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The Pathological Indications of Diabetes Mellitus

Patricia Gast

ROCHESTER INSTITUTE OF TECHNOLOGY

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THE PATHOLOGICAL INDICATIONS OF DIABETES MELLITUS

By

Patricia Gast

Date:

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APPROVALS

Adviser: Glen Hintz

Date: 5/17/85

Associate Adviser: Robert Wabnitz

Date: 5/17/85

Associate Adviser: Robert Heischman

Date: 5/20/85

Assistant to the Dean
for Graduate Affairs Fred Meyer

Date: 8/21/85

Dean, College of
Fine & Applied Arts: Dr. Robert H. Johnston Ph. D.

Date: 8/23/1985

I, Patricia Gast, prefer to be contacted each time a request for reproduction is made. I can be reached at the following address.

Date: 5/17/85

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INTRODUCTION

The purpose of my thesis is to develop and produce a series of illustrations demonstrating various pathological conditions manifested on the microscopic level by the disease diabetes mellitus, and intended for use as educational material for medical students.

The conditions I have chosen to illustrate are pathognomonic (diagnostic and characteristic) of diabetes mellitus; and the illustrations themselves are conceptualizations, dimensionalizing visual information ordinarily presented as a flat plane (two-dimensional), and are drawn from actual pathological specimens. The illustrations are intended to be used to teach medical students to recognize and understand the pathological changes that occur as a result of diabetes mellitus.

In addition to the educational purpose of the illustrations, it is also my intention to produce works that are not only scientifically accurate, but aesthetically pleasing as well. Thus I have attempted to produce works that can be appreciated on two levels. First, as <u>medical</u> art, the works can be appreciated as accurate, clear, and effective communication of some medical or scientific fact, idea, or concept. Second, as medical <u>art</u>, the works can be appreciated as illustration in terms of composition, color, perspective, rendering techniques, etc.

This concern with aesthetic quality as well as accuracy stems from my own personal experience and my evolving philosophy of art. I have always been struck by the inherent beauty[1] that I have found in Creation (i.e. Nature and all life) on all levels, from the universal and the cosmic to the macroscopic and the microscopic; and I have a sincere desire to share that beauty with others:

> The appreciation of beauty (i.e. aesthetic appreciation — having a sense of the beautiful or characterized by a love of beauty) is a common denominator linking the artist and the viewer. The artist may perceive beauty and respond to it through the creative process, producing a piece of art which has the quality of beauty, and this quality in turn is perceived and responded to by the viewer. Thus, beauty plays a role in generating and sustaining dialogue between the artist and the viewer.
>
> ...The occurrence of...[the] exaltation [of the mind or spirit of the perceiver of beauty] is what gives special or more than ordinary significance to a piece of art. The experience of exaltation and the subsequent recognition of special meaning and significance often leads to inspiration of both the artist and the viewer: the artist is inspired to create and the viewer is inspired to more fully respond.[2]

Also, I have been influenced and inspired by the anatomical drawings in the notebooks of Leonardo Da Vinci, particularly in their alliance of beauty and accuracy (i.e. what

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[1]Beauty can be defined as a quality present in a person or thing that gives aesthetic pleasure to the senses and pleasurably exalts the mind or spirit.

[2]Patricia Gast, "Beauty," paper for Graduate Forum, Rochester Institute of Technology, 14 May 1984.

was considered accurate at the time)[3] which played an integral part in the quest for scientific (anatomical) knowledge.[4] I have found such a concern with accuracy and aesthetic value to be of essential importance to the role of the medical illustrator and to the role of medical illustration today:

> Basically, the medical artist is an illustrator, trained and experienced in presenting complex medical problems, so that they are easily understood, in a visually clear, concise and pleasing manner.[5]

> [The medical artist] must constantly strive for good draftsmanship and scientific accuracy, but then he must remain aware that if the 'story' can be enhanced, images can be taken out of context or size relationships with their surroundings and still be valid. Straying from literal reality didn't bother the expressionists, and I contend that this is usually what makes a medical illustration rather than just a medical picture.[6]

Furthermore, I have been inspired by Leonardo Da Vinci, the artist, particularly as the "uomo universale" or the "Ren-

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[3]Leonardo Da Vinci was influenced by contemporaneous anatomical theories, particularly that of Galenism, which colored his interpretation of what he saw. His later drawings in which he relied totally upon his own observations are his most accurate. Charles D. O'Malley and J.B. de C.M. Saunders, ed., Leonardo Da Vinci on the Human Body: The Anatomical, Physiological, and Embryological Drawings of Leonardo Da Vinci, (New York: Greenwich House, Crown Publishers Inc., 1982), pp.20-30.

[4]Ibid., pp.20-30.

[5]Lou Barlow, "The Medical Artist in Pharmaceutical Advertising," The Journal of Biocommunication, 1, no.1 (June 1974):29.

[6]Barry Baker in "Barry Baker, Medical Illustrator," interview by William Winn, The Journal of Biocommunication, 4, no.2 (July 1977):38.

aissance man", pursuing a variety of interests and making contributions in those areas. "While it is doubtful that Leonardo ever thought of himself as an anatomist,...it is noteworthy that he pushed his investigations far beyond the point of artistic usefulness; and it is possibly correct that Leonardo thought of these studies as a separate discipline rather than auxiliary to art."[7] This Renaissance mentality is echoed by modern medical illustrators:

> It's a combination of study, of observing specimens, of attending hospitals, meetings, consulting....I have to be a specialist in all specialties. One day I might be working on something in the field of brain surgery, another day I might be working on intestinal disorders, another day on heart disease...so I have to know these various subjects, and that is the most difficult and important, and also I might say, the most interesting and fascinating part of my work.[8]

> We must...paint with our minds....I believe that intelligent illustrators make good illustrators....We must know our subject matter!...There shouldn't be a day in our lives that we don't learn something about the structure and function of our incredible body. The next drawing that we produce should reflect new knowledge and be a better illustration than the last one. Ours is not a job, it is a career. A lifelong pursuit...and there is a real joy in that pursuit![9]

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[7] O'Malley and Saunders, Leonardo Da Vinci on the Human Body, p.18.

[8] Dr. Frank H. Netter, "Michelangelo of Medicine," PRN (Physician's Radio Network) Guide, 11, no.6 (November 1984):30.

[9] Robert Demarest, "Painting With Our Minds," The Journal of Biocommunication, 11, no.4 (November 1984):2.

It is mainly out of personal interest that I have chosen to illustrate the pathological indications of diabetes mellitus. Some members of both the maternal and paternal sides of my family, as well as a few of my friends, have been or are now affected with this disease. It is to them that I would like to dedicate this thesis.

DIABETES MELLITUS (AN OVERVIEW)

Diabetes mellitus is a chronic disorder afflicting 12 million Americans[10] and 30 million people worldwide.[11] It is characterized by abnormalities in the metabolism of carbohydrate, protein, and fat (lipid), with hyperglycemia (the state of excessive levels of glucose in the blood) brought on by a combination of environmental and genetic factors. Hyperglycemia may be due to a lack of insulin (the hormone which is synthesized and secreted by the beta cells of the islets of Langerhans in the pancreas, and which regulates the glucose concentration in the blood) or due to an excess of factors which oppose insulin's action (insulin resistance). Diabetes mellitus encompasses a group of genetically and clinically heterogeneous disorders in which glucose intolerance is a common denominator.[12,13] The major effects of diabetes include the development of the following pathological conditions: atherosclerosis (large blood vessel damage (disease)), arteri-

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[10] Earl Ubell, "A Cure for Diabetes?," Parade Magazine, (April 21, 1985):14.

[11] WHO (World Health Organization) Expert Committee on Diabetes Mellitus: Second Report, Tecnical Report Series 646, Geneva (1980):7.

[12] Ibid., p.8.

[13] The Physician's Guide to Type II Diabetes (NIDDM): Diagnosis and Treatment, American Diabetes Association, Inc., (1984):3.

osclerosis (small blood vessel damage), microangiopathy (capillary damage), nephropathy (kidney disease, particularly glomerulosclerosis), retinopathy (damage of the blood vessels of the eye), and neuropathy (damage to the peripheral nerves).[14,15]

There are two major types of diabetes mellitus: Type I (insulin-dependent diabetes mellitus or IDDM), formerly classified as juvenile-onset or ketosis-prone diabetes mellitus,[16] accounting for 10 to 20 percent of known cases of diabetes in the United States, or an estimated one million plus people;[17] and Type II (non-insulin-dependent diabetes mellitus or NIDDM), formerly classified as maturity-onset or ketosis-resistant diabetes, accounting for 80 to 90 percent of known cases of diabetes in the United States,[18] or an estimated 10 million people. The new classifications are the result of recent research into the pathogenic mechanisms and differing courses and outcomes of diabetes. There are further subdivisions and other types (see Table 1).

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[14] Ibid., p.3.

[15] Stanley L. Robbins, M.D., and Ramzi S. Cotran, M.D., Pathologic Basis of Disease, (Philadelphia: W.B. Saunders Company, 1979), p.327.

[16] IDDM may occur at any age and NIDDM may also occur among young people. Markku Laakso, M.D. and Kalevi Pyörälä, M.D., "Age of Onset and Type of Diabetes," Diabetes Care, 8, no.2, (March/April 1985):117.

[17] This estimate includes unreported cases of diabetes. Approximately 50 percent of the 10 million with NIDDM don't know they have it. Ubell, "A Cure For Diabetes?," p.15.

[18] The Physician's Guide, p.1.

TABLE 1

Classification of Diabetes Mellitus and Other Categories of Glucose Intolerance*

A. Clinical classes

Diabetes mellitus

Insulin-dependent type —— Type I

Non-insulin-dependent type —— Type II
(a) non-obese
(b) obese
Other types including diabetes mellitus associated with certain conditions and syndromes:
(1) pancreatic disease
(2) disease of hormonal etiology
(3) drug- or chemical-induced condition
(4) insulin receptor abnormalities
(5) certain genetic syndromes
(6) miscellaneous

Impaired glucose tolerance
(a) Non-obese
(b) Obese
(c) Impaired glucose tolerance associated with certain conditions and syndromes

Gestational diabetes

B. Statistical risk classes
(subjects with normal glucose tolerance but substantially increased risk of developing diabetes)

Previous abnormality of glucose tolerance

Potential abnormality of glucose tolerance

*Classification scheme prepared by the Diabetes Data Group of the National Institutes of Health, USA, modified from version appearing in WHO Expert Committee on Diabetes Mellitus, p.13.

Type I is characterized by a clearly defined insulin deficiency, i.e. lack of production of enough insulin; whereas Type II is characterized by a relative insulin insufficiency, i.e., a delay in or inappropriate insulin secretory response and/or resistance or insensitivity to insulin in the peripheral tissues.[19]

Hereditary influences contribute significantly to the development of both major variants. Genetic markers such as the presence of HLA haplotypes in relatives of insulin-dependent diabetics and the presence of ICA's (islet cell antibodies) in non-insulin-dependent diabetics and their relatives may eventually help to identify those persons at high risk of developing diabetes (genetic pre-disposition) and attempt prevention by avoiding contributing environmental influences. Such environmental influences include obesity (overnutrition and hyperinsulinemia), pregnancy, and infection (viruses such as enterovirus coxsackie B4, mumps, and rubella), as well as alcohol, protein malnutrition, nutritional imbalance, severe or prolonged stress, drugs and hormones, and physical inactivity (insensitivity to insulin and the number of insulin receptor sites in muscle are related to physical fitness).[20,21] "It is abundantly clear that interactions between genetic and

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[19] Robbins and Cotran, Pathologic Basis of Disease, p.327.

[20] Ibid., p.327.

[21] WHO Expert Committee on Diabetes Mellitus: Second Report, pp.21-6.

environmental factors provide the basis of the multifactorial causes of diabetes. In any given subject it is the relative proportion of these factors that determines the eventual development of the disease."[22]

The onset of diabetes (both IDDM and NIDDM) has been divided into the following stages: suspected prediabetes, prediabetes (or diabetes pre-mellitus), chemical diabetes, and overt (clinical) diabetes. The first three stages are considered asymptomatic (i.e., there is no manifestation of the classic symptoms of diabetes: excessive thirst (polydipsia), excessive urination (polyuria), glucose in the urine (glycosuria)). In suspected prediabetes there is a suspected genetic predisposition (depending on how closely related to a diabetic in the family, the prevalence of diabetes in the family, and the presence of genetic markers), but no significant abnormalities are manifested. In prediabetes there is no abnormality of carbohydrate metabolism demonstrable in a glucose tolerance test. In chemical diabetes no symptoms are present, fasting blood glucose levels are normal, but glucose tolerance is impaired. In overt (clinical) diabetes the characteristic symptoms are present as well as abnormal random blood glucose values.[23]

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[22] WHO Expert Committee on Diabetes Mellitus:Second Report, p.25.

[23] R.F. Camerini-Davalos, H.S. Cole, and J.A. Jimenez, "Prediabetes," in Diabetes Mellitus:Theory and Practice, ed. by Max Ellenberg, M.D. and Harold Rifkin, M.D., (New York: McGraw-Hill Book Company, Blakiston Publication,1970),pp.508-10.

> These four stages from suspected prediabetes to overt symptomatic diabetes, are not necessarily progressive in a forward direction, but the condition may revert to earlier stages (as from chemical diabetes to prediabetes), and this may take place without change in body weight or treatment. In fact, during the early stages, diabetes must be regarded as a 'fluid' condition that can progress or revert depending upon different factors (diabetogenic and antidiabetogenic).[24]

Diabetes is diagnosed from the presence of overt symptoms (polydipsia, polyuria, glycosuria, rapid weight loss) and from the results of specific tests such as the oral glucose tolerance test, blood tests (for plasma glucose concentration), and urine tests (for glycosuria). New methods of diagnosis are being researched and developed which are geared toward diagnosing diabetes in the earlier asymptomatic stages. One such method is the measurement of the basement membrane width of muscle capillaries, the thickening of which is one of the pathological conditions (microangiopathy) of diabetes mellitus.[25]

Type I diabetes (IDDM) is treated with insulin therapy (either self-injections or the new insulin pump) and diet. Type II is treated with diet and/or drugs which increase insulin receptivity of the peripheral body tissues. Such treatment relieves the symptoms but does not cure the disease.

> Excess mortality attributable to diabetes has, in the past decade, caused more deaths than all wars combined. In the United States it is the fourth lead-

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[24] Ibid., p.509.

[25] Ibid., pp.518, 521.

> ing cause of death, and in at least thirty other developed countries it is also a leading cause of death. It is also a major cause of morbidity and mortality in many developing countries.[26]

Research and development are an integral part of diabetic care. New developments include islet cell transplants,[27] pancreas transplants,[28] and the use of new drugs such as Cyclosporin A which completely reverses IDDM in juvenile diabetics if administered soon enough after onset.[29,30]

> Basic research should not be ignored in the hunt for immediate improvements of worldwide health care for diabetics. Particular areas where further knowledge could lead to improvements in diabetic care include methods of insulin secretion, mechanisms of insulin action and resistance, mechanisms of glucose homeostasis, and mechanisms of insulin-receptor interactions and their modification by drugs. Perhaps more urgent is the need to know the precise biochemical lesions that lead to the characteristic complications of diabetes [underlining mine].[31]

Education is a keystone in the management of diabetes since diabetes is an example of a chronic disorder in which

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[26] WHO Expert Committee on Diabetes Mellitus:Second Report, p.18.

[27] Ubell, "A Cure For Diabetes?,"pp.15,16.

[28] S.O. Bohman, G. Tyden, H. Wilczek, G. Jaremko, et.al., "Prevention of Kidney Graft Diabetic Nephropathy by Pancreas Transplantation in Man,"Diabetes, 34, no.3 (March 1985):306.

[29] Ubell, p.15-16.

[30] U. Keller, Ch. Beglinger, and W. Berger, "Identification of subjects with a high risk of developing Type I (insulin-dependent) diabetes," Diabetolgica, 28 (1985):57.

[31] WHO Expert Committee on Diabetes Mellitus, p.63.

"the affected person must take major responsibility for his own health with the support of the medical profession and the community."[32] According to the WHO (World Health Organization), "little effort has been expended to date on finding the best means of assisting learning in diabetics, whether individually or collectively, or of informing the community about diabetes."[33] There is a need for education, even of the medical community,[34] about diabetes, particularly in the area of the specific pathological conditions (indications) and the mechanisms which cause them, in order to develop methods of prevention or possible cures.

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[32] WHO Expert Report on Diabetes Mellitus, pp.7-8.

[33] Ibid., p.58.

[34] "Health care personnel need to have a basic knowledge of the scientific background of diabetes, adapted to their professional level....Teaching should be effected during in service training in hospitals and the community.... Education about diabetes must be incorporated into the basic training programmes for each cadre and continued at all levels." Ibid.,pp54-5.

SPECIFIC PATHOGNOMONIC CONDITIONS (PATHOLOGICAL INDICATIONS) OF DIABETES MELLITUS

Pathognomonic conditions are those conditions which are characteristic of and diagnostic of a particular disease, in this case diabetes mellitus. Certain structural anomalies and related functional anomalies take place as a result of diabetes. (See Appendix A for a brief overview of the microscopic structure and function of the normal kidney). Among the most important and most observable of these anomalies are those which take place in the kidney, specifically the lesions (tissue abnormalities) which are indicative of glomerulosclerosis. Lesions indicative of atherosclerosis and arteriosclerosis, although found in other parts of the body, are of special interest and importance in the kidney, and together with glomerulosclerotic lesions are considered part of diabetic nephropathy. "Nephropathy is a major complication of diabetes mellitus and results in renal failure in at least one third of Type 1 diabetics within fifteen to thirty years of the onset of the disease."[35]

The diabetic glomerular lesions are characterized by

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[35]E.N. Ellis, M.W. Steffes, F.C. Goetz, D.E.R. Sutherland, and S.M. Mauer, "Relationship of renal size to nephropathy in Type 1 (insulin-dependent) diabetes," Diabetologica, 28 (1985):12.

an accumulation of basement membrane material. There are two main types of glomerular lesions: diffuse and nodular.

The diffuse type (diffuse glomerulosclerosis) consists of the deposition of PAS (Periodic Acid Schiff stain)-positive material diffusely throughout the glomerulus, in the capillary walls and the mesangium, with a progressive narrowing and eventual obliteration of vessels. Some consider it to be pathognomonic of diabetes while others do not.[36,37] However, diffuse glomerulosclerosis has been found within a few years after onset and in the initial stages of progressive renal failure (nephropathy).

The nodular type (nodular glomerulosclerosis), formerly known as Kimmelsteil-Wilson disease, is definitively considered to be pathognomonic of diabetes mellitus. It is characterized by the appearance of an ovoid or spherical focal nodule, either at the periphery of the glomerulus or within the mesangial core of the glomerular lobules, which is eosinophilic, PAS-positive, has a laminated appearance and is hyalinized.[38,39] Nodules of progressively increasing size are depos-

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[36] Elexious Thompson Bell, M.D., Diabetes Mellitus: A Clinical and Pathological Study of 2529 Cases, (Springfield, Illinois: Charles C. Thomas, 1960), p.46.

[37] "Diabetic Nephropathy," in CIBA Collection of Medical Illustrations Volume 6 Kidneys, Ureters, and Urinary Bladder, (CIBA Pharmaceutical Company, 1972), p.149.

[38] Diabetes Mellitus Volume V, ed. by Harold Rifkin, M.D., and Philip Raskin, M.D., (Bowie, Maryland: Prentice-Hall Publishing and Communications Company, 1981), p.265.

[39] Robbins and Cotran, Pathologic Basis of Disease, pp.338-9.

ed by the endothelial cells (of the capillaries) or the mesangial (intercapillary) cells, and these nodules may eventually distort or obliterate the capillaries of the glomerulus or the entire glomerulus. One, several, or all of the lobules in the individual glomerulus may be involved as may any number of glomeruli up to involvement of the entire kidney.[40] Also, the glomerular space may become filled with laminated crescents of hyalinized fibrous tissue so that eventually the entire glomerular structure assumes a hyaline sclerotic appearance.

Recent research has suggested the theory that diffuse glomerulosclerosis eventually gives rise to nodular glomerulosclerosis. The basement membrane material accumulated in both types contains mucopolysaccharides and glycoprotein fibrils like normal basement membrane but with trapped mesangial cells and other chemical alterations such as a higher concentration of albumin, which may be specific (diagnostic) for diabetes as demonstrated by cuurent research.[41] The glomerular basement membrane although thickened tends to be leaky, functioning imperfectly as a filtration barrier. This phenomenon is thought to be due to a structural defect in organization.[42]

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[40]Ibid., p.338.

[41]Alfred F. Michael and David M. Brown, "Increased Concentration of Albumin in Kidney Basement Membranes in Diabetes Mellitus," Diabetes, 30 (1981),p.843.

[42]Robert G. Spiro, "Chemistry and Metabolism of the Basement Membrane," in Diabetes Mellitus: Theory and Practice, ed. by H. Rifkin, M.D. and M. Ellenberg, M.D., (New York: McGraw-Hill Book Company, Blakiston Publication,1970), p.219.

Both types of lesions are associated with a characteristic clinical syndrome, the five stages of progressive renal failure: In the first stage, early hypertrophy-hyperfunction, there is an increase in renal size (i.e. an increase in the size of the glomeruli, particularly in the volume of the basement membrane material)[43] accompanied by an increase in function (specifically, an increase in the glomerular filtration rate (GFR)). These changes may stem from metabolic effects of diabetes and are slowly reversible by metabolic control.[44] In the second stage glomerular lesions are present but there are no signs of clinical disease. These lesions develop over many years as there is a gradual increase in the thickness of the glomerular basement membrane with a corresponding increase in the duration of diabetes, followed by changes in the glomerular mesangium (deposition of basement membrane-like mesangial matrix and proliferation of mesangial cells) There is also hyperfunction, thought to be due to imperfect metabolic control. In the third stage, incipient diabetic nephropathy, ther is an abnormally elevated urinary albumin excretion (proteinuria) with a slow gradual increase over the years accom-

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[43]R. Osterby and H.J.G. Gunderen, "Quantitative electron microscopic studies of glomerular basement membrane material in diabetes mellitus," in New Approaches to Insulin Therapy, ed. by Karl Irsigler, Kathryn N. Kunz, David R. Owens, and Horst Regal, (Baltimore: University Park Press, 1981),p.349.

[44]C.E. Mogensen, C.K. Christensen, and E. Vittinghus, "The Stages in Diabetic Renal Disease With Emphasis on the Stage of Incipient Diabetic Nephropathy," Diabetes, 32 (1983):65.

panied by a rise in blood pressure. This stage signals the future decline in renal function. The fourth stage is overt diabetic nephropathy in which there is persistent proteinuria. If the high blood pressure remains untreated there is an accompanying fall in the GFR; however, if it is treated (long-term anti-hypertensive treatment) the fall rate is reduced by 60%.[45] In the fifth and final stage, end-stage renal failure, there is uremia (retention in the blood of constituents normally excreted in the urine). "As many as 25% of the population entering end-stage renal failure programs in the United States are diabetic."[46] A number of mechanisms have been postulated as causing changes in early diabetes that produce late diabetic nephropathy:

> (1) Increased basement membrane material, found early as an increase in the filtration surface area could be regarded as a forerunner of later increase in basement membrane thickness, eventually producing clinical glomerulosclerosis; (2) hemodynamic changes, predominantly an increase in filtration pressure, may produce glomerular structural disruption...(3) abnormal extravasation of plasma protein, probably in connection with increased pressure, may also be of pathogenic importance.[47]

These mechanisms may work alone or in combination.

Atherosclerosis and arteriosclerosis often accompany diabetic glomerulosclerosis. Atherosclerosis begins to appear in most diabetics within a few years of onset and consists of thickening of the artery walls with deposition of fat and hyalin, which leads to vessel occlusion. Like glomerulosclerosis it develops gradually with no clinical

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[45]Ibid., p.65. [46]Ibid., p.65. [47]Ibid., p.74.

manifestations. Arteriosclerosis (or arteriolosclerosis) affects the smaller blood vessel (arterioles). The lesion is characterized by amorphous hyalinization of the arteriole wall, deposits of PAS-positive mucopolysaccharides, endothelial cell proliferation and narrowing of the lumen. It affects all the vascular beds but particularly those in the kidneys. Recent research has indicated that there are differences between the endothelial cells[48] of the larger vessels and the smaller vessels as well as differences between the such cells in different organs.[49] There is disagreement as to whether athero- and arteriosclerotic lesions are the product of deranged metabolism or an inherited genetic consequence of diabetes.

Study of the structural abnormalities of the diseased glomerulus is carried out in order "to gain insight into the events that lead to decline and finally extinction of the glomerular function....to gather diagnostic criteria.... to look for the structural counterpart of functional deviations."[50] Such study would hopefully uncover ways of preventing the progressive deterioration that marks diabetic nephropathy.

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[48]Endothelial cells form the inner lining of all blood vessels. Among their functions are the mediation of the passage of nutrients and other solutes from the blood to the tissues, the maintenance of an open vessel lumen, and the formation of a single cell-layer tightly adherent to the basement membrane of the vessel wall.

[49]Bruce R, Zetter, "The Endothelial Cells of Large and Small Blood Vessels, Diabetes 30 (Suppl.2) (November 1981): 24-7.

[50]R. Osterby, H.J.G. Gundersen, A. Horlyck, J.P.Kroustrup, et. al.,"Diabetic Glomerulopathy: Structural Characteristics of the Early and Advanced Stages," Diabetes, 32 (Suppl.2) (June 1983):79,82.

METHOD (EXECUTION)

After arriving at the concept of a series of educational illustrations for medical students I undertook extensive reading and collection of reference materials in order to familiarize myself with the disease diabetes mellitus, particularly its pathological aspects, and thus be able to effectively reach my intended audience. As a medical artist I have found it to be of great importance to have some knowledge and comprehension of what one is illustrating in order to effectively communicate it to others:

> Our job is to communicate knowledge; our illustrations are made to teach.... They do this, if they are effective, because of our ability to understand the subject, understand the audience, and understand the problem. By relying on a vast store of knowledge stored in our resource books, our libraries, and our brains, we abstract the material, delete much of it, emphasize the salient points and, finally paint or portray it.[51]

My initial research led me to choose those pathological conditions which are pathognomonic (diagnostic and characteristic) of diabetes mellitus. At first I set out to illustrate such conditions from various areas of the body (e.g. kidneys, eyes, blood vessels, the pancreas) as diabetes is a systemic disease affecting these organs in particular. How-

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[51] Demarest,"Painting With Our Minds,"p.2.

ever, the limited availability of specimens and the plethora of information found in what was available, as well as time constraints induced me to concentrate only on the pathognomonic conditions found in the kidney. As such it is an important area not only because of the prevalence of diabetic nephropathy (kidney disease), but also because it is an area of future research, particularly on the cellular (microvascular) level, in attempting to understand the pathological processes that take place in hopes of eventual prevention.[52]

I acquired four microscope slides of pathological specimens of diabetic kidney tissue from Dr. Bernard Panner of the Pathology Department of the School of Medicine and Dentistry at the University of Rochester. After an initial overview with Dr. Panner in which he briefly pointed out the typical lesions, I then carefully looked over each slide myself using light microscopes (see Appendix B) both at Rochester Institute of Tecnology and at the University of Rochester (Strong Memorial Hospital). Using my own observations and photomicrographs of typical lesions as reference, I selected those areas on the specimen slides which showed the particular lesion I was interested in as well as an interesting composition. I then did drawings of these areas using a camera lucida (see Appendix C) for the purpose of establishing proper proportions and maintaining accuracy:

> Few users of the microscope possess the requisite talent to make accurate free-hand drawings of the specimens observed under their instruments and those

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[52] Bruce R. Zetter, "The Endothelial Cells of Large and Small Blood Vessels," Diabetes, 30 (Supp.2), (November 1981):27.

> who do possess this ability realize the difficulty of judging the size and proportion of parts. For these reasons... mechanical aid is necessary...by means of some form of camera lucida to bring the microscopic image and the drawing paper and pencil in the same plane.... The procedure is to draw the outline, the various parts, and the coarser detail of the object, and then fillin the fine detail by direct observation through53 the microscope.

I originally started doing free-hand drawings of the specimens but found them too time-consuming as I had limited time on the microscope (three hours at a time once or twice a week) and had placed the constraint of accuracy upon myself. It was suggested to me that I use a camera lucida. From my own experience with the camera lucida I would have to say that it still requires a great deal of drawing skill in order to do the drawings at a reasonable speed and to do them accurately (i.e. it is easy to lose one's place as only the point of the drawing implement can be seen, and as such it appears magnified so that one's movements must be adjusted accordingly; it is somewhat along the lines of blind contour drawing).

All of the camera lucida drawings were done at 400x magnification ("high-dry" power, i.e. the highest magnification possible without oil immersion) for the sake of clarity as well as uniformity. The power of magnification also determined the actual size of the camera lucida drawings; the drawings are somewhat smaller than what is seen through the eye-

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George Herbert Needham, M.S., F.R.M.S., The Practical Use of the Microscope: Including Photomicrography, (Springfield, Illinois:Charles C. Thomas, 1958), pp.398-9.

piece due to the optical properties of the system. This size discrepancy led me to experiment with a variety of drawing implements in order to get as sharp and detailed an image as possible as well as one I could work from later in rendering the actual full-size pieces. This experimentation included 3H and 4H graphite pencils, Prismacolor pencils, Thinex colored pencils, a mechanical pencil (0.5mm lead), and a ballpoint pen (0.3mm tip). The 0.3mm ballpoint gave the best results in terms of clarity and sharpness, whereas those drawings with specific structures coded with colored pencil were easier to refer to later in rendering. The best solution was a ballpoint drawing with certain areas indicated in colored pencil (see Figures 1,2 ,3).

These small camera lucida drawings were then enlarged with a "Lucy" enlarger and transferred to board (double-sided Strathmore illustration board). This particular board was chosen as a quality surface which would handle a variety of media. Unfortunately, there is no way of exactly measuring the degree of enlargement obtained with the Lucy, and therefore I cannot give an exact value for the magnification of the full-size illustrations. In comparison to printed photomicrographs of similar subjects I would estimate them to be about 1100-1200x magnification.

As the full-size pieces were rendered, costant referral to the actual microscopic section was necessary in order to establish structure, render finer detail accurately, as well as to serve as a guide in three-dimensionalizing the structures seen. Occasionally oil immersion (1000x magnifica-

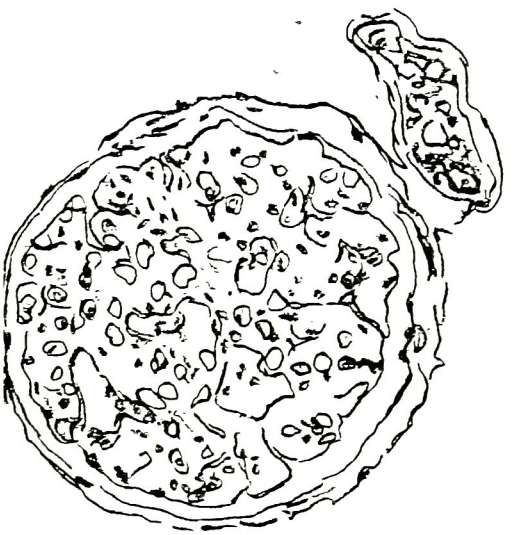


Figure 1

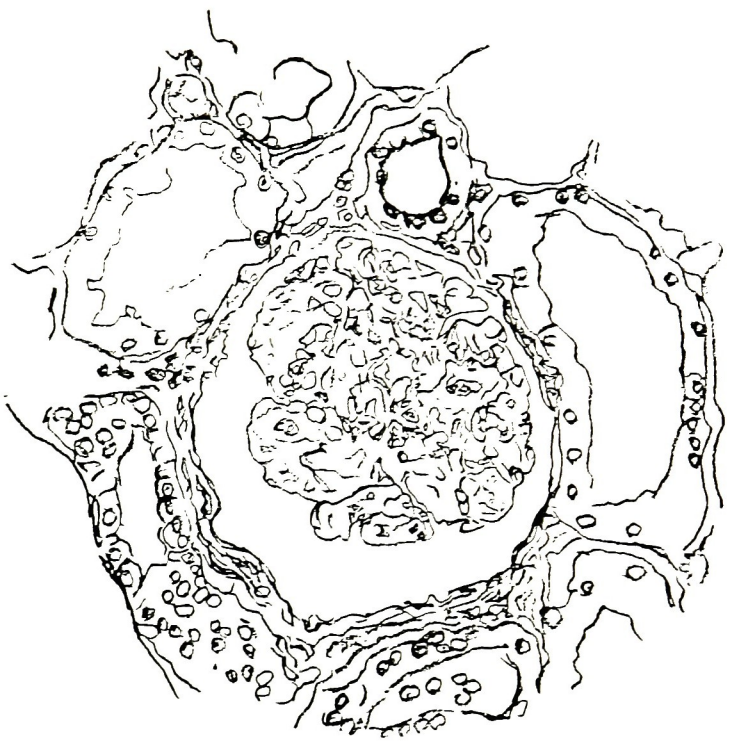


Figure 2

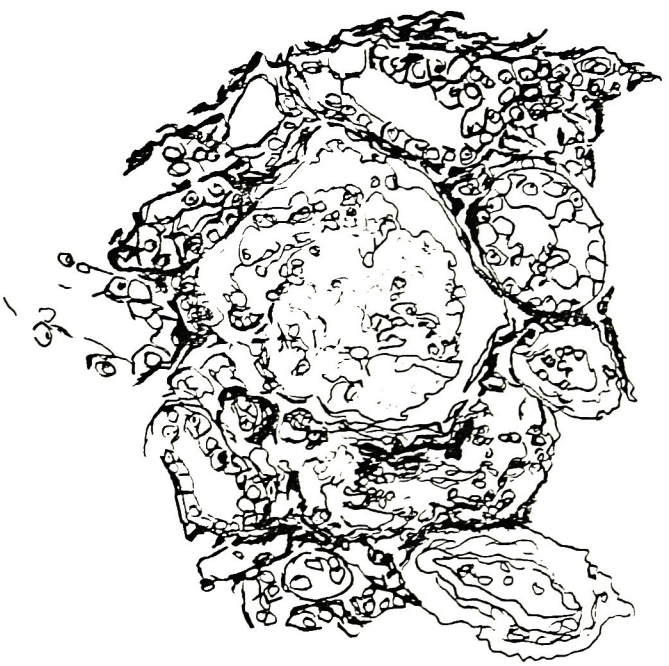


Figure 3

tion was used to delineate finer detail not clearly observable at 400x magnification.

The dimensionalizing was the most challenging part of the drawing process, whereas the camera lucida was the most trying in terms of patience, tediousness and size. Other artists' three-dimensional conceptualizations of kidney (glomeruli) and other tissues were referred to as a guide. However, they were all conceptualizations of healthy tissue and thus were more idealized in form as well as color. After I had done my illustrations I found a few conceptualizations of diseased tissue, again somewhat idealized, and not at all like my approach. My approach was to represent the diseased glomerulus as a cross section with depth (i.e. one point perspective or "tunnel vision"). I also chose to render only that which was discernible with the light microscope; there are other finer structures present in the glomerulus and surrounding tissues, discernible with the electron microscope. I refrained from illustrating such structures because they were not relevant to what I was illustrating, might cause confusion, and would not fit within the size dimensions I was working with. More importantly, I did not have access to an electron microscope nor to specimens prepared for the electron microscope, and as it was my wish to work from actual specimens in order to achieve a degree of originality as well as my goals of accuracy and aesthetic value, it would be ridiculous to attempt to include such structures in my illustrations.

The colors I used were based on the microscopic stains used for the specimens, namely, hematoxylin (purple to blue),

eosin (red), and PAS (Periodic Acid Schiff) (red-purple to magenta). The four specimen slides were each stained differently to emphasize different structures (see Appendix B). However, in order to establish continuity and to avoid confusion, I kept the color scheme (i.e., coloration for specific tissue types) the same throughout the series of illustrations, with a few minor variations.

The rendering procedure for each illustration was basically the same. Basic washes were laid down for each area and were gradually built up. Details such as granulation of nuclei and cytoplasm were stippled in colored ink, and cell boundaries were indicated with colored pencil. The laminated appearance of hyalinized basement membrane was achieved with a fine brush. Fine brushes were also used for subtle blending in small areas as well as crisping up of edges of airbrushed areas. A Paasche AB airbrush was used to apply watercolor in areas that required very fine gradations, particularly those areas of tubules, vessels, and capsules that showed depth. All of the airbrushing was done free-hand; no masks or friskets were used.

For each of the full-size illustrations I made an accompanying pen and ink line drawing with pertinent structures numbered along with a key indicating the appropriate labels. This was done to preserve the integrity of the illustrations from an aesthetic standpoint as well as a practical one. Labels on the actual illustrations would be distracting as well as confusing and would defeat the purpose of letting the illustrations stand on their own as art. Also, my exhibit audience

would not be as well versed in the subject matter as my intended audience (medical students). The pen and ink drawings were made from reduction on the Lucy of the actual illustrations. This was done as a time-saving device and to ensure accuracy and ease of recognition of the pertinent structures. The drawings were made on Bienfang layout paper with a rapidograph pen, and numbers and lettering were done with transfer type. The paper was then cut and dry-mounted on board to achieve a smooth surface, durable thickness, and uniformity in accord with the label cards provided by the Bevier Gallery.

Each of the full-size illustrations was checked for accuracy by Dr. Bernard Panner, pathologist at the University of Rochester (Strong Memorial Hospital). Each of the illustrations was double-matted (white outer mat with a 1/8" border of an inner mat in a color related to the particular illustration (pink or blue)). For the exhibit, the matted illustrations were put in silver aluminum frames which gave a clean, polished look to the pieces without being distracting, and in keeping with the nature of the illustrations. Each piece was hung with its accompanying pen and ink label drawing next to it in order to facilitate direct comparison.

Originally I had proposed to do five to six comparison pieces, each normal versus abnormal, of various affected parts of the body. However, due to the limited availability of specimens, the time factor involved, and the richness of material in what I was able to acquire, led me to decide to illustrate only the pathological conditions of the kidney. As it was, the illustrations became a series on the progressive deterio-

ration of the glomerulus and surrounding tissues due to the pathological manifestations of diabetes mellitus. Because of this progression, I felt that only one comparison piece (normal versus abnormal) was necessary. In fact the remainder of the illustrations are comparisons of various stages of abnormality with the initial illustration of the normal glomerulus.

Piece #1: "Normal and Diseased Renal Glomerulus"

This piece is a basic comparison between the appearance of normal renal glomerulus and the diseased diabetic glomerulus. The illustration of the normal glomerulus is an adaptation of a photomicrograph from Bailey's Textbook of Histology, as I did not have access to slides of normal kidney tissue. By adaptation I mean that I used the basic contours of the glomerulus in the photomicrograph and then dimensionalized it with my rendering (essentially the same technique used with the actual specimen slides). I also rendered the normal glomerulus in carbon dust (black and white) in order to set it off from the abnormal tissues depicted in the comparison diseased glomerulus as well as in the remainder of the illustrations in the series. The normal glomerulus has wide, open capillaries, a normal mesangium with the appropriate number of pericytes and mesangial cells, and a healthy adjacent distal tubule. The diseased glomerulus has reduced and blocked capillaries, proliferation of mesangial cells and hyalinization of the mesangium, as well as increased basement membrane material, and an adjacent atrophied tubule.

Piece #2:"Diffuse Glomerulosclerosis"

This piece shows a typical example of a glomerulus with diffuse glomerulosclerosis, as well as surrounding tissues which do not yet appear to be very diseased (Bowman's capsule, proximal and distal convoluted tubules).

Piece #3:"Diffuse Glomerulosclerosis and Arteriosclerosis

This piece shows another example of a glomerulus with diffuse glomerulosclerosis, however, this time with surrounding tissues showing more evidence of disease, particularly the tubules and the arterioles. This specimen was reticulin-stained in order to show the presence of reticular fibers in the basement membranes. Although the fibers appear black to an intense purple in less dense areas I chose to render them in purple for the purpose of clarity and color relationships.

Piece #4:"Arteriosclerosis"

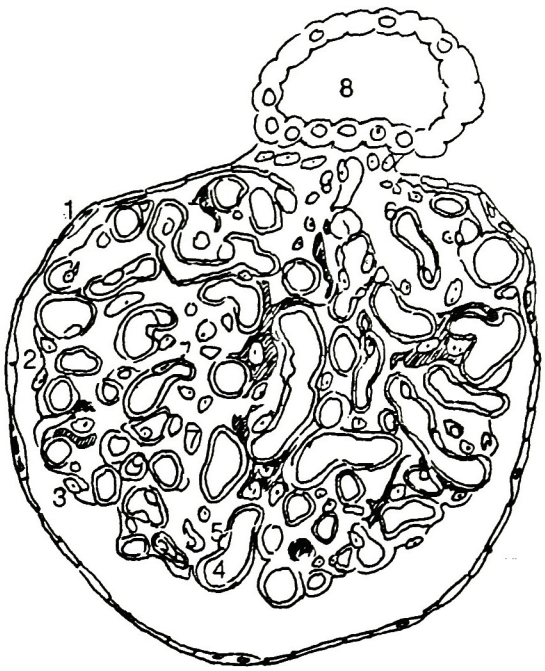
This piece focuses on a diseased arteriole with thicked walls and a hyaline deposit, as well as progressively diseased (atrophied) tubules, and extremely thickened base ment membranes.

Piece #5:"Nodular Glomerulosclerosis"

This piece shows two examples of glomeruli with nodular sclerotic lesions. Also present is diifuse glomerulosclerosis which gives credence to the theory that the diffuse type eventually gives rise to the nodular type. It was pointed out to me by Dr. Panner that the second glomerulus is a rather spectacular example of a nodular lesion, and not a typical one.

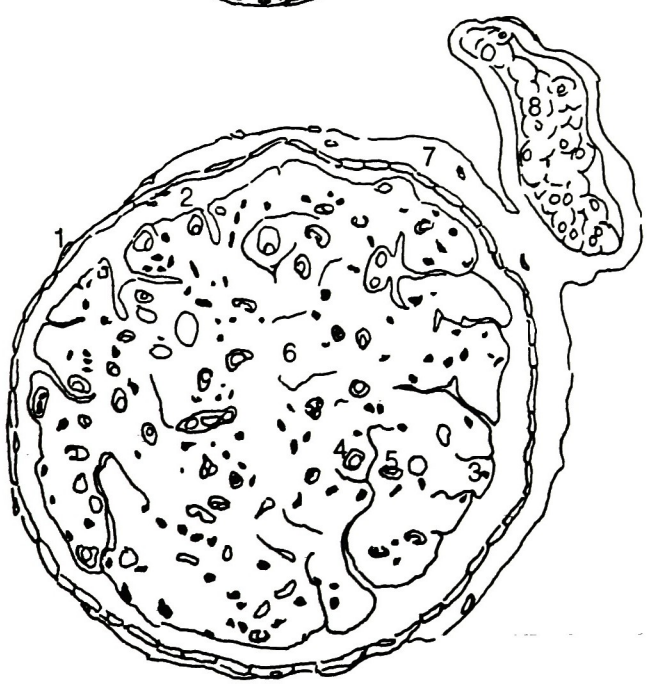
Piece #6:"Severe Glomerulosclerosis (Obliteration of Glomerulus and Tubules"

This piece is an example of the advanced stage of glomerular sclerosis, with obliterated (hyalinized) glomerulus and tubules, extremely thickened basement membranes, and the presence of chronic inflammatory cells.



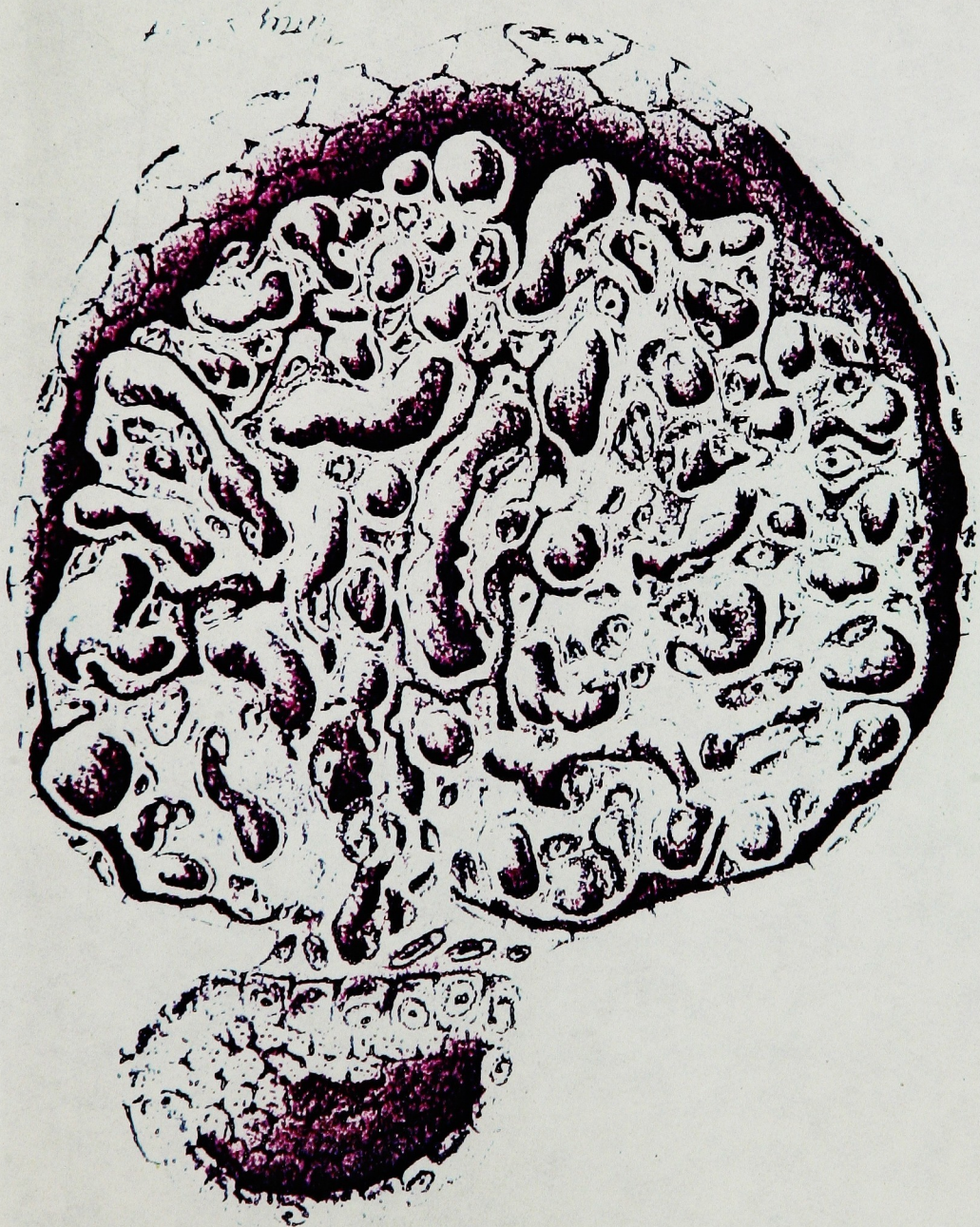
NORMAL RENAL GLOMERULUS

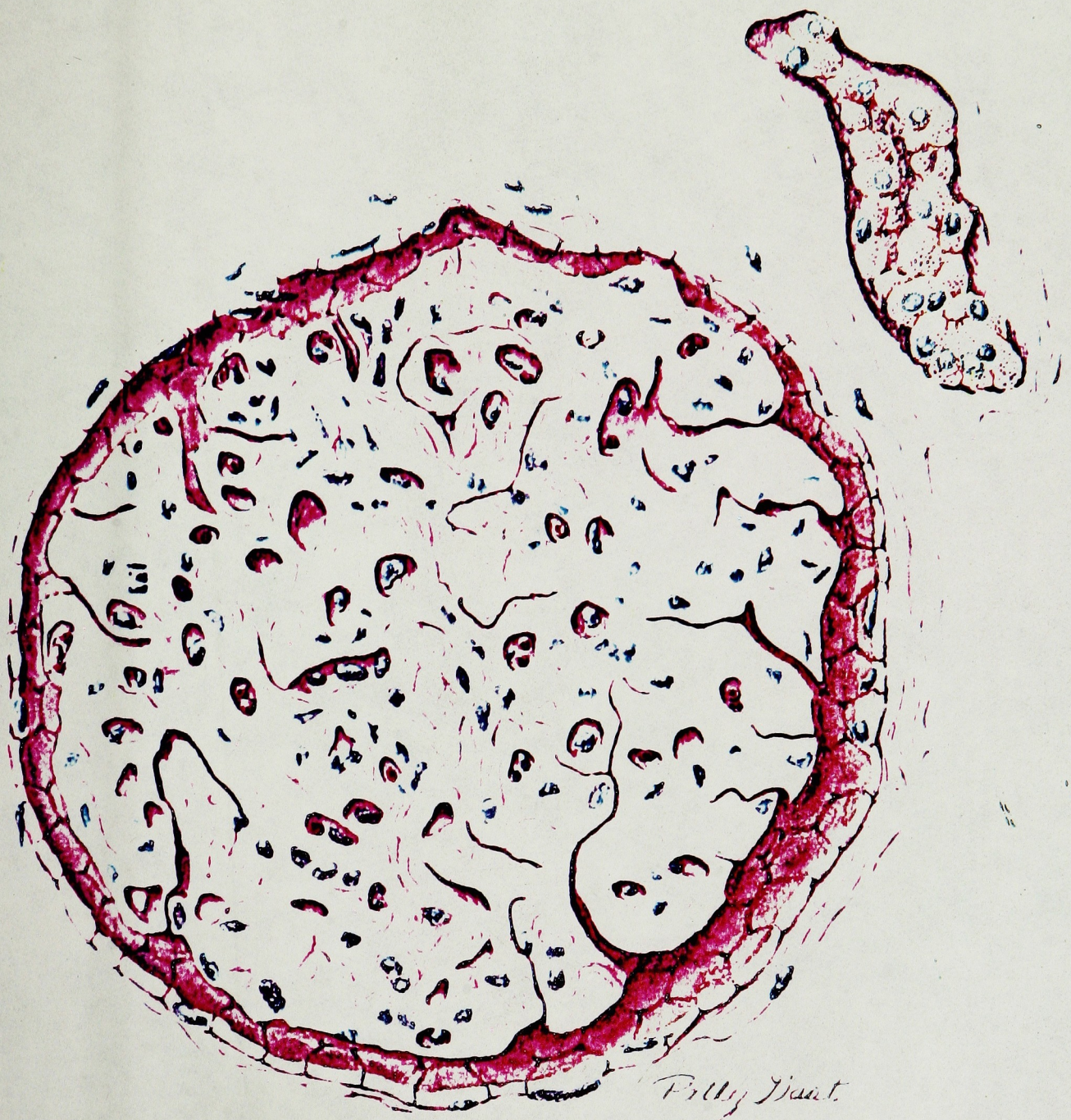
1 Parietal Epithelium
2 Urinary Space
3 Podocyte
4 Capillary
5 Endothelial Cell
6 Capillary Basement Membrane
7 Mesangial Cell
8 Distal Convoluted Tubule



DISEASED GLOMERULUS

1 Parietal Epithelium
2 Urinary Space
3 Podocyte
4 Capillary
5 Endothelial Cell
6 Sclerotic (Hyalinized) Tissue
7 Thickened Basement Membrane
8 Atrophied Distal Tubule

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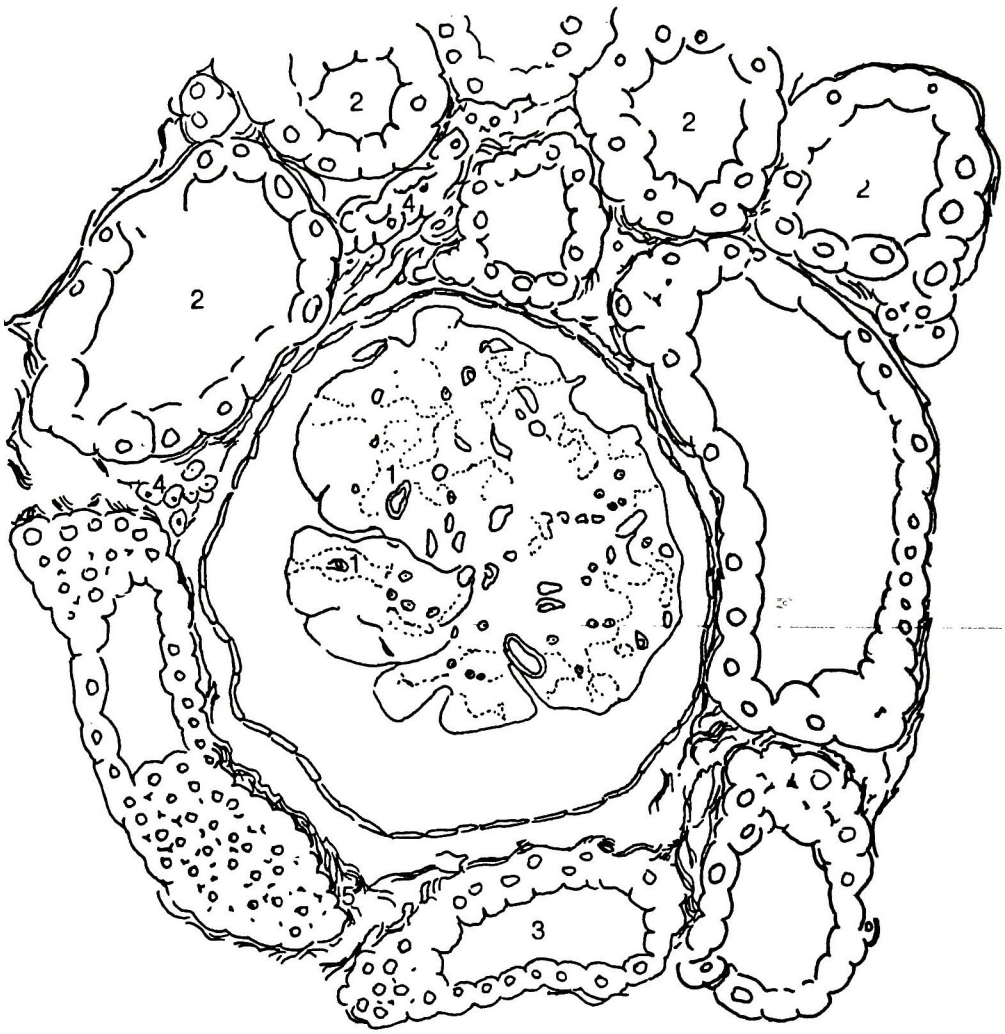


DIFFUSE GLOMERULOSCLEROSIS

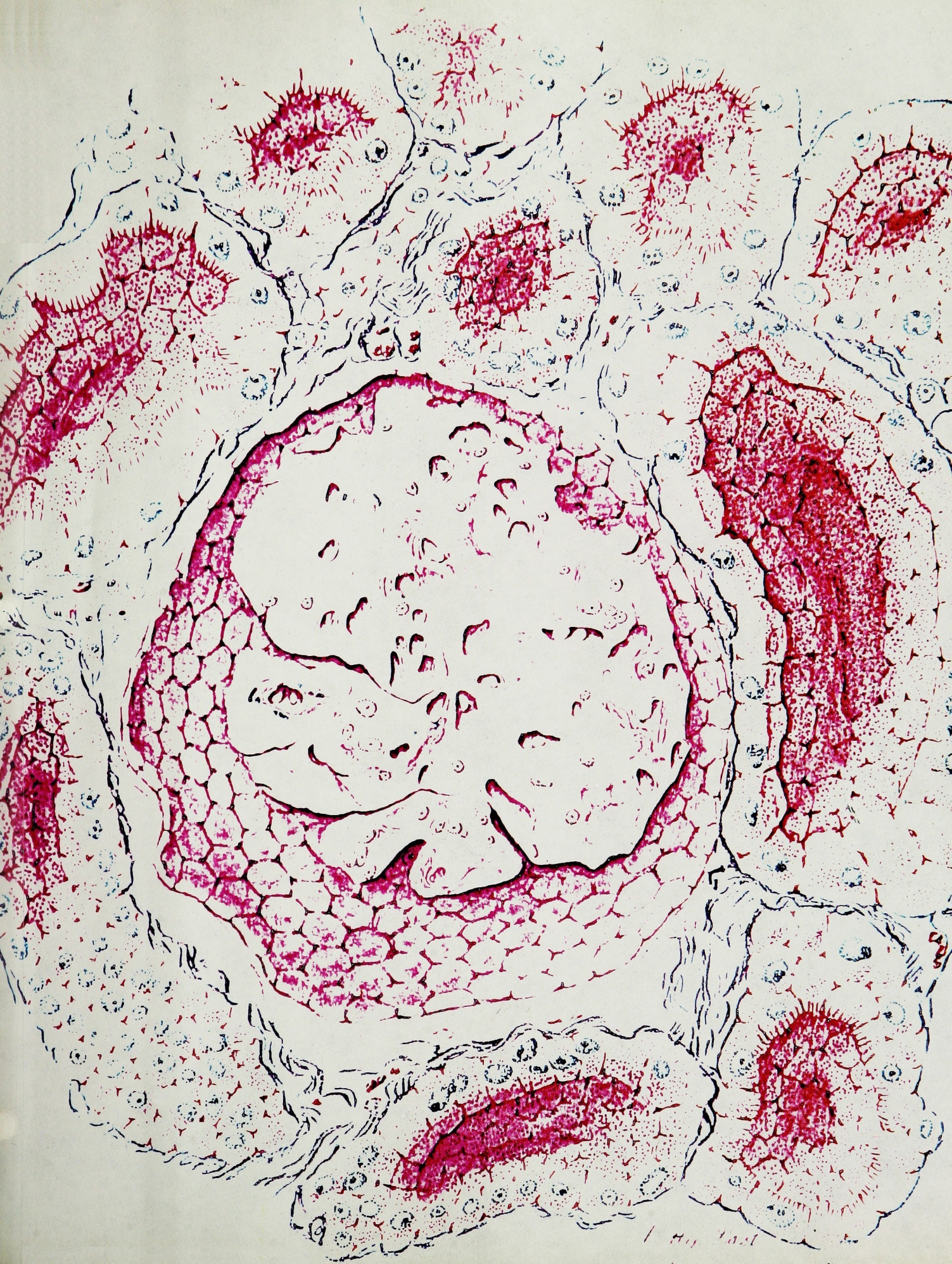
1 Diffuse Sclerotic (Hyalinized) Tissue

2 Proximal Convoluted Tubules

3 Distal Convoluted Tubule

4 Atrophied Tubules

5 Thickened Basement Membranes (Reticulin-Stained)



DIFFUSE GLOMERULOSCLEROSIS AND ARTERIOSCLEROSIS

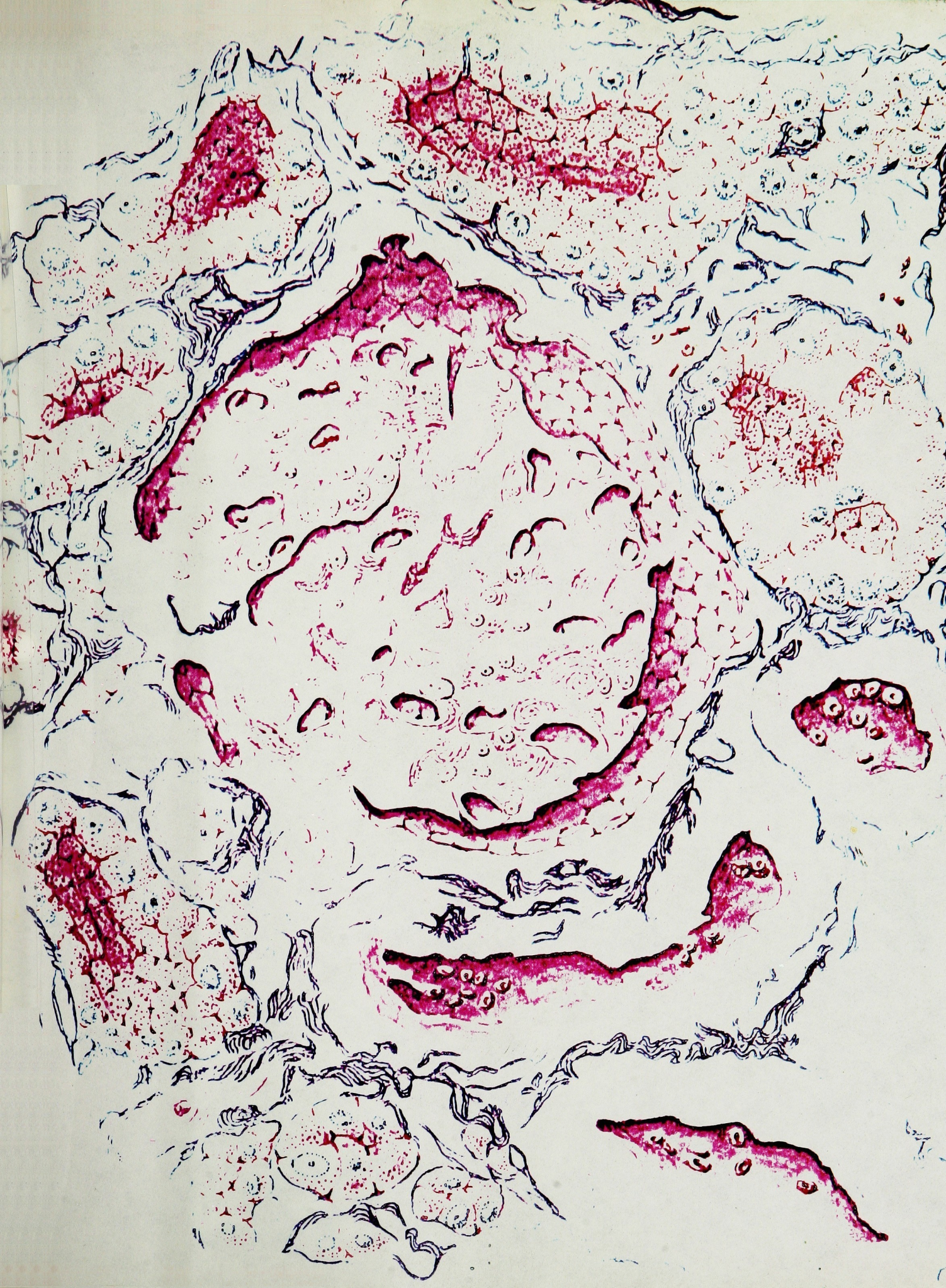
1 Diffuse Sclerotic (Hyalinized) Tissue

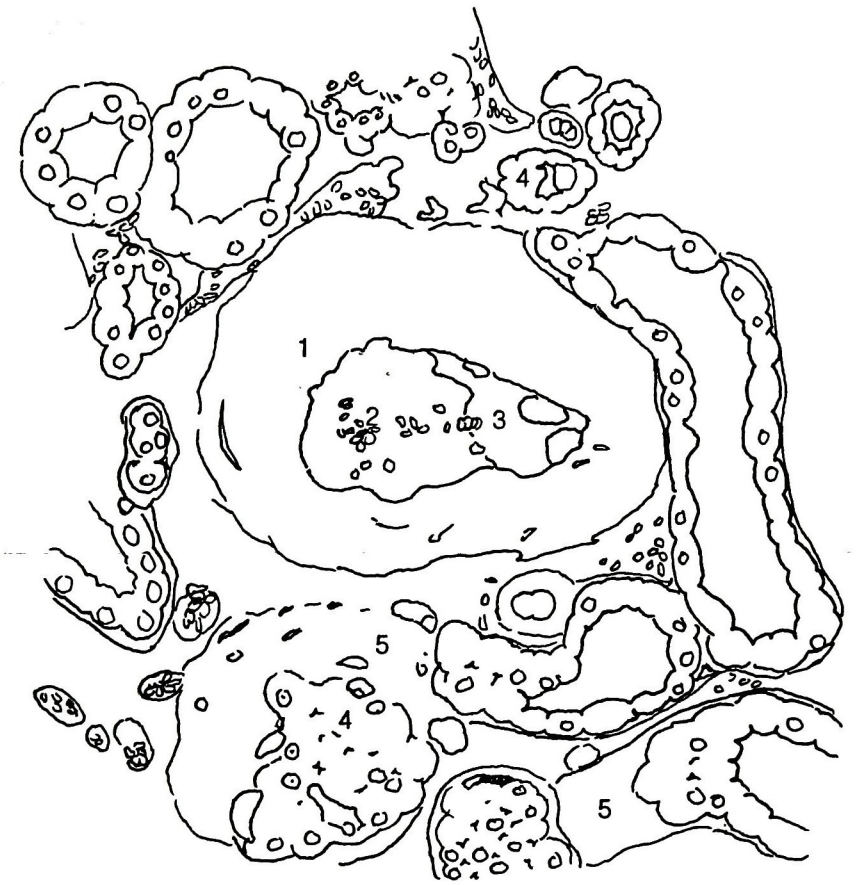
2 Sclerotic Arteriole

3 Hyaline Deposit

4 Atrophied Proximal Convoluted Tubule

5 Thickened Basement Membranes (Reticulin-Stained)





ARTERIOSCLEROSIS

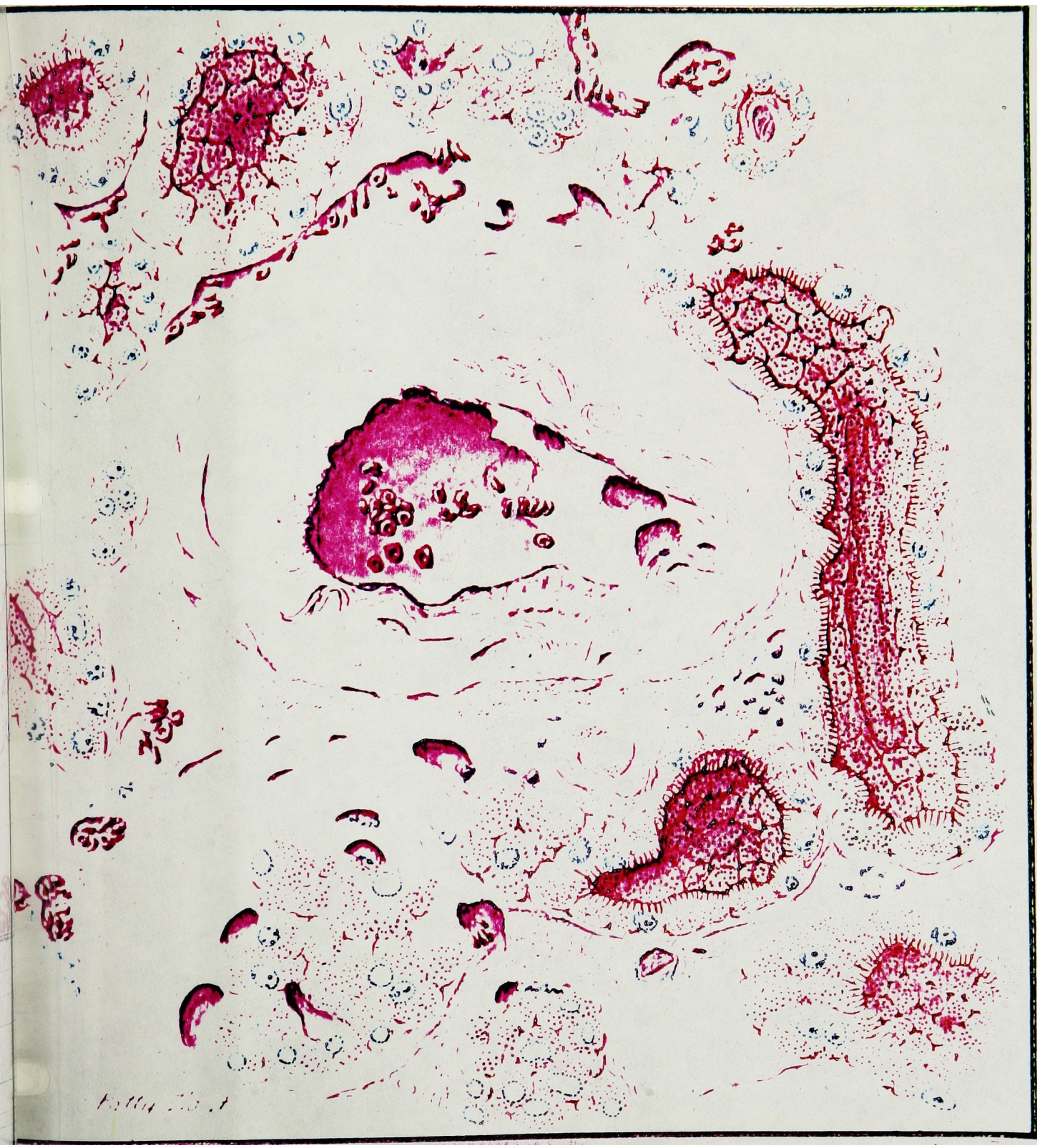
1 Sclerotic Arteriole

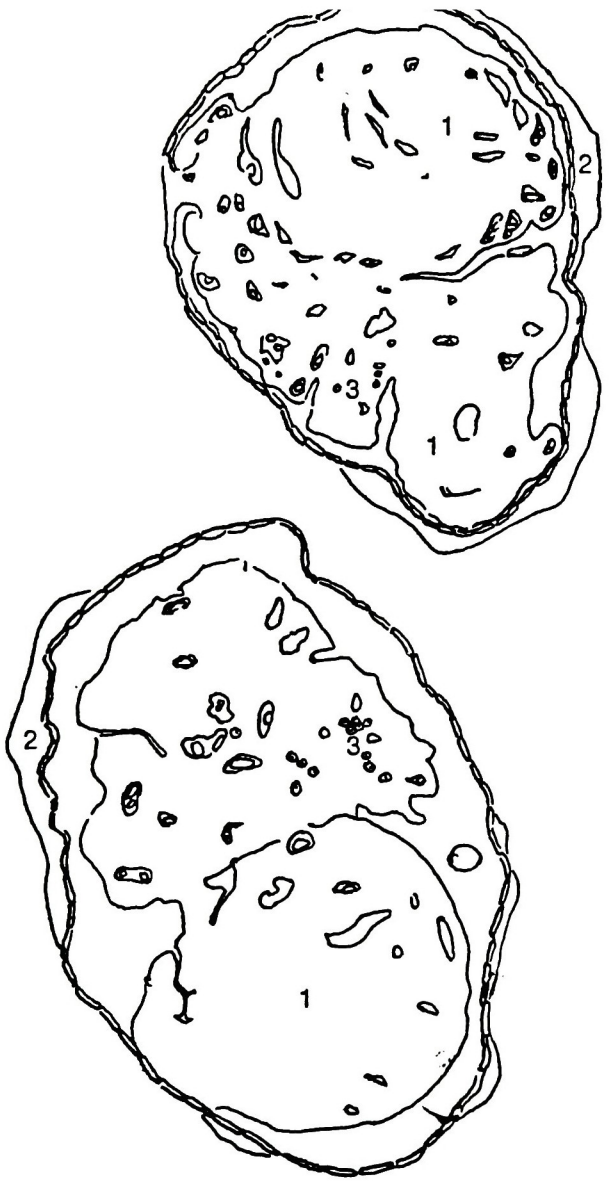
2 Red Blood Cells

3 Hyaline Deposit

4 Atrophied Tubules

5 Thickened Basement Membranes



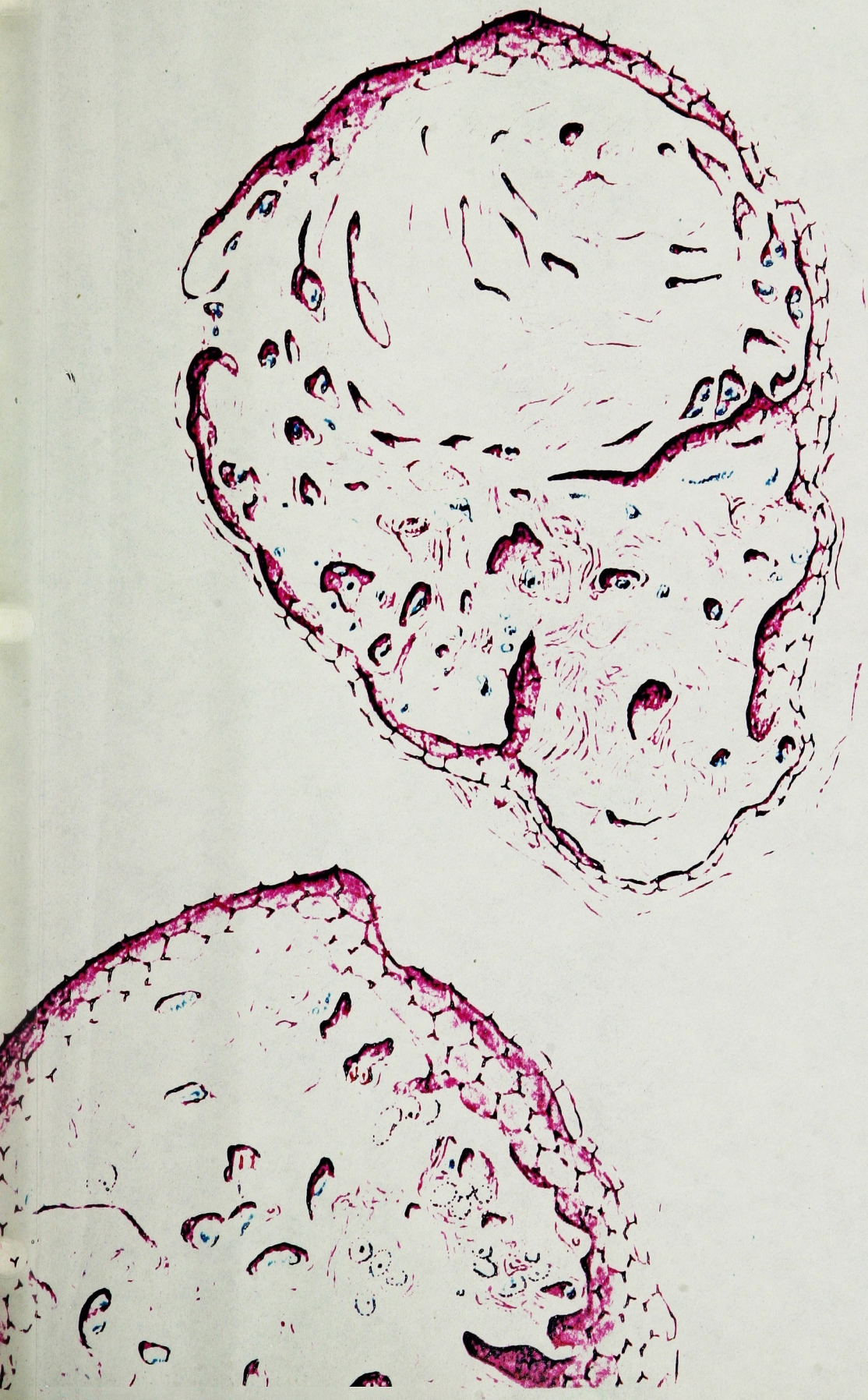


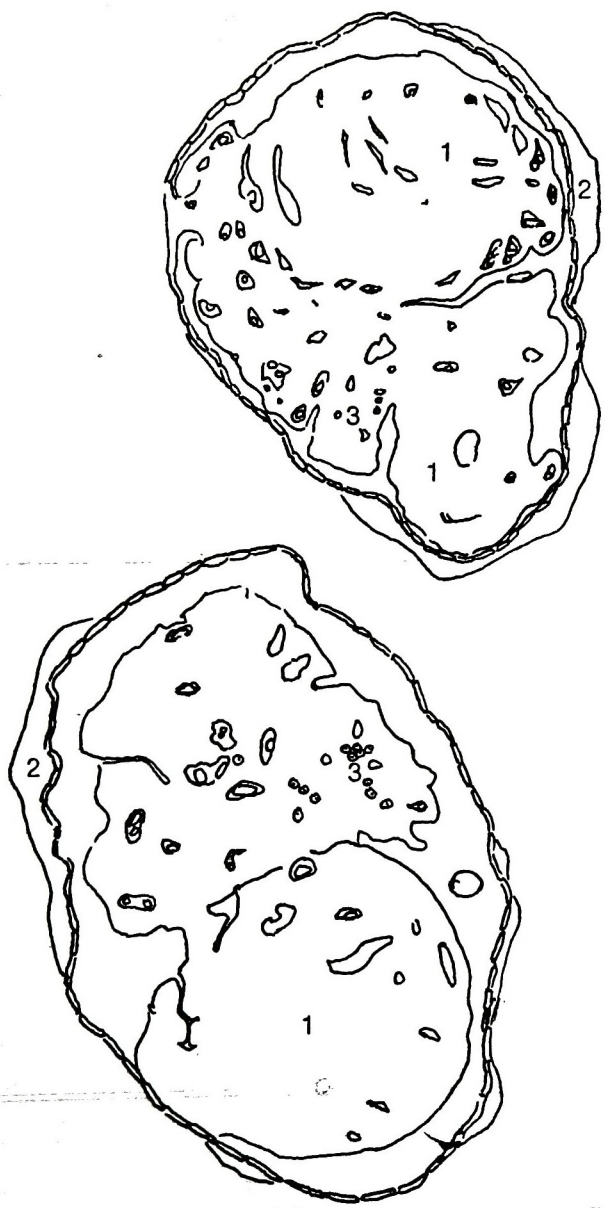
NODULAR GLOMERULOSCLEROSIS

1 Sclerotic Nodule

2 Thickened Basement Membranes

3 Diffuse Glomerulosclerosis



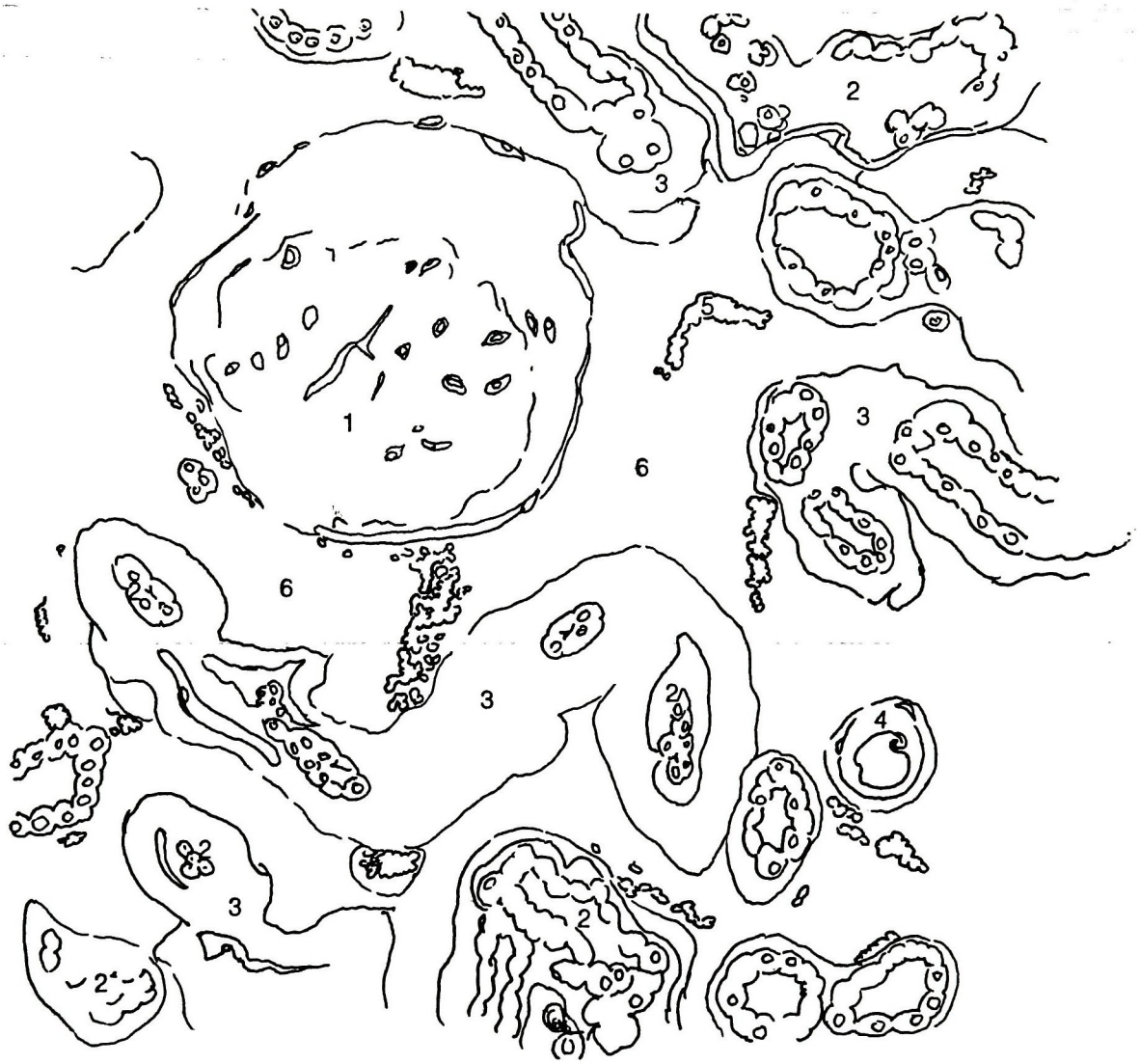


NODULAR GLOMERULOSCLEROSIS

1 Sclerotic Nodule

2 Thickened Basement Membranes

3 Diffuse Glomerulosclerosis



SEVERE GLOMERULOSCLEROSIS
(OBLITERATED GLOMERULUS AND TUBULES)

1 Obliterated (Hyalinized) Glomerulus

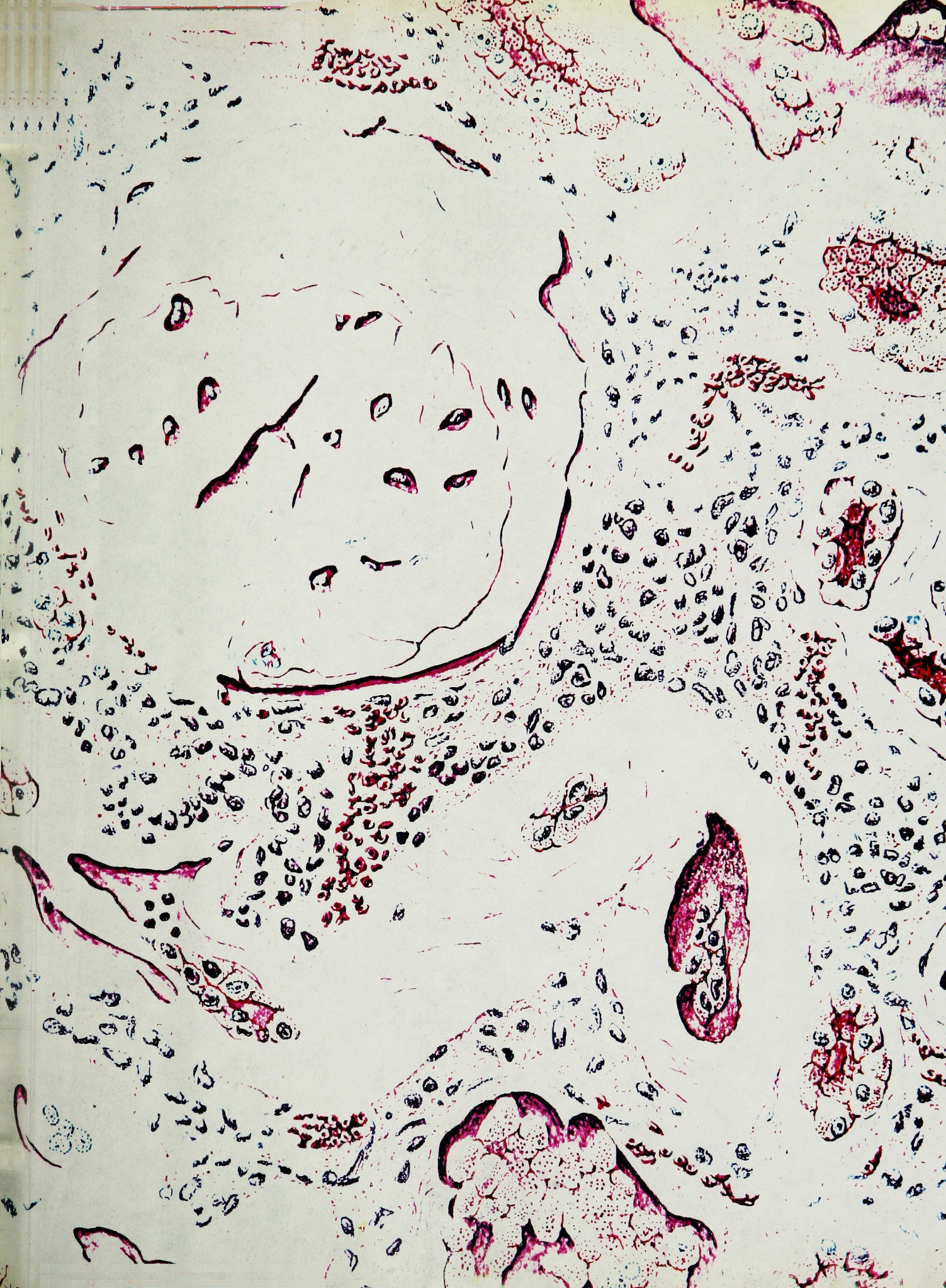
2 Obliterated (Atrophied) Tubules

3 Thickened (Hyalinized) Basement Membranes

4 Sclerotic Blood Vessel

5 Red Blood Cells

6 Chronic Inflammatory Cells



CONCLUSION

I feel that my thesis work has fulfilled its purpose of the development and production of a series of illustrations demonstrating various pathological conditions manifested by diabetes mellitus on the microscopic level, and intended for use as educational materials for medical students. In addition, I also feel that my goals of accuracy and aesthetic value were achieved in the works. I found this thesis work particularly challenging to my creative skills and technical abilities as a medical artist, especially in the conceptualizing (dimensionalizing) of the microscopic sections.

I have also learned a tremendous amount about the disease diabetes mellitus and its scientific and social implications (much of which could not be covered in this paper). In the midst of my research and learning I made the wonderful discovery that there is an actual need for the kind of work I did in this thesis as well as the pertinence of the area (kidney) I chose to illustrate to the most current research being conducted for diabetes mellitus. In other words there is a great need for education about diabetes, particularly its pathological aspects, among the medical profession and the health care community, in order to develop methods of prevention or possible cures. It is hoped that this thesis work is but a small step in that direction.

APPENDIX A

Microscopic Structure and Function of the Kidney

The kidney, as part of the excretory system, functions to eliminate toxic materials (metabolytes), and to maintain the fluid (water) and salt (ion) balance of the body. The glandular tissue of the kidney consists of closely packed uriniferous tubules, the functional units of the kidney, between which are blood vessels and some interstitial connective tissue.

Each uriniferous tubule consists of two parts: the nephron which is responsible for the formation of urine, and the collecting tubule which serves as the excretory duct carrying urine to the renal pelvis (from which it goes to the ureter and eventually the bladder). The nephron begins as a cup-shaped expansion (Bowman's capsule) which encloses a tuft of capillaries (the glomerulus). The glomerulus consists of a number of capillary loops connecting an afferent arteriole with an efferent arteriole (see Figure A-1).[1] Bowman's capsule is double-walled with an outer (parietal) layer consisting of squamous epithelial cells, and an inner (visceral) layer of podocytes in intimate contact with the glomerular capillaries,[2] and the area between the two walls forms the uriniferous space where plasma ultrafiltrate from the blood passing through the

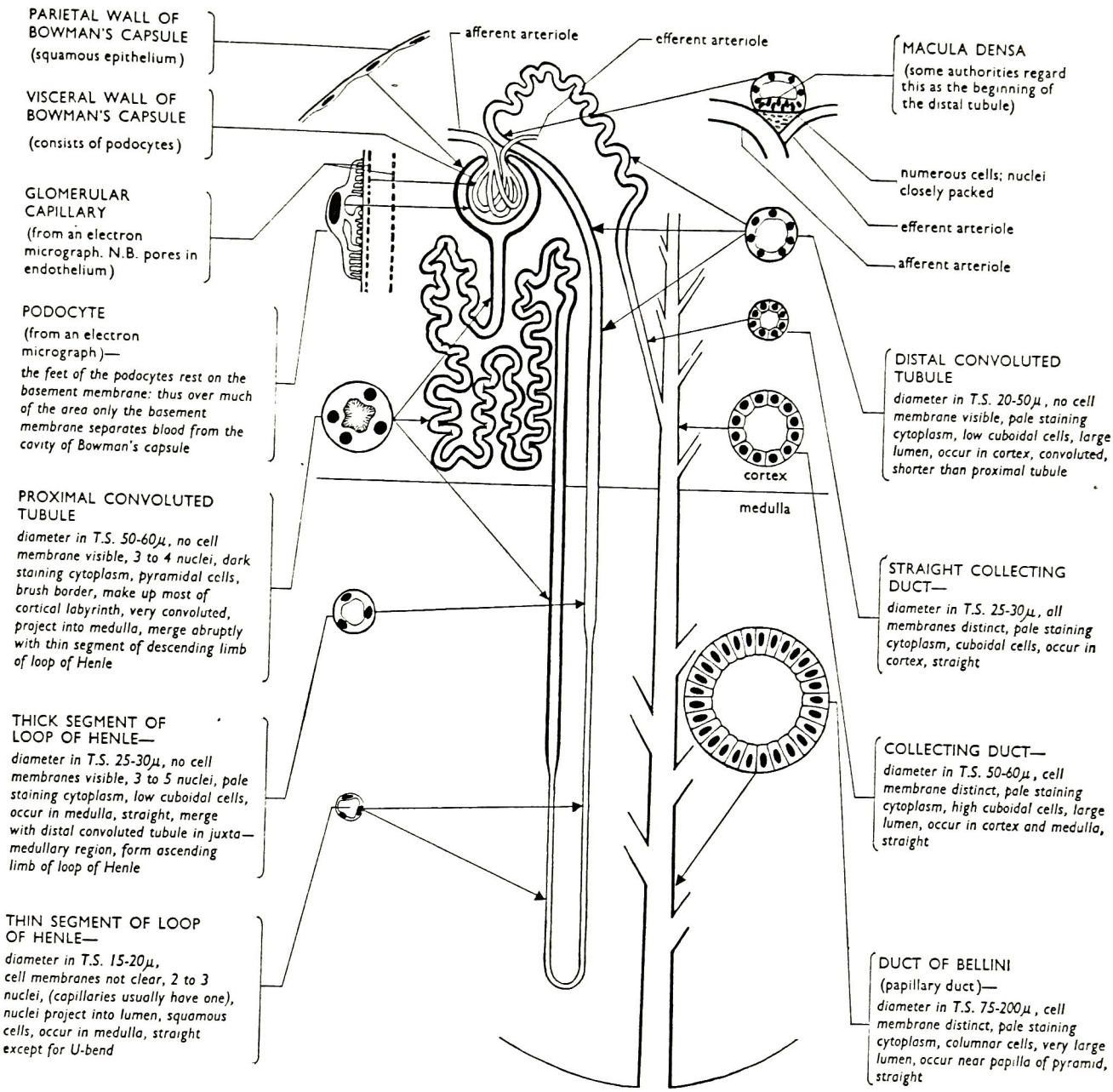


DIAGRAM OF NEPHRON

A nephron consists of Bowman's capsule, glomerulus, proximal convoluted tubule, loop of Henle and distal convoluted tubule.

[From An Advanced Atlas of Histology]

Figure A-1

glomerular capillaries is collected. This space opens into the proximal convoluted tubule which consists of pyramidal cells with a brush border, and in which glucose, amino acids, and some sodium, chloride, and bicarbonate ions are resorbed together with water and passed to peritubular capillaries.[3] This tubule then continues as the straight proximal tubule (thick proximal segment of Henle's loop), the thin segment of Henle's loop, the thick distal segment of Henle's loop (ascending), and finally the distal convoluted tubule which empties into the initial collecting tubule. The tubule system of the nephron sets up a series of concentration gradients which serve to facilitate the resorption of water, the balance of ions, and the regulation of blood pH.

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[1]Deep within the area betwee the capillary loops are mesangial cells that are enveloped by a glycoprotein layer that is fused with the basal lamina (basement membrane) of the endothelial cells of the capillary loops, and they have a role in the removal of material that piles up at the basement membrane during filtration. Wilfred M. Copenhaver, Ph.D., Douglas E. Kelly, Ph.D., and Richard L. Wood, Ph.D., Bailey's Textbook of Histology, 17th ed.,(Baltimore: The Williams and Wilkins Company, 1978), pp.579-80.

[2]The podocytes and the endothelial cells of the glomerular capillaries are separated only by a thin basal lamina.

[3]Thomas S. Leeson, M.D., Ph.D., and C. Roland Leeson, M.D., Ph.D., A Brief Atlas of Histology, (Philadelphia: W.B. Saunders Company, 1979), p.194.

APPENDIX B

The Compound Light Microscope and Microscopic Stains

The compound light microscope is a compound magnifying system with magnification taking place in two stages: First, the objective lens forms an intermediate (primary) image of the object under view. The eyepiece (ocular) forms the secondary, further enlarged image. (See Figure B-1).

"The observer looks at the first, or primary, image with a lens that produces an enlarged secondary image, called a virtual image "[1] which is perceived by the eye. The total amount of image enlargement, or magnification produced is found by multiplying the magnifying power of the objective by that of the eyepiece.

Specimens to be examined through a microscope are mounted on a glass microscope slide (3" x 1" x 1mm) and covered with a cover glass. The specimen is usually colored by means of various stains to produce contrast and emphasize various structures. Two of the most widely used stains are hematoxylin (purple to blue in color and indicates structures such as cell nuclei depending upon their biochemical composition) and eosin (red in color and an acid dye(cytoplasm)). These stains are often used in combimation. PAS (Periodic Acid Schiff) a reddish purple, stains structures containing carbohy-

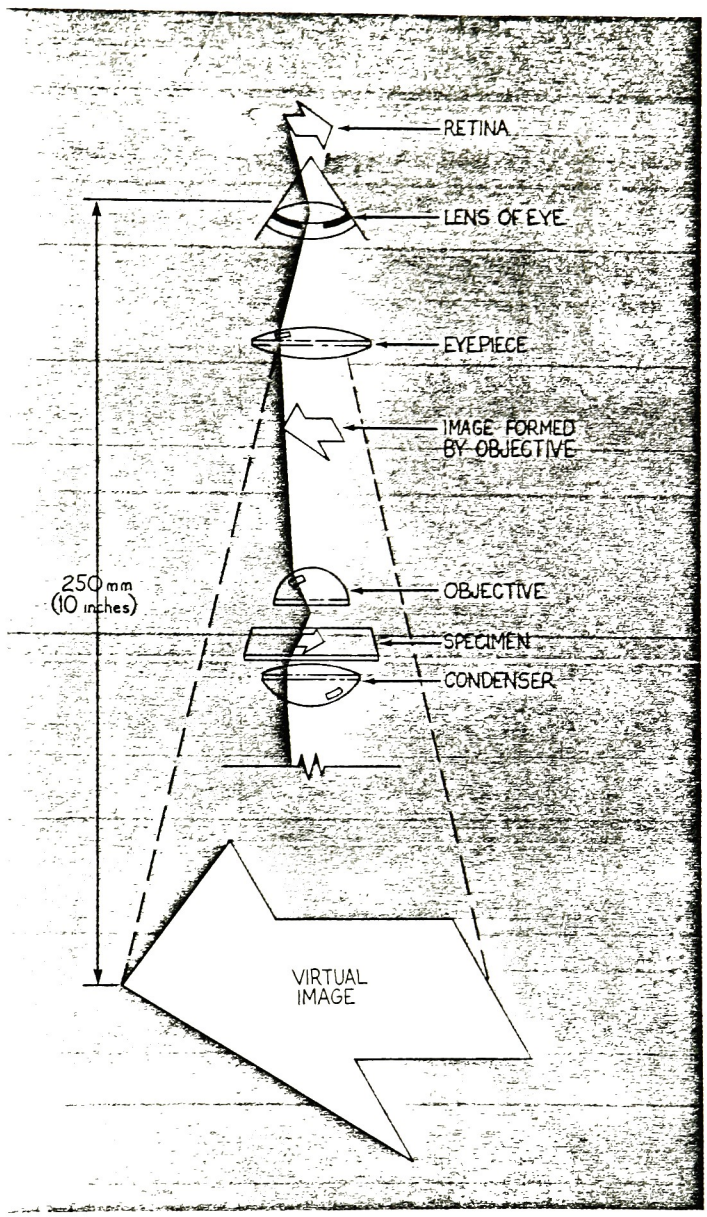

Fig. 1-2
COMPOUND MAGNIFIER–
In the compound microscope, the intermediate image formed by the objective is enlarged by the eyepiece.

Figure B-1

[From Photography Through the Microscope]

drates and polysaccharides. Reticulin stain is specific for reticular fibers which are small branching fibers forming a net-like supporting framework or reticulum. Reticular fibers also stain with PAS because they contain carbohydrates in their surface coat.

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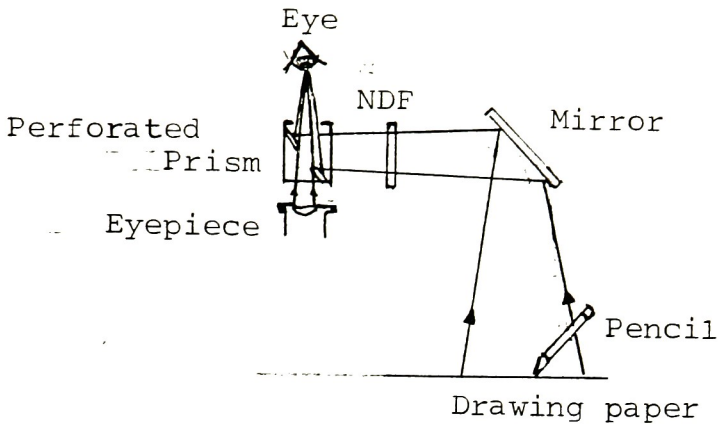
[1] Photography Through the Microscope, Eastman Kodak Company, 1980, pp.3-4.

APPENDIX C

The Camera Lucida

The camera lucida is an optical device enabling the projection of the drawing paper into the microscopic image. It was originally devised by Ernst Abbe and was based on the total reflection at a prism interface with a central opening in combination with a mirror at some distance from the microscope tube (see Figure C-1). In between the mirror and the prism is a neutral density filter which balances the brightness of the microscopic image with that of the drawing paper, otherwise one image would dominate over the other. When a correct balance has been reached, lines drawn with a pencil or other drawing implement become clearly visible in the microscopic image. In a later development of this device a semi-transparent prism is used which produces a better quality image.[1,2]

The set-up used is illustrated in Figure C-2.[3] The mirror and prism are included in a cylindrical bar attached to the microscope tube above the objective lens and below the eyepiece. In my case the set-up included a separate light control box with a meter and control knob, which regulated the amount of light (brightness) of the microscopic image; and a high-intensity desk lamp which determined the brightness of the drawing paper. By adjusting the light control knob and by moving the desk lamp either closer (brighter) or further away (less bright), the brightness of the two



NDF = Neutral Density Filter

Figure C-1
After diagram in Light Microscopic Techniques in Biology and Medicine, p.242.

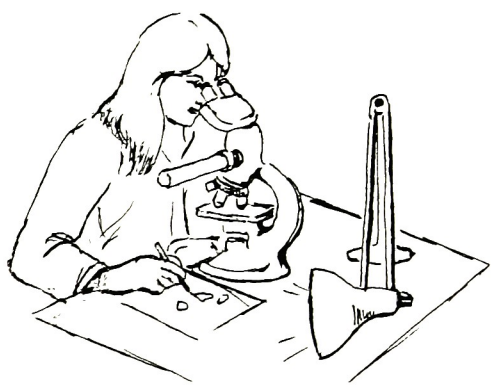


Figure C-2

ness of the drawing paper. By adjusting the light control knob and by moving the desk lamp either closer (brighter) or farther away (less bright), the brightness of the two images was equalized.

A separate light control was necessary for the microscopic image because successive higher magnifications require greater intensity of light. Also, if I wanted to observe just the microscopic image I could turn up the brightness of that image and override the drawing paper image or I could turn off the desk lamp and achieve the same effect.

A piece of drawing paper was taped down (in order to avoid shifting while drawing) next to the microscope. Once the desired microscopic image was found and brought into focus at the desired magnification, and the light intensity was equalized, a simple outline drawing was done tracing (following) the microscopic image.

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[1]J. James, Light Microscopic Techniques in Biology and Medicine, (Netherlands: Martinus Nijhoff Medical Division, 1976), pp.241-3.

[2]George Herbert Needham, M.S., F.R.M.S., The Practical Use of the Microscope: Including Photomicrography, (Springfield, Illinois: Charles C. Thomas, 1958), p.401.

[3]I was instructed in the use of the camera lucida by Dr. Albert Ritterson of the Department of Parasitology, School of Medicine and Dentistry at the University of Rochester, who graciously allowed me to use his set-up once a week for three to four hours.

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