Health Administration patients. J Rehab Res Dev 2006;43:741-8.
[229] Tsan GL, Hoban KL, Jun W, et al. Assessment of diabetic teleretinal imaging program at the Portland Department of Veterans Affairs Medical Center. J Rehab Res Dev 2015; 52(2): 193-200.

of an effective strategy to reduce the prevalence of both sight-threatening visual loss and blindness among American citizens. It is of course another example of the benefit of systems similar to the English NHS.

In the U.S., private companies, stimulated by needs to improve HEDIS DR screening scores as well as opportunities for profits, have been developed to provide DR screening programs in efforts to provide higher percentages of diabetic patients who are evaluated for DR in a manner similar to the HIS and VA described above. But these programs are limited to those patients capable of funding with their insurance, and even Medicare requires a co-payment unaffordable to many.

Retinopathy care in India

As mentioned earlier, a 2014 nationwide survey of over 5,000 diabetic individuals in India revealed a DR prevalence of almost 22%, and the typical variables of duration of systemic disease, age, and glucose control quality were significantly associated with the likelihood of developing retinal vascular changes[230]. Specific prevalence figures vary somewhat from region to region and study to study, but it is quite clear that increasing numbers of patients with DM will lead to more cases of DR, and that both disorders will increase the healthcare burden for India's population of 1.24 billion persons[231]. Seventy percent of Indian citizens live in rural areas where average incomes are less than one US dollar/day and the ratio of physicians to patients is six times lower than in the urban areas, so

[230] Gadkari 2014, Op. cit., p.58.
[231] Holtz, Op. cit., 87.

the diagnosis and management of both DM and DR are compromised[232]. In 2015 the International Council of Ophthalmology published recommended guidelines for the screening and treatment of DR while recognizing the realities of the differing environments[233]. Thus, a broad spectrum of eye caregivers ranging from ophthalmologists and optometrists to primary physicians to any field worker or health volunteer who had significant training in retinopathy grading were deemed capable of screening of diabetic patients. However, the impact of the recommendations remains unclear, as a substantial gap between plans and outcomes persists.

In 2013, a realistic overview of DR care in India was published[234]. Awareness of DR as a serious entity was generally poor, and little had been done to initiate mass awareness programs across the nation. As an example of a systemic "disconnect", a prior population-based study was cited in which 80% of non-medical responders stated a belief that annual eye exams were essential but less than half had ever visited an eye care professional, and only 10% knew that uncontrolled DM was a risk factor for DR[235]. In an additional study from Chennai it was noted that 63% of diabetic patients in rural areas and 75% in urban environments had never

[232] Central Intelligence Agency. *The World Factbook: India.* Retrieved from http://www.cia.gv/cia/publications/factbook/goes/ind.html.
[233] International Council of Ophthalmology. *Vision 2020 The Right to Sight India. Guidelines for Diabetic Care in India.* San Francisco 2015, International Council of Ophthalmology, pp. 1-40.
[234] Ramasamy K, Raman R, Tandon M. Current state of care for diabetic retinopathy care in India. Curr Diab Rep 2013;13:460-8.
[235] Namperumalsamy P, Kim R, Kaliaperumal K, et al. A pilot study on awareness of diabetic retinopathy among non-medical persons in South India. The challenge for eye care progams in the region. Ind J Ophthalmol.2004;52:247–51.

had an eye exam for DR, whereas 45% of rural and 50% of urban diabetics with sight-threatening DR had never been evaluated previously[236].

In a more recent report regarding diabetic patients being followed in a tertiary eye hospital in southern India, the importance of knowledge regarding both DM and DR was further documented[237]. A 45-point questionnaire was administered verbally to 288 diabetic patients in outpatient clinics and inpatient wards. Forty-two percent had "good knowledge" regarding DM, but only 10% regarding DR; 72 % were aware that DM could affect eyes, but only 17 % were aware of DR as a specific entity, the latter figure being consistent with additional prior reports[238]. Importantly, among the relatively small percentage of diabetic patients with awareness of DR, their odds of having good practice patterns regarding the systemic disease were much better than those of patients unaware of it. Similarly, the odds of patients with good knowledge regarding DM also having good DR practice patterns were four times those with little knowledge regarding the systemic disease.

Improving knowledge and awareness of DM and its microvascular complications is a fundamental goal in improving the health of diabetic patients and in reducing the impact of visual impairment due to DR. But, bearing in mind that blindness can be prevented in the vast majority of patients who are treated in a

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[236] Rani PK, Raman R, Paul PG, et al. Use of eye care services by people with diabetes – South Indian experience. Br J Ophthalmol. Letter to the editor, Published online May 18, 2005. Available: http://bjo.bmj.com/content/82/4/ 410/reply#bjophthalmol_el_756.
[237] Srinivasan NK, Deepa J, Rebekah G, et al. Diabetes and diabetic retinopathy: Knowledge, attitude, practice (KAP) among diabetic patients in a tertiary eye care center. J Clin Diag Res 2017;11(7):1-7.
[238] See Dandona R, Dandona L, John RK, McCarty CA, Rao GN. Awareness of eye diseases in an urban population in southern India. Bull World Health Organ. 2001;79(2):96-102., Mahesh G, Elias A, Sandhya N, et al. Chengamanad Diabetic Retinopathy Awareness Study (CDRAS). Kerala J Ophthalmol. 2006;28:14-21.

timely fashion, what about the care process for the Indian diabetic patient? Since treatment can only be applied when patients in need are identified, patients with DM must be screened. Currently there is no national screening program for DR, and different ad-hoc methods have been employed in diverse locations[239]. Less than two percent of primary care physicians use direct ophthalmoscopes, and only half of those dilate patients' eyes, so screening in that fashion is ineffective[240]. Eye camps for diabetic patients have been employed in parts of India for several years, and they provide an additional benefit of community awareness in the region[241]; and in one report, approximately 20% of screened diabetic patients exhibited signs of DR, although only six percent of those had any evidence of prior DR treatment[242]. A more recent plan for DR screening in India involved the use of telemedicine conducted by cameras enclosed in mobile vans; images were produced and conveyed to a centralized reading center for analysis, and a report returned to the patient within an hour[243]. This system was demonstrated as quite cost-effective if employed on a biannual basis[244]

Once patients with DM and retinopathy are detected, what about the delivery of therapy? Again, the issues of distribution of both patients and caregivers have a

[239] Ramasamy 2013, Op. cit, 460.
[240] Raman R, Paul PG, Padmajakumari R, Sharma T. Knowledge and attitude of general practitioners towards diabetic retinopathy practice in South India. Commun Eye Hlth 2006;19(57):13–4.
[241] Rani PK, Raman R, Agarwal S, et al. Diabetic retinopathy screening model for rural population: awareness and screening methodology. Rural Remote Heal. 2005;5:350.
[242] Namperumalsamy P, Nirmalan PK, Ramasamy K. Developing a screening program to detect sight-threatening diabetic retinopathy in south India. Diabetes Care. 2003;26:1831–5.
[243] Liesenfeld B, Kohner E, Piehlmeier, et al. A telemedical approach to the screening of diabetic retinopathy with digital fundus photography. Diabetes Care 2000;23:345–48.
[244] Rachapelle S, Legood R, Alavi Y, et al. The cost-utility of telemedicine to screen for diabetic retinopathy in India. Ophthalmology 2013;120:566-73.

major impact that remains uncorrected. Nationally, there is an approximate ratio of 1 ophthalmologist for every 107,000 people, but this ranges from 1:9,000 in urban areas to 1:608,000 in more rural locations[245]; and the percentages of ophthalmologists that manage DR is unclear, although there were 585 ophthalmologists who had become members of the Vitreoretinal Society of India by 2012[246]. Once patients reach a location with appropriate facilities, state-of-the-art DR management is generally practiced, and only minor practice pattern discrepancies exist between India practitioners and those surveyed by the American Society of Retina Specialists[247]

Observations regarding international healthcare systems

At the time of this writing, "tools" for state-of-the art therapy for DR are available in the majority of locations around the world, but they are employed only in tertiary centers with appropriate facilities, and therefore their use is quite limited in most regions, especially low-middle income countries. Although the abilities to detect sight-threatening DR have been profoundly expanded by the introduction of mobile telemedical devices, "tools" for providing the means of connecting appropriate patients with therapeutic facilities remain problematic. Clearly, most societies have yet to construct satisfactory approaches to the epidemic of DM and DR along with nephropathy and neuropathy.[248,249] The proverbial "elephant in the

[245] Kumar R. Ophthalmic manpower in India — need for a serious review. Int Ophthalmol.1993;17:269–75.
[246] Ramasamy 2013, Op. Cit., 463.
[247] Ibid, 467.
[248] Hossain P, Kawar B, El Nahas M: Obesity and diabetes in the developing world--a growing challenge. *N Engl J Med.* 2007;356(3):213–5.

room" is the increasingly gigantic number of diabetic individuals in the world, especially in low-middle income countries in which 80% of diabetic patients are living.[250] Regardless of precise diagnostic criteria, the number continues to grow in association with obesity, which in turn is due to dietary modifications as described earlier. And roughly a quarter of diabetic patients without optimal Hemoglobin A1c levels will ultimately develop significant DR.

What would constitute an ideal (or significantly improved) healthcare system for DR? Criteria would include universal access to adequate DM management without excessive financial burden to patients; currently, among the three countries under discussion, this is available in England, said to be in force in India but not functional; and unavailable in the U.S. Second, programs for patient education regarding the importance of optimal DM management and the realities of DR; currently, these are available in all three countries but underutilized. Third, capabilities to screen remotely large numbers of diabetic patients for DR; in the three countries being discussed, these are routinely available only in England. Fourth, a means of connecting all patients in need of DR treatment to appropriate caregivers offering optimal therapeutic facilities; this currently is most optimal in England. Finally, establishment of efficient lines of communication between DM caregivers and those involved in eye care; again, although far from perfect, it is most available in England but fragmented in the U.S. and India. In all countries, the roles

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[249] Bello AK, Levin A, Lunney M, et al. Status of care for end stage kidney disease in countries and regions worldwide: international cross sectional survey. BMJ 2019;367:5873.
[250] Sabanayagam C, Yip W, Ting DSW, et al. Ten emerging trends in the epidemiology of diabetic retinopathy. Opyhalmic Epidemiol 2016;23(4):209-222. DOI: 10.1080/09286586.2016.1193618

of social and environmental circumstances including poverty and public health realities should be recognized, as they are important determinants of the quality of care that could be provided.

Creation of optimal healthcare systems for DM and DR will require improvements in the classic linkages of state policies, patient engagement and compliance, and involvement of medical personnel – a system that brings acknowledged contemporary state-of-the-art diagnostic and treatment capabilities to combat the current maldistribution of affected patients with their caregivers. These three variables are discussed in sequence in the following paragraphs.

Regarding "state policies", a 2000 UN General Comment No.14 "Right to Health"[251] specified that "the highest attainable standard of physical and mental health" should be broadly interpreted and not limited to the right to healthcare but to extend to recognition and improvements in the underlying socioeconomic determinants of health such as safe water, adequate food, reasonable sanitation, and access to healthcare information. The right to health was stated to be composed of four elements: availability, accessibility, acceptability, and quality[252].

A 2006 UN Resolution 61/225[253] asked for "all nations to develop national policies for the prevention, care and treatment of diabetes…taking into account

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[251] United Nations (2000) General Comment No. 14: The right to the highest attainable standard of health. New York, United Nations, pp. 1-22. Cited in: Di Iorio CT, Carinci F, Benedetti MM. The diabetes challenge: from human and social rights to the empowerment of people with diabetes. In: DeFranzo RD, Ferrannini E, Zimmet P, et al (eds), *International Textbook of Diabetes Mellitus, 4th Ed,* Hoboken, NJ, John Wiley and Sons, 2015 p 1105.

[252] Ibid.

[253] United Nations Resolution 61/225: World Diabetes Day. New York 2007, United Nations 83rd Plenary session, pp.1-2. Cited in Di Iorio CT, Carinci F, Benedetti MM. The diabetes challenge: from human and social rights to the empowerment of people with diabetes. In: DeFranzo RD, Ferrannini E,

internationally agreed development goals, including the Millennium Development Goals." Delegates participating at the WHO 65th World Health Assembly "approved the development of a global monitoring framework for the prevention and control of non communicable diseases (NCDs), including indicators and a set of global targets." At the same meeting, the Assembly approved a global target of a 25% reduction of deaths from NCDs.

In the U. S. in Section 403 of the 2010 Affordable Care Act, an opportunity to identify populations at risk for type-2 DM was presented, and in 2012, the Institute of Medicine (IOM) recognized the need for improved public health measures to manage a growing toll of chronic diseases including DM and called for data acquisition regarding such illnesses and their determinants.[254] Three years later, a review of NIH funding to prevent chronic disease was published.[255] Nevertheless, although acquisition of such data may be worthwhile globally, most patients with DM live in countries in which implementation of practices for most patients remains impossible.

In a more recent 2106 report[256], the Director-General of the WHO described a "2030 Agenda for sustainable development", in which member states set a target to reduce premature mortality from NCD's including diabetes by one-third, to achieve universal health coverage, and to provide access to affordable essential

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Zimmet P, et al (eds), *International Textbook of Diabetes Mellitus, 4th Ed,* Hoboken, NJ, John Wiley and Sons, 2015 p 1105.

[254] Institute of Medicine. *Living Well with Chronic Illness. A Call for Public Action.* 2012, Washington, D.C.

[255] Calitz C, Pollack KM, Millard C, et al. National Institute of Health funding for behavioral interactions to prevent chronic diseases. Am J Prev Med 2015;48(4):462-471.

[256] WHO 2016, Op. cit.

medications. In the same report and regarding DM, technologies "generally available in publically-funded primary healthcare facilities" were assessed, and the percentages of countries with capabilities for offering accessible dilated retinal evaluations varied enormously, ranging from 26% in the "African region" to approximately 45% in the "western Pacific" and "region of the Americas" regions to 75% in the "European region". The income levels in various global regions were major factors that influenced this disparity. Dilated retinal examinations were available in only 19% of low-income countries compared to 29% in "lower middle" income levels to 48% in "upper middle" income levels to 67% in "high income" regions. This maldistribution of capabilities to deliver optimal evidence-based care for DR and DM is not unique for these two disorders. But, hopefully, the economic impact of the complications of diabetes will stimulate strategies for states to improve the recognition and management of diabetic patients. In spite of worthy but ambitious WHO recommendations, I have demonstrated that the abilities of individual nations to implement them have varied considerably. Differences between three discussed countries' abilities to deliver contemporary care for DR have been provided. Currently, optimal care for DR is available in tertiary medical centers in most urban areas of the world, but a vast percentage of patients with DM and DR remain unmanaged, especially if they are poor and live in a low-income country.

Regarding "patient engagement", personal culpability is a major factor impacting many if not most cases of DR. Patients diagnosed with DM enter the

proverbial "kingdom of the sick",[257] a region from which no exit to normality exists. Still, although this reality should be acknowledged, the personal responsibilities of patients with DM cannot be overestimated, because adequate control of serum sugar levels remains an essential feature of strategies to reduce the impact of DR and the additional macro- and microvascular complications of DM. A critical component of this management is the recognition of the disease in question, and unfortunately a substantial percentage of patients with DM are unaware of its presence; and many with known DM have little knowledge regarding optimal processes of care[258]. And the costs as well as availability of diabetic medicines are additional variables that impact self-management. So although such individuals should not be blamed for all deficiencies in personal health practices, optimal patient self-care remains a cornerstone of the therapeutic process, a statement validated in studies mentioned previously.

The St. Vincent Declaration mentioned earlier stated that a reduction in the burden of diabetes would require active partnership between patients with diabetes and care providers, particularly in categories of disease management and education[259]. This policy advocated a fundamental principle of "patient empowerment", defined as "the ability of a person affected by a disease to be an

[257] Sontag S. *Illness as a Metephor and AIDS and its Metaphors.* 1978, New York, Picador USA.
[258] In the U.S. the epidemic of DM has resulted to the ubiquitous appearance of multitudes of media advertisements of drugs to lower hemoglobin A1C, whereas information regarding the critical importance of diets remains relatively unavailable to the public.
[259] Di Iorio CT, Carinci F, Benedetti MM. The diabetes challenge: from human and social rights to the empowerment of people with diabetes. In: DeFranzo RD, Ferrannini E, Zimmet P, et al (eds). *International Textbook of Diabetes Mellitus, Fourth Edition*, 2015, Hoboken NJ, John Wiley & Sons, 1105-12.

active member of his/her management team"[260]. It addressed different dimensions of care including education regarding both medical and public health conditions and the ability of a person to make decisions on treatments. Optimal patient empowerment should allow a person to effectively self-manage both DM and DR by adherence to agreed self-care regimens including maintenance of optimal serum glucose levels, normal blood pressure, and meaningful weight loss. Chronic disease programs that rely on self-management education have been tested in randomized controlled trials that have demonstrated significant improvements in the areas of healthy behaviors and communication with healthcare providers[261].

Concepts of patient empowerment are most difficult in regions characterized by poor sanitary facilities, malnutrition, poverty, and the lack of education. Still, even in an excellent system such as the English Diabetes Screening Program mentioned earlier, patient willingness to participate is a critical variable. In a 2016 report[262], reasons for non-attendance at DR screening programs in London were tabulated. A vast majority of those offered screening accepted it, but 258 who registered but never appeared for screening were later identified, and an attempt was made to contact them to learn why. A substantial number of patients could not be reached, but reasons for non-attendance were documented for 146 (57%). Personal explanations for non-acceptance included conflicting commitments,

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[260] Santurri LE: Patient empowerment: improving the outcomes of chronic diseases through self-management education. The MPHP 439 Online Text Book,, 2006, Case Western Reserve University, at: http://www.cwru.edu/med/epidbio/mphp439/Patient_Empowerment.htm

[261] Ibid.

[262] Stratton R, Du Chemin A, Stratton M, et al. System-level and patient-level explanations for non-attendance at diabetic retinopathy screening in Sutton and Merton (London, UK): a qualitative analysis of a service evaluation. BMJ Open 2016;6: e010952.

anxiety regarding the screening test, disengagement with diabetes care in general, and forgetting. System-level factors included inaccurate registration data, untimely communications, eligibility errors, and practical problems such as a lack of recognition of homebound patients. The essential point is that patient responsibility is necessary for optimal care to occur. And unfortunately, non-attending patients have been shown to have a greater likelihood of sight-threatening DR[263].

Regarding "involvement of medical personnel", caregiver responsibility remains a cornerstone of DM and DR management. The IOM has listed six characteristics of optimal medical care: it should be safe, effective, patient-centered, timely, efficient, and equitable[264]; and the Agency for Healthcare Research and Quality (AHRQ) has established quality indicators and guidelines for good healthcare[265]. The essential features of contemporary evidence-based care for patients with DM and DR have been mentioned earlier. Caregivers should know what should be done to manage these disorders. The major limitation in the care process is the inadequate matching of patients with those capable of recognizing DR and providing care, and profound differences in capabilities to do so are quite evident, as mentioned earlier. Many of the mentioned contemporary strategies have distanced patients from specialists, and training more primary healthcare workers to acquire screening and counseling skills could alleviate some of the current

[263] Forster AS, Forbes A, Dodhia H, et al. Non-attendance at diabetic eye screening and risk of sight-threatening diabetic retinopathy: a population-based cohort study. Diabetologia 2013;56(10):2187-93.
[264] Institute of Medicine. Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, D.C: National Academy Press; 2001.
[265] Agency for Healthcare Research and Quality.

problems. Bonding of diabetic patients with personal caregivers is recognized as a critical variable in the therapeutic process.

The story of DR does not end here. In addition to making desirable improvements in societal programs described above, biologic research for better therapies needs to continue to be explored. In particular, the appropriate role of anti-VEGF medications requires considerably more study. Still, efforts to reduce the prevalence of DM and its many determinants are fundamental goals to prevent vascular complications.

In this chapter, I described a history of increasing awareness of the epidemic of DM and DR by international health care entities and plans for strategies to combat the disorders, including the important implementation of telemedicine. This was followed by a comparative analysis of healthcare systems in England, the U.S., and India and an overview of their efforts. This history of DR management systems in three countries demonstrated that scientific "medical" studies regarding the disorder have far outpaced global capabilities to manage it. Optimal evidence-based care is available in all of the regions, but it is limited by a variety of social and economic factors. Generalizing: In England, an excellent program is in place, and a major Impediment to care appears to be patient compliance. In the U.S., care remains fragmented due to many patients' lack of financial resources and their compliance. In India, excellent programs exist in major medical centers that feature contemporary eye hospitals, but the percentages of patients without access to care are enormous and may be growing. Thus, although the scientific basis for reducing vision loss and additional complications of diabetes has been well established, the

implementation of these care processes remains inadequate, with responsibilities continuing to fall upon all three contributing factors: the “state”, the patients, and the caregivers. I will now present a concluding chapter summarizing these facts as variables supporting my thesis.

Chapter 6.

Conclusions

This manuscript was written in an effort to support the thesis that most of the world's health care systems have responded inadequately to the epidemics of DR and its cause, DM, especially in view of availability of evidence-based management strategies that have been developed over decades. I drew upon my personal experience to describe the manifestations of DR but conducted a thorough literature search regarding the additional aspects of this effort to support my claims.

My analysis demonstrated that the global distribution of health care systems to combat DM and DR is exceptionally limited. Although contemporary exemplary plans are available in most corners of the world, they are limited in the percentages of populations that can be served. In general, they are available only in environments containing sophisticated equipment and personnel in which only patients with appropriate medical insurance or funding are managed. An exception to this generality exists in the UK, Iceland, and selected western European countries, but in India, the U.S., and regions containing most of the world's populations, it remains true.

The implications of this research are that although optimal strategies to manage the disorders in question (as well as nephropathy, neuropathy, and many additional chronic diseases) are available in selected parts of the world, their broader implementation will require the development of "universal" national health care systems that are appropriately funded and capable of identifying affected

patients and providing the means for care. These of course are optimal goals and the likelihood of their being accomplished will depend upon the political environments and funding capabilities among the many nations. In the opening section of this dissertation, I mentioned that this story of DR could represent a metaphor for other chronic diseases. State-of-the-art therapies for both nephropathy and neuropathy have been developed in a fashion parallel to that of DR.[266,267268] And the Institute of Medicine has recognized the need for public health action for improved management strategies for chronic diseases.[269]

I also earlier quoted that disease represented "an occasion and agenda for an ongoing discourse concerning the relationship among state policy, medical responsibility, and personal culpability".[270] My research has supported this impression: adequate state policies are necessary for optimal universal health care; evidence-based medicine should be understood and practiced by available caregivers; and patients have responsibilities to appropriately manage their systemic disease. It is said in the idiom that "talk is cheap", [271] and so it is with these three variables. Relatively few countries provide optimal funding of health care systems, even when they are self-designated as "universal health care". Many caregivers remain unable to provide exemplary care because of inadequate access

[266] Blagg CR. The early history of dialysis for chronic renal failure in the United States: A view from Seattle. Am J Kid Dis 2007;49(3):482-496.
[267] Bello AK, Levin A, Lunney M, et al. Studies of care for end stage kidney disease in countries and regions worldwide. International cross sectional survey. BMJ 2019;367:5873.
[268] Skljarerski V. Historical aspects of diabetic neuropathies. In Veves A, Malik RA (eds). *Diabetic Neuropathy. Clinical Management (2nd Ed).* 2007, Totawa NJ, Humana Press, pp. 1-5.
[269] Institute of Medicine. *Living Well with Chronic Disease. A Call for Public Action. 2012, Washington D.C, Institute of Medicine.*
[270] Rosenberg 1992, Op. cit.
[271] Origin of the idiom is uncertain.

to patients, funding, or education. And few patients are genuinely compliant in managing their diabetes. Each of these factors is amplified in regions of relative poverty and poor hygiene.

My research efforts described differences among three national health care systems, but they can be extrapolated to additional regions. Based on my analysis, it appears likely that the epidemic of DR-related vision loss will be significantly reduced *only* in locations that provide comprehensive health care services to most diabetic patients and that the majority of the world's diabetic patients will remain underserved.[272]

[272] Cavan D, Marakoff L, Fernandes JdeR, et al. The diabetic retinopathy barometer study: global perspectives on access to and experiences of diabetic retinopathy screening and treatment. Diab Res Clin Prac. 2017:129:16-24.

Figure 1. Diagram of the Helmholtz Ophthalmoscope, (courtesy of the Wellcome Collection)

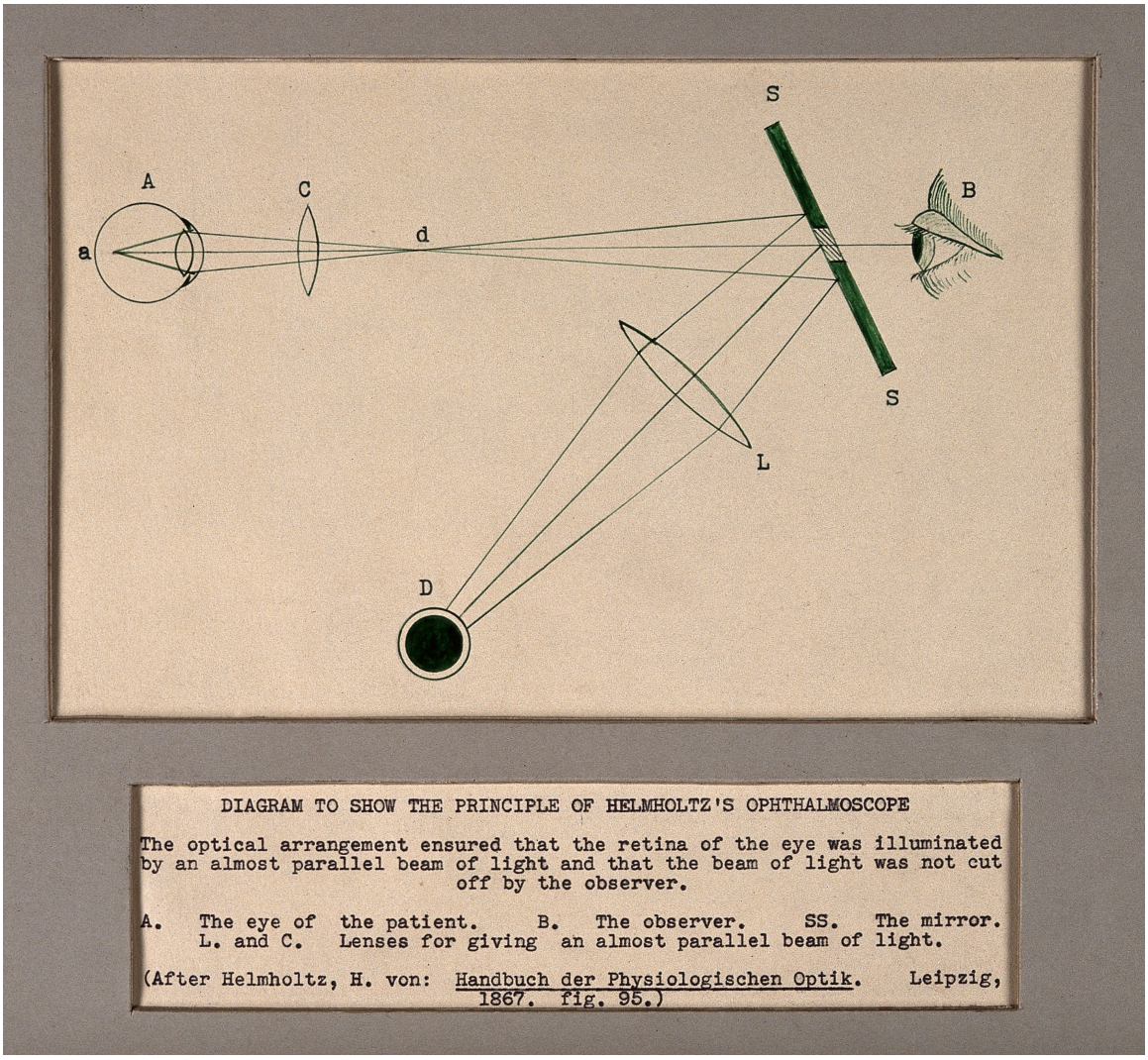


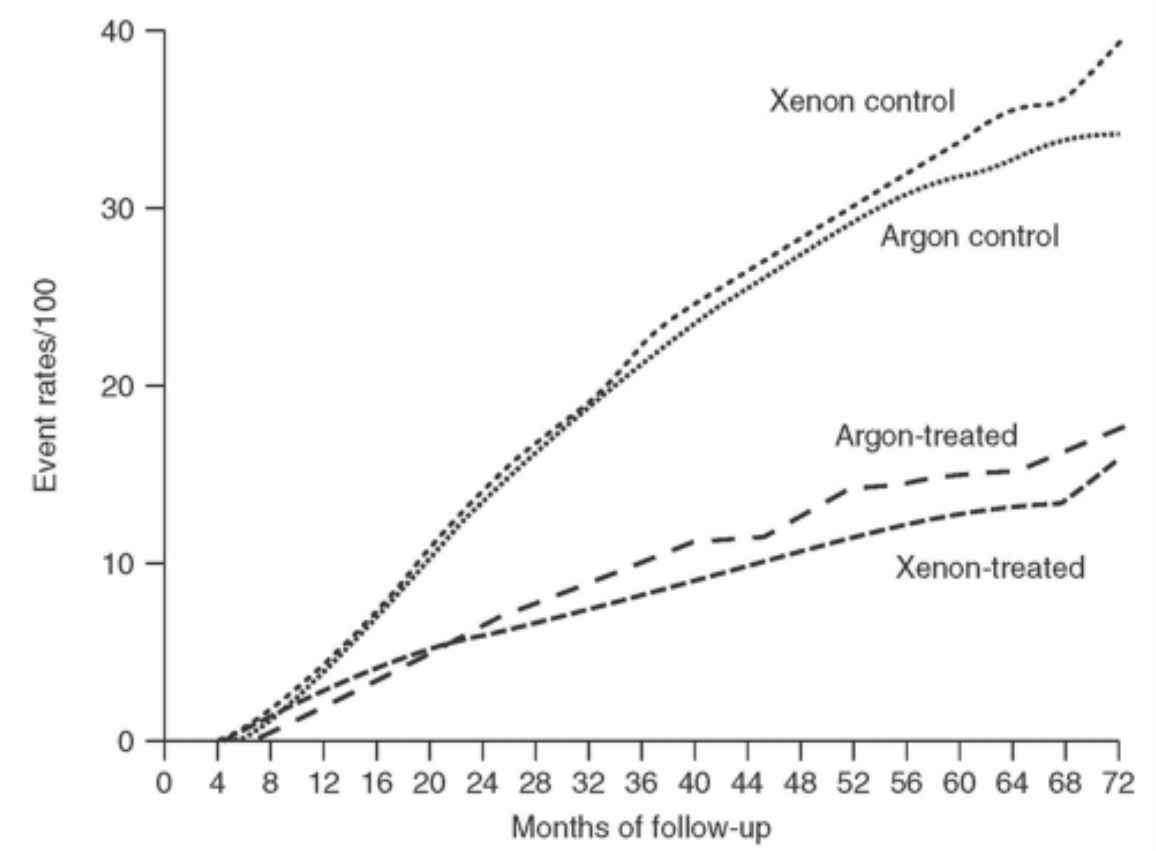
DIAGRAM TO SHOW THE PRINCIPLE OF HELMHOLTZ'S OPHTHALMOSCOPE

The optical arrangement ensured that the retina of the eye was illuminated by an almost parallel beam of light and that the beam of light was not cut off by the observer.

A. The eye of the patient. B. The observer. SS. The mirror. L. and C. Lenses for giving an almost parallel beam of light.

(After Helmholtz, H. von: Handbuch der Physiologischen Optik. Leipzig, 1867. fig. 95.)

Figure 2. The Diabetic Retinopathy Study[17]: Initial Outcomes for treatment of severe diabetic retinopathy. The "event" was a severe loss of vision on two consecutive 4-month follow-up visits.



CURRICULUM VITAE

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PERSONAL DATA

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Birth date: 8/16/40, Syracuse, New York

Domestic status:
Married: Alice Roberts Michels (Married 11/13/92)
Children: Laura Wilkinson Gable, born 2/9/66
Melinda Wilkinson Lee, born 11/29/67
Stepchildren: James Randolph "Randy" Michels, born 1/31/76
Allison Michels Pettinelli, born 10/2/78

EDUCATION HISTORY

Undergraduate
Stanford University, 1958-1962; BA (Psychology) 1962

Medical School
Johns Hopkins University Medical School, 1962-1966; MD 1966

Postgraduate Training:
Internship: Johns Hopkins Hospital (Medicine), 1966-1967
Residency: Wilmer Institute, Johns Hopkins (Ophthalmology), 1967-1970
Fellowship: Bascom Palmer Eye Institute (Vitreoretinal), 1970-1971
Harvard School of Public Health "Program for Chiefs of Clinical Services", 1993
Johns Hopkins Department of the History of Medicine (M.A. track) 2016-present.

Certification:
American Board of Ophthalmology, 1972-present, including 2010 "recertification"
Maryland State Medical Association, 1966 - present
Oklahoma State Medical Association, 1971-2002

PROFESSIONAL ACTIVITIES

Current Academic Appointments:

Chairman Emeritus, Ophthalmology, Greater Baltimore Medical Center, 2016-present.

Emeritus Status at Johns Hopkins University, pending.

Past Academic Appointments

Chairman, Dept. of Ophthalmology, Greater Baltimore Medical Center, 1992-2016.

Professor, Dept. of Ophthalmology, Johns Hopkins University, 1996 – 2016

Associate Professor, Dept. of Ophthalmology, Johns Hopkins University, 1993 - 1996

Clinical Professor, Dept. of Ophthalmology, University of Oklahoma, 1977-1992.

Vice-Director, Dean A. McGee Eye Institute, Oklahoma City 1975-1992

Director, Vitreoretinal Service, Dean A. McGee Eye Institute, 1975-1992

Current Clinical Staff Appointments:

Greater Baltimore Medical Center (Emeritus Staff), 1992 - present

The Johns Hopkins Hospital (Active then Courtesy Staff), 1992 – present

Additional Professional Appointments:

Chair, EyeCare America Steering Committee, 2014-2019.

Member, Data and Safety Monitoring Committee, Diabetic Retinopathy Clinical Research Network (DRCRnet), 2012-present.

Member, EyeCare America Steering Committee, 2000-2019.

Member, Data and Safety Monitoring Committee, Age Related Eye Disease Study (AREDS II), 2005-present.

Past Professional Appointments

Member, American Academy of Ophthalmology Seniors' Committee, 2012-2016

Study Director, FDA LASIK Quality of Life Collaboration Project (Patient Reported Outcomes with Lasik (PROWL)) 2009-June, 2015.

Member, Executive Committee, Pan American Ophthalmological Society 2009-11.

Secretary for English Language, Pan American Ophthalmological Society 2009-11.

President, American Ophthalmological Society, 5/2009 – 5/2010.

Immediate Past President, American Academy of Ophthalmology, 2008

Member, Board of Trustees, American Academy of Ophthalmology, 1999-2002, 2006-2008, 4/1/09-12/31/09.

Chairman, American Academy of Ophthalmology Eye Care America Diabetes Project Committee, 2000-2009.

President, American Academy of Ophthalmology, 2007.

President-Elect, American Academy of Ophthalmology, 2006.

Secretary-Treasurer, American Ophthalmological Society, 1999 – 2007.

Member, Board of Trustees, American Society of Retina Specialists, 2002 – 2006.

President, Retina Society, 2004 & 2005.

Member, Data and Safety Monitoring Committee, NAPP Trial, 2002 – 2006.

Member, American Academy of Ophthalmology Committee for Research, Regulatory, and External Scientific relations, 2000 – 2005.

Chairman, American Board of Ophthalmology, 2004.
Director, American Board of Ophthalmology, 1997 – 2004.
Member, American Academy of Ophthalmology Committee for Ophthalmic Technology Development, 1994-2000.
Member, American Academy of Ophthalmology Committee for Research, Regulatory Agencies and Federal Systems, 1990-1998.
Associate Examiner, American Board of Ophthalmology, 1986-1997.
Treasurer, Retina Society, 1997 – 2000.
Chairman, Credentials Committee, Retina Society, 1992-1996.
Voting Consultant, FDA Ophthalmic Devices Panel, l993-2009.
Chairman, Food and Drug Administration (FDA) Ophthalmic Devices Panel, 1990-1993.
Member, Food and Drug Administration (FDA) Ophthalmic Devices Panel, 1986-l993.
Member, RAND/Academic Medical Center Consortium on Cataract Surgery, 1990-l992.
Member, National Eye Institute Vision Research Review Committee, 1992-1993 (Brevity due to FDA conflict).
Member, NEI Data and Safety Monitoring Committee, Silicone Oil Study, 1985-1991.

Professional Society Memberships:

American Ophthalmological Society
Retina Society
Macula Society
American Society of Retinal Specialists (ne Vitreous Society)
Club Jules Gonin
Association for Research in Vision and Ophthalmology (ARVO)
Schepens International Society
Pan American Ophthalmological Society
Society of Heed Fellows
American Eye Study Club
Joseph Weil Society
Bascom Palmer Alumni Association
American Eye Study Club
Wilmer Residents Association

Current and Past Editorial Staff Appointments:

Associate Editor, Retina, 2007 - present
Editorial Board, Retina, 1985-present.
Associate Secretary, American Academy of Ophthalmology, Modules Program, 1988-1992.
Editorial Review Board, American Academy of Ophthalmology, Clinical Modules for Ophthalmologists, 1983 – 1988.
Chairman, American Academy of Ophthalmology Preferred Practice Patterns: Retina

Panel, 1992-2001.
Member, American Academy of Ophthalmology Preferred Practice Patterns: Retina Panel, 1989-2001.

Current Reviewer for Ophthalmology Publications:
Ophthalmology
American Journal of Ophthalmology
JAMA Archives of Ophthalmology
Retina
British Journal of Ophthalmology
European Journal of Ophthalmology
Indian Journal of Ophthalmology

Past Granted Research:
Principle Investigator, Macular Photocoagulation Study, University of Oklahoma, 1979-1992.
Principle Investigator, Endophthalmitis Vitrectomy Study, University of Oklahoma, 1990-1992.

Current Research Interests:
History of medicine
Evidence-based medicine, outcomes research
Diabetic retinopathy: pathogenesis, epidemiology, screening, treatment, and prevention
Pathogenesis and prevention of retinal detachment
Posterior segment complications of intraocular surgery
Age-related macular degeneration: screening, treatment

Honors and Awards:
American Academy of Ophthalmology Honor Award, 1982.
American Academy of Ophthalmology Senior Honor Award, 1991.
Society of Heed Fellows Honor Award, 1991
Residents' Teaching Award, Greater Baltimore Medical Center, 1994
American Academy of Ophthalmology Secretariat Award, 2003
Residents' Teaching Award, Greater Baltimore Medical Center, 2005
American Academy of Ophthalmology Life Achievement Award, 2005
Gertrude Pryon Award (American Society of Retinal Specialists), 2009
Residents' Teaching Award, Greater Baltimore Medical Center, 2010
Presidential Guest of Honor, American Academy of Ophthalmology annual meeting, 2011
Inaugural recipient of the Wilkinson-Welch-Hoover Endowed Chair in Ophthalmology, GBMC, 2015
Special Recognition Award, American Academy of Ophthalmology, 2015
Retina Hall of Fame, Charter member, 2016.

Named Lectures:
11th Mahlon Barlow Memorial Lectureship, Baltimore, 1982

2nd Ronald G. Michels Memorial Lectureship, Baltimore, 1992
15th Taylor Smith Lecture, Aspen, 1994
2nd Walter J. Stark Sr. Lecture, Oklahoma City, 1994
12th Delbert P. Nachazel, Jr Lecture, Detroit, 1999
25th Tullos O. Coston Lecture, Oklahoma City, 2004.
37th Doheny Lecture, Los Angeles, 2006.
17th D. Jackson Coleman Lecture, New York, 2007.
4th Jerry and Donna Knauer Lecture, Beaver Creek, 2007.
31st Taylor Asbury Lecture, Cincinnati, 2007
8th Stanley Truhlsen Lecture, Omaha, 2009
20th Gertrude Pryon Award Lecture, New York, 2009
23rd William Holland Wilmer Lecture, Baltimore, 2011
21st Edward W. D. Norton Lecture, Miami, 2015

Visiting Professorships:

Albany (NY) Medical Center	University of Arkansas
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Baylor University	University of California, SF
Duke University	University of Iowa
Devers Eye Clinic, Portland	University of Kansas
Emory University	University of Minnesota
Georgetown University	University of Oklahoma
Mayo Clinic	University of Pennsylvania
Mass Eye and Ear Infirmary	University of Pittsburgh
Penn State University	University of Southern California
Royal Oak, MI	University of Tenn, Memphis
Tulane University	University of Texas, San Antonio
Vienna Eye Clinic I	University of Cincinnati
Wills Eye Hospital	Vanberbilt University
Wake Forest University	

PUBLICATIONS

1. Donahoo, J.S., Wilkinson, C.P., Weldon, C.S.: The Production of Lymphocytopenia by Selective Irradiation in Dogs, J Surg Res 7:475-480, 1967.

2. Duke, J.R., Wilkinson, C.P., Sigelman, S.: Retinal Microaneurysms in Leukemia, Brit J Ophthalmol 52:368-374, 1968.

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5. Gass, J.D.M., Wilkinson, C.P.: A Follow-Up Study of Presumed Ocular Histoplasmosis, Trans Am Acad Ophthalmol Otolaryngol 76:672-694, 1972.

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10. Wilkinson, C.P., Anderson, L.S., Little, J.H.: Retinal Detachment Following Phacoemulsification, Ophthalmology 85:151-156, 1978.

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12. Wilkinson, C.P.: Retinal Detachment Following Phacoemulsification, Am J Ophthalmol 87:628-631, 1979.

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44. Wilkinson, C.P.: Closed Vitreous Surgery for Complications of Intraocular Lens Implantation. I. Indications; In: Basic and Advanced Vitreous Surgery. Blankenship, G.W., Binder, S., Gonvers, M., Stirpe, M. (eds). Liviana Press, Padova, Italy, 1986, pages 136-140.

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