TYPE A BEHAVIOR AND CENTRAL SEROUS CHORIORETINOPATHY*

BY *Lawrence A. Yannuzzi,* MD

INTRODUCTION

SOME OF THE CLINICAL FEATURES OF IDIOPATHIC DETACHMENT OF THE MACULA, or central serous chorioretinopathy (CSC), have been known since 1866, when von Graefe[1] originally described the disorder that he named "relapsing central luetic retinitis." For more than a century thereafter, the syndrome has been referred to by a series of descriptive terms thought to be related to its pathogenesis as well as its clinical and fluorescein angiographic manifestations.[2-73] As early as 1927, personality traits and psychic disturbances were implicated as contributing or precipitating factors in the development of the disorder.[7] Several studies alluded to psychological reactions such as anxiety, or environmental factors such as stress, as coincidental or causative features of CSC.[16,19,20,28,30,32,34-41,43,58] No study to date has attempted to examine in a quantitative and comparative fashion the specific behavioral patterns alleged to be associated with CSC.

The type A behavior pattern is known to be an established risk factor for coronary heart disease (CDH).[74-105] The major components of this multidimensional personality construct are (1) a competitive drive, (2) a sense of urgency, (3) an aggressive nature, and (4) a hostile temperament. A person exhibiting a simple preponderance of these personality traits is classified as type A, whereas a person who does not is categorized as either indeterminate or type B.

The purpose of this study was as follows:

- To determine the frequency of type A behavior pattern in patients with CSC compared with control groups.
- To formulate a concept that relates this type of behavior pattern to CSC as one risk factor in its pathogenesis.
- To establish specific goals for future research, including the prediction of patients prone to development of CSC and the determination of practical approaches to pharmacologic and psychologic treatment modalities.

*From the LuEsther T. Mertz Retinal Research Laboratory of the Manhattan Eye, Ear and Throat Hospital, New York and The Edward S. Harkness Eye Institute of the Columbia University Medical Center, New York.

TR. AM. OPHTH. SOC. vol. LXXXIV, 1986

METHODOLOGY

PATIENT SELECTION

The patients in this study were selected from the private practice of the author and from the retinal and general clinics of his associated teaching hospital. The spectrum of patients derived from the combined private practice and hospital service sources offered the opportunity to recruit persons of varied racial and socioeconomic status.

All patients fulfilled a strict definition of CSC, notably an idiopathic neurosensory detachment of the macula associated with focal or multifocal, pinpoint leaks at the level of the retinal pigment epithelium (RPE) evident on fluorescein angiography. Patients with macular detachment were not included in the study if they met one or more of the following exclusionary criteria:

- Age greater than 50 years
- Macular disease such as age or drusen-related degeneration, angioid streaks, choroidal ruptures, the presumed ocular histoplasmosis syndrome, pathologic myopia, or inflammatory uveal-vitreal disorders such as Harada's disease
- Neurosensory macular detachment associated with clinical or fluorescein angiographic manifestations indicative of subretinal neovascularization, including subretinal hemorrhage, lipid exudation, cystoid macular edema, or "lacy," vascular, subretinal leakage
- Serous detachment of the RPE greater than ½ disc diameter in size.

A consecutive series of newly diagnosed patients with CSC was compared with two independent control groups chosen from the same patient population. From the population of new patients referred privately to the author or seen at the clinics of his associated teaching hospital, patients with painless, reduced central vision and other chorioretinal diseases (group I), or nonchorioretinal ocular conditions (group II) were studied. The qualifying visual acuity reduction ranged from *less* than 20/20 to *better* than 20/200. Patients with acuity reduction due solely to refractive errors were included in control group II. The methodology for selecting matched controls for this study complied with standard epidemiologic procedures, matching for age, sex, race, and patient source (private office or hospital service). All patients were recruited between January 1982 and December 1983.

PATIENT EXAMINATION

Ocular

All patients were given the standard ophthalmologic examination for a

new patient, including an ophthalmic and medical history, a measurement of the uncorrected and corrected Snellen visual acuity, a refraction, Goldmann applanation tonometry, a slit-lamp biomicroscopic examination, and a peripheral retinal examination with indirect ophthalmoscopy. Patients with CSC or other chorioretinal diseases (control group I) had a slit-lamp biomicroscopic examination of the macula with a contact lens (Goldmann) and a central visual field examination. Most of these patients also had an examination of the peripheral retina with indirect ophthalmoscopy and scleral depression. A fluorescein angiogram was performed in each patient with CSC and in any patient in control group I exhibiting an exudative detachment of the macula or other indication for the procedure.

Behavior Assessment

The most consistently effective procedure for the assessment of the type A behavior pattern is the so-called structured interview,[104,105] which consists of a set of 25 to 30 questions and observations. The content of the response by the person interviewed is secondary to the manner in which the person responds. The structured interview is consequently a subjective, global assessment of the presence or absence of type A behavior pattern and its specific components as judged by trained personnel.

Several questionnaires have been developed in an attempt to increase the objectivity and efficiency of the structured interview.[86,95,100-103,106,107] These questionnaires have been found to have a highly significant correlation with the structured interview assessment. In addition, they maximize convenience, minimize cost, and enhance standardization. The best and most widely used questionnaire for assessment, quantification, and simplification of the type A behavior pattern is the Jenkins Activity Survey (JAS), the method used in this study.[100-103,108]

Nearly 50,000 people have been administered the JAS. It was originally developed in conjunction with the Western Collaborative Group Study of 2195 men between the ages of 39 and 52. The JAS questions have been established from algorithms developed by cross-validations against assessments based on the structured interview. The JAS scores have been demonstrated to have a high level of agreement with the structured interview, good reliability in test-retest situations, and predictive value for the incidence of CHD on a prospective basis.[100-103] The JAS and the structured interview agree on the determination of type A behavior pattern at the rate of 73%. For JAS scores over 10 and under 10, the agreement was 91% and 89%, respectively.[106,107]

This self-administered, multiple-choice questionnaire was given to each patient in the CSC and control groups. The 52 weighted questions

were scored to yield a composite type A scale and an assessment of three subscales derived from factor analysis: factor S (speed and impatience), factor J (job involvement), and factor H (hard-driving competitiveness). Factor analysis was incorporated into the JAS to ascertain whether the multifaceted type A behavior pattern is a single syndrome or a loose aggregation of traits or subsyndromes.[103] The three factors were derived by orthogonal rotations of the principal axes factor analysis. This procedure develops factors that are uncorrelated and hence conceptually independent. The model also insures that any person possessing one factor has no greater chance of having any of the other two factors.[107] Thus, the three-factor analytically derived dimensions are relatively independent of the components of the type A behavior pattern. Factor S is defined by 21 questions (Nos. 1, 2, 6-10, 12-14, 17, 18, 22, 23, 25, 26, 30, 32, 35, 39, 44); factor J by 24 questions (Nos. 3, 4, 10, 11, 17, 21, 24, 25, 30-34, 36-38, 41, 44, 47-52); and factor H by 20 questions (Nos. 2, 3, 7, 15-20, 22, 24, 26, 27, 29, 31, 42, 43, 45, 46, 51).[108]

Normative data were based on the raw scores of these persons. The mean score was transformed to 0 and the standard deviation was set at 10.[108] The scores are on a continuous scale ranging from approximately +30 to −30; the higher the positive scale, the greater the degree of type A behavior. Factor analysis has been standardized in the same way as the composite scale, with linear transformation such that the mean score of each factor is 0 and the standard deviation is 10.[108] A score of unity is assigned to each response pertinent to the composite behavior group or to a subscale. A score of 0 is recorded for every other alternative response to that question; that is, a person scores a point every time he or she checks an answer that is statistically distinctive of the behavioral group or to the subscale. The JAS is also constructed and coded so that only one of the possible two to five alternatives to a question is scored. A complete description of the JAS composite and subscale scoring, the factor loadings, and the reliability scale has been described by Jenkins and Zyzanski.

The scoring of the questionnaires was carried out by The Psychological Testing Corporation of New York.[108] The persons who graded the questionnaires were not aware of the classification of the patients in the study. Patients scoring in the upper third of the weighted scale were classified as type A, and patients scoring in the lower third were categorized as type B. Patients scoring in the middle third of the scale were considered to exhibit neither type A nor type B behavioral patterns. A similar grading system was employed for the three subscale factor analyses.

Data Analysis

The frequencies of the composite type A behavioral scale and the three

subscale categories (factor S, factor J, and factor H) were compared between pairs of patient groups using a two-by-two contingency table analysis. The statistical significance of the difference between groups was estimated by the chi-square test, with 1 degree of freedom.

RESULTS

BEHAVIORAL ASSESSMENT

A total of 117 consecutive, newly diagnosed patients with CSC were invited to fill out the JAS. One hundred ten (94%) of these patients were entered in the study. Three patients refused to participate, and four failed to complete the questionnaire adequately for analysis. The clinical profile of the patients with CSC was similar to that reported in other series.[109-111] Eighty-nine of 110 (81%) of the patients were men. The age range was 33 to 50 years, with a mean age of 42.3 years. The majority of patients (96 or 87%) were white. Six (5%) were Hispanic and six (5%) were Asian. Only two (2%) of the patients were black (Table I).

Eight patients selected for control group I were not included: three refused to participate and five failed to complete the questionnaire adequately. A total of 110 patients were studied in this group. The specific diagnosis of patients with other chorioretinal diseases (control group I) is listed in Table II. The single entity most frequently represented was diabetic retinopathy, present in 31 (28%) of the patients. A double-digit frequency was also noted with rhegmatogenous retinal detachment (16 patients, 15%), nondiabetic retinal vascular occlusive disease (14 patients, 13%), and various diseases of the macula associated with disciform degeneration (14 patients, 13%). Several other chorioretinal diseases listed in Table II accounted for 4% to 6% of the cases on control group I. Any chorioretinal disease that occurred less frequently was listed in the miscellaneous category.

In control group II, 11 selected patients were not included: 3 refused to participate, 7 did not properly complete the questionnaire, and 1 lost the questionnaire. A total of 110 patients were studied in this group. The various nonchorioretinal ocular conditions found in control group II are listed in Table III. Matched private patients were selected from the practice of an anterior segment specialist who shared an office with the author. Matched service patients were selected from the general screening clinics of the author's affiliated teaching hospital. This group was composed of patients with diseases of the anterior segment of the eye and refractive errors. Refractive errors accounted for nearly half of these

TABLE I: CSC: CLINICAL CHARACTERISTICS (110 PATIENTS)

Sex	
Male	89 (81%)
Female	21 (19%)
Age (yrs)	
Range	33-50
Mean	42.3
Race	
White	96 (87%)
Hispanic	6 (5%)
Asian	6 (5%)
Black	2 (2%)

TABLE II: CONTROL GROUP I: OTHER CHORIORETINAL DISEASES (110 PATIENTS)

Diabetic retinopathy	31 (28%)
Rhegmatogenous retinal detachment	16 (15%)
Nondiabetic retinal vascular occlusive disease	14 (13%)
Disciform macular degeneration	14 (13%)
Inflammatory disease	7 (6%)
Hereditary disease	5 (5%)
Preretinal membrane disease	4 (4%)
Trauma	4 (4%)
Miscellaneous	15 (14%)

TABLE III: CONTROL GROUP II: NONCHORIORETINAL OCULAR CONDITIONS (110 PATIENTS)

Refractive error	54 (49%)
External and corneal diseases	26 (24%)
Cataract	17 (15%)
Trauma	4 (4%)
Miscellaneous	9 (8%)

TABLE IV: CSC: JAS COMPOSITE SCORES* (110 PATIENTS)

Type A behavior		66 (60%)
Type B behavior		20 (18%)
Type A/type B ratio	3.4	

*Non-type A behavior occurred in 24 patients (22%).

TABLE V: CSC: JAS SUBSCALE SCORES (110 PATIENTS)

Factor S (speed and impatience)		
Factor S		50 (45%)
No factor S		21 (19%)
Factor S/no factor S ratio	2.4	
Factor J (job involvement)		
Factor J		31 (28%)
No factor J		39 (35%)
Factor J/no factor J ratio	0.8	
Factor H (hard-driving competitiveness)		
Factor H		70 (64%)
No factor H		16 (15%)
Factor H/no factor H ratio	4.4	

TABLE VI: CONTROL GROUP I: JAS COMPOSITE SCORES (110 PATIENTS)

Type A behavior		45 (41%)
Type B behavior		32 (29%)
Type A/type B ratio	1.4	

TABLE VII: CONTROL GROUP I: JAS SUBSCALE SCORES (110 PATIENTS)

Factor S (speed and impatience)		
Factor S		29 (26%)
No factor S		42 (38%)
Factor S/no factor S ratio	0.7	
Factor J (job involvement)		
Factor J		29 (26%)
No factor J		48 (44%)
Factor J/no factor J ratio	0.6	
Factor H (hard-driving competitiveness)		
Factor H		55 (50%)
No factor H		23 (21%)
Factor H/no factor H ratio	2.4	

TABLE VIII: CONTROL GROUP II: JAS COMPOSITE SCORES (110 PATIENTS)

Type A behavior		33 (30%)
Type B behavior		43 (39%)
Type A/type B ratio	0.8	

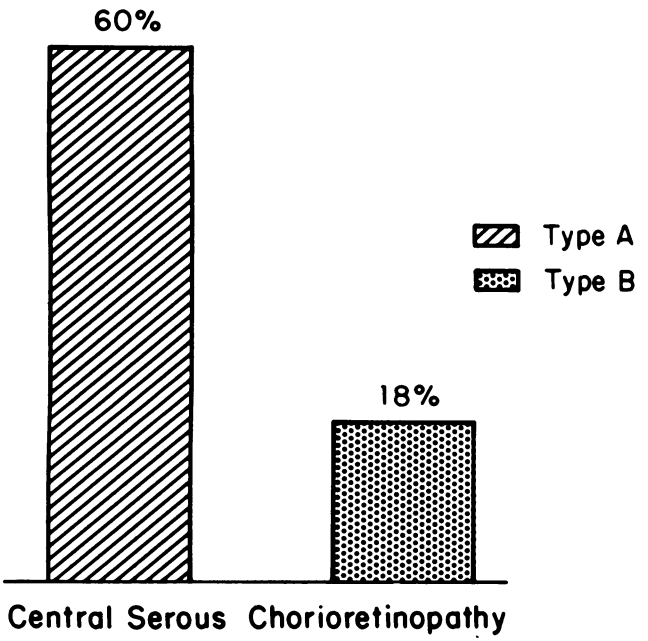

FIGURE 1

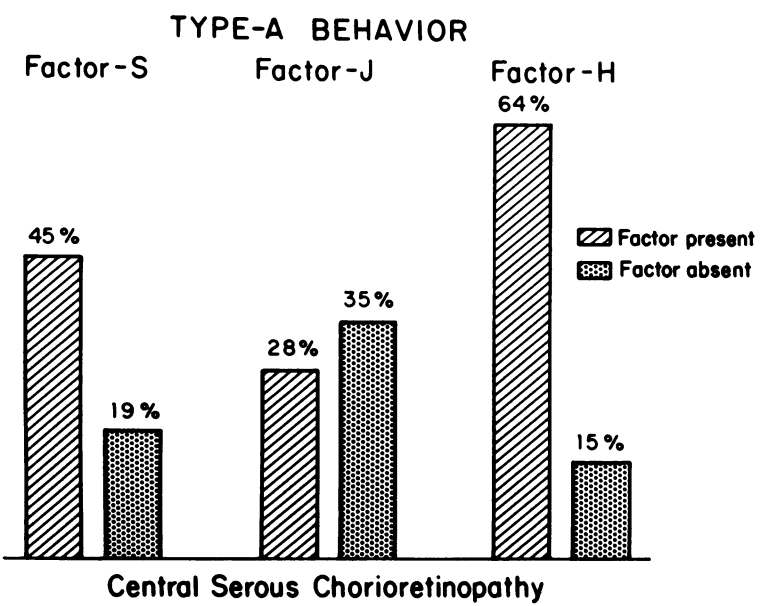

FIGURE 2

patients (54 patients, 49%). Other diagnoses included external and corneal diseases (26 patients, 24%), cataract (17 patients, 15%), and trauma (4 patients, 4%). The remaining entities were seen less frequently and classified as miscellaneous.

The results of the JAS scoring of patients with CSC are listed in Table IV and illustrated in Fig 1. Of the patients with CSC, 66 (60%) scored in the upper third of the scale, indicative of a type A behavior pattern. Only 20 (18%) of the CSC patients scored in the lower third of the scale, signifying a type B behavior pattern. The ratio between type A and type B in this group was 66/20, or 3.4.

Further factor analysis of the three subscales—factor S, factor J, and factor H—appears in Table V and Fig 2. A total of 50 patients (45%) exhibited factor S (speed and impatience), while only 21 (19%) did not, producing a factor S/no factor S ratio of 50/21, or 2.4.

With regard to factor J (job involvement), only 31 (28%) of the patients with CSC scored in the upper third of the subscale compared with 39 (35%) who scored in the lower third of the subscale. This resulted in a factor J/no factor J ratio of 0.8.

The factor H (hard-driving competitiveness) subcomponent of type A behavior revealed the largest difference. Seventy (64%) of the patients with CSC exhibited factor S; only 16 (15%) did not. This resulted in a factor S/no factor S ratio of 4.4.

The JAS results for control groups I and II are listed in Tables VI through IX and illustrated in Figs 3 through 6. The general composite type A pattern for control group I was identified in 45 (41%) of the patients, while the type B pattern occurred in 32 (29%). The type A/type B ratio was 1.4 (Table VI, Fig 3). Subcomponent JAS analysis for group I

TABLE IX: CONTROL GROUP II: JAS SUBSCALE SCORES (110 PATIENTS)

Factor S (speed and impatience)		
Factor S		30 (27%)
No factor S		47 (43%)
Factor S/no factor S ratio	0.6	
Factor J (job involvement)		
Factor J		34 (31%)
No factor J		53 (48%)
Factor J/no factor J ratio	0.6	
Factor H (hard-driving competitiveness)		
Factor H		47 (43%)
No factor H		28 (25%)
Factor H/no factor H ratio	1.7	

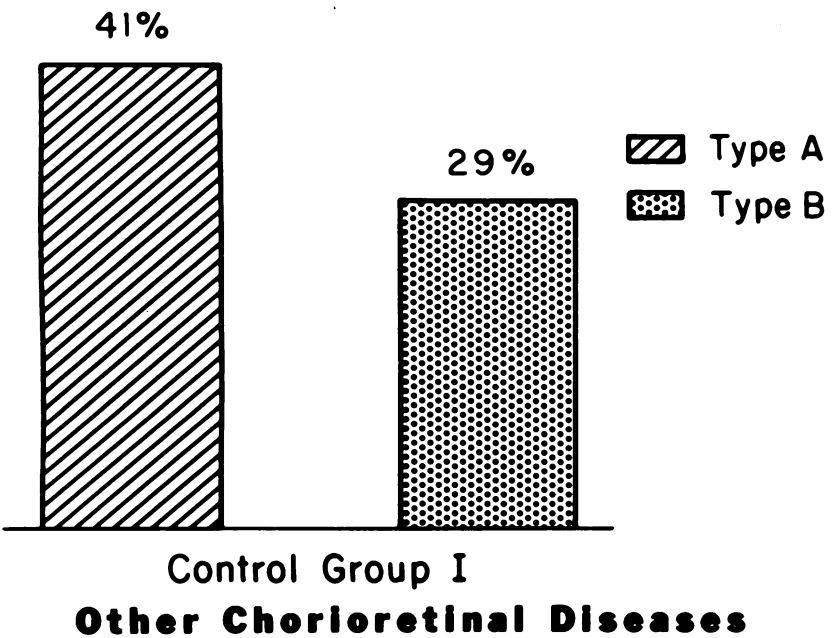

FIGURE 3

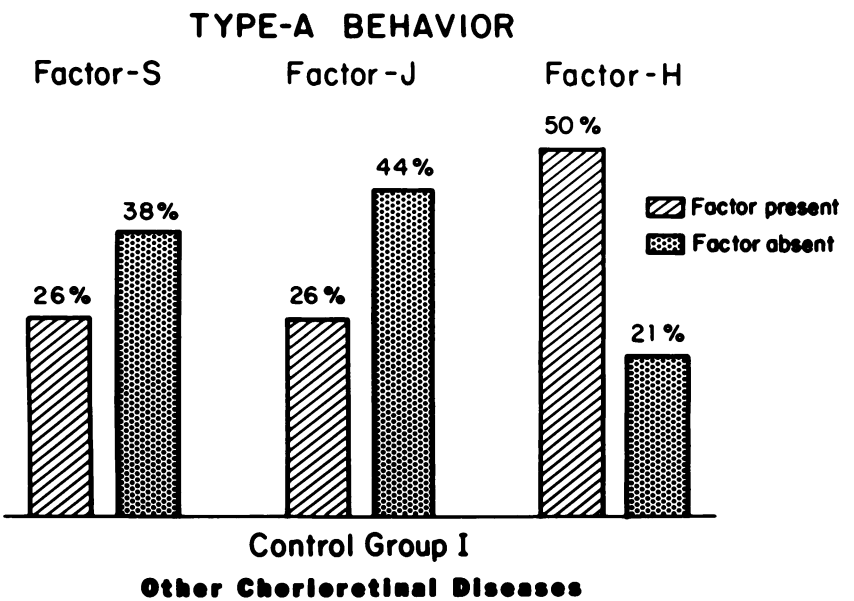

FIGURE 4

is noted in Table VII and Fig 4. For control group I, the factor S/no factor S ratio was 29/42, or 0.7. The factor J/no factor J ratio was 0.6, and the factor H/no factor H ratio was 2.4. Analysis of control group II revealed a composite type A/type B ratio of 0.8 (Table VIII, Fig 5). Subcomponent analysis of this control group is listed in Table IX and Fig 6. Subscale ratios were 0.6 for factor S, 0.6 for factor J, and 1.7 for factor H for control group II. A summary of the composite type A behavior and the three subcomponent factor scores for the three study groups is found in Table X and Figs 7 through 9.

STATISTICAL ANALYSIS

Statistical analysis of the data (Table XI) reveals that type A behavior is significantly more common in CSC patients than in either control group I patients ($\chi^2 = 6.1$, $P < 0.025$) or control group II patients ($\chi^2 = 17.7$, $P < 0.001$). When both control groups were combined for comparison with the CSC patients, there was also a highly significant difference with regard to type A behavior ($\chi^2 = 14.1$, $P < 0.001$). A comparison of control group I with control group II revealed no significant difference in type A behavior ($\chi^2 = 3.5$, $P > 0.05$).

Subscale analysis indicated that factor S is significantly more likely to occur in the CSC patient than in the two control groups separately or combined (group I: $\chi^2 = 11.5$, $P < 0.001$; group II: $\chi^2 = 13.4$, $P < 0.001$; group I plus group II: $\chi^2 = 15.9$, $P < 0.001$).

Distribution of factor J is equal among the three study groups, since none of the comparisons is statistically significant (CSC *vs* group I: $\chi^2 = 0.5$, $P > 0.5$; CSC *vs* group II: $\chi^2 = 0.3$, $P > 0.5$; CSC *vs* group I plus group II: $\chi^2 = 0.5$, $P > 0.5$).

Some variation in the component analysis was noted with regard to factor H. Analysis of this JAS subscale reveals no difference between CSC patients and control group I ($\chi^2 = 2.0$, $P > 0.1$). CSC patients are more likely to exhibit factor H than persons in control group II ($\chi^2 = 5.8$, $P < 0.025$). A statistically significant difference is also present when the CSC patients are compared with the combined control groups ($\chi^2 = 4.6$, $P < 0.05$).

No significant difference is present between control group I and control group II when these study patients are compared for any of the three subscale factors (type A composite: $\chi^2 = 3.5$, $P > 0.05$; factor S: $\chi^2 = 0.05$, $P > 0.5$; factor J: $\chi^2 = 0.03$, $P > 0.5$; factor H: $\chi^2 = 1.1$, $P > 0.1$).

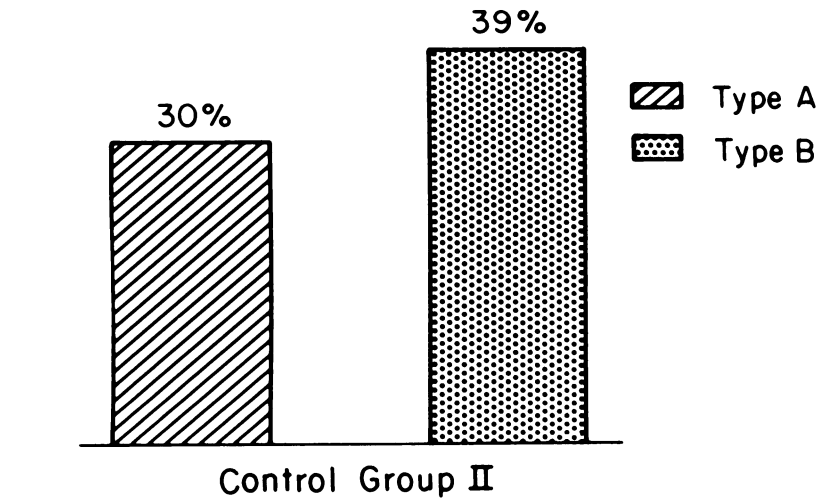

FIGURE 5

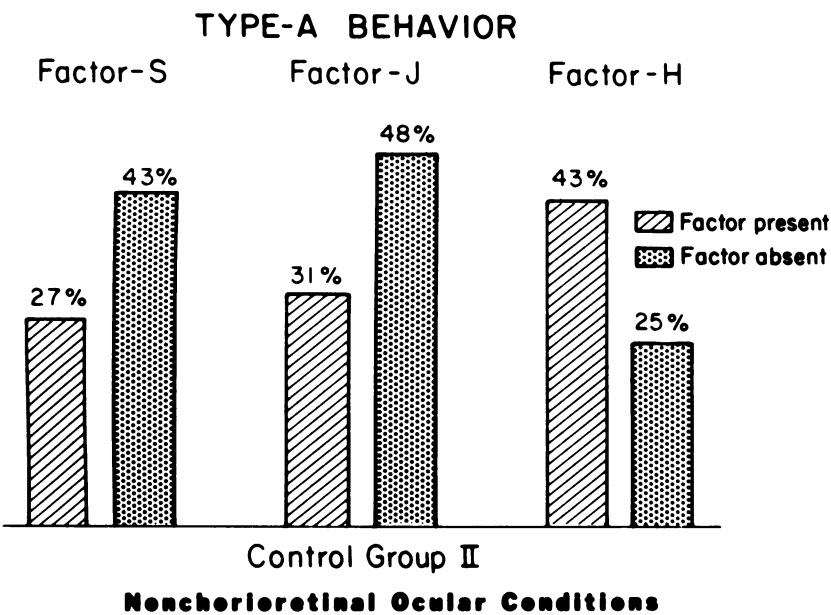

FIGURE 6

TABLE X: FREQUENCY OF JAS COMPOSITE AND SUBCOMPOSITE SCORES: CSC PATIENTS AND CONTROL GROUPS

PATIENT GROUPS	TYPE A		TYPE B		FACTOR S		NO FACTOR S		FACTOR J		NO FACTOR J		FACTOR H		NO FACTOR H	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
CSC (n = 110)	66	60	20	18	50	45	21	19	31	28	39	35	70	64	16	15
Control group I (n = 110)	45	41	32	29	29	26	42	38	29	26	48	44	55	50	23	21
Control group II (n = 110)	33	30	43	39	30	27	47	43	34	31	53	48	47	43	28	25

TABLE XI: TYPE A BEHAVIOR AND CSC: STATISTICAL RESULTS*

BEHAVIOR ANALYSIS	CSC v CONTROL GROUP I		CSC v CONTROL GROUP II		CSC v CONTROL GROUP I AND CONTROL GROUP II		CONTROL GROUP I v CONTROL GROUP II	
	χ^2	*P* VALUE	χ^2	*P* VALUE	χ^2	*P* VALUE	χ^2	*P* VALUE
Type A behavior composite analysis	6.1	< 0.025†	17.7	< 0.001†	14.1	< 0.001†	3.5	> 0.05
Factor S analysis	11.5	< 0.001†	13.4	< 0.001†	15.9	< 0.001†	0.05	> 0.5
Factor J analysis	0.5	> 0.5	0.3	> 0.5	0.5	> 0.5	0.03	> 0.5
Factor H analysis	2.0	> 0.1	5.8	< 0.025†	4.6	< 0.05†	1.1	> 0.1

*Control group I: other chorioretinal diseases; Control group II: nonchorioretinal ocular conditions.
†Statistically significant at $P < 0.05$.

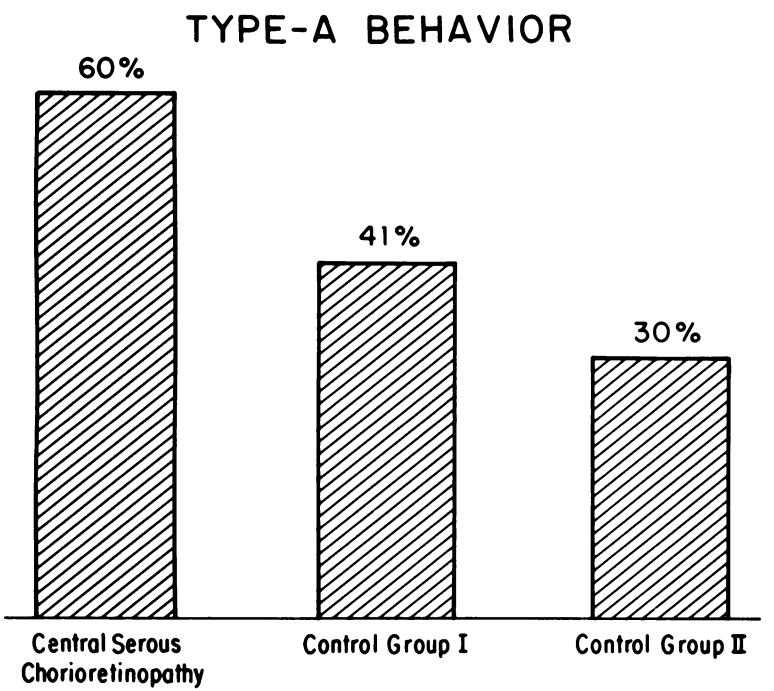

FIGURE 7

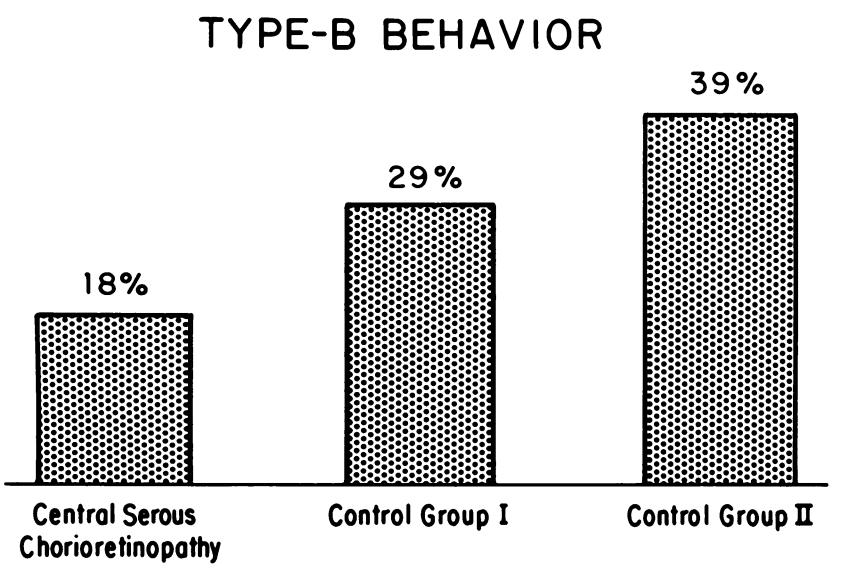

FIGURE 8

DISCUSSION

CENTRAL SEROUS CHORIORETINOPATHY

Historical Review of the Psychogenic-Related Hypothesis

A review of the ophthalmic literature, beginning with von Graefe's original description of "relapsing central luetic retinitis" in 1866, documents ophthalmology's futile attempt to understand the exact pathogenesis of CSC.[1-73,109-133] The huge list of names used to describe CSC is a chronicle of diseases prevalent in particular historical periods, a diary of presumptive fundus tissue layers of primary involvement, and a record of various pathogenetic concepts (Table XII). An inadequate appreciation of the exact clinical manifestations of CSC by earlier ophthalmologists and an obscure understanding of its pathogenesis have led to this multiplicity of terms. New names for the disorder were proposed by numerous authors, a practice that has continued until the present. The earlier designations were meant to suggest the possibility of specific causative agents, such as syphilis[1,3] and tuberculosis.[6,14] The retina,[39] the choroid,[53,57] and more recently the RPE,[67] singly or in combination, have been implicated as the principal site or sites of disturbance.

Most theories on the pathogenesis of CSC have assumed a single

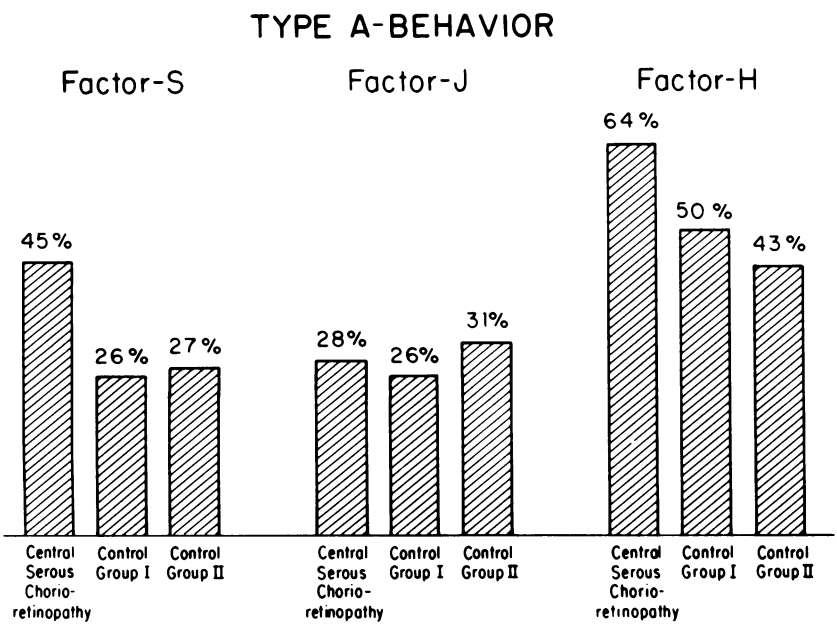

FIGURE 9

etiologic cause, such as vitreous traction,[55] hypotony,[56] a vitamin deficiency,[56,129] malnutrition,[56,129] an infective agent,[1,3,6,14,46,48,51] an allergic reaction,[25,112,114] or a toxic effect.[13,26,49,86,129] Some investigators[13,57,115,120-123] proposed more complex, multietiologic mechanisms. Light damage to the retina in predisposed persons was thought to be a causative factor for CSC as early as 1934.[13,26] Curiously, this phototoxic mechanism is actually a known or presumptive etiologic factor in other forms of macular disease today. Other ophthalmologists[7,8,16,19-21,28,29,34-38,41,44] hypothesized the existence of a vasomotor instability of the retina that induces spasm and stasis of the perifoveal capillaries and the macular exudative changes characteristic of CSC.

Several investigators have made reference to certain emotional disturbances or to a constitutional angioneurosis as a coincidental or causative factor in the pathogenesis of CSC. This so-called psychogenic-related hypothesis was first suggested by Horniker[7] in 1927. He proposed that psychic disturbances precipitated retinal angiospasm and secondary exudative manifestations in the macula. This angiospastic concept led to the characterization of a "vasoneurotic" type of patient at risk to develop CSC.[16] This view that psychological factors were related to angiospasm of retinal capillaries in susceptible persons was shared by Horniker's American contemporaries, Gifford and Marquardt,[19] and later by others.[20,21,28,30,34-36,44]

Subsequent reports by Zeligs[28] and Harrington[30] in the 1940s elaborated further on this psychogenic hypothesis of CSC. Harrington noted clinical evidence of an autonomic vasomotor instability in 100 cases of CSC. Zeligs believed that anxiety was a precipitating factor in a series of combat Marines with "central angiospastic retinopathy." He also theorized that focal spasm of perifoveal retinal arterioles and macular edema accented a more generalized vasospastic state in these patients.

In the 1950s, several investigators made similar observations relating psychological factors to CSC. A vague neurogenic or sympathetic nervous system response secondary to emotional disturbances or stress was thought to be related to the pathogenesis of CSC. In separate reports, Klein[38] implicated stress and Wolkowitz[42] associated emotional shock with CSC. Schlaegel and Hoyt[43] were not convinced that vasomotor instability was a principal causative factor, but they did feel that anxiety and other emotional disturbances played an important but ill-defined role in CSC. In France, Hartman[35] was certain that virtually every case of CSC was precipitated by acute psychological trauma. Bennet[9] concluded that CSC in England was related to stress and that psychotherapy was indicated as a means of treatment. Harrington[30] had previously noted

benefits of psychotherapy in a few of his cases, and Schlaegel and Hoyt[43] had also recommended psychotherapy in selected patients, since no other form of treatment was known to be effective for CSC.

While the psychogenic-related hypothesis for CSC was enthusiastically supported by various investigators for more than 30 years, it abruptly ceased as an etiologic explanation by 1970. Only one article can be found in the literature after the 1950s, a case report by Lipowski and Kiriakos[58] in 1971. The support of this concept was destined to fall abruptly from the ophthalmic literature for several reasons.

In earlier studies, conflicting clinical findings were reported in patients with CSC. Virtually all series contained descriptions of cases that were not consistent with the present definition. Even in the latter part of the 1960s, clinical manifestations of CSC were described in standard references of the period as "a faintly grey macula," "yellow-white flecks on the surface of the retina," and "hemorrhage outside or in the cyst," findings which are not currently applicable to the syndrome.[43,56] Indeed, some of the described manifestations, such as preretinal blood, represent exlusionary criteria for CSC as it is strictly defined today.

Distinct histopathologic changes, such as preretinal or epiretinal membrane formation, cystoid edema, and detachment of the neurosensory retina and RPE, were not consistently recognized in the older literature. These important manifestations, essential in the differential diagnosis of macular disease, were not fully and widely appreciated in these earlier studies.

With the advent of fluorescein angiography in the 1960s, better recognition of the primary and secondary alterations in the fundus in CSC was possible. Ophthalmology was now equipped with a means of recognizing subtle clinical manifestations in the macula and of differentiating closely related macular disorders. A major advance in the understanding of the pathophysiologic mechanism of CSC occurred when Maumenee[117] first noted a leak at the level of the RPE with fluorescein angioscopy, nearly 100 years after von Graefe's original description. Maumenee's important observation was followed by one of the most significant contributions to the study of macular diseases, the legendary series of articles on the pathogeneis of disciform detachment of the neuroepithelium published by Gass[57,120-123] in 1967. This series was highlighted by a monograph on the clinical and fluorescein angiographic nature of CSC.[57] This article was a response to an appeal voiced by Wise and associates[124] for a more precise clinical and angiographic description of the syndrome. The Gass publications represented a milestone in the study of CSC. These papers were actually a symbol of ophthalmology's transition into a modern era

with regard to the diagnosis of macular disease. Instead of a collection of vague maculopathies, a more pure strain of CSC and related disorders could now be generated in clinical studies.

Coincidental with the refinement of macular diagnostics was an increasing trend in ophthalmology to rely exclusively on clinical trials designed with rigid definitions, prospectivity, randomization, and matched controls. The psychogenic-related hypothesis for CSC, lacking scientific data produced by studies with such carefully designed methodology, fell into disfavor.

Clinical Features

Over the past 20 years, numerous articles have been published that provide additional information on the visual symptoms, the demographic characteristics, the natural history, the clinical and fluorescein angiographic manifestations, and the treatment of CSC.[54,57,59-73,109-111,115-162] Some aspects of the maculopathy have been fairly well established: the syndrome has a definite predilection for men. Its onset is generally between the ages of 30 and 50 years. It is usually seen in persons with a mild degree of hyperopia. It tends to be bilateral and recurrent. There may be a racial predisposition, with a higher incidence in white persons, Hispanics, and possibly Orientals, and an extremely low incidence in black persons.[111]

The literature on CSC has also described extensively the clinical and fluorescein angiographic manifestations, involving the neurosensory retina, the RPE, and the choroid.

Retinal Pigment Epithelium. Although the precise pathophysiologic event leading to macular detachment has not been identified, many ophthalmologists today believe that the site of primary pathology begins at the level of the RPE. Often a discoloration or elevation in the RPE is noted on clinical examination. This leads to an alteration in the normally impermeable state of the posterior blood-retinal barrier and to serous leakage underneath and through the RPE to produce detachment of the neurosensory retina. The nature of the defect leading to focal leakage in CSC is still poorly understood. It could be a physical disruption in continuity, a focal area of inflammation or ischemia, a localized immunologic or biochemical reaction, a physiologic breakdown in the junctional complexes or diffusion barriers (zonula occludens and zonula adherens), or other unknown factors. The initial disturbance in the RPE is thought to be "nonvascular"; that is, it is not believed to be associated with proliferation of choroidal vessels under the RPE (choroidal neovascularization) or so-called subretinal neovascularization. However, in some patients with CSC, choroidal vascular ingrowth or subretinal neovascularization may

develop as a secondary manifestation from a nonspecific disturbance of the RPE. The primary nonvascular nature of CSC distinguishes it from age-related macular degeneration or any other maculopathy associated with disciform scarring, such as the presumed ocular histoplasmosis syndrome, angioid streaks, and pathological myopia. In addition to focal or multifocal leaks and serous detachments, the RPE may also develop irregular areas of atrophy in CSC. Atrophic tracts descending to the inferior hemisphere from the posterior pole leading to a dependent detachment have also recently been described in CSC.[67]

Neurosensory Retina. The retina and choroid are also involved in CSC. The retina appears to be only secondarily affected. In addition to macular detachment, other retinal changes, including cystoid edema, telangiectatic capillary change, lipid deposition, cystic degeneration, pigment deposition, and peripheral dependent detachment, may develop in patients with CSC. Many of these retinal manifestations are newly recognized features of the syndrome. Some of them, such as cystoid macular edema, retinal capillary telangiectatic vascular change, and lipid deposition, were previously thought to be exclusionary criteria for CSC.[67] No clinical or fluorescein angiographic evidence exists to support the concept of retinal angiospasm.

Choroid. A nonproliferative vascular disturbance in the choriocapillaris leading to alterations in the RPE also poses as an alternative primary histopathologic mechanism for CSC. The pathophysiologic change in the choriocapillaris could be mediated through a physiologic, biochemical, ischemic, immune, inflammatory, or degenerative process that is not clinically or angiographically discernible. While choroidal ischemia, tumors, neovascularization, and inflammation can lead to macular detachment, these specific precursors are, by definition, not associated with idiopathic detachment of the macula. Some cases of CSC may become associated with secondary manifestations in the choroid, such as folds, choriocapillaris atrophy, and even neovascularization with disciform scarring.[67]

TYPE A BEHAVIOR AND CENTRAL SEROUS CHORIORETINOPATHY

As stated previously, the recent ophthalmic literature that has characterized the clinical and angiographic manifestations of CSC has been conspicuously devoid of any studies investigating the psychogenic-induced hypothesis for CSC. However, several investigators, including Gass,[110] have made reference to a stressful personal situation as a common precursor of the acute detachment in patients with CSC. Following the doubt or the denial of the clinical pedigrees of earlier CSC studies, the

only remaining evidence in support of the psychogenic-related hypothesis for CSC was impressions such as that of Gass and anecdotal, poorly defined clinical reports in the older literature. Yet, for lingering doubters, a rationale for associating psychological factors with CSC has survived.

A widely held impression has always existed that patients with CSC exhibited an unusual personality. While the exact behavioral pattern believed to be associated with CSC has never been characterized precisely, patients have been noted to be energetic, dynamic, hurried, pressured, or emotionally stressed. These observations by ophthalmologists examining patients with CSC have been received with a great deal of skepticism by research physicians, who are more oriented to laboratory or statistical data. Rigorous epidemiologically designed concepts have not been available to establish a consensus position between ophthalmic clinicians and academicians. Nor has there been any biophysiologic explanation available to associate behavior with ocular disease. However, toward the end of the 1950s, behavioral mechanisms associated with systemic disease began to gain recognition and respect. Most notably, a group of cardiologists proposed that a particular behavioral pattern could serve as an independent risk factor for CHD.

TYPE A BEHAVIOR AND CORONARY HEART DISEASE

The origins of the belief that personality, emotions, and life's experiences play a role in the pathogenesis of CHD were found in a Latin monograph authored by William Harvey[163] in 1628. In 1897, Sir William Osler[164] suggested that there was a connection between behavior and the development of atherosclerosis and angina pectoris. Several other prominent cardiologists have made reference over the past 150 years to an association between CHD and behavioral patterns such as a high-pressure existence, an aggressive nature, and an intense achievement drive.

Without question, the most significant contributions relating to psychosocial perspective of a person with CHD were initiated by Friedman and Rosenman[74] in the late 1950s. These investigators described a constellation of psychological characteristics with consistency and ubiquity in their CHD patients. They assimilated these observations into a personality profile that became known as the type A behavior pattern. The behavioral pattern of these patients was originally described as ". . . an action-emotion complex that is exhibited by those individuals who are engaged in a chronic and incessant struggle to achieve more and more in less and less time (thus giving rise to a sense of time urgency or "hurry sickness") and who also usually (but not always) exhibit a free-floating but well-rationalized hostility."[84]

The initial report of Friedman and Rosenman[74] essentially described a behavioral pattern characterized by a relentless, self-induced struggle to overcome real or imagined obstacles, inspired by time, events, and other people. The struggle is evidently mediated with obligatory speed and impatience; a sense of time urgency; a pervasive, competitive, and aggressive force; and an easily aroused temperament.

While more sophisticated terminology offered by behavioral investigators has refined and expanded the original definition of the type A behavior pattern, the pattern has basically persisted in its original form with only minor modification. For example, Jenkins and associates suggest that the pattern results from an "interplay of psychological traits and situational pressures," while Bortner and Rosenman[106] state that the pattern occurs when "a susceptible person is challenged by a suitable environment." These broader boundaries for the type A behavior pattern have expanded the original concept from individual personality traits that interact with environmental factors to a behavior that also exhibits a set of observable responses to life's daily experiences.

The type A behavior pattern is consequently not merely a personality description. It includes all of the behavioral dispositions just described, but it also embraces behavioral characteristics such as muscle tenseness, hyperaltertness, hyperkineticism, vigorous or explosive speech, and an accelerated pace in most activities. Table XIII lists several typical type A behavioral characteristics.[74,89,105,106]

Those persons who manifest an opposite style of behavior are designated as type B. The type B behavior pattern is not simply conceptualized as an absence of type A characteristics. A more distinct definition of the type B personality requires certain behavioral characteristics: the type B person is a relaxed, unhurried, mellow, content individual. A type B person rarely is caught in the struggle to achieve in a competitive environment. This person is relatively immune to environmental constraints imposed by time, organizations, or interpersonal relationships. Table XIV is a list of typical type B characteristics.[74,89,106,109]

Two aspects of type A behavior pattern warrant further elucidation and emphasis. First, not all features of the pattern need to be exhibited for a person to be classified as type A. Within the sphere of type A behavior, life's situations will elicit a variable response with respect to its particular features. Maximum response by some type A persons and minimal reaction by others are provoked by a given situation depending on the person's values and needs. The same is true for type B behavior.

Second, it is necessary to distinguish the type A behavior pattern from ill-defined psychological concepts such as anxiety or stress. The impor-

TABLE XII: CHRONOLOGIC LIST OF NAMES USED TO DESCRIBE IDIOPATHIC DETACHMENT OF NEUROSENSORY RETINA

Relapsing central luetic retinitis (1866)[1]	Retinal edema (1938)[18]
Central retinitis (1892)[2]	Central angiospastic retinopathy (1939)[19]
Luetic retinitis (1916)[3]	Central serous choroidosis (1942)[22]
Recurrent retinitis (1916)[4]	Central serous retinitis (1943)[23]
Central annular retinitis (1923)[5]	Foveomacular retinitis (1944)[24]
Preretinal edema (1925)[6]	Allergic retinosis (1945)[25]
Central vasoneurotic retinopathy (1927)[7]	Solar retinitis (1945)[26]
Central angioneurotic retinopathy (1929)[8]	Central serous choroiditis (1946)[27]
Juvenile exudative retinitis (1930)[9]	Central serous retinosis (1951)[33]
Central chorioretinitis (1933)[10]	Angiospastic retinopathy (1952)[34]
Central serous chorioretinitis (1933)[11]	Central serous retinopathy (1955)[39]
Retinal capillaritis (1934)[12]	Serous disciform detachment of the macula (1959)[45]
Central photodynamic chorioretinitis (1934)[13]	Central serous chorioretinopathy (1965)[53]
Idiopathic flat detachment of the macula (1936)[15]	Idiopathic central serous choroidopathy (1967)[57]
Central angiospastic retinitis (1937)[16]	Central serous choroidopathy (1975)[62]
Juvenile disciform degeneration of the macula (1937)[17]	Central serous pigment epitheliopathy (1984)[67]

TABLE XIII: TYPE A BEHAVIORAL CHARACTERISTICS

Extreme competitiveness
Intense and sustained drive to achieve
Aggressive nature
Easily aroused anger
Hostile temperament
Sense of impatience and haste
Propensity to accelerate the execution of physical and mental tasks
State of restlessness
Perception of all responsibilities with the element of challenge
Extraordinary mental and physical alertness
Persistent desire for recognition and advancement
Frequent involvement with deadlines and multiple simultaneous tasks

TABLE XIV: TYPE B BEHAVIORAL CHARACTERISTICS

Passive interest in achievement
Relaxed state
Unhurried pace
Mellow affect
Easily satisfied style
Deferent nature
Introverted personality

tance of this distinction has been addressed by behavioral scientist David Jenkins:

"The term stress is used in a variety of ways, sometimes to refer to a painful stimulus or upsetting situation, and at other times to refer to a personal reaction of alarm, discomfort, or pain. The divergent ways in which the notion of stress has been treated in the hands of many researchers in this field has thwarted the progress of psychosomatic research and has raised the level of skepticism among biological scientists toward all social and psychological research into disease etiology. In contrast to stress, however defined, the Type-A behavior pattern is neither a stressor situation nor a distressed response. It is rather a style of overt behavior with which some people confront life situations, either pleasant or troubling, provided that some element of challenge is felt to be present."[89]

Thus, a given life's experience eliciting type A behavior in a type A person may be associated with pain or pleasure; that is, it may be stressful or pleasant. It is solely the element of challenge that is perceived with consistency by the type A person.

The JAS questionnaire used in this study on the relationship between the type A behavior pattern and CSC has been demonstrated to have a high level of agreement with the structured interview, good reliability in test-retest situations, and predictive value in the incidence of CHD on a prospective basis.[100-103,108]

The JAS questionnaire not only measured the degree in which the respondent manifested the type A behavior pattern with a general or composite score, but it also indicated three separate subscores corresponding to three distinct dimensions or subcomponents of the behavioral pattern. The typical characteristics of the three JAS subscale behavioral components are listed in Table XV.[89,108] The first subscale score derived from the JAS factor analysis is factor S (speed and impatience). Factor S is a measure of a person's style of behavior. Factor J, the second subscale determined by the JAS, relates to a person's job involvement. The third subcomponent measured by the JAS is factor H, which reflects a person's characteristics and values.

The recognition of type A behavior pattern as a risk factor in CHD was based on the work of the Western Collaboratorive Group Study.[75-77] In this huge study, middle-aged, employed men assessed as type A were found to have more than twice the frequency of CHD as men assessed as type B. This significant difference prevailed for all manifestations of CHD independent of all other risk factors.[77] Following this study, a huge number of epidemiologic, clinical, and laboratory studies on the role of

behavior and the central nervous system (CNS) in the development of CHD appeared from cardiologists and behavioral scientists.[78-103,165-219] Although the initial study of type A behavior involved men, subsequent work was quick to note that women exhibited the same behavioral patterns and a remarkable similarity with regard to cardiovascular disease.[169,192] The association between type A behavior and CHD has been confirmed by studies from other countries, including the Soviet Union, Poland, Belgium, Israel, Sweden, Australia, and The Netherlands.[89] This cross-cultural concurrence linked type A behavior and CHD in various ethnic communities and cultures.[89]

A second major prospective clinical trial—The Framingham Study—showed convincingly that persons who manifested the type A behavior were at significantly greater risk for all forms of CHD.[86,87] Numerous other studies have demonstrated significant relationships between type A behavior and an increased rate of myocardial infarction, recurrent myocardial infarction, silent myocardial infarction, and death related to CHD.

Because much of the early research was flawed by methodologic and conceptual defects, considerable skepticism was voiced by behavior and medical scientists regarding the effects of the type A behavior pattern on CHD. A raging controversy exists to the present with respect to the importance of type A behavior as an influence on the course of CHD. Two recent studies questioned the relationship between the type A score and the incidence of CHD[211] and between the score and cardiac mortality.[212] These reports elicited a series of responses by experts in the field who challenged their design, execution, and conclusions.[213-220] These critics alluded to other studies that revealed conflicting results, supporting the association between type A behavior and cardiac morbidity and mortality.

Realizing the need for an impartial and objective review of the subject, the National Heart, Lung, and Blood Institute in 1981 organized a panel of more than 50 distinguished biomedical and behavioral scientists to evaluate the theory and available research linking behavior to heart disease.[94] A summary statement on the association of the type A behavior pattern with CHD was issued by the panel:

"The review panel accepts the available body of scientific evidence as demonstrating that Type-A behavior . . . is associated with an increased risk of clinically apparent CHD in employed, middle-aged US citizens. This risk is greater than that imposed by age, elevated values of systolic blood pressure and serum cholesterol, and smoking and appears to be of the same order of magnitude as the relative risk associated with the latter three of these other factors."[94]

TYPE A BEHAVIOR: BIOPHYSIOLOGIC CONSIDERATIONS

A search for the pathophysiologic mechanism responsible for the relationship between the type A behavior pattern and CHD has resulted in numerous laboratory and clinical studies.[74,84,165-198] The principal concept for all biobehavioral scientists investigating the systemic effects of the type A behavior pattern is a belief that an intense and sustained level of this behavioral pattern has the potential to arouse the adrenomedullary-sympathetic system to levels that predispose to disease states. Research has consequently been directed primarily at the study of the activity of the adrenomedullary-sympathetic system.[178,179,182-186] The rationale for this approach to research is also based on the assumption that the CNS plays a major role in the regulation of the cardiovascular system and in the development of physiologic disturbances and pathologic structural changes. Converging lines of experimental and clinical research have now clearly established that the type A behavior pattern can stimulate the adrenomedullary-sympathetic system and modulate numerous physiologic mechanisms.

Psychological factors are generally known to affect pulse rate, blood pressure, serologic levels of free fatty acids and lipids, platelet aggregation, blood clotting mechanisms, endocrine function, and sympathetic nervous system activity. Recent studies have indicated that type A persons, compared with type B controls, show evidence of increased sympathetic activity in response to challenging situations, as reflected by cardiovascular and neuroendocrine determinations.[167,177-179,184,185,187] The numerous biophysiologic changes associated with the type A behavior pattern are listed in Table XVI. Type A persons, for example, show an enhanced sympathetic arousal by measurement of skin temperature, muscle vasodilation, pupillary dilatation, pulse rate, and blood pressure changes in laboratory studies.[91,178] An elevation of plasma catecholamines during socially competitive situations has also been reported in type A persons when compared with type B persons.[169,177,184,187] In response to environmental challenges, epinephrine and norepinephrine urinary excretion levels are higher in type A patients than in type B persons, presumably because of the more reactive behavioral state. Elevated serum free fatty acids, cholesterol, triglycerides, and cortisol levels; increased platelet aggregation; sludging of erythrocytes and blood clotting; increased testosterone, cortisol, and 3-methoxy-4-hydroxymandelic acid urinary excretion; and increased platelet epinephrine content have also been reported to be higher in type A persons.[165-169,173,176,178,182,193] One report indicated that type A students produced 40 times as much cortisol and 4 times as much epinephrine as their type B classmates.[187]

TABLE XV: JAS FOR TYPE A BEHAVIOR SUBCOMPONENT CHARACTERISTICS

Factor S (speed and impatience)
Rushes others
Interrupts conversation
Is easily irritated
Has easily aroused temper
Has tense facial muscles
Speaks, eats, and walks fast
Shows signs of restlessness (taps fingers, jiggles knee, sits at edge of seat)
Factor J (job involvement)
Has high-pressured work
Has challenging job
Has frequent overtime schedules
Has frequent deadlines
Is promotion-motivated
Has strong emotional demands
Factor H (hard-driving competitiveness)
Is a hard-driving force
Is exceedingly conscientious
Is highly responsible
Is compulsively serious
Is highly competitive
Has an intense effort
Is highly energetic
Is obsessively achievement-oriented

TABLE XVI: PHYSIOLOGIC CHANGES ASSOCIATED WITH THE TYPE A BEHAVIORAL PATTERN

Arcus senilis[165]
Increased pupillary size[185]
Increased conjunctival sludging[173]
Increased muscle vasodilation[178]
Increased skin temperature[179]
Increased pulse rate[179]
Increased blood pressure[91]
Increased serum free fatty acids[166]
Increased serum cholesterol[167]
Increased serum triglycerides[173]
Increased serum phospholipids[170]
Increased platelet aggregation[176]
Increased blood clotting[165]
Increased plasma cortisol[178]
Increased plasma norepinephrine[177]
Increased plasma epinephrine[187]
Increased platelet epinephrine[185]
Increased urinary excretion of cortisol[187]
Increased urinary excretion of norepinephrine[169]
Increased urinary excretion epinephrine[187]
Increased urinary excretion 3-methoxy-4-hydroxymandelic acid[173]
Increased urinary excretion of testosterone[193]

Other studies[194-198] have associated biochemical changes induced by the type A behavior pattern with atherosclerosis. Free fatty acids have been shown to be elevated in response to emotional stimuli or increased catecholamine secretion.[168,181,182] Infusion of epinephrine has also been found to increase serum levels of free fatty acids.[166,168] A rise in circulatory catecholamines has been reported to be associated with atherogenesis.[172] Although the type A behavior pattern is associated with an enhanced discharge of catecholamines during life's challenging situations, there is still no clear evidence that this rise is the mechanism linking the pattern with CHD. Angiographic studies of coronary artery diseases have not shown convincing evidence of a relationship between the type A behavior pattern and the presence of coronary artery obstruction. Some studies have found angiographic evidence of coronary disease associated with type A behavior, and others have not. It must be concluded on the basis of available evidence that the role of circulating catecholamines in the development of the primary cause of CHD—the formation of an atheroma—is still unclear.

Some evidence exists that genetic factors may play a role in the development of the type A behavior pattern.[199-203] Type A behavior has long been considered to be solely the product of environmental influences. In contrast, recent studies suggest that some children are genetically predisposed to certain components of the pattern, especially quickness to anger, competitiveness, and the need to be in control. These studies have revealed a type A component similarity in twins and in their parents, notably factor H (hard-driving competitiveness).[201,203] A resemblance of type A behavior in parents and their children has also been noted. This similarity correlated most closely with type A fathers and sons.[201,202] These observations imply that a paternal, environmental, or hereditary influence may be important in the development of the type A behavior pattern, as well as any of its associated medical disorders.

The relationship of type A behavior with illnesses other than CHD has not been studied extensively. In the Western Collaborative Group Study, type A subjects were at greater risk of accidents, suicides, and homicides.[89,75-77] This observation, according to the investigators, was thought to be associated with type A behavior reactive state. It has been suggested that patients with peptic ulcer disease tend to exhibit type A behavior.[204-206] This concept, however, has not been thoroughly investigated. Only two reports on the type A behavior pattern appear to have made reference to ocular changes.[74,185] In a report on the association between type A behavior and blood and cardiovascular findings, the frequency of arcus senilis and the serum cholesterol and CHD were

significantly higher in type A persons than in type B persons.[74] Another study[185] noted an increase in pupillary size as a physiologic marker of type A behavior, indicative of increased sympathetic nervous system activity.

The role of behavior, in general, as a biologic response modifier is under investigation in allied medical sciences.[217-235] Numerous studies have implicated a relationship between mental state and disease. Psychological factors have been found to contribute to asthmatic attacks. Studies have indicated that psychological factors can influence survival in patients with heart disease and breast cancer.[29,220,222,223,227,228] Also, a well-established body of evidence associates immune function with emotional stress.[229,233] This psychological reaction has been linked with reduced lymphocytes in humans.[230] Depression has been associated with disinhibition of the hypothalamic and pituitary-adrenal axis, thereby producing excessive steroid secretion.[231] Recent research has also indicated that stress-induced reductions in lymphocyte cytotoxicity may be mediated through circulating opiate peptides or other nonadrenal pathways.[232] Increasing evidence connecting emotional states with immune functions and oncogenesis seems worthy of serious consideration and additional study. These studies lend support to the concept that a person's behavior can induce physiologic changes that may influence his or her physical state.

Type A Behavior and Treatment of CHD

The ultimate goal of clinical research is to utilize newly acquired information in the practical therapy of the investigated medical disorder. In the case of the established relationship between type A behavior and CHD, methods of modifying the behavioral pattern in an attempt to ameliorate or prevent CHD have been under investigation for several years. Behavior intervention studies utilizing recurrent myocardial infarction as the outcome variable have been the most useful in assessing the value of type A behavior modification as a treatment modality for CHD.[207-210] The methodology for modification of the type A behavior pattern was designed to consider the multidimensional nature of the pattern, including cognitive (attitudinal or perceptual processes), behavioral, physiologic, and environmental components, in management training techniques.

All of these factors, interacting in a complex system, were addressed by the most recent and extensive type A behavior treatment study, The Recurrent Coronary Prevention Program. This study was a 5-year prospective trial to investigate morbidity and mortality in a large series of type A and type B persons with CHD. An elaborate, cognitive social learning model and individual and group behavioral instruction programs

stressed the importance of (1) passive and relaxed activity in social relationships, (2) active listening, (3) a relaxed, calm mental activity, (4) a slower, softer speech pattern, and (5) a reduced pace. Environmental factors, such as the atmosphere at work and the conditions at home, were addressed to solve existing problems. The physiologic aspect of treatment was designed to improve biochemical studies, particularly those associated with the sympathetic nervous system. Catecholamine secretion, serum cholesterol levels, and behavioral responses to challenging tasks were monitored. The results of the study were based on several measurements, including self-reports, retesting, and biochemical assays. In this study, funded by the National Institutes of Health, a type A group that was given psychological guidance was compared with a type A control group that received only advice on diet, exercise, and appropriate medication. The findings clearly indicated that the type A behavior pattern could be successfully altered and that the modification was associated with a reduced risk of reinfarction and death. The statistical significance increased to such a high level that the 5-year program was terminated after 4 years.[210]

Clinical Study

This study of the prevalence of the type A behavior pattern in patients with CSC is the first systematic investigation of the relationship between a specific behavioral pattern and macular disease. In fact, it is the first cross-sectional study to investigate the possible association between any particular form of behavior and ocular disease, employing strict clinical definitions and matched controls. Patients with CSC were assessed with the JAS to have type A behavior 60% of the time. Only 18% of these patients with CSC were classified as type B. The ratio of type A/type B is 3.4, indicating that a patient with CSC in this series is more than three times as likely to be type A than to be type B. By comparison, the Western Collaborative Group Study indicated that in patients with CHD, the incidence of type A behavior was slightly more than twice the incidence of type B behavior (type A/type B ratio 2.2).[75-77] The frequency of type A behavior in CSC patients also suggests that the JAS may be a relatively simple and quantitative predictor of patients at risk of developing this maculopathy.

Two groups of patients taken from the same population and matched for age, race, and sex were also compared. One group consisted of patients who had other chorioretinal disease (control group I), and the other group had nonchorioretinal ocular conditions, including refractive errors (control group II). Each of these patients had symptoms of painless reduc-

tion of central vision within a range characteristic of the CSC patients.

Comparative statistical analysis of these patients with respect to type A composite behavior revealed the following:

- Type A behavior pattern was significantly more frequent in patients with CSC than in control group I ($\chi^2 = 6.1$, $P < 0.025$).
- Type A behavior pattern was statistically more frequent in patients with CSC than in control group II ($\chi^2 = 17.7$, $P < 0.001$).
- Type A behavior pattern was statistically more frequent in patients with CSC than in the combined control groups (group I plus group II) ($\chi^2 = 14.1$, $P < 0.001$).
- Type A behavior pattern was equally distributed between control group I and control group II.

The JAS questionnaire not only measured the degree to which the respondent manifested the type A behavior pattern with a general or composite score, but also indicated three separate subscores corresponding to three distinct dimensions or subcomponents of the behavioral pattern.

Further comparative analyses of the JAS subscales, factor S (speed and impatience), factor J (job involvement), and factor H (hard-driving competitiveness) were carried out in an attempt to identify specific components of type A behavior associated with CSC. The subscale analysis indicated the following:

- Factor S was statistically more frequent in patients with CSC than in group I ($\chi^2 = 11.5$, $P < 0.001$).
- Factor S was statistically more frequent in patients with CSC than in group II ($\chi^2 = 13.4$, $P < 0.001$).
- Factor S was statistically more frequent in patients with CSC than in the combined control groups (group I plus group II) ($\chi^2 = 15.9$, $P < 0.001$).
- Factor J was equally distributed among CSC and the two study groups singularly or combined.
- Factor H was equally distributed between CSC patients and group I.
- Factor H was statistically more frequent in CSC patients than in group II ($\chi^2 = 5.8$, $P < 0.025$).
- Factor H was statistically more frequent in CSC patients than in the combined control groups (group I plus group II) ($\chi^2 = 4.6$, $P < 0.05$).
- Factor S, factor J, and factor H were equally distributed between control group I and control group II.

These data indicate that factor S, which characterizes a person's style of behavior, may be an important risk factor for CSC in the type A behavior

pattern. A slightly less relevant risk factor is factor H, which reflects personal traits and values. Of no significance is factor J, which measures a patient's employment setting.

Finally, in patients with CSC, the incidence of factor S was nearly 2.5 times greater (ratio, 2.4), and the incidence of factor H more than 4 times greater (ratio, 4.4).

Experimental Evidence

Experimental evidence relating the type A behavior pattern biophysiologic phenomena to CSC can be found in the ophthalmic literature. In one study involving recurrent CSC during successive pregnancies, circulating hormonal agents were suggested to be causative factors. Some reports have implicated the use of systemic corticosteroids as possible precipitants of the neurosensory detachment.[158,161,162] In one of these studies, recurrent detachment corresponded to three separate treatments with steroids.[162] Resolution occurred following reduction of steroid treatment on each occasion. These studies suggest that circulating biochemical agents may be important in the pathogenesis of CSC in humans.

Experimental evidence also links sympathetic drugs with the pathogenesis of CSC in animals.[40,68-73] An animal model of CSC was first produced biochemically by Ikeda and co-workers,[40] who injected rabbits with repeated doses of intravenous epinephrine, acetylcholine, and histamine. Other investigators[68-70] subsequently concluded that intravenous epinephrine was most suitable for producing experimental CSC in this animal model. Clinical and fluorescein angiographic studies of these animals revealed changes that were similar to CSC in humans.

Yoshioka and associates[71-73] confirmed earlier work on experimental CSC in monkey eyes. Intravenous epinephrine in one monkey and combined intravenous epinephrine and intramuscular prednisolone in another were administered on successive days for slightly more than 1 month. Serous detachments of the neurosensory retina in the macula, associated with multiple pinpoint leaks from the level of the RPE ("inkblot" and "mushroom") were produced experimentally in these animals.[72] The angiographic findings were characteristic of CSC. Following resolution of the detachment, a recurrence was easily induced with repeated injections. Furthermore, no clinical or angiographic abnormalities in the choroid, retina, or optic nerve were observed in these monkeys. The absence of hypertensive retinopathy and choroidopathy changes in these animals are of particular importance, since these retinal and choroidal vascular manifestations are known to be associated with exudative detachment of the macula.

These monkey eyes were also examined with light and electron microscopy.[73] A disappearance of the diaphragms of fenestrated and endothelial cells was noted in the inner surface of the choriocapillaris. The damaged endothelial cells were beneath degenerated RPE cells. The choroidal endothelial defects were covered with fibrin-platelet clots, which were also noted in Bruch's membrane. There were no signs of inflammation or intercellular separation of the damaged RPE cells. No clinical, angiographic, or histopathologic differences were noted between the monkey given epinephrine and the one administered combined epinephrine and prednisolone.

From their observations the authors concluded the following:

- The animals were biochemically stressed with epinephrine to produce experimental CSC.
- The steroid injections did not seem to influence the experimental model.
- The most likely explanation for pathogenesis of the detachment was a biochemically mediated (adrenergic) alteration in the macula, resulting in damage and hyperpermeability to the choriocapillaris, degeneration of a few RPE cells, and consequent breakdown in the posterior blood-retinal barrier in a multifocal distribution.

These studies provide important clinical and experimental evidence linking elevated catecholamine levels, the well-documented physiologic effects associated with the type A behavior pattern, and ocular tissue pathology, specifically neurosensory macular detachment with RPE leakage or CSC. The association of CSC with a sympathetic response also suggests new approaches to the treatment of the disorder.

Type A Behavior and Treatment of CSC

Currently, no definitive, universally accepted form of treatment for CSC exists. Xenon arc or laser photocoagulation under fluorescein angiographic guidance can be employed directly to RPE leaks to accelerate resolution of the neurosensory detachment.[60,109,124,134-151] No clear evidence exists on the basis of clinical trials that this form of treatment benefits long-term visual prognosis. Only one study has suggested that laser photocoagulation treatment may reduce the recurrence rate of CSC.[151]

Medical therapy for CSC has been disappointing. Corticosteroids, administered subconjunctivally or systemically, have not proved to be of definite value, although this mode of medical therapy was advocated for several years as the only available means of treatment.[153-155,157] Most ophthalmologists do not currently recommend this form of treatment.

Antihistaminics, vasodilators such as nicotinic acid, nitrates, papaver-

ine, a nonsteroid antiinflammatory drug, salicylates, adrenocorticotropic hormone, diuretics, and osmotic dehydration with oral glycerin (50%) have also been suggested as possible medical forms of treatment.[56,153,160] Retrobulbar injections of tolazoline (Priscoline) and subconjunctival injections of milk, albumin, and salt solutions have also been recommended.[129,156] Patients have been advised to minimize vasoconstriction by avoiding coffee, tea, tobacco, and cold weather. Even cervical sympathectomy, administration of insulin-free pancreatic extract, oral potassium iodide, thyroid extract, typhoid vaccine, and antisyphilitic and antitubercular drugs have been championed as therapeutic regimens for CSC by some clinicians.[129] No clinical trial has supported the efficacy of any of these agents to date.

Perhaps the most frequent form of pharmacologic treatment advocated by practicing ophthalmologists today is the use of sedatives, barbituates, or tranquilizers. CSC patients presumed to be under stressful or anxiety-provoking situations have been managed in this fashion. Prescribing ophthalmologists believe that modulation of the CNS is of value to patients with CSC. Anecdotal reports of benefits from this method of treatment by today's practicing ophthalmologists and by yesterday's psychosomatic ophthalmic investigators have not been confirmed by clinical trials involving well-defined CSC patients. The extent of type A behavior in CSC patients who are in obvious need of tranquilization is not known. This study suggests that many may be type A persons. This impression, however, must be regarded as speculative until additional studies further elucidate the precise, psychological framework of patients with CSC.

The results of this study on the prevalence of type A behavior in patients with CSC provide new rationale for treatment of the macular disorder, a psychological and/or pharmacologic approach. The Recurrent Coronary Prevention Program did show a significant reduction in the morbidity and mortality of CHD patients with type A behavior if they participated in a behavior intervention program. A large-scale individual and group behavior modification trial would be required to justify this method of treatment for CSC.

A more practical pharmacologic approach to the treatment of CSC is also suggested by this study. Pharmacologic modulators of sympathetic activity may be classified into four groups: (1) alpha-adrenergic receptor and beta-adrenergic receptor blocking agents, (2) centrally acting agents, (3) adrenergic neuron blocking agents, and (4) calcium channel blockers.[234] Beta-adrenergic receptor blocking agents are commonly used in CHD patients to inhibit the effects of epinephrine. These drugs are also used to treat the symptomatic and physiologic states in which distur-

bances manifest themselves by stimulation of various peripheral receptors. For example, the pulse rate and blood pressure changes that can occur with stress or its anticipation can be partially controlled by beta blockers. These drugs have been used for diverse reactions, such as stage fright in performers, tachycardia in ski jumpers, and stress in surgeons.[235] In these situations, performance has apparently not been impaired by these drugs. If well-documented elevations of catecholamines in biochemical assays are consistently found in patients with type A behavior and CSC, there would be a rationale for the use of beta blockers in treatment of these patients. These agents are now under investigation for treatment of patients with type A behavior and CHD. In one study, patients treated with beta blockers converted from a type A to a type B behavior pattern. In another study, a beta blocker was compared with a diuretic in an attempt to modify type A behavior in a group of matched hypertensive patients. After therapy, subjects treated with the beta blocker exhibited significantly less type A behavior than those treated with the diuretic. This type of medical therapy may prove to be of value in the treatment of patients with type A behavior and CSC. The author has already begun to randomize newly diagnosed patients with CSC and type A behavior for treatment *vs* nontreatment, utilizing the beta blocker propranolol in a clinical trial. Duration of the neurosensory detachment, recurrence rate, secondarily induced degenerative changes, and vision will be used as measurements of the efficacy of this treatment.

Type A Behavior and CSC: Future Research

Additional clinical and experimental studies are obviously needed to evaluate the hypothesis of type A-related CSC. The strength of the association between type A behavior and CSC should first be confirmed by clinical studies of patients from other geographic areas and cultures. It could be argued that type A persons might be more inclined to seek immediate medical attention for minor ailments or dysfunctions because of their hyperreactive state. Yet, it is as plausible to anticipate type A persons to do the opposite, since they are constantly in a hurried state, too preoccupied with pressures and deadlines to meet daily personal needs. Assumptions such as these must be validated in future studies to establish a more acceptable relationship between type A behavior and CSC.

The use of the JAS in a prospective study as a predictor of patients prone to developing CSC would also be of importance to the hypothesis. Patients with CSC would also be of importance to the hypothesis. Patients with CSC should be studied for the physiologic changes associated

with the type A behavior pattern, such as an elevated pulse rate, pupillary dilatation, platelet aggregation, and increased serum lipid levels and catecholamine secretion. The type A behavior pattern would be more convincing as a risk factor in CSC if a biologic gradient could be established, correlating the psychological and physiologic severity of the behavior pattern with the macular disorder.

Clinical trials investigating the efficacy and safety of pharmacologic and behavioral modulations of type A behavior physiologic reactivity are also needed to judge the merits of the hypothesis. The development of potent pharmacologic agents that influence this reactivity by blocking peripheral receptors provides an attractive rationale for carefully designed studies to assess the type A behavior pattern and CSC. These drugs have opened new horizons for future studies. The prime example for future research in this area is the potential therapeutic use of a beta blocker. It is important to keep in mind that all beta blockers are not alike in their metabolism, CNS effects, duration of action, and selectively for β_1 and β_2 receptors.[234] Investigators must recognize these differences and their dose-response relationships in clinical research. The study of these agents should initially be linked to the active disease state, such as the acute neurosensory detachment in CSC. Their role as preventative agents in CSC could be subsequently considered if data from preliminary studies warrant it.

Future experimental work is also needed to further investigate the relationship between type A behavior and CSC. The appropriateness of the experimental monkey model for CSC should first be confirmed. It is important that the pathologic features of experimental hypertensive choroidopathy do not exist in these animals. A series of injections of epinephrine may induce systemic hypertension.[236-240] The choroidal vasculature responds to systemic hypertension differently than does the retinal circulation, because the latter is autoregulated and the former is controlled by sympathetic nerve tones.[237-239] As a result, choroidal vascular changes usually precede retinal vascular changes in acute systemic hypertension.[237] Although monkeys with experimentally induced CSC have revealed no clinical or histopatologic signs of hypertensive retinopathy or choroidopathy, macular detachment could have been caused by this mechanism.[236] Choroidal ischemia sufficient to induce retinal detachment may be very subtle and detectable only by fluorescein angiography.[240] Such ischemia may leave no residual clinical abnormality in the fundus. Future pharmacologic studies to clarify the relationship between the type A behavior pattern and CSC should be limited to primates, since large differences in drug metabolism and sympathetic regulated physiologic change make the transfer of observations from nonprimates highly

unreliable. To further investigate the mechanism of experimental macular detachment in monkeys, the author has begun to use several drugs intravenously, including epinephrine, alone and in combination with selected α- and β-adrenergic blocking agents.

A Multifactorial Etiologic Hypothesis

The results of the present study and the experimental monkey model suggest an association between the type A behavior pattern and CSC, with elevated catecholamines as the connecting link or risk factor. However, association does not necessarily indicate causation. Disorders of the macula, like cardiovascular diseases or any chronic degenerative illness, are complex, multidimensional abnormalities, unlikely to be caused by a single factor. The high incidence of type A behavior as measured by the JAS in the CSC group compared with the control groups is undeniable support of previous observations of psychological factors associated with CSC. As with cardiovascular diseases, the influence of behavior is likely to represent one of several factors in its pathogenesis. Experience with retinal research has made ophthalmologists aware that no single approach to the understanding of the pathogenesis and treatment of a macular disease is likely to succeed. Age, sex, race, and the refractive state of the eye are other likely risk factors in the etiology of CSC. Also likely contributors to the pathogenesis of CSC are environmental and genetic or host factors. The susceptibility of a particular host on a genetic basis appears to be evident in the epidemiology of CSC, namely its racial and sex distributions. The type A behavior pattern alone certainly cannot explain the obvious resistance of black persons to CSC in all series. The male predilection is also consistent for CSC throughout the world. The same is likely to be true for the low hyperopic state of the eye in CSC. These clinical observations emphasize the host susceptibility and resistance typically expressed in a complex disease.

Modern epidemiologic theory strongly emphasizes the concept of multifactorial etiology and multiplicity of response. Any of the potential risk factors to CSC, including the type A behavior pattern, may act independently of the others, predisposing a person to the disorder. The influence of each of these factors is likely to be subtle and complex. A direct and overriding connection between type A behavior or any other potential risk factor and CSC is not likely. The overall risk of CSC is likely to be greater in persons possessing two or more risk factors than among those with only one or none (Fig 10). The multifactorial concept of disease also implies that the type A behavior pattern is neither a necessity nor a prerequisite for the development of CSC. Consistent with the multiplica-

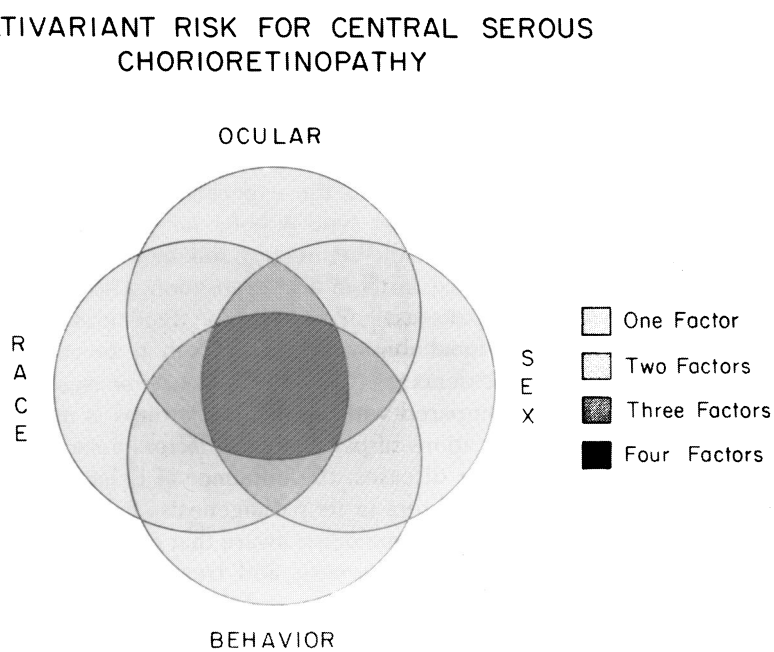

FIGURE 10

tive model is the realization that a patient with CSC or any other complex disease may have none of its known risk factors. In essence, type A behavior-related CSC hypothesis implies that a broad conceptual framework is needed for the pathogenesis of CSC. The independent and interactive influences of psychological, physiologic, ocular, environmental, and genetic factors associated with CSC must be identified for a complete understanding of its etiology and for the rational development of new treatment strategies.

Meanwhile, this study provides sufficient grounds to suggest that the role of behavioral factors should no longer be ignored in the clinical investigation of CSC. The fact that earlier studies were equivocal, largely because of poor definition and methodology, should invoke caution in future investigations. Adequate regard to all potential sources of error that might produce artifact rather than actual knowledge is mandatory in the investigation of the relationship between type A behavior pattern and CSC. Scrupulous regard to experimental design is obviously needed, especially in sampling procedures and patient definitions. Doubtful as-

sumptions should also be avoided to eliminate errors that may yield confusing or conflicting results or inevitable bias.

The broader scope of CSC patient management implied by this report is not merely a reversion to an antedated position; rather, it is a fresh, expanded look at an old impression, incorporating a more scientific approach with modern methods of ophthalmic and behavioral examinations and investigative techniques to legitimize a previously ill-defined concept. Earlier ophthalmologists were highly perceptive in suspecting phototoxicity as a mechanism for macular disease.[13,26] This paper implies that they may have also exhibited keen insight with regard to behavioral factors in the pathogenesis of CSC. The mechanism and the degree of the behavioral influence on CSC must undoubtedly remain open to question, until further evidence supports the concept that an intense and/or sustained behavioral pattern can influence or evoke, through physiologic means, the development of pathologic disturbance in the eye.

CONCLUSION

The results of this clinical study are consistent with the experimental epinephrine monkey model for CSC. It suggests that the eye as an organ system and the macula as an ultimate target area can be intermittently or continuously stimulated adversely by type A behavior and its physiologic consequences, most notably a sympathetic discharge. Coexistent with one or more risk factors, such as age, race, sex, refractive state, or unknown tissue susceptibilities, CSC can evolve. The multifactorial concept allows that not everyone possessing the type A behavior pattern risk factor develops CSC because of host specificities. In this respect, the type A hypothesis for CSC clearly states that the disorder is not caused by a solitary etiologic factor producing a specific constellation of macular manifestations. Rather, its pathogenesis is more likely related to the interrelationship between finely balanced components of a complex biopsychological system involving a person's genetic endowment, environment, and behavioral pattern. By virtue of the concept proposed, it seems appropriate to assess patients with CSC more broadly, assimilating psychological and clinical features of the disorder in the understanding of its pathogenesis. The concept also offers new possible lines of investigation for its *treatment*, utilizing pharmacologic regulators of sympathetic agents, and for its *prevention*, through early identification of CSC-prone persons.

ACKNOWLEDGMENT

I wish to thank Susan Leibo, MPH, for epidemiologic assistance, Edith Zang, PhD, for her biostatistical analysis, Ms Ursula Schell for proof reading the text, Russ Sobel, MS for library research, Ms Margaret Boboyak for secretarial support, and Ms Janet Kennaugh for typing the manuscript.

REFERENCES

1. Von Graefe A: Kurzere Abhandlugen, Notizen und casaistische Mitheilugnen vermischten Inhalts: VI. Ueber zentrale recidivirende Retinitis. *Albrecht Von Graefes Arch Klin Exp Ophthalmol* 1866; 12:211-215.
2. Asayama J, cited by Klein BA: 1892 Retinitis centralis. *Am J Ophthalmol* 1953; 36:1-13.
3. Fuchs E: Ein Fall von zentraler residivierender syphilitischer Netzhaut Enzundung. *Zentralbl Prakt Augenheilkd* 1916; 40:105-108.
4. Masuda T: Clinical studies on central retinitis. *Acta Soc Ophthalmol Jpn* 1916; 20:151-158.
5. Kraupa E: Die Retinitis centralis annularis. *Z Augenheilkd* 1923; 50:335-343.
6. Guist G: Über preretinales Oedema. *Z Augenheilkd* 1925; 54:37-49.
7. Horniker E: Su di unaforma di retinite centrale di origine vasoneurotica. *Ann Ottalmol* 1927; 55:578-600, 830-840, 865-883.
8. ———: Ueber eine Form von zentraler retinitis auf angioneurotischer Grundlage. *Albrecht Von Graefes Arch Klin Exp Ophthalmol* 1929; 123:286-360.
9. Junius P: Erschernungsformen und Ablauf juvenilen retinitis exudatina macularis. *Augenheilkd* 1930; 70:129-148.
10. Ko HU: About the nature of the so-called chorioretinitis centralis (Masuda's). *Acta Soc Ophthalmol Jpn* 1933; 37:977-982.
11. Horniker E: Bemerkungen zur Arbeit von Dr Sakae Kitahara "Über klinische Beobachtungen bei der in Japan haufig vorkommenden Chorioretinitis centralis serosa." *Klin Monatsbl Augenheilkd* 1933; 98:487-489.
12. Baelliart P: Capilarites et lesions lacunaires de la retine. *Ann Ottalmol* 1934; 171:97-111.
13. Ko HU: An experimental study of the nature of Masuda's chorioretinitis: III. A study of the relationship existing between chorioretinitis centralis photodynamica and the function of the kidney. *Acta Soc Ophthalmol Jpn* 1934; 38:1060-1073.
14. Kitahara S: Ueber klinische Beobachtungen bei der in Japan haufig vorkommenden Chorioretinitis centralis serosa. *Klin Monatsbl Augenheilkd* 1936; 97:345-362.
15. Walsh FB, Sloan LL: Idiopathic flat detachment of the macula. *Am J Ophthalmol* 1936; 19:195-228.
16. Horniker E: Central angiospastic retinitis. *Klin Monatsbl Augenheilkd* 1937; 98:487-497.
17. Verhoff FH, Grossman HP, Herman P: Pathogenesis of juvenile disciform degeneration of the macula. *Arch Ophthalmol* 1937; 18:561-585.
18. Baelliart P: L'Edeme de la retine. *Ann d'Oculst* 1938; 175:133-140.
19. Gifford SR, Marquardt G: Central angiospastic retinopathy. *Arch Ophthalmol* 1939; 21:211-228.
20. Streiff EB: Ueber Chorioretinitis centralis serose und ihre Abgrenzung gegenuber der Retinitis centralis angioneurotica. *Klin Monatsbl Augenheilkd* 1939; 103:524-530.
21. Lowenstein A: Retinopathia centralis angiospastica (angioneurotica) and serosa allergica and their relation to detachment of the retina. *Br J Ophthalmol* 1941; 25:369-383.
22. Duggan WF: Choroidosis centralis serosa: Diagnosis, pathology, physiology and therapy. *Am J Ophthalmol* 1942; 27:123-138.
23. Stenstrom S: Retinitis centralis serosa (Masuda's Krankheit). *Acta Ophthalmol* 1943; 21:97-106.
24. Cordes FC: A type of foveomacular retinitis observed in the US Navy. *Am J Ophthalmol* 1944; 27:803-816.
25. Bettman JW: Allergic retinosis. *Am J Ophthalmol* 1945; 28:1323-1328.
26. Redman SI: A review of solar retinitis as it may pertain to macular lesions seen in persons of the armed forces. *Am J Ophthalmol* 1945; 28:1155-165.
27. Bonnet P, Panfique L, Bonamour M: La choroidite sereuse centrale. *Arch Ophthalmol* 1946; 6:13-34.

28. Zeligs MA: Central angiospastic retinopathy: A psychosomatic study of the occurrence in military personnel. *Psychosom Med* 1947; 9:110-117.
29. Baelliart P: Le tonus des arterioles retinennes: Un regard sur la circulation peripherinquet. *Medicine* 1948; 28:1761-1769.
30. Harrington DO: Psychosomatic interrelationship in ophthalmology. *Am J Ophthalmol* 1948; 31:1241-1251.
31. Crukrasz I: Contribution to the chorioretinitis centralis serosa Kitahara. *Ophthalmology* 1951; 33:25-29.
32. Nichols JUV: On the character and management of circulatory disturbances of the retina. *Am J Ophthalmol* 1952; 35:12-19.
33. Keeney A: Central serous retinosis and its relation to other acquired impairments of central vision. *J Ky Med Assoc* 1951; 49:148-152.
34. Augustin M: La retinopathic centrale angiospastique. *Bull Med Suppl* 1952; 15:230-241.
35. Hartman DM: La retinopathie centrale angiospastique. *Bull Soc Ophtalmol Fr* 1952; 00:110-120.
36. Henry F: Angiospastic retinopathy. *Am J Ophthalmol* 1952; 35:1509-1510.
37. Buxeda R: Central angiospastic retinopathy. *Am J Ophthalmol* 1952; 35:1769-1775.
38. Klein B: Macular lesions of vascular origin: II. Functional vascular condition leading to damage of the macula. *Am J Ophthalmol* 1953; 36:1-13.
39. Bennet G: Central serous retinopathy. *Br J Ophthalmol* 1955; 39:605-618.
40. Ikeda I, Komi T, Nakaji K, et al: Chorioretinitis central serous. *Acta Soc Ophthalmol Jpn* 1956; 60:1261-1266.
41. Mitsui Y, Sakamaski R: Central angiospastic retinopathy. *Am J Ophthalmol* 1956; 41:105-114.
42. Wolkowitz MI: Central serous retinopathy: Clinical and experimental studies. *Am J Ophthalmol* 1956; 42:531-545.
43. Schlaegel TF, Hoyt M: *Psychosomatic Ophthalmology*. Baltimore, Williams & Wilkins, 1957, pp 260-295.
44. Wagener HP: Central angiospastic retinopathy and central serous chorioretinitis. J Am Med Sci 1957; 233:220-232.
45. Maumenee AE: Serous and hemorrhagic disciform detachment of the macula. *Trans Pac Coast Ophthalmol Soc* 1959; 80:139-160.
46. Reiger H: Zur Atiologic der Retinitis exudative externa centralis. *Albrecht Von Graefes Arch Klin Exp Ophthalmol* 1960; 00:000-000.
47. Collier M: Les problems etio pathogeniques poses par la retinopathie centrale angiospastique. *Bull Soc Med* (Paris) 1962; 46:1-17.
48. Djakri SE, Dillinas N: L'importance de la lambliase comme facteur etiologique dans la chorioretinite centrale sereuse. *Ophthalmologica* 1963; 147:264-272.
49. Delman M, Leubuscher K: Transient macular edema due to griseofulvin. *Am J Ophthalmol* 1963; 56:658.
50. Edwards TS, Priestly BS: Central angiospastic retinopathy. *Am J Ophthalmol* 1964; 57:988-996.
51. Si-Boen-Lian: The etiologic agent of serous central chorioretinitis. *Ophthalmologica* 1964; 148:263-267.
52. Fujisawa Y: Clinical studies on retinal and chorioretinal lesions by fluorescein fundus photography: I. Chorioretinitis centralis serosa. *Acta Soc Ophthalmol Jpn* 1965; 69:1317-1328.
53. Klein B: Macular diseases: Clinical manifestations. Central serous retinopathy and chorioretinopathy. *Trans Am Acad Ophthalmol Otolaryngol* 1965; 69:614-620.
54. Straatsma B, Allen PA, Petit TH: Central serous retinopathy. *Trans Pac Coast Ophthalmol Soc* 1966; 47:107-127.
55. Tolentinto FI, Freeman HM, Schepens CC: Vitreoretinal traction in serous and hemorrhagic macular retinopathy. *Arch Ophthalmol* 1967; 78:23-30.

56. Duke-Elder WS: *System of Ophthalmology: Diseases of the Retina*. St Louis, CV Mosby, 1967, vol 10, pp 121-137.
57. Gass JDM: Pathogenesis of disciform detachment of the neuroepithelium: II. Idiopathic central serous choroidopathy. *Am J Ophthalmol* 1967; 63:587-615.
58. Lipowski ZV, Kiriakos RZ: Psychosomatic aspects of central serous retinopathy. *Psychosom Med* 1971; 12:398-401.
59. Wessing A: Central serous retinopathy and related lesions. *Mod Probl Ophthalmol* 1971; 9:148-161.
60. Theodossiadis G, Tonges D: Treatment of central serous retinopathy: A comparative study with and without light coagulation. *Ophthalmologica* 1974; 169:416-431.
61. Spitznas M: Pathogenesis of central serous retinopathy: A new working hypothesis. *Albrecht Von Graefes Arch Klin Exp Ophthalmol* 1986; 224:321-324.
62. Schatz H: Central serous choroidopathy and serous detachment of the retinal pigment epithelium. *Int Ophthalmol Clin* 1975; 15:159-168.
63. Dellaporta A: Central serous retinopathy. *Trans Am Ophthalmol Soc* 1976; 74:144-153.
64. Nanjiani M: Longterm followup of central serous retinopathy. *Trans Ophthalmol Soc UK* 1977; 97:656-661.
65. Carr RE, Noble KG: Central serous chorioretinopathy (central serous retinopathy). *Ophthalmology* 1980; 87:841-846.
66. Cassel GH, Brown GC, Annesley WH: Central serous chorioretinopathy: Seasonal variation. *Br J Ophthalmol* 1984; 68:724-726.
67. Yannuzzi LA, Shakin J, Fisher Y, et al: Peripheral retinal detachment and retinal pigment epithelial atrophic tracks secondary to central serous pigment epitheliopathy. *Ophthalmology* 1984; 91:1554-1572.
68. Nagayoski K: Experimental study of chorioretinopathy by intravenous injection of adrenaline. *Acta Soc Ophthalmol Jpn* 1971; 75:1720-1727.
69. Miki T, Sunada I, Higaki T: Studies on chorioretinitis induced in rabbits by stress (repeated administration of epinephrine). *Acta Soc Ophthalmol Jpn* 1972; 76:1037-1045.
70. Yasuzumi T, Miki T, Sugimoto K: Electron microscopic studies of epinephrine choroiditis in rabbits: I. Pigment epithelium and Bruch's membrane in the healed stage. *Acta Soc Ophthalmol Jpn* 1974; 78:588-598.
71. Yoshioka H, Sugita T, Nagayoski K: Fluorescein angiographic findings in experimental retinopathy produced by intravenous adrenaline injection. *Folia Ophthalmol Jpn* 1970; 21:648-652.
72. Yoshioka H, Katsume Y, Akune H: Experimental central serous chorioretinopathy in monkey eyes: II. Fluorescein angiographic findings. *Ophthalmologica* 1982; 185:168-178.
73. Yoshioka H, Katsume Y: Experimental central serous chorioretinopathy: III. Ultrastructural findings. *Jpn J Ophthalmol* 1982; 26:397-409.
74. Friedman M, Rosenman RM: Association of specific overt behavior pattern with blood and cardiovascular findings. *JAMA* 1959; 169:1286-1296.
75. Rosenman RH, Friedman M, Jenkins C, et al: Clinically unrecognized myocardial infarction in the Western Collaborative Group Study. *Am J Cardiol* 1967; 19:776-782.
76. ———: Recurring and fatal myocardial infarction in the Western Collaborative Group Study. *Am J Cardiol* 1967; 19:771-775.
77. Rosenman RH, Friedman M, Straus R, et al: Coronary heart disease in the Western Collaborative Group Study: A follow-up experience of 4½ years. *J Chronic Dis* 1970; 23:173-190.
78. Hinkle LE: *Thrombosis: Risk Factors and Diagnostic Approaches*. Stuttgart, FK Shatterauer Verlag, 1972, pp 15-65.
79. Wardwell WI, Bahnson CB: Behavioral variables and myocardial infarction in the Southeastern Connecticut Heart Study. *J Chronic Dis* 1973; 26:447-461.

80. Jenkins CD, Rosenman RH, Zyzanski SJ: Prediction of clinical coronary heart disease by a test for the coronary-prone behavioral pattern. *N Engl J Med* 1974; 290:1271-1275.
81. Caplan RD, Cobb S, French JRP, et al: *Job Demands and Worker Health*. US of Dept of Health, Education, and Welfare publication No. (NIOSH) 75, 1975.
82. Rosenman RH, Brand RJ, Jenkins CD, et al: Coronary heart disease in the Western Collaborative Group Study: Final follow-up experience of 8½ years. *JAMA* 1975; 233:872-877.
83. Rosenman RH, Brand RJ, Scholtz RI, et al: Multivariate prediction of coronary heart disease during 8.5-year follow-up in the Western Collaborative Group Study. *Am J Cardiol* 1976; 37:903-910.
84. Friedman M: Type-A behavior pattern: Some of its pathophysiological components. *Bull NY Acad Med* 1977; 53:593-604.
85. Brand RJ: Coronary prone behavior as an independent risk factor for coronary heart disease, in TM Dembroski, SM Weiss, JD Shields, et al (eds): *Coronary-Prone Behavior*. New York, Springer-Verlag, 1978, pp 11-24.
86. Haynes SB, Levine S, Scotch NA, et al: The relationship of psychological factors to coronary heart disease in the Framingham Study: I. Methods and risk factors. *Am J Epidemiol* 1978; 107:362-383.
87. Haynes S, Feinleib M, Levine S, et al: The relationship of psychosocial factors to coronary heart disease in the Framingham Study: II. Prevalence of coronary heart disease. *Am J Epidemiol* 1978; 107:384-402.
88. Cohen JB: The influence of culture on coronary-prone behavior, in SM Dembroski, JL Weiss, JD Shields, et al (eds): *Coronary-Prone Behavior*. New York, Springer-Verlag, 1978, chap 12.
89. Jenkins CD: Behavioral risk factors in coronary artery disease. *Ann Rev Med* 1978; 29:543-562.
90. Manuk SB, Craft S, Gold KJ: Coronary-prone behavior pattern and cardiovascular response. *Psychophysiology* 1978; 13:403-409.
91. Manuk SB, Garland FN: Coronary-prone behavior pattern, task incentive and cardiovascular response. *Psychophysiology* 1979; 16:136-143.
92. Van Egeren LP: Social interactions, communications and the coronary-prone behavior pattern: A psychophysiological study. *Psychosom Med* 1979; 41:2-18.
93. Williams RB, Haney TL, Lee KL, et al: Type-A behavior, hostility, and coronary atherosclerosis. *Psychosom Med* 1980; 42:539-549.
94. The review on coronary-prone behavior and coronary heart disease. *Circulation* 1981; 63:1199-1215.
95. Chessney MA, Rosenman RH: Type A behavior: Observation on the past decade. *Heart Lung* 1982; 11:12-18.
96. Anderson JR, Waldron I: Behavioral and content components of the structured interview assessment of type A behavior pattern in women. *J Behav Med* 1983; 6:123-134.
97. Barefoot JC, Dahlstrom WG, Williams RB: Hostility, CHD incidence and total mortality: A 25-year follow-up study of 255 physicians. *Psychosom Med* 1983; 45:59-63.
98. Haynes SG, Feinleib M, Eaber ED: Type A behavior and the ten-year incidence of coronary heart disease in the Framingham Heart Study, in RH Rosenman (ed): *Psychosomatic Risk Factors and Coronary Heart Disease*. Berne, Hans Huber, 1983, pp 80-92.
99. Ontega DF, Pipal JE: Challenge seeking and the type A coronary-prone behavior pattern. *J Pers Soc Psychol* 1984; 46:1328-1334.
100. Jenkins CD, Rosenman RH, Friedman M: Development of an objective psychological test for the determination of the coronary-prone behavior pattern in employed men. *J Chronic Dis* 1967; 20:371-379.
101. ———: Replicability of rating the coronary-prone behavior pattern. *Br J Prev Soc Med* 1968; 22:16-22.

102. Jenkins CD, Rosenman RH: Progress toward the validation of a computer scored test for the type A coronary-prone behavior pattern. *Psychosom Med* 1971; 33:193-202.
103. Jenkins CD, Zyzanski SJ, Rosenman RH: Coronary-prone behavior: One pattern or several? *Psychosom Med* 1978; 40:25-43.
104. Rosenman RH: The interview method of assessment of the coronary-prone behavior pattern, in TM Dembroski, SM Weiss, JL Shields, et al (eds): *Coronary-Prone Behavior*. New York, Springer-Verlag, 1978, chap 5.
105. Chesney MA, Eagleston JR, Rosenman RH: The type A structured interview: A behavioral assessment in the rough. *J Behav Assess* 1980; 2:255-271.
106. Bortner H, Rosenman RH: The measurement of pattern A behavior. *J Chronic Dis* 1967; 20:525-533.
107. Bortner RW: A short rating scale as a potential measure of pattern A behavior. *J Chronic Dis* 1969; 22:87-91.
108. Jenkins CD, Zyzanski SJ, Rosenman RH: *The Jenkins Activity Survey*. New York, The Psychological Testing Corporation, 1979.
109. Schimizu K: *Fluorescein Microangiopathy of the Ocular Fundus*. Tokyo, Igaku-Schoin, 1973, chap 5.
110. Gass JDM: *Stereoscopic Atlas of Macular Diseases: Diagnosis and Treatment*. St Louis, CV Mosby, 1977, chap 5.
111. Yannuzzi LA, Gitter KA, Schatz H: *The Macula: A Comprehensive Text and Atlas*. Baltimore, Williams & Wilkins, 1979, pp 145-165.
112. Lothman L: Clinical manifestations of allergy in ophthalmology. *Year Book of EENT*. Chicago, Year Book Medical Publishers, 1941, pp 38-41.
113. Doggart JH: Diseases of the retina: Symptoms of macular derangement. *Trans Ophthalmol Soc UK* 1946; 75:180-191.
114. Berens C, Sayad WY, Girard LJ: Symposium on ocular allergy. The uveal tract and retina: Consideration of certain experimental and clinical concepts. *Trans Am Acad Ophthalmol Otolaryngol* 1952; 56:220-241.
115. Norton EWD, Gass JDM, Smith JL, et al: Symposium on macular diseases: Diagnosis. Fluorescein in the study of macular diseases. *Trans Am Acad Ophthalmol Otolaryngol* 1956; 69:631-642.
116. Norten EWD, Smith JL, Curtin JT, et al: Fluorescein fundus photography: An aid in the differential diagnosis of posterior ocular lesions. *Trans Am Acad Ophthalmol Otolaryngol* 1964; 68:755-765.
117. Maumenee AE: Symposium on macular diseases: Clinical manifestations. *Trans Am Acad Ophthalmol Otolaryngol* 1965; 69:605-613.
118 .———: Symposium on macular diseases: Pathogenesis. *Trans Am Acad Ophthalmol Otolaryngol* 1965; 69:691-699.
119. Burns CA, Blodi FC, Williamson BK: Acute lymphacytic leukemia and central serous retinopathy. *Trans Am Acad Ophthalmol Otolaryngol* 1965; 69:307-309.
120. Gass JDM: Pathogenesis of disciform detachment of the neuroepithelium: I. General concepts and classifications. *Am J Ophthalmol* 1967; 63:573-585.
121. ———: Pathogenesis of disciform detachment of the neuroepithelium: III. Senile disciform macular degeneration. *Am J Ophthalmol* 1967; 63:617-644.
122. ———: Pathogenesis of disciform detachment of the neuroepithelium: IV. Fluorescein angiographic study of senile disciform macular degeneration. *Am J Ophthalmol* 1967; 63:645-659.
123.———: Pathogenesis of disciform detachment of the neuroepithelium: V. Disciform macular detachment secondary to focal choroiditis. *Am J Ophthalmol* 1967; 63:661-687.
124. Wise GN, Campbell CJ, Wendler PF, et al: Photocoagulation of vascular lesions of the macula. *Am J Ophthalmol* 1968; 66:452-459.
125. Norholm I: Central serous retinitis. *Acta Ophthalmol* 1969; 47:890-899.
126. Rosen ES: *Fluorescence Photography of the Eye: A Manual of Dynamic Clinical Ocular Fundus Pathology*. Woburn, Mass, Butterworths, 1969, chap 5.

127. Schimizu K, Tobari I: Central serous retinopathy: The dynamics of the subretinal fluid. *Mod Probl Ophthalmol* 1971; 9:152-157.
128. Funabashi T: Histologic basis for fluorographic characteristics of central serous retinopathy. *Jpn J Clin Ophthalmol* 1971; 24:89-95.
129. Burton T: Central serous retinopathy, in FC Blodi (ed): *Current Concepts in Ophthalmology*. St Louis, CV Mosby, 1972, pp 1-28.
130. Coscas G: Maculopathies oedemateuses. *Bull Soc Ophtalmol Fr* 1972; 6:154-161.
131. Norton EWD: The value of fluorescein angiography in the study of choroidal and pigment epithelial disease. *Trans Am Acad Ophthalmol Otolaryngol* 1973; 77:321-322.
132. Lowder CY, Gutman FA, Zegarra H, et al: Macular and paramacular detachment of the neurosensory retina associated with systemic diseases. *Trans Am Ophthalmol Soc* 1981; 79:346-370.
133. Schatz H, Burton TC, Yannuzzi LA, et al: *Fundus Fluorescein Angiography*. St Louis, CV Mosby, 1978, pp 643-653.
134. Peabody RR, Zweng HC, Little HL: Treatment of persistent central serous retinopathy. *Arch Ophthalmol* 1968; 79:166-169.
135. Spalter HF: Photocoagulation of central serous retinopathy. *Arch Ophthalmol* 1968; 79:247-253.
136. Orzalesi N, Serra A: Nouve acquisizini sulla pathogenesis e la terapia della retinopathia sierosa centrale. *Boll Oculist* 1969; 48:471-496.
137. Zweng HC, Little HL, Peabody RR: *Laser Photocoagulation and Retinal Angiography*. St Louis, CV Mosby, 1969, pp 297-312.
138. Schimizu K, Tobari I: Fluorography and photocoagulation of central serous retinopathy. *Jpn Clin Ophthalmol* 1968; 23:438-480.
139. Mitsui Y, Matsubara M, Kanagawa M: Xenon light exposure as a treatment of central serous retinopathy. *Jpn Clin Ophthalmol* 1970; 23:453-460.
140. Uyama M, Okuma M: Photocoagulation of central serous retinopathy. *Folia Ophthalmol Jpn* 1970; 21:454-474.
141. Gass JDM: Photocoagulation of macular lesions. *Trans Am Acad Ophthalmol Otolaryngol* 1971; 75:580-608.
142. Annesley WH, Tasman WS, LeWin DP, et al: A retrospective evaluation of photocoagulation for idiopathic central serous choroidopathy. *Mod Probl Ophthalmol* 1974; 12:234-259.
143. Klein M, VanBuskirk M, Friedman E, et al: Experience with non-treatment of central serous choroidopathy. *Arch Ophthalmol* 1974; 91:247-250.
144. Watzke RC, Burton TC, Leverton PE: Ruby laser photocoagulation therapy of central serous retinopathy: I. A controlled clinical trial. II. Factors affecting prognosis. *Trans Am Acad Ophthalmol Otolaryngol* 1974; 78:205-211.
145. Berrochal JA: Current world-wide management of central serous retinopathy. *Mod Probl Ophthalmol* 1974; 12:239-243.
146. Gass JDM: Photocoagulation treatment of idiopathic central serous choroidopathy. *Trans Am Acad Ophthalmol Otolaryngol* 1977; 83:456-467.
147. Landers MB, Shaw HE, Anderson WB, et al: Argon laser treatment of central serous chorioretinopathy. *Ann Ophthalmol* 1977; 9:1567-1572.
148. Lyons DE: Conservative management of central serous retinopathy. *Trans Ophthalmol Soc UK* 1977; 97:214-216.
149. Schatz H, Yannuzzi LA, Gitter K: Subretinal neovascularization following argon laser photocoagulation treatment for central serous chorioretinopathy. *Trans Am Acad Ophthalmol Otolaryngol* 1977; 83:893-906.
150. Leaver P, Williams C: Argon laser photocoagulation of central serous retinopathy. *Br J Ophthalmol* 1979; 63:674-677.
151. Robertson DM: Direct, indirect and sham laser photocoagulation in the management of central serous chorioretinopathy. *Am J Ophthalmol* 1983; 95:457-466.
152. Gilbert MC, Owens SL, Smith PD, et al: Long-term follow-up of central serous chorioretinopathy. *Br J Ophthalmol* 1984; 68:815-820.

153. McLean JM, Gordon DM, Koteen H: Clinical experience with ACTH and cortizone in ocular diseases. *Trans Am Acad Ophthalmol Otolaryngol* 1951; 55:565-575.
154. Purnell JE, Leopold IH: Cortisone in ocular diseases: Further studies. *Am J Ophthalmol* 1952; 35:663-670.
155. Hobbs HE: Macular degeneration treated with cortisone. *Proc R Soc Med* 1953; 46:213-218.
156. Bialasiewicz A: Über therapeutische Erfolge bei Retinitis centralis serosa mit Priscoline-injektionen. *Klin Monatsbl Augenheilkd* 1957; 131:536-537.
157. Okamota T, Tominaga K, Watanabe T, et al: Statistical observations in retinitis centralis in 1963. *Folia Ophthalmol Jpn* 1965; 16:218-225.
158. Williamson J, Naki G: Macular lesions during systemic therapy with depotetracosactrin. *Br J Ophthalmol* 1970; 45:405-419.
159. Chumbly LC, Frank R: Central serous retinopathy and pregnancy. *Am J Ophthalmol* 1974; 77:158-160.
160. Pecora JL: Ibuprofen in the treatment of central serous chorioretinopathy. *Am J Ophthalmol* 1978; 10:1481-1483.
161. Wakakura M, Ishikawa S: An evaluation of corticosteroid treatment for central serous chorioretinopathy. *Rinsho Ganko* 1980; 34:123-129.
162. ———: Central serous chorioretinopathy: Complications of systemic corticosteroid treatment. *Br J Ophthalmol* 1984; 68:329-331.
163. Harvey W: 1628 Exercetatio de motei cordis et sanguonis in anisnalibus, cited in MR Eastwood, H Trevelyn: Stress and coronary heart disease. *J Psychosom Res* 1971; 15:289-292.
164. Osler W: The Lumlerian lectures on angina pectoris and allied states. (Delivered before the Royal College of Physicians.) *Lancet* 1910; 1:696-700, 839-844, 974-977.
165. Rosenman RH, Friedman M: Association of a specific overt behavior pattern in women with increased blood cholesterol and clotting time, arcus senilis, and incidence of clinical coronary disease. *Circulation* 1959; 20:759-778.
166. Gordon RS, Cherkes A: Unesterified fatty acids in human blood plasma. *J Clin Invest* 1956; 35:206-212.
167. Bogdanoff MD, Estes H, Trout D: Acute effect of psychologic stimuli upon plasma non-esterified fatty acid levels. *Proc Exp Biol Med* 1959; 100:503-504.
168. Gordon PV, Gordon RS: Rapid increase in plasma unesterified fatty acids in man during fear. *J Psychosom Res* 1959; 4:5-9.
169. Friedman M, St George S, Byers SO, et al: Excretion of catecholamines, 17-ketosteroids, 17-hydroxycorticoids, and 5-hydroxyindole in men exhibiting a particular behavior (pattern A) associated with high incidence of clinical coronary artery disease. *J Clin Invest* 1960; 39:758-764.
170. McElroy WT, Spitzer JJ: Effects of adrenergic blocking agents on plasma free fatty acid concentration. *Am J Physiol* 1961; 200:318-322.
171. Byers SO, Friedman M, Rosenman RH, et al: Excretion of 3-methoxy-4-hydroxymandelic acid in men with behavior pattern associated with high incidence of coronary artery disease. *Fed Proc* 1962; 21:999-1001.
172. Engleman K, Mueller PS, Sjoerdsma A: Elevated plasma free fatty acid concentrations in patients with pheochromocytoma. *N Engl J Med* 1964; 270:865-870.
173. Friedman M, Rosenman RH, Byers SO: Serum lipids and conjunctival circulation after fat ingestion in men exhibiting Type A behavior pattern. *Circulation* 1964; 29:874-886.
174. Friedman M, Byers SO, Rosenman RH, et al: Coronary-prone individuals (Type A behavior pattern): Some biochemical characteristics. *JAMA* 1970; 212:1030-1037.
175. Haft JI: Cardiovascular injury induced by sympathetic catecholamines. *Prog Cardiovasc Dis* 1974; 17:73-86.
176. Simpson MT, Olewine DA, Jenkins CD, et al: Exercise-induced catecholamines and platelet aggregation in the coronary-prone behavior pattern. *Psychosom Med* 1974; 36:476-487.

177. Friedman M, Byers SO, Diamant J, et al: Plasma catecholamine response of coronary-prone subjects (type A) to specific challenge. *Metabolism* 1975; 4:205-210.
178. Williams RB: Physiological mechanisms underlying disease, in WD Gentry, RB Williams Jr (eds): *Psychological Aspects of Myocardial Infarction and Coronary Care*. St Louis, CV Mosby, 1975, chap 8.
179. Dembroski TM, MacDougall JM, Shields JL: Physiologic reaction to social challenge in persons evidencing the type A coronary-prone behavior pattern. *J Human Stress* 1977; 3:211-230.
180. Friedman M: Type A behavior pattern: Some of its pathophysiologic components. *Bull NY Acad Med* 1977; 53:593-604.
181. Chait A, Brunzell JD, Johnson DG, et al: Reduction of plasma triglyceride concentrations by acute stress in man. *Metabolism* 1979; 28:553-561.
182. Von Euler US: Quantitation of stress by catecholamine analysis. *Clin Pharmacol Ther* 1964; 5:398-404.
183. Glass DC, Krakoff LR, Contrada R, et al: Effect of harassment and competition upon cardiovascular and catecholamine responses in type A and B individuals. *Psychophysiology* 1980; 17:453-461.
184. Glass DC, Krakoff LR, Finkelman J, et al: Effect of task overload upon cardiovascular and plasma catecholamine response in type A and B individuals. *Basic Appl Soc Psychol* 1980; 1:199-207.
185. Schneider RH: New markers for type A behavior: Pupil size and platelet epinephrine. *Psychosom Med* 1985; 47:89.
186. Von Eiff AW, Frederick G, Neus H, et al: Effects of beta blockers on type A coronary-prone behavior. *Klin Wochenschr* 1982; 60:1315-1316.
187. Williams RB, Lane JD, Kuhn CM, et al: Type A behavior and elevated physiological and neuroendocrine responses to cognitive tasks. *Science* 1982; 218:483-485.
188. Kravitz DS, Durell LA, Davis JE, et al: Propranolol medication among coronary patients: Relationship to type A behavior and cardiovascular response. *J Human Stress* 1983; 8:4-12.
189. Schmilder R, Friedrich G, Neus H, et al: The influence of beta blockers on cardiovascular reactivity and type A behavior pattern in hypertension. *Psychosom Med* 1983; 45:417-421.
190. Holmes DS, McGilley BM, Houston BK: Task related arousal of type A and type B persons: Level of challenge and response specifically. *J Pers Soc Psychol* 1984; 46:1322-1327.
191. Malcom AT, Janisse MP, Cyck DG: Type A behavior, heart rate and pupillary response: Effects of cold pressor and ego threat. *J Psychosom Res* 1984; 28:27-34.
192. Mayes BT, Sime WE, Ganster DC: Convergent validity of type A behavior pattern scales and their ability to predict physiological responsiveness in a sample of female public employees. *J Behav Med* 1984; 7:83-108.
193. Zumoff B, Rosenfeld RS, Friedman M, et al: Elevated daytime urinary excretion of testosterone glucuronide in men with type A behavior pattern. *Psychosom Med* 1984; 46:223-225.
194. Blumenthal J, Williams R, Cong Y, et al: Type A behavior pattern and coronary atherosclerosis. *Circulation* 1978; 58:634-639.
195. Zyzanski SJ, Jenkins CD, Ryan C, et al: Psychological correlates of coronary angiographic findings. *Arch Intern Med* 1976; 136:1234-1237.
196. Frank K, Heller S, Kornfeld D, et al: Type A behavior pattern and coronary angiographic findings. *JAMA* 1978; 240:761-763.
197. Dimsdale J, Hackett T, Hutter A, et al: Type A behavior and angiographic findings. *J Psychosom Res* 1979; 23:273-276.
198. Dimsdale J, Hackett T, Catanzano D, et al: The relationship between diverse measure for Type A personalities and coronary angiographic findings. *J Psychosom Res* 1979; 23:289-293.

199. Bortner RW, Rosenman RH, Friedman M: Familial similarity in pattern A behavior. *J Chronic Dis* 1970; 23:39-43.
200. Rosenman RH, Rabe RH, Boshani NO, et al: Heritability of personality and behavior pattern. *Acta Genet Med Gemellol* 1974; 23:37-42.
201. Matthew KA, Krantz DS: Resemblance of twins and their parents in pattern A behavior. *Psychosom Med* 1976; 28:140-144.
202. Rahe RH, Hervig L, Rosenman RH: The heritability of type A behavior. *Psychosom Med* 1978; 40:478-486.
203. Matthews KA, Rosenman RH, Dembroski T, et al: Familial resemblance in components of the type A behavior pattern: A reanalysis of the California twin study. *Psychosom Med*. In press.
204. Watkins MG: Relation of chronic peptic ulcer to coronary sclerosis. *Gastroenterology* 1958; 89:292-301.
205. Davis DT, Wilson ATM: Observations on life history of patients with chronic peptic ulcer. *Lancet* 1937; 2:1353-1360.
206. Paulley JW: Ulcers, heart disease, and type-A behavior. (Letter) Lancet 1979; 2:1238-1239.
207. Rahe RH, Ward HW, Hayes V: Brief group therapy in myocardial infarction rehabilitation: Three-to-four year follow-up of a controlled trial. *Psychosom Med* 1979; 41:229-242.
208. Thoresen CE, Telch JM, Eagleston JR: Approaches to altering the type A behavior pattern. *Psychosom Med* 1981; 22:472-482.
209. Friedman M, Thoresen CE, Gill J, et al: Feasibility of altering type A behavior pattern after myocardial infarction: Recurrent coronary prevention project study: Methods, baseline results and preliminary findings. *Circulation* 1982; 66:83-92.
210. ———: Alteration of type A behavior and reduction in cardiac recurrences in post-myocardial infarction patients. *Am Heart J* 1984; 108:237-248.
211. Case RB, Heller SS, Case NB, et al: Type A behavior and survival after acute myocardial infarction. *N Engl J Med* 1985; 312:737-741.
212. Shekelle RB, Hulley SB, Neaton JD, et al: The MRFIT behavior pattern study: II. Type A behavior and incidence of coronary heart disease. *Am J Epidemiol* 1985; 122:559-570.
213. Kelterer MW: Type A behavior and survival after myocardial infarction. (Letter) *N Engl J Med* 1985; 313:449-450.
214. Pickering TG: Type A behavior and survival after myocardial infarction. (Letter) *N Engl J Med* 1985; 333:450.
215. Halperin PJ, Littman AB: Type A behavior and survival after myocardial infarction. (Letter) *N Engl J Med* 1985; 313:450.
216. Abbott AV, Peters RK, Vogel ME: Type A behavior and survival after myocardial infarction. (Letter) *N Engl J Med* 1985; 333:450-451.
217. Dimsdale JE, Hackett TP: Effect of denial on cardiac health and psychological assessment. *Am J Psychiatry* 1982; 139:1477-1480.
218. Abbott AV, Vogel M: Psychological influences on mortality after myocardial infarction. *N Engl J Med* 1985; 312:50-51.
219. Ruberman W, Weinblatt E, Goldberg JD, et al: Psychological influences on mortality after myocardial infarction. *N Engl J Med* 1984; 311:552-559.
220. Rahe RH, Lind E: Psychosocial factors and sudden cardiac death: A pilot study. *J Psychosom Res* 1971; 15:19-24.
221. Vailliant GE: Natural history of male psychological health: Effects of mental and physical health. *N Engl J Med* 1979; 301:1249-1254.
222. Helsing LJ, Comstock GW, Szklo M: Causes of death in a widowed population. *Am J Epidemiol* 1982; 116:524-532.
223. Shekelle RB, Raynor WJ, Ostfeld AM, et al: Psychological depression in 17-year risk of death from cancer. *Psychosom Med* 1981; 43:117-125.

224. Kabasa C, Maddi SR, Kahn S: Heartiness and health: A prospective study. *J Pers Soc Psychol* 1982; 42:168-177.
225. Hoffman JW, Benson H, Arns PH, et al: Reduced sympathetic nervous system responsivity associated with the relaxation response. *Science* 1982; 215:190-192.
226. Klous RE, Lustman PI: Psychiatric illness and contraction abnormalities of the esophagus. *N Engl J Med* 1983; 309:1332-1342.
227. Levy SM, Herberman RB, Malush AM, et al: Prognostic risk assessment in primary breast cancer by behavioral and immunologic parameters. *Health Psychol* 1985; 4:99-113.
228. Pettingale KW, Morris T, Greer S, et al: Mental attitudes to cancer: An additional prognostic factor. (Letter) *Lancet* 1985; 1:750.
229. Hamburg DA: Frontiers of research in neurobiology. *Science* 1983; 222:969.
230. Keller SE, Weiss JM, Schleifer SJ, et al: Stress-induced suppression of immunity in adrenalectomized rats. *Science* 1983; 221:1301-1304.
231. Pepper GM, Krieger DT: Hypothalamic-pituitary-adrenal abnormalities in depression: Their possible relation to central mechanisms regulating ACTH release, in RM Post, JC Ballenger (eds): *Neurobiology of Mood Disorders*. Baltimore, Williams & Wilkins, 1984, pp 245-270.
232. Shavit Y, Lewis JW, Terman GW, et al: Opioid peptides mediate the suppressive effect of stress on natural killer cell cytotoxicity. *Science* 1984; 223:188-189.
233. Marx JL: The immune system "belongs to the body." *Science* 1985; 222:1190-1192.
234. Schapiro A, Grim C: Pharmacologic agents as modulators for stress, in SM Weiss, KA Matthews, et al (eds): *Bethesda, National Institutes of Health*, 1984, pp 213-217.
235. Surwit R: Pharmacologic and behaviorl modulators of cardiovascular reactivity, in SM Weiss, KA Matthews, et al (eds): *Bethesda, National Institutes of Health*, 1984, pp 175-195.
236. Kishi S, Tso MO, Hayreh SS: Fundus lesions of experimental hypertensive choroidopathy: I. A pathologic study of experimental hypertensive choroidopathy. *Arch Ophthalmol* 1985; 103:1189-1206.
237. Laties AM, Jacobowitz D: A comparative study of the autonomic innervation of the eye in monkey, cat and rabbit. *Anat Rec* 1966; 156:383-395.
238. Ernst JT: The effect of systolic hypertension on rhesus monkey eyes after ocular sympathectomy. *Am J Ophthalmol* 1977; 84:341-344.
239. Wecter JJ, Schachar RA, Ernst JT: Control of intraocular blood flow: II. Effect of sympathetic tone. *Invest Ophthalmol Vis Sci* 1973; 12:332-334.
240. Gaudic A, Coscas G, Bird AC: Choroidal ischemia. *Am J Ophthalmol* 1982; 94:489-498.