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STRESS POLYCYTHEMIA
THE INFLUENCE OF STRESS ON THE HEMATOCRIT

RALPH J. FALKENSTEIN

1969

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STRESS POLYCYTHEMIA

The Influence of Stress on the Hematocrit

Ralph Jay Falkenstein

A.B., Columbia College

A Thesis

Presented to the Department of Medicine,
Yale University

In Partial Fulfillment of the Requirements
for the Degree of Doctor of Medicine

New Haven, Connecticut
April 1, 1969

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DEDICATION

For My Wife and Parents



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ABSTRACT

A study of 16 male patients with confirmed Stress Polycythemia showed a significant clustering of life-changing and stressful events in the year preceding definitive diagnosis as compared to two control years, arbitrarily chosen. Hematocrit values were noted to fluctuate and lower values were invariably correlated with calmer periods in the patient's life.

Psychological tests administered to these patients indicated that their scores on trait-anxiety and neuroticism were significantly higher than matched and standardized controls. It was also noted that these patients had a very high incidence of other presumed psychosomatic diseases-peptic ulcers and ulcerative colitis.

Although definitive Stress Polycythemia was not uncovered in the male in-patient psychiatric population at Yale-New Haven Hospital between 1960 and 1966, hematocrit values were generally lower at time of discharge than at time of admission.

Finally, medical students, undergoing acute stress, showed a definite increase in hematocrit during that time as compared to quiescent control periods. It would again appear that the hematocrit spectrum shifts toward higher values in time of stress and excitement.

An attempt was made to establish an animal model for Stress Polycythemia. Acute physical excitation of rabbits invariably resulted in a modest but consistent increase in venous hematocrit. There was no evidence that this "stress" polycythemic syndrome was associated

with shifts in either plasma water or age-specific red cells. The administration of reserpine prior to rabbit manipulation abolished the hematocrit response. Neither epinephrine nor norepinephrine without physical manipulation produced an increased hematocrit.

INTRODUCTION

HISTORICAL PERSPECTIVE

That body states and functions may wax and wane according to the moods and fortunes of the individual was realized long before Freud's study of the mind led him to develop the concept of psychoanalysis. It was William Beaumont in 1833 who, by direct visualization through a gastric fistula, conclusively showed the influence of emotional upsets upon gastric functioning.¹

The classical treatment of the physiological accompaniments of emotional states was written by Cannon, whose studies on the pain, hunger, fear, and rage in animals ushered in the modern era of study of the influence of psychic processes upon the physiological state of the organism.² Cannon also realized the necessity for the development of new techniques in studying psychophysiological phenomena. Clearly, the use of such methods as gastric fistuli were not readily applicable to human subjects and new tools had to be devised. The initial approach to this new area of medicine took the form of correlating biographical, medical, and psychological data and attempting to show correlations between emotional stress and the onset, variability, and possible termination of the related disease process, if, indeed, such a relationship existed at all. Subsequently, in the 1950's, the development of numerous psychological tests enabled the researcher to study, on an empirical basis, the influence of psychodynamic processes upon behavior and physiology.

In my study, I have used both the old and the newer approach to investigate psychophysiological relationships in the cardiovascular

system, with specific emphasis on the problem of Stress Polycythemia.

PSYCHOPHYSIOLOGICAL RESEARCH

The terms psychophysiological and psychosomatic are used in this paper to include those conditions where physio-pathological or anatomopathological changes are evident, or where symptoms or laboratory tests suggest that such changes have occurred, and in which psychological factors are believed to play an important role in their genesis or aggravation. The notion of psychosomatic illness is so commonly linked with the concept of "stress" that it is well to consider what will be meant by the latter term. In its widest application, it refers to the phenomenon of adverse environmental circumstances resulting in bodily changes believed to be mediated through pathways of mental activity. What is decisive is not necessarily the circumstances itself but the way in which it is perceived and dealt with. In other words, it is the interaction between the extrinsic event and the intrinsic personality reacting to it. The interaction is specific for an individual. In addition, this interaction, while specific, may vary at different times and exposures.

There have been numerous studies to attempt to delineate personality patterns in persons with diseases which are believed to have considerable emotional overlay; namely, peptic ulcers and hypertension.^{3,4} While certain personality characteristics, modes of perceiving the environment, and patterns of reacting to stress were found to occur more frequently in these patients than in control populations, similar

personality characteristics and modes of functioning were also seen in many people of the control group. Therefore, these studies which demonstrated the characteristics and modes of functioning probably have their greatest value in suggesting hypotheses rather than definitely relating psychological factors and the disease process. The studies whereby such hypotheses are tested fall into the psychophysiological realm in that behavioral variables are independently manipulated while physiological parameters are monitored.

Another complicating feature of psychophysiological research is that for any etiological significance to be placed upon an association found between personality and physical illness, the former should be determined before the development of the latter. This is to insure that the illness itself has not produced the personality attributes. To date, there has not been any such study in the realm of psychosomatic disease.

One further problem in conducting medical research, which has special reference to the study of psychosomatic disease, is determining precisely the date of onset of the illness. Just as it is impossible to date the first appearance of malignant cells in a neoplastic growth, so one cannot accurately determine the inception of an ulcer crater, an elevated blood pressure, or an elevated hematocrit. Every patient will be examined and perhaps diagnosed at different stages and progressions of the same disease process. So the observed inception will depend on numerous factors, including the symptomatology of the patient, the acumen of the physician and the exact point in time when the

individual sees the physician. The best that one can hope to accomplish is to note any significant differences in the individual's life pattern as it refers to events, behavior, etc. preceding either the onset of symptoms or the actual diagnosis.

While the syndrome of Stress Polycythemia has received increasing attention within the past few years, the stress aspects have not been studied, save to state that they seem to exist. In this paper an attempt has been made to describe groups of behavioral traits in a pragmatic frame of reference, based on what is clearly observable in the interview situation, the patient's record, and reported by the patient to be a constant behavior pattern from early life. This study was undertaken with the understanding that "the patterns of response to an environmental stress will be handled differently depending on genetic predisposition, early learning experiences, how the stress is interpreted, what the emotional response is to the interpreted stress, and the 'organ systems' or pathways through which this response gains expression"⁵ were not, and could not possibly be, fully known with the level of understanding currently available.

REVIEW OF LITERATURE

Polycythemia refers to an absolute increase in the number of circulating erythrocytes. This may be either primary or secondary in nature.

The original description of Primary or Polycythemia Vera appeared in the European literature in 1892 by Vaquez.⁶ Osler described it as a new clinical entity in 1903.⁷ However, he introduced the idea that "there are two classes, relative in which the condition is due to a diminution in the quantity of the plasma of the blood and true, in which there is an actual increase in the number of red blood corpuscles."⁷ Terminology

became more complex when Gaisbock described his "polycythemia hypertonica" in 1922.⁸ Although he recognized both the true and relative forms of polycythemia, he considered his "polycythemia hypertonica" as a true form of polycythemia. He regarded the presence of hypertension as the most important manifestation separating his syndrome from the Vaquez type of true polycythemia. He also considered the absence of splenomegaly as a diagnostic criterion. Gaisbock observed plethora, apoplectic habitus, small strokes, arteriosclerosis, erythromelalgia, claudication, and neurasthenia as common features of "polycythemia hypertonica".

Judging from the absence of medical reports on this subject, this syndrome all but escaped recognition for the next 30 years. In 1952, Lawrence and Berlin reported 18 cases of apparent polycythemia in which blood volume measurements revealed a decrease in plasma volume and a normal circulating red cell mass, (using P³² labeled red blood cells).⁹ Fe⁵⁹ turnover data were not characteristic of polycythemia vera or of secondary polycythemia and showed a rate of incorporation that was within normal limits. Of the 18 patients described, there were some fairly common findings: 16 were males (primarily between 40 and 50 years old), 11 showed the ruddy cyanosis so common in polycythemia vera, 9 were hypertensive with a blood pressure greater than 150/90, 8 were thought to be overweight, 6 complained of dizziness but none showed the splenomegaly and pancytosis seen so commonly in polycythemia vera. In many respects these patients fit into the group of patients described by Gaisbock in which there was polycythemia and hypertension but no splenomegaly. Lawrence and Berlin were at a loss for an explanation of the etiology of what they found. However, they

noted that "about one half of the patients were thought to have some significant anxiety state or to be mildly psychoneurotic. . . and the psychiatric background of some of these patients indicated that they had been subjected to undue nervous stress and strain."⁹ They concluded by saying "one is tempted to relate the blood volume changes in these patients to some form of emotional stress and to class this condition as a psychosomatic phenomenon".⁹ Although it was known that anoxic stress could produce hemoconcentration, this was the first report of the possible effect of nervous stress causing a decreased plasma volume while the total red cell volume remained normal. To this clinical picture, Lawrence and Berlin gave the name of "the Polycythemia of Stress" or "Relative Polycythemia".

Subsequent studies confirmed the observation made by Lawrence and Berlin and awareness of the syndrome increased. Russell and Conley stated that "at the Johns Hopkins Hospital the most common type of polycythemia encountered, apart from dehydration and the erythrocytosis associated with arterial oxygen unsaturation, is that resembling this syndrome."¹⁰ Of the 25 patients reported, they noticed similar findings to those of Lawrence and Berlin: 23 were males, the mean age at the time of discovery was 45, 8 complained of dizziness, 12 were overweight, 12 were hypertensive with blood pressure greater than 150/90, and 15 were felt to be plethoric. More importantly, impressive evidence of anxiety and tension characterized the history of 17 patients; also, 8 had received medical treatment for symptoms related to emotional stress or anxiety. There was X-ray proof that

5 of these patients had peptic ulcers, and of the 22 patients whose smoking habits were recorded, 21 smoked cigarettes (12 smoking one or more packs per day). That these patients did not have Polycythemia Vera was conclusively shown by the absence of an increased red cell mass, leukocytosis, thrombocytosis, and splenomegaly. Likewise, organic disease resulting in a secondary polycythemia was also ruled out by procedures such as pulmonary function studies, arterial oxygen saturation, and intravenous pyelograms when they were indicated.

Russell and Conley felt that the recurring pattern of manifestations justified the classification of these cases as a unique syndrome and suggested the titles of "Benign Polycythemia" and "Gaisbock's Syndrome." They also pointed out that these patients be clinically separated from those with other forms of polycythemia since both treatment and prognosis are radically different. Long term follow-up of these patients showed the benign nature of this polycythemia. A higher incidence of vascular complications attributable to the increased viscosity of the blood, as suggested by several authors, was not evidenced. In addition, the use of phlebotomy in improving the prognosis of this syndrome was of doubtful value, as compared to that in Polycythemia Vera. On the other hand, the use of radiation, including P^{32} , is contraindicated in view of the resistance of normal erythropoietic tissue to this agent and because of the potential hazards of radiation therapy.

Kaung and Peterson studied a similar group of 10 male patients.¹¹ The diagnosis was made by using the Cr^{51} -labeled red cell technique to determine total blood volume. Plasma volumes and red cell mass

were then calculated from the venous hematocrit. Although they also noted the high prevalence of plethora, obesity, and hypertension, they emphasized that thromboembolic phenomena were encountered in 5 of the 10 patients. This included 3 cerebral thromboses, 4 coronary thromboses, one arterial embolism to the leg, and one venous thrombosis of the leg. Moreover, they claimed "only one of our 10 patients was noted to be anxious and presented a picture of a person under emotional stress. The others were calm, cooperative, and apparently well adjusted."¹¹ However, no attempts were made to uncover hidden stress or to pursue psychological make-up of the group. Kaung and Peterson felt that the term "Pseudo-polycythemia" best fits this diagnosis.

Hall described a group of 20 male patients whom he diagnosed as having "Gaisbock's Disease" from Cr⁵¹ blood determinations as well as the absence of pannyelosis and a benign long-term clinical picture.¹² His clinical summary revealed the following: 17 were plethoric, 14 had a blood pressure greater than 140/90, 9 had headaches, 8 were obese, 7 complained of dizziness, and 13 suffered some form of vascular disease, the most common being of the heart. Hall felt that the emotional mood of 9 of his 20 patients could be described as "nervous or tense".

Hall was the first to make specific mention of the clinical course of this syndrome. He states that followup of 12 of his patients from one to 10 years (average, 4.8 years) showed that there was never any real change in the basic disorder or any persistent change in the hematocrit value. The latter was attributed to the chronicity of the

hemoconcentration. While almost half of his population was nervous or tense, Hall objected to the term of "Stress Polycythemia" used by Lawrence and Berlin because "too little is known about the subject to permit the use of the word 'stress' in an etiologic sense".¹² He emphasized that the term "pseudo-polycythemia" used by Kaung and Peterson was the best of the present terminologies. In an attempt to further clarify terms, Hall referred to the state whereby an elevated hematocrit value that was due solely to the combination of a normal total red blood cell volume with a low total plasma volume be referred to as "pseudopolycythemia", while Gaisbock's syndrome be used to define either pseudopolycythemia or a similar condition with the addition of an increased red blood cell volume.

Table 1 is a modified outline from Modan¹³ and Berlin¹⁴ which gives the most recent classification of the different types of polycythemia.

Hall concurs with Russell and Conley that, in the absence of polycythemia from dehydration and arterial oxygen unsaturation, "Stress " or "Pseudopolycythemia" is the most common of all the above listed forms seen.

In 1967, Stevens and Chabot¹⁵ studied a group of 12 white male patients, varying in age from 37 to 58, who had a predominance of all of the symptoms mentioned in the other previous studies. They termed their group "Intermediate Polycythemia" rather than Gaisbock's syndrome, as they felt the blood picture of most of their patients combined the features of polycythemia vera (an increased red cell volume) with those of relative polycythemia of "stress" (decreased plasma volume), but is

TABLE 1 - CLASSIFICATION OF POLYCYTHEMIC SYNDROMES

TRUE ERYTHROCYTOSIS
(Polycythemia)

Erythropoietin Increased

1. Anoxic types
 - a) Pulmonary insufficiency
High altitude
Pickwickian Syndrome
 - b) Hemoglobinopathies
Hemoglobin Chesapeake
Ranier
Ypsilanti
Yakima
Hiroshima
Kempsey

- c) Other
Methemoglobinemia

2. Humoral or Hormonal Types

- a) Tumors
Cerebellar Hemangioma
" Hemangioblastoma
Hypernephroma
Renal Adenoma
Uterine Fibromyoma
- b) Other
Hydronephrosis
Renal Cysts

Erythropoietin not increased

1. Polycythemia Vera
2. Humoral or Hormonal
 - a) Tumors
Ovarian Carcinoma
Hepatoma
Pheochromocytoma
Adrenocortical carcinoma
 - b) Other
Adrenal cortical hyperplasia

3. Erythrocytosis of Childhood

FALSE ERYTHROCYTOSIS
(Relative Polycythemia)

1. "Stress" Polycythemia
2. Dehydration
3. Small plasma volume

neither. It thus appeared that terminology and definitions continued to splinter patients into specific and not universally accepted groups. To better standardize diagnosis, Kaung and Peterson felt that blood volume data should best be expressed in relation to body surface rather than body weight, as is commonly done. In fact, they found that some of their patients with relative polycythemia had a normal red blood cell volume when it was related to weight but slightly increased when it was related to surface area - a fact that would make some investigators shift these patients from the relative polycythemia group to the Gaisbock syndrome niche.

Perhaps the most poignant point in making blood volume determinations was made by Blum and Zbar.¹⁶ They showed that plasma volume could not properly or accurately be calculated from the total red cell volume and the venous hematocrit, as Lawrence and Berlin had done. Implicit in that procedure is the assumption that the venous hematocrit is equal to the total-body hematocrit; the proven and known facts have indicated that the total-body hematocrit-to-venous hematocrit ratio approximates 0.9 and to use the venous hematocrit in such calculations would result in a spuriously low plasma volume. Blum and Zbar further suggested that a reduction in the plasma volume was not the only means of yielding a high venous hematocrit without true polycythemia. If the ratio of total-body hematocrit to venous hematocrit is reduced below 0.9 because of a shift of red cells from smaller to larger vessels, this would result in an elevated venous hematocrit and give an incorrectly high reading of the total-body hematocrit, if the venous hematocrit is considered alone. Therefore, according to Blum and Zbar, "Plasma

volume measurements suggest two mechanisms for a high venous hematocrit without polycythemia: 1) a reduction in the plasma volume and 2) a shift in the distribution of red cells."¹⁶

The etiology as well as the mechanism for hemoconcentration in Stress Polycythemia remains an enigma. Until 1966 there were no reports in the literature on possible mechanisms causing relative polycythemia. Prankerd was the first to suggest several hypotheses and these included:¹⁷

a) DISORDER OF CELL ELECTROLYTES - if there were a total deficiency of cell electrolytes there would have to be a fall in cell and plasma water to maintain normal osmolarity. This is unlikely since electrolytes in these patients are normal.

b) DISORDER OF RENAL HANDLING OF WATER - a diabetes insipidus-like syndrome. This, too, is unlikely since the patients show no thirst or polyuria and their renal concentrating and diluting mechanisms behave normally.

c) DISORDER INVOLVING BODY VOLUME PERCEPTORS - it may be that some mechanism regulating plasma volume (perhaps in the hypothalamus) is set at a permanently lower level than normal. This is highly hypothetical.

d) ALDOSTERONE EXCRETION - Prankerd has claimed to have measured the 24-hour aldosterone secretion of patients with relative polycythemia on normal diets and to have found that they secrete significantly less than people with normal plasma volumes. He also states that these patients failed to respond to 3 days of salt restriction, (a diet ostensibly containing less than 0.5 gm. of salt)

by not increasing their aldosterone excretion in the manner of normal subjects. Furthermore, the administration of aldosterone in a dose of 0.5 mg daily for 3 days resulted in the fall in hematocrit of one of the patients being investigated. While this sounds encouraging, Prankerd does not give any values or figures to substantiate his work.

However, investigations by Finch and Blackerd¹⁹ revealed both normal urinary 17-ketosteroids and plasma cortisol levels both before and after intravenous ACTH in stress polycythemic patients. The patients also showed a normal response to a Tilt Test.

Lawrence and Berlin invoked stress as the most likely etiology of Stress Polycythemia, although they were unable to go further than that.⁹ That stress is in some way integrally involved is undeniable. Stevens and Chabot noted that all 12 of their patients manifested anxiety and tension, extending over a period of several years by their histories. Three of the twelve were significantly depressed and two had received psychiatric therapy.¹⁵ These figures correlate well with the incidence of psychological symptomatology of most previously reported studies.

However, it was Mendels in 1967 who made the first systematic attempt to explore the psychological aspects of this syndrome.¹⁹ Mendels presents a case study of an anxious and depressed male who was worked-up and found to have Stress Polycythemia, and he indicates a clear temporal relationship between the clinical manifestations of anxiety (and the response to stress) and blood volume. The patient

presented with the common complaint of intermittent dizziness of 3 months duration and upon admission to the psychiatry service had a hematocrit of 57% and a hemoglobin of 20.5 gm/100 cc. Blood volume studies clinched the diagnosis. His hematocrit was carefully followed in the hospital and peaks were noted to be closely associated with increases in his overt anxiety, and the declines coincided with remission in his clinical state. Upon abatement of his symptomatology and discharge from the hospital 8 weeks after admission his hematocrit decreased from 57% to 44% and his hemoglobin from 20.5 gm/100 cc to 15.5 gm/100 cc. It was also noted that between his discharge from the hospital and his first outpatient appointment 10 days later his hematocrit rose to 54% and his hemoglobin to 19.0 gm/100 cc. This would seem to correlate well with the greater pressures he undoubtedly encountered outside the hospital.

In addition to receiving psychotherapy, a close watch was kept on the patient's fluid intake and output in order to determine whether there was an association between these and the plasma concentration. No significant association was found.

In view of the intricate but elusive role of stress in this syndrome and the paucity of relevant studies, patient studies were undertaken to obtain more definitive data. It was also the purpose of the study to more accurately describe the psychological and psychiatric aspects and to further delineate the natural history of the disease.

PART I - HUMAN INVESTIGATION

1. STRESS POLYCYTHEMIC PATIENTS

METHODS

From an original sample of 34 diagnosed cases of Stress Polycythemia (including 3 women) known to the Hematology Service of the Yale-New Haven Hospital, 16 men were contacted and interviewed. The others either could not be reached, would not consent, or were not granted approval by their family physician to participate, principally because a psychiatrically oriented interview might be too disturbing. Two of the cases not participating were in psychiatric treatment and a third was said to have been suicidal and refusing psychiatric care at the time the inquiries were made.

Eleven of the 16 patients were interviewed twice, at an interval of 2 years. The remaining 5 were interviewed but once. A questionnaire outline, adapted from "The Social Readjustment Rating Scale"²⁰ of Holmes and Rahe, formed the basis of the interview. While the interview was conducted in an open-ended fashion, the interviewer insured that at the end of the interview answers to all items on the questionnaire outline had been obtained. In addition, tape recordings of the entire interview were secured in half of the cases for subsequent analysis.

The aim of the questionnaire was first to obtain an objective recording of the major and minor medical and psychiatric illnesses of the patient together with an account of stressful life events (i.e., divorce, death of family member, occupational stress). Careful attention was paid to dates and in each instance the patient's hospital records were

checked to insure validity. Those patients who were interviewed for the second time were again asked to relate the above data, and in all cases, despite a 2-year hiatus, the correlations with previous statements were extremely high. The second purpose of the questionnaire was to elicit information of a subjective nature about the patients' emotional life with particular attention to his situation at the time of onset. There was extensive interaction between subject and interviewer, with the interviewer making inquiries in a friendly but persistent fashion. All the data was reviewed to establish the presence or absence of a psychiatric diagnosis.

At the end of each approximately 75-minute interview session, the patients were weighed and measured and venous blood samples were drawn to measure the hematocrit, hemoglobin count and white blood cell count. These values were correlated with those taken at other times and recorded in the patient's hospital record. The latter values were also correlated with the various personal life events related by the patient. While it is impossible to know exactly when the patient's hematocrit rose to polycythemic levels, the recognition of new symptoms common to Stress Polycythemia (i.e., dizziness, headache) has been shown to be a good measure of illness onset.

To further assess the psychodynamics of this group of patients, psychological tests were administered. Such tests were used in the hope that 1 or 2 traits might show an overwhelming preponderance among these patients. Naturally, the use of tests in this way is restricted, at most, to the repertoire of features the inventory is designed to measure. There is no

room for originality or for the finding of a feature not in the inventory. It was felt that the 3 most revealing features which could be tested for were trait anxiety, neuroticism, and extraversion. With this in mind, the "Taylor Manifest Anxiety Scale"²¹ was used to measure trait anxiety and the "Maudsley Personality Inventory"²² used to test the other 2 features. Both private and service patients who visited the Dermatology Clinic were used as a control group. Samples of these tests appear in Appendix I and II.

In order to note the similarity of the symptoms of Stress Polycythemic patients at Yale-New Haven Hospital with those previously reported in the literature,^{8,9,10,11,12,15} a complete review of findings was tabulated.

RESULTS

From a collective study of these 16 white males, certain common features could be recognized, compared with the literature descriptions, and then further findings and conclusions drawn. The pertinent clinical findings are tabulated in Table 2.

In summary, the following was observed from the data in Table 2:

1. The ages at which Stress Polycythemia was diagnosed, ranged from 26 to 63 years old, with the average being 42 years.
2. 12 of the 16 men were judged to have a ruddy complexion, with 8 of these being frankly plethoric.
3. 12 of the 16 men were overweight; 7 had a weight excess of greater than 10% above the accepted limit.

TABLE 2 - CLINICAL FINDINGS

Case	Age	Years of Observation	Ruddy Complexion	Weight % Excess*	High Blood Pressure +	Sustained Hypertension #	Other Major Medical Problems
1. (S.D.)	50	14	++	-	-	-	Duodenal ulcer Hypercholesterolemia
2. (H.S.)	63	12	+	19%	165/95	Yes	Myocardial Infarction Angina X2
3. (A.P.)	53	3	++	18%	180/130	Yes	Duodenal Ulcer
4. (M.L.)	67	4	0	7%	-	-	Duodenal Ulcer
5. (R.S.)	64	9	++	26%	180/100	Yes	Gout
6. (C.C.)	54	12	++	-	-	-	Duodenal Ulcer Myocardial Infarction X2 Ulcerative Colitis
7. (N.H.)	35	5	+	-	-	-	Thrombophlebitis
8. (J.S.)	47	5	++	6%	150/100	-	Myocardial Infarction Duodenal Ulcer
9. (A.D.)	52	11	++	16%	-	-	-
10. (W.S.)	40	6	+++	11%	195/120	Yes	Duodenal Ulcer
11. (B.D.)	63	9	+	6%	-	-	Duodenal Ulcer Ulcerative Colitis
12. (Ha.S.)	29	3	+	9%	-	-	Duodenal Ulcer Ulcerative Colitis
13. (L.W.)	64	4	+	8%	175/90	Yes	-
14. (A.J.)	57	1	0	32%	170/100	Yes	-
15. (M.B.)	70	10	0	-	-	-	Myocardial Infarction
16. (D.C.)	58	12	+++	46%	150/95	-	Myocardial Infarction Duodenal Ulcer

*Normal values from Metropolitan Life Insurance Co. data, 1958

+Blood pressure greater than 150/90 mmHg, recorded at interview

#Blood pressure greater than 150/90 mmHg, as noted from medical record

4. Half of the men had a blood pressure greater than 150/90 mm Hg, as measured at the time of interview. However, of these, only 6 had a well-documented history of sustained hypertension.

5. A remarkably high incidence of duodenal ulcers - 9 out of 16 - All but one of these was documented by X-rays.

6. 3 patients with ulcerative colitis; 2 of the 3 appearing in people who also had duodenal ulcers.

The pertinent laboratory findings appear in Table 3.

The pertinent findings from Table 3 include:

1. The peak hematocrit readings ranged from 51% to 60%, with the median being 54%. These peak readings occurred at different points in the course of the patient's polycythemia, but most peak values were noted at the time the definitive diagnosis was made.

2. When seen by the interviewer in 1966 and 1968, the patients' all had hematocrits which were either equal to or less than the peak - none were higher.

3. The range of hematocrits taken at both interviews was 45% to 55%, values extending from the normal range to those slightly above normal.

4. A comparison of hematocrits for each patient in 1966 and 1968 showed very similar values, with only one reading being as much as 4 units different.

5. Hemoglobin values were generally elevated, with a range of 15.5 gm. to 20.8 gm.

6. With the possible exception of 1 patient, the white blood count was within normal limits.

TABLE 3 - LABORATORY FINDINGS

Case	Peak Hct.	Hct.-1966+	Hct.-1968+	Hb-1968	WBC-1968	Blood Volume*, cc/kg		
						Total	Red Cell	Plasma
1	60%	50%	50%	17.6 gm	10,100	-	-	-
2	55%	50%	47%	16.6	9,500	-	-	-
3	56%	50%	50%	18.9	9,200	51	29.6	21.4
4	56%	52%	53%	19.6	5,600	58.6	29.1	29.5
5	54%	48%	52%	17.5	7,800	71.5	31.8	40.7
6	55%	55%	53%	18.8	8,100	55.8	30.6	25.2
7	56%	52%	50%	18.5	5,200	-	-	-
8	57%	45%	46%	17.5	7,000	-	-	-
9	55%	49%	52%	17.8	6,500	56.6	31.7	24.9
10	54%	52%	51%#	15.5	11,200	-	-	-
11	56%	48%	45%	-	-	-	-	-
12	52%	-	50%	17.4	6,900	-	-	-
13	54%	-	50%	16.8	5,700	-	-	-
14	54%	-	49%	18.6	4,700	-	-	-
15	53%	-	46%	16.3	6,800	-	-	-
16	53%	-	52%	20.8	10,300	-	-	-

*Total blood volume was determined by Cr⁵¹-labelled red cell technique. Plasma volume and red cell mass were calculated from the total body hematocrit determined from the venous hct.
 +Venous blood specimens were centrifuged in the micro hematocrit centrifuge at 13,000 RPM for 4 minutes, according to the micro method.
 #Phlebotomized within the past month.
 Normal blood volume measurements at Yale-New Haven Hospital: Red Cell Volume: 29 to 32 ml/kg
 Plasma Volume: 43 to 46 ml/kg

7. Plasma volumes on all 5 patients on whom they were done were low, but all the red cell volumes were within normal limits.

Particular attention was focused on the various medical, emotional, and environmental events which the patient experienced during the last 20 years of his life. A graph or "life chart" of each patient was prepared, plotting the appearance in time of these critical life events and the definitive diagnosis of Stress Polycythemia. In 12 of the 16 patients there was noted to be a significant clustering of events, requiring a definite adjustment in the ongoing life of the patient, which occurred 1 year prior to the definitive diagnosis of Stress Polycythemia. Representative graphs of 2 patients in whom a temporal relationship was found appears in Appendix III. Table 4 summarized these events for all the patients.

A glance at Table 4 and the patient's "life chart" shows that in most cases the patients experienced a significant clustering of life-altering and stressing events preceding the year that the diagnosis was made. At no other time in the patients' history did so many and so important life events occur. However, it should be recognized that some of the symptomatology described above (i.e., headaches, dizziness) were part of the polycythemic syndrome itself and could not properly be included as a cause leading up to the development of Stress Polycythemia. However, the close temporal relationship (less than 1 year) between the onset of these symptoms and the diagnosis in most cases would still encompass the majority of life-changing events described.

TABLE 4 - LIFE EVENTS

<u>PATIENT</u>	<u>NEW EVENTS OCCURRING WITHIN 1 YEAR IN WHICH STRESS POLYCYTHEMIA WAS DIAGNOSED</u>	<u>LCU VALUE</u>
1	Father died Son born Duodenal ulcers diagnosed	155
2	Severe angina pains appeared Coronary thrombosis X2	106
3	Severe headaches & vertigo Insomnia Operation for submandibular gland stone Angina pains commenced	122
4	-	0
5	Acute prostatitis attack First gouty arthritis attack Distressing day of "mental confusion and amnesia" Mother died	169
6	Severe business stress Uncle died (very close)	102
7	Hospitalized for thrombophlebitis Fired from job "Migraine" headache, spells & insomnia began	116
8	Clinical depression (seen by psychiatrist) Marital difficulties started Peptic ulcer diagnosed	161
9	-	0
10	Peptic ulcer diagnosed Varicose veins stripped Problems building own house Onset of headaches, dizziness & tinnitus Flare-up of marital difficulties Promoted at work	170
11	Diverticulitis diagnosed	53

TABLE 4 - LIFE EVENTS (continued)

<u>PATIENT</u>	<u>NEW EVENTS OCCURING WITHIN 1 YEAR IN WHICH STRESS POLYCYTHEMIA WAS DIAGNOSED</u>	<u>LCU VALUE</u>
12	Hospitalized for thrombophlebitis Moved twice Son born	132
13	-	0
14	Severe headaches Son left home Found to be suffering from narcolepsy	98
15	Daughter left home and got married Myocardial Infarction	92
16	Attack of atypical facial neuralgia Fired from job X2	147

The LCU values which appear in Table 4 refer to the "life change units" which are used in quantitatively grading the responses made to the "Schedule of Recent Experience" questionnaire prepared by Holmes and Rahe and described in their article on "The Social Readjustment Rating Scale",²⁰ which, as I described previously, formed the basis of my questionnaire. Their "Schedule of Recent Experiences" documents, by year of occurrence, changes in residence, occupation, finances, personal status, family, social activities, and health status. The numerical counterparts to life events, ranging from 100 for death of spouse to 11 for minor violations of the law, were determined by statistical analyses in questionnaires administered to over 5000 individuals. From this work a "life crisis" was defined as any clustering of life changing events whose individual values summed to 150 LCU or more in 1 year.²³ Where a "life crisis" persisted for longer than 1 year, successive years had separate LCU totals greater than 150.

While there were a few life events found among the polycythemic group which were not considered in the "Schedule of Recent Experience" (SRE) (i.e., angina pains, tinnitus), my probing into the patient's history was so similar that each of the life events uncovered was quantitated similarly to that of the SRE.

A look at the Stress Polycythemic patient scores showed that of the 11 patients that were noted to have a significant "clustering" of life events, 10 had an LCU score over 100. In addition, 4 patients had scores over 150, classifying them as having had a "life crisis".

In order to see what the importance of the LCU values might have had in the temporal relationship to the onset of Stress Polycythemia, it was decided to take a control year and determine the LCU magnitude. Arbitrarily and before the patients were interviewed, the year ending 3 years before the year of the diagnosis was chosen. The results of this study appear in Table 5.

TABLE 5 - LIFE EVENTS

<u>PATIENT</u>	<u>NEW EVENTS OCCURRING 3 YEARS PRIOR TO THAT IN WHICH STRESS POLYCYTHEMIA WAS DIAGNOSED</u>	<u>LCU</u>
1	Changed jobs	36
2	-	0
3	Peptic ulcer diagnosed Sister died	116
4	-	0
5	-	0
6	-	0
7	-	0
8	Sister died of cancer Father died	126
9	-	0
10	Quarrels with wife increased	35
11	Flare-up of duodenal ulcer Subtotal gastrectomy	106
12	Birth of son	39
13	Feuding with relatives	29
14	-	0
15	Myocardial Infarction	53
16	-	0

A look at the results of Table 5 reveals that none of the patients experienced even a mild "life crisis" as defined by Holmes and Rahe. In fact, one half of the patients did not receive any LCU values for the entire year. Only 2 of the 16 patients scored higher values in the third year prior to the diagnosis than they did in the year preceding the definitive diagnosis.

A comparison of Tables 4 and 5 shows:

1) A combined total of 1560 LCU for the 1-year period preceding diagnosis for all 16 patients as compared to 540 LCU for the third year period which preceded diagnosis. Analysis by the Wilcoxin matched-pairs sign ranks test yields $T = 11$ and $p < 0.01$.

2) An absolute number of 40 life changing events for all 16 patients in the year prior to diagnosis, as compared to an absolute number of 11 three years prior. $X^2 = 16.5$ for 1 degree of freedom and $p < 0.005$.

3) It should be noted that 3 patients did not have any LCU in the year preceding diagnosis. Of these, 2 again did not have any LCU two years prior to that one and the third patient had a mere 29 LCU.

PSYCHOLOGICAL TESTS

Psychological tests were administered to better ascertain the presence, absence, magnitude, and relevance of certain features in the patients' psychodynamic functioning. While these tests could not absolutely prove that these factors were involved with the appearance of Stress Polycythemia, they do have value in suggesting hypotheses relating psychological factors and Stress Polycythemia. The "Taylor Manifest Anxiety Scale"²¹ measured trait anxiety and the "Maudsley Personality Inventory"²² measured neuroticism and extraversion/intraversion (see

Appendix I and II). The scores of the Stress Polycythemic patients are compared with the values for control groups established by the designers of the tests as well as the results from male outpatients visiting the Dermatology Clinic at Yale-New Haven Hospital. As suggested in an article by Bernstein,²⁴ the interviewer left the room at the time the tests were given and returned when he was certain the patient had completed them.

Table 6 shows the resulting scores of the "Manifest Anxiety Scale" of the Stress Polycythemia patients and compares them to the normative percentile established by Taylor. The normative percentage equivalents were charted after scores of 1,259 college males, over the course of 2 years, took the test. Taylor states "Since we have dealt almost exclusively with college students, I have normative data only from this group. My impression from the few non-college groups we have tested and from other sources are that the norms are roughly the same, but, of course, it would be unwise, even so, to use the college norms as anything but an informal guideline."²⁵

TABLE 6 - MANIFEST ANXIETY SCALE (MAS)

<u>PATIENT</u>	<u>RAW SCORE</u>	<u>CORRESPONDING CONTROL CUMULATIVE PERCENT</u>
1	31	97
2	20	79
3	24	88
4	18	73
5	28	94
6	19	76
7	20	79
8	21	81
9	21	81
10	24	88
11	16	64
12	18	73
13	27	93
14	21	81
15	10	27
16	24	88

The mean score was 21.4 with a standard deviation of 5.0

Table 7 contains the scores of the Dermatology patients who consented to take the test; again results are compared to the percentages of the control college population.

TABLE 7 MAS - DERMATOLOGY PATIENT

<u>PATIENT</u>	<u>DIAGNOSIS</u>	<u>RAW SCORE</u>	<u>CORRESPONDING CONTROL CUMULATIVE PER CENT</u>
1 (E.C.)	Psoriasis, severe	7	21
2 (B.R.)	Psoriasis, moderate	18	73
3 (L.K.)	Psoriasis, minimal	26	92
4 (F.H.)	Epithelioma of neck	1	2
5 (A.B.)	Post-radiation Fibrosis	22	85
6 (W.P.)	Tinea/seb dermatitis	8	27
7 (E.D.)	Psoriasis, moderate	20	79
8 (S.A.)	Asteatotic eczema	14	55
9 (R.M.)	Actinic Keratoses/ Tinea versicolor	4	8
10 (J.U.)	Actinic Keratosis	10	35
11 (R.T.)	Eczematous reaction	4	8
12 (N.L.)	Psoriasis, moderate	4	8
13 (J.B.)	Exfoliative dermatitis	10	35
14 (A.J.)	Psoriasis, moderate	18	73
15 (R.W.)	Xerosis	19	76
16 (G.R.)	Atopic dermatitis	10	35

The mean score was 12.2 with a standard deviation of 7.5. A comparison of the scores registered by the 2 groups by the Mann-Whitney yielded a $p < 0.001$.

The cumulative per cent column can be understood by considering an individual scoring at, for example, the 88 per cent. This means that his score is as high or higher than 88 per cent of the normative group and is exceeded by only 12% of the normative group.

As a group, the Stress Polycythemics had a mean score of 21.4. According to the normative data established, this would place the group in about the 83rd percentile, leaving only 17 per cent scoring higher.

Our control group of dermatology patients, ranging in age from 23 to 72 with a mean of 50.7 years, had a mean score of 12.2 with a standard deviation of 7.5. In relation to the normative data, this would place them in about the 47th percentile, placing them about mid-way on the scale.

In order to study the levels of neuroticism and extraversion/introversion of the polycythemic patients, the "Maudsley Personality Inventory" (MPI) was administered. Again, both the normative data supplied by the designers as well as Dermatology patients served as controls. Again, American college students served as the norms for the MPI. However, Eysenck also included for the sake of comparison, the mean scores with standard deviations of different groups of people (i.e., hospitalized psychosomatics, neurotic patients). The results of this study are found in Table 8.

TABLE 8 - MAUDSLEY PERSONALITY INVENTORY (MPI)

<u>PATIENT</u>	<u>NEUROTICISM</u>		<u>EXTRAVERSION</u>	
	<u>RAW SCORE</u>	<u>PERCENTILE</u>	<u>RAW SCORE</u>	<u>PERCENTILE</u>
1	34	89	20	18
2	20	49	28	48
3	26	70	26	40
4	24	64	30	57
5	36	92	28	48
6	20	49	34	74
7	26	70	38	90
8	28	74	30	57
9	21	55	11	2
10	23	60	25	34
11	24	64	26	40
12	36	92	28	48
13	44	100	20	18
14	25	67	12	3
15	23	60	21	20
16	40	97	30	57

The mean neuroticism score was 28.1 with a standard deviation of 7.5. This placed the group at the 74th percentile in relation to the normative data. The extraversion scale revealed a mean of 25.4 and a standard deviation of 7.2. The corresponding percentile was about the 37th.

The MPI was given to the control group; the results appear in Table 9.

TABLE 9 - MPI, DERMATOLOGY PATIENTS

<u>PATIENT</u>	<u>NEUROTICISM</u>		<u>EXTRAVERSION</u>	
	<u>RAW SCORE</u>	<u>PERCENTILE</u>	<u>RAW SCORE</u>	<u>PERCENTILE</u>
1	5	8	37	85
2	28	74	28	48
3	38	95	28	48
4	6	10	12	3
5	28	74	20	18
6	9	17	21	20
7	30	80	26	40
8	19	46	26	40
9	12	23	36	80
10	31	82	20	18
11	8	15	36	80
12	13	26	42	97
13	12	23	18	13
14	18	42	10	1
15	28	74	36	80
16	5	8	19	15

The dermatology patients' mean score of 18.1 with a standard deviation of 10.9 in neuroticism placed them in the 42nd percentile. This score placed them within a 2 point range of the average scores of both the American university student norm group (mean 20.66) of 1064 and the English norm group of 1800 people (mean 19.89). $P < 0.02$ by Mann-Whitney Test.

In the introversion-extraversion scale, their mean score of 25.9 with a standard deviation of 9.5 placed them in the 40th percentile. Again comparing them with the data supplied by Eysenck, this fits them within 1 point of the English norm group (mean 24.91) and 3 points of the American university students (mean 28.73). $P \approx 0.91$ by Mann-Whitney Test.

PSYCHOLOGICAL OBSERVATIONS

Four of the patients were diagnosed as having chronic depressive reactions of moderate severity. In 3 of these cases the depressive reaction went back to just before the time when the diagnosis of Stress Polycythemia was made. As one of these men put it, "All my troubles started around then." Six were diagnosed as chronic anxiety reactions either in the mild or moderate category of severity. None were psychotic and all cooperated well during the interview. Sociopathic tendencies were not found in this sample nor was there evidence for the use of phobic, dissociative or obsessive-compulsive defenses. The modal defenses were denial, somatization and conversion of anxiety into body movement. When these defenses were not successful, depressive affects appeared.

All took their jobs and responsibilities very seriously and were concerned about their relationships to other people. When questioned about how they used their spare time, most replied that "they had to be on the move or be doing something." One patient characterized himself as a "nervous Henry who couldn't sit still for 2 minutes." All of the 16 men smoked upwards of 5 cigars a day or from 1/2 to 2 packs

of cigarettes a day.

There were 6 patients in the sample who were not classed as having any psychiatric diagnoses. These patients shared the same general characteristics as the others but seemed to have better control of their anxieties.

Three of the patients had been under psychiatric treatment - 2 for a period of about 1 month and 1 for several years. However, none of these had an ongoing relationship with a psychiatrist at the time they were interviewed.

Discussion

The diagnosis of Stress Polycythemia made at Yale-New Haven Hospital was based primarily on the appearance of a benign clinical course. The absence of splenomegaly, leukocytosis, thrombocytosis, and the presence of a normal leukocyte alkaline phosphatase, pulmonary function test, renal function and abnormal blood volume determinations served as ancillary evidence in confirming the diagnosis where necessary.

While the sample of 16 subjects is small, statistically demonstrable and consistent trends suggested by the data have been noted. It is likely that with a larger sample these trends would have been more striking and it might have been possible to make even more correlations. The validity of any conclusions suggested by the present data must depend upon the results of more extensive testing in a larger sample.

The clinical data described in this paper is very similar to that studied in other series (9, 10, 11, 12, 13) in regards to the average age of onset, the overwhelmingly predominant male population, and the incidence of plethora, hypertension, obesity, dizziness, and emotional

overlay. That this is a "typical" Stress Polycythemic population can hardly be denied. However, the extremely high incidence of concomitant duodenal ulcers (9 of 16) and ulcerative colitis (3 cases) is reported here for the first time.

Wintrobe's (26) value for the normal male hematocrit is $47\% \pm 7$. If hematocrits are viewed as a spectrum, the hematocrits of most of these Stress Polycythemic patients fall into the upper limits of normal with only a few readings above. This is very characteristic of values for Stress Polycythemic patients as reported in other studies 9,10,11,12,13.

It is well known that hematocrit readings fluctuate from day to day as well as at different times in the same day. This is believed to be particularly true of people with Stress Polycythemia. An examination of the hematocrit values obtained in 1968 reveals a range of 45% to 53%, all within the normal range but skewed toward the upper limits.

Study of the hematocrit values shows that the hematocrits are not continuously elevated as Hall¹² states and that it is possible for a patient with values in the upper limits of "normal" and/or the polycythemic range to demonstrate temporal redistributions of hematocrit values which are more commonly found in the normal distribution.

Table 10 was constructed to demonstrate the life events which accompanied the overall lower hematocrit readings of 1968, as contrasted to those events in the years already described (Tables 4 and 5).

TABLE 10 - LIFE EVENTS IN THE PAST YEAR

<u>PATIENT</u>	<u>EVENTS IN THE PAST YEAR (1967-68)</u>	<u>TABLE 10 LCU</u>	<u>TABLE 4 LCU</u>	<u>TABLE 5 LCU</u>
1	Son married	29	155	36
2	Mother had stroke	44	161	126
3	Son married	29	122	116
4	-	0	0	0
5	Retired	45	169	0
6	"Intermittent claudication" problems arose Wife hospitalized for diver- ticulosis	97	102	0
7	Changed jobs voluntarily	20	116	0
8	-	0	161	126
9	Son married Daughter married	58	0	0
10	Sister died	63	170	35
11	-	0	53	106
12	-	0	132	39
13	Brother died	63	0	29
14	Glaucoma diagnosed	53	98	0
15	-	0	92	53
16	Myocardial infarction	53	147	0
TOTAL		554	1560	540

The LCU total value obtained for 1967-1968 approximates very closely that achieved 3 years prior to the diagnosis of Stress Polycythemia. The mean hematocrit of the 16 patients in 1968 was 50%; this contrasts to the mean hematocrit of 53.5% achieved in the year prior to diagnosis, when the total LCU was 1560. These results are similar to those of Mendel's¹⁹ who noted a definite correlation between life events and concomitant rises and falls of the hematocrit.

Such findings would question the concept of a "normal" hematocrit for an individual or for the population as a whole. Studies undertaken to establish normative data have always used serial readings of quiescent

individuals. It would appear that a long-term prospective study observing people at different periods of physical and psychic equalibria would show a different spectrum of hematocrit values. The hematocrit, like blood pressure, appears to be labile and greatly influenced by everyday occurrences.

The prevalence of Stress Polycythemia in the general population has never been documented. All of the patients in this study facilitated diagnosis by seeking medical attention. The majority of patients reluctantly seek the advice of physicians and greatly complicate an accurate determination of the prevalence of most diseases. However, stress seems closely correlated to higher hematocrit values, and the prevalence of Stress Polycythemia is probably greater than heretofore realized.

The finding that the LCU values are significantly higher in the year preceding diagnosis of Stress Polycythemia than in control years suggests a strong relationship. However, finding such a correlation does not establish an etiologic relationship. Rahe and Meyer et al²⁷ feel that most, if not all, disease have their onset in a setting of mounting frequency of social stress. These authors feel that any set of environmental factors which significantly alter the steady state of the individual increases the probability that bodily resistance to disease will be lowered and postulate that the life crisis represents a necessary but not necessarily sufficient precipitant of major health changes. If this is the case, anxiety and stress may be a necessary factor in Stress Polycythemia but the precipitating factor may still be undetermined. If

an etiologic relationship exists between a summation of emotional stresses and the appearance of Stress Polycythemia, it must be complex and factors not appreciated at the present time must be involved.

In assessing this data, a word on the retrospective nature of these studies is in order. The obvious problem is memory, or the reliability and validity of recall of life events and health changes. An overestimate or underestimate of these could influence the nature and meaning of the associations demonstrated. One could speculate that variability in memory might operate falsely to confirm or deny the significance of the association of health change and life change. Two studies having relevance for this problem^{28,29} suggest that memory for some life events and health changes for a comparable time span is relatively good, and for others relatively poor. Thus, at the moment, there is no systematic body of data which would permit a conclusion whether or not the bias of memory would change the significance of the finding.

An attempt to further clarify the problem of memory was carried out with SRE data³⁰. The subjects in the study were asked to complete the SRE and then again 8 months later. Analysis of the data indicated a highly significant agreement to the items subscribed to in the first and second replies. So, while it is not possible to estimate the completeness of recall, it does seem that what is being recalled is consistent. This was also well seen in the patients interviewed twice and asked to recall relevant data.

While it is difficult to draw character profiles using so small a population, it was hoped that certain traits or constellations of

traits or of personality could be elicited. For this reason, both the TaylorMAS and the MPI were administered. All the subjects that were asked to complete these tests were told that they were contributing to medical research and that interest lay in groups of patients (not the individuals themselves). As they had nothing to lose by cooperating and nothing to gain by falsifying their responses, we may presume that the majority of patients made an honest effort to do what they were asked.

The Taylor "Manifest Anxiety Scale" is the best measure available to measure "trait anxiety", defined as "anxiety as a life pattern" and distinct from "state anxiety" or "anxiety at the time of measurement".³¹ Scores on anxiety trait were shown to be uninfluenced by any stress which the interview itself might cause.³¹ The results of the administration of the MAS shows that the Stress Polycythemic patients scored in the 83rd percentile as compared to normative data. If this figure is accurate, it would indicate that these patients have a significantly above normal trait anxiety to merit attention. Kendall³² noted that the reliability of the MAS has been shown to be very high, ranging in different studies from 0.81 to 0.96 and 0.91 in his own study. The problem in drawing conclusions has resulted from undecided and unagreed upon validity of the scale. Kendall feels that the MAS is valid "only as an extremely coarse measure of manifest anxiety".³²

Siegmán feels that the greatest problem in accurately interpreting results is "the individual differences in self-awareness and sensitivity to one's symptoms".³³ It is this self-evaluation rather than the individual's reluctance to admit anxiety symptoms which he feels is

the most significant variable. From the results of the Stress Polycythemic patients, it would appear that a significant amount of trait anxiety was present and that the patients were aware of this and were able to express it. Further, the MAS has been shown to be impervious to changes in stimulus conditions which either preceded or were present during the actual testing.³⁴ The meaning and validity of the quantitative data, nevertheless, cannot be absolutely ascertained.

In attempting a rough assay of trait anxiety among our population, it is important to note that their mean score of 21.4 was much higher than the 12.2 mean of the dermatology patients or the 13.06 mean reported by Kendall³² in his control 93 subjects. While no absolute number of value can be assigned, it is an observation which requires attention and further investigation.

The problem of controls in psychological research is very difficult because of the uniqueness of individuals and also because of variability in them over time. The selection of dermatology outpatients as controls was made chiefly on the basis of similar overall disability of the patients. People with Stress Polycythemia can, by and large, conduct normal lives, in that their activity is not limited in any way. It was felt that similar living circumstances prevailed in the overwhelming majority of dermatology outpatients, and, in order to avoid any selection of patients, this clinic population would be most appropriate as a control group.

The age range and mean age of the controls matched almost exactly that of the experimental group. In addition, the control group consisted of people almost totally from the middle class, much as did

the polycythemics. Also, the interview setting was much the same since both groups were required to come to the hospital and were then left alone in a room to complete the tests. Nevertheless, it was clearly recognized that there is a substantial emotional overlay in patients with skin disorders, as there obviously is with patients with any disease, that could not be measured or its significance truly known.

The Maudsley Personality Inventory (MPI) was constructed to measure 2 pervasive and relatively independent dimensions of personality - extraversion - intraversion (E) and neuroticism-stability (N)²². Eysenck defined neuroticism as "the general emotional instability of a person, his emotional overresponsiveness, and his liability to neurotic breakdown under stress." Extraversion, as opposed to intraversion, refers to the "outgoing, uninhibited, impulsive and sociable inclinations of a person."

In neuroticism, the Stress Polycythemic population scored a mean of 28.1 which placed them in the 74th percentile. The extraversion mean was 25.4, corresponding to the 37th percentile of the normative data. For the neuroticism scale reliability coefficients lie between 0.85 and 0.90 and for the extraversion scale these values lie between 0.75 and 0.85, with the majority above 0.80. Test-retest reliabilities on about 100 cases were found to be 0.81 and 0.83 respectively³⁵. These figures are very significant.

Sainsbury³⁶ administered the MPI to outpatients attending a general hospital and arrived at several conclusions which have relevance in this study. From a study of over 1300 patients he concluded that the chronicity of a disease did not account for the high neuroticism score found in people with psychosomatic disease. It is rather the

patient's psychodynamic state which accounts for his score. Secondly, Sainsbury showed that there was no tendency for outpatient departments to select neurotic patients. This was shown by demonstrating that the mean neurotic score of his outpatient control group was similar to that of the general population, while his "psychosomatic group" had a markedly higher mean than both.

Sainsbury's control population of 546 had a mean neuroticism score of 18.38 and a mean extraversion score of 25.74. This is extraordinarily similar to the means obtained in the dermatology patients, 18.1 for neuroticism and 25.9 for extraversion. Further similarity is noted to Eysenck's control sample of 1800 patients who had a mean neuroticism of 19.89 and mean extraversion of 24.91.³⁵ Even though our sample of controls is small, it does seem to be representative of other norms.

Further comparisons to Sainsbury's study shows that his psychosomatic population had a mean neuroticism score of 23.81 and 23.16 for extraversion. The Stress Polycythemic patients had mean scores of 4.3 higher and 2.3 higher, respectively. The mean score of 28.1 in neuroticism places them 7.5 points above the American norms and 4.3 points above Eysenck's group of 459 psychosomatics who were tested.

From his study of psychosomatic disease, Eysenck developed 2 hypotheses relating neuroticism and extraversion to psychosomatic disorders.³⁷

1. "The level of neuroticism will be higher in patients with psychosomatic disease than in control groups without psychosomatic disease."

2. "If, as is commonly believed, psychosomatic disease results from the prolonged physiological effects of an emotion, such as anxiety, patients with these diseases will be less extraverted than a non-psychosomatic control group; because it has been found that anxious and depressed patients are intraverted."

It is Eysenck's contention that "average scores (on the MPI) may be said to be those between the 31st and 70th percentiles (of the normative data). Individuals scoring above or below these cutting-off points would be depicted as above or below average on the trait under consideration."³⁵ Thus, the Stress Polycythemic population would suit the first of his hypotheses but not the second.

The probability is great that had other groups of people been tested with disease believed to be of psychosomatic origin similar findings to those of the polycythemics would have been uncovered. Reports of this nature are, however, rare. Kanter and Hazelton³⁸ administered the MPI to 35 males with duodenal ulcers. They noted a mean score on neuroticism of 30.0 and 26.7 for extraversion. These findings are very near those uncovered in this study and support the first contention of Eysenck that psychosomatic patients have a significantly higher level of neuroticism, as measured by the MPI, than do controls.

In making psychological observations on these patients it should be noted that, in the 1 or 2 interviews conducted with these patients, it was very unlikely that more than the surface of the patients' personalities was explored. Furthermore, the need for objectivity probably resulted in an under-reporting of psychological stress. It

is highly probable that longer exposure to the patients would have unearthed more psychopathology and would have identified more stress. Nevertheless, careful study of the tapes and observations on the reactions and conduct of the patients during the interview was very helpful in attempting to make profiles.

Many investigators have sought to account for different psychosomatic disorders in terms of differences in personality. The principal exponents of the view that each disorder is characterized by a typical or distinctive personality are Dunbar³⁹ and Kissen⁴⁰. However, the consensus is that the similarities in the personality profiles obtained from patients with various psychosomatic illnesses is more evident than the differences. It appears that almost all of the patients with psychosomatic diseases show a great deal of what is commonly referred to as "neurotic tendencies" in their personality. Therefore, it seems likely that the failure to discover a clear association between these diseases and a characteristic type of personality has been because the traits previously described in these patients are those common to most "neurotics".

No attempt has been made to rigidly classify these patients. Nevertheless, it was felt that 25% of them were undergoing depressive reactions of moderate severity and 38% were experiencing anxiety reactions, mild or moderate in severity. No other psychiatric diagnoses were made. While these percentages are rather high, it should be noted that these are the most common reactions found in the general population and their significance, therefore, influenced by sampling error.

It was also noted that the life styles of these men were similar in that they were strivers, took their obligations seriously, and tended to deny and somatize their anxiety. Their susceptibility to psychosomatic disease was undeniable in view of the fact that 56% had X-ray proof of duodenal ulcers and 19% had had ulcerative colitis with blood and mucus being passed per anum. Whether such a high incidence of psychosomatic disease suggests some common defense or lack of defense against life stress can only be hypothesized. Nevertheless, it exists.

Long-term follow-up has proved to be the best way of confirming the diagnosis of Stress Polycythemia. Except for Kaung and Peterson,¹¹ who emphasized the high complication rate of thromboembolic phenomena, all other investigators have reported few, if any, sequelae. A benign clinical course has repeatedly been attributed to Stress Polycythemia.

Follow-up of our patients ranged from 1 to 14 years, averaging 7.5 years. All but one of the patients felt in good health or better and were able to continue working and living in what they described as their normal pattern. The one exception was "forced to retire" and curb his activities because of frequent daily attacks of dizziness, tinnitus and malaise. To date, a definite explanation of his complaints has not been determined, but it has generally been attributed to psychic distress. Four other patients have complained of frequent dizziness but none have felt incapacitated by this.

Five of the 16 patients have experienced a total of 7 myocardial infarctions. Of these 5 occurred before the diagnosis of Stress Polycythemia, 3 occurring within 1 year preceding diagnosis. Two

patients had documented calf thrombophlebitis, both occurring within the year prior to diagnosis. No other thromboembolic phenomena were noted.

The only other features commonly mentioned by these patients were thirst and excessive sweating. Nine patients stated that they were always much more thirsty, and consequently ingested more liquids, than other people around them. None were able to give a temporal relationship to the diagnosis of Stress Polycythemia, but most felt that they had always consumed more fluids than others. Four of these same 9 patients also complained of excessive noticeable sweating throughout the years. Such findings may be coincidental but merit special attention as they could have some significance to the hemoconcentration which occurs.

CONCLUSIONS

Several conclusions might now be extracted from the preceding discussion. The final acceptance of these conclusions must necessarily await the more extensive analysis of a greater variety of data in a larger sample than was possible in the present study. Nevertheless, it is believed that there is sufficient data at hand to permit the following interpretations.

Stress Polycythemia seems to have its onset in a setting characterized by a significant clustering of changing and stressful life events. This clustering has been referred to as the psychosocial "life crisis". It would appear that in these individuals naturally occurring life situations which alter or threaten the status quo of the individual

and evoke attempts at adaptive behavior also evoke the physiological disorder, Stress Polycythemia. While these life-changing events appear to be closely linked, it has not been proved that they are absolutely necessary to initiate the disorders. Certainly, the majority of the population experience life-altering experiences without developing Stress Polycythemia.

Psychological testing seemed to indicate that these individuals perceived these changes differently than controls as manifested by their higher scores in trait anxiety and neuroticism. It would appear that these individuals have a noticeable upsurge of feelings of anxiety on a relatively larger number of occasions, under more circumstances and in a larger number of different situations than do their peers. It is this relatively unfluctuating condition which probably exerts a constant influence on their behavior. While they are more likely to experience anxiety, the intensity of their feelings will be a function of the nature of the situation and their personal characteristics. As Hinkle⁴¹ stated, "it seems likely that those who perceive their life situations as threatening, demanding and unsatisfactory may become more susceptible to illness because of the physiological changes evoked during attempts to adapt to the threats they perceive."

An absolute or quantitative measure of trait anxiety and neuroticism cannot be properly assigned to the patients. However, the questionnaires proved very successful in confirming the suspected characteristics which were observed from previous clinical observation.

It would appear from the preceding information that Lawrence and Berlin's⁹ original observation that stress is integrally involved is correct. The exact relationship awaits further psychological and physiological experimentation.

2. PSYCHIATRIC PATIENTS

In the previous section studies showed that none of the 16 patients were thought to have significant enough emotional impairment to warrant hospitalization. In view of the fact that Mendels' case report is of a hospitalized patient,¹⁹ it was felt worthwhile to attempt to determine the prevalence of Stress Polycythemia in a male psychiatric population.

METHODS

The records of two-thirds of all the male patients under 30 years and all the male patients over 30 years who had been admitted to the In-patient Psychiatric Service of Yale-New Haven Hospital between 1960-1966 were studied. The patients were divided into age categories and their hematocrits followed throughout their hospital stay. In view of the urgency which necessitated admission it was assumed that the patient was most acutely stressed upon admission and progressively improved until favorable discharge was granted.

RESULTS

Of the 190 male patients randomly selected for study, only 117 could be followed completely and a proper hematologic evaluation of them made. Of the 73 not followed, 10 were in the hospital for too short a period for more than one hematocrit value to be obtained, 4 left the hospital against medical advice, 11 could not be studied because their

charts were not located, and 48 cases had no accompanying hematocrit values or had an insufficient number of values from which to draw any conclusions. The diagnoses of the 117 psychiatric patients included: depressive reaction, anxiety reaction, involuntional depression, various neuroses, schizophrenia (various types), psychotic reactions, personality disorders, suicidal gestures, adjustment reaction, and chronic brain syndrome. The age distribution of the patients was as follows:

11-19 years.....	11 patients
20-21 years.....	43 "
30-39 years.....	17 "
40-49 years.....	21 "
50-59 years.....	13 "
60-69 years.....	11 "
70-75 years.....	1 "

The range of hematocrits upon admission was:

Hematocrit 32-39.....	6 patients
Hematocrit 40-49.....	95 "
Hematocrit 50-53.....	16 "

The range of hematocrits upon discharge was:

Hematocrit 38-39.....	7 patients
Hematocrit 40-49.....	107 "
Hematocrit 50-53.....	3 "

Table 11 is a listing of patients whose hematocrits varied by more than 4 percentage points from time of admission to discharge.

TABLE 11

<u>PATIENT</u>	<u>DIAGNOSIS</u>	<u>ADMISSION HCT.</u>	<u>DISCHARGE HCT.</u>	<u>DIFFER.</u>
1	Depressive reaction	50	44	6
2	Passive-aggressive personality	49	39	10
3	Involuntional depression	48	41	7
4	Depressive reaction	48	42	6
5	Manic-depressive psychosis	50	45	5
6	Schizophrenia, paranoid type	50	44	6
7	Manic-depressive psychosis	50	45	5
8	Manic-depressive psychosis	50	45	5
9	Depressive reaction	51	45	6
10	Depressive reaction	48	43	5
11	Depressive reaction	45	39	6
12	Psychotic reaction	49	43	-6
13	Schizophrenia	50	45	5

The data presented on the preceding page shows that the overwhelming majority of patients had hematocrits in the normal range both on admission and on discharge. However, there were 16 patients who had hematocrits above 50 on admission; this was reduced to 3 patients at discharge.

An analysis of all the data showed that there were 13 patients who had hematocrits 5 or more units higher on the day they were admitted than on the last reading before they were favorably discharged. Of these, 7 patients had initial hematocrit readings of 50 or greater. Among the latter group, the greatest variant was found to be 6 units, a hematocrit reading of 50 on admission fell to 44 on discharge 2 1/2 months later.

The most dramatic change was registered by a 42 year old white male, whose hematocrit dropped 10 percentage points from 49% to 39% in a matter of 3 months. A review of his medical record revealed that he was plethoric and had documented duodenal ulcers. In addition, he had undergone several severe life crises within the year preceding admission; these included a divorce, being fired from his job, and an amnesic episode 1 month prior to admission - all of which precipitated his admission. A weekly study of his hematocrit showed that his values gradually decreased and never rose again. Unfortunately, this patient was not available for follow-up study.

DISCUSSION

While absolute diagnosis of Stress Polycythemia rests with long-term follow-up and the laboratory demonstration of a normal total

blood volume and red cell mass with a smaller than normal plasma volume one should suspect that diagnosis if a stressful situation is resolved and at the same time there is a concomitant decrease of an elevated hematocrit. Plasma volume studies were not done on any of the patients, nor were records following their weights kept. However, hematocrits were taken on a weekly basis and occasionally even more frequently.

Except for 1 patient whose hematocrit was 53% and remained there for the duration of his hospital stay, none of the patients could be considered to be truly polycythemic. Yet the other 15 patients who were admitted with hematocrits greater than 50% experienced an average drop of 4% at time of discharge. Also, over one-half of the patients who experienced a drop of 5% or greater were among this group. That there is a temporal relationship between the decreased hematocrit and improvement in the clinical condition is undeniable but whether there is a causal relationship or whether this represents a Stress Polycythemic-like response is unproveable. Had the one patient whose hematocrit dropped 10 percentage points had a higher initial hematocrit it might have been able to postulate, with the aid of the clinical and medical data, that he had Stress Polycythemia. However, it would be unwise to say so with the material and information we have available.

Examination of the data showed that while there were 13 patients whose hematocrits decreased by 5 or more percentage points only 4 of the 117 patients showed an increase in hematocrit of more than 5 points, and one of these increases occurred after substantial blood loss from a suicide attempt prompted admission. The other 3

hematocrits rose from 38% to 43%, 41% to 47% and 46% to 51%. It appears from this data that the majority of patients tend to remain within 5 percentage points of their admission hematocrit till discharged. However, there were 13 patients whose hematocrits dropped by 5 or more points as compared to only 4 whose were raised by that amount. Yet no definitive conclusion as regards Stress Polycythemia can be drawn from this.

In conclusion, it was not possible to state that a single case of Stress Polycythemia was uncovered in this sample of 117 hospitalized males. The point which must be made is that the male patient in his 40's or 50's with a hematocrit greater than 50% and accompanied by ruddy complexion, hypertension, or psychophysiologic findings should be closely followed and, if doubt exists, total blood red cell and plasma volume studies done. If this had been done and if ancillary medical information had been more informative, it might have been possible to uncover a maximum of 7 Stress Polycythemic patients.

3. MEDICAL STUDENTS

The specific measure of hematocrits before and after an acute stress situation and its possible variance during this time has never been reported. The normal hematocrit values which appear in textbooks represent quiet-state values. Whether these values can accurately be applied in stressful and excited states is not known.

METHOD

In order to assess the effects of such an acute stressful situation on the hematocrits of a sample population, all second-year

medical students at the Yale School of Medicine were asked to allow their blood to be drawn around the time preceding National Medical Boards, an extremely important and stressful period. For the 10 male students who responded, hematocrits, weight and blood pressure readings were recorded 4 times: about a month prior to National Boards, the afternoon before Boards were given, immediately at the conclusion of Boards* or a day after the conclusion#, and a week later. To help establish "the normal hematocrit" for each participating student, in addition to noting the amount of individual fluctuation, 3 control readings were taken within a 3 week period about 2-5 months after National Boards. In all cases venous blood was drawn, and the micro method used in centrifuging and reading the results.

RESULTS

The hematocrit results appear in Table 12.

TABLE 12 - HEMATOCRIT READINGS OF MEDICAL STUDENTS

<u>STUDENT</u>	<u>Hct 1 Month Prior</u>	<u>Hct day before Boards</u>	<u>Hct after Boards (* or #)</u>	<u>Hct 1 week after</u>	<u>HCT. CONTROLS</u>		
					<u>1</u>	<u>2</u>	<u>3</u>
1. (C.V.)	43%	48%	46%*	42%	44%	44%	44%
2. (H.C.)	45%	50%	49%*	46%	47%	47%	47%
3. (H.F.)	41%	44%	41#	41%	42%	41%	41%
4. (D.D.)	43%	46%	43#	42%	43%	41%	42%
5. (N.C.)	42%	44%	42%*	42%	40%	42%	41%
6. (A.K.)	45%	47%	45%	44%	45%	45%	45%
7. (L.M.)	42%	44%	42%#	-	43%	43%	43%
8. (R.C.)	43%	45%	46#	46%	44%	43%	44%
9. (R.J.)	48%	48%	47#	-	47%	47%	48%
10. (J.B.)	50%	48%	50%*	-	48%	50%	49%

A study of the student hematocrits shows.

(1) in 8 of the 10 cases there was a rise of between 2 to 5 percentage points from one month prior to the Boards to the reading the

the day before Boards.

(2) In 7 of these 8 cases the hematocrit subsequently went down after Boards to a level comparable to that a month before. In fact, in all but 1 student the values for 1 month prior and 1 week after are within 1 percentage point. Only 1 student showed an additional rise in hematocrit after Boards.

(3) In the above-mentioned 7 students, the hematocrit value taken just before Boards was the highest hematocrit of the 6 or 7 different trials recorded for each patient.

(4) All of the control values are within 2 percentage points of each other.

DISCUSSION

It is interesting to see such a consistent rise in the hematocrits just before such a stressful event as the National Medical Boards. Exactly what caused this increase is not known. The possibility exists that different factors were at work in different students. There may have been a temporary increase in red cell circulation for unknown reasons, or an actual hemoconcentration similar to that seen in Stress Polycythemia may have occurred. The latter may have been caused in some way by the anxiety of the situation or by an excessive loss of water (especially by perspiration secondary to the anxiety). None of the students complained of "noticeable" excessive perspiration, and all of the students remained within 5 pounds of their body weight throughout the 7 trials. Food and water intake were not reported to be abnormal at any time. To stabilize things further, most of the hematocrits were drawn at the same time of the day for the trials.

The 2 point increase noted in 4 of the students and the 3 point increase seen with 2 other students might well be explained away by a combination of the daily fluctuation of hematocrits known to occur as well as to laboratory error in determining the values. The latter problem was eliminated as much as possible by having the same person read all the values. However, it would be difficult to invoke these same factors to account for the 5 percentage point gain noted in 2 of the students. These 2 increases were clear-cut and showed a temporal relationship to the National Board Examination, assuming, as we did, that the most stressful time would be the day before when all the uncertainties and doubts confronted the students straight-on.

The results seem to have borne out the hypothesis but the etiologic explanation remains unknown. The question which must be raised is whether or not standard hematocrit values can be justly applied to individuals not in a resting state. It would appear that the hematocrit spectrum shifts toward higher values in times of stress and excitement.

PART II - ANIMAL INVESTIGATION

In order to learn and understand more about disease in himself man has long tried to simulate similar conditions in animals. To date there have not been any reports in the literature attempting to establish an animal model for Stress Polycythemia. The problems encountered in trying to simulate a model are magnified by the psychophysiologic nature of the disease, and the obvious differences in mental and psychic energies. Nonetheless, if the etiology and mechanisms of this disease are to be understood, animal studies will help provide the first answers and guide subsequent investigation.

1. THE ANIMAL MODEL

METHODS AND MATERIALS

Rabbits 3 to 5 pound were chosen as the experimental animal because, like man, they do not have any splenic blood reserves which can be mobilized by exercise, epinephrine, and hemorrhage.⁴² The rabbits were subjected to a "stress situation" by flipping them over 3 times in the air while holding onto the scruff of their necks. Hematocrit readings were taken about 15 minutes prior to the turning over while the rabbits were in a calm and undisturbed state, immediately after they were flipped over and placed on the laboratory desk, and at different times after the latter reading. Blood for these readings was obtained from a marginal ear vein by a razor cut and collected in a microcapillary tube, which was centrifuged and a hematocrit reading taken on a manual microcounter. Before the rabbits were used in further investigation they were always put through this test. All values were obtained and recorded in duplicate.

RESULTS

In all the trials all 45 rabbits, 35 males and 10 females, showed an increase in their hematocrits immediately following their "stress situation" of being flipped over. The increases over their recorded hematocrits prior to being flipped over ranged from 1.5 to 4.5 percentage points. This increase gradually returned to the pre-stress values within 2 to 3 minutes.

Just as the hematocrit reading for a particular rabbit changed

slightly each day, the increment due to the "stress situation" varied daily, although the usual increase ranged from 2.0 to 3.5 percentage points above the reading before the stress. Table 1 shows some of the readings obtained using this protocol.

TABLE 1 - ANIMAL MODEL

<u>RABBIT #1</u>		<u>RABBIT #2</u>		<u>CONTROL #1</u>
Pre-stress Hct.	36.0	Pre-stress Hct.	39.0	Time 0 Hct. 40.0
	36.0		39.0	40.0
"Stress" Hct.	39.0	"Stress" Hct.	42.0	Time 15 min Hct. 40.0
	39.0		41.5	40.5
5-Min. Post Hct.	36.0	2-Min. Post Hct.	41.5	Time 20 min Hct. 40.5
	36.5		41.5	40.0
60-Min. Post Hct.	36.0	30-Min. Post Hct.	39.0	Time 75 min Hct. 40.0
	35.5		39.0	40.0

DISCUSSION

The average increase of 3 percentage points in Table 1 represents a substantial increase in the red blood cell concentration being sampled from the ear (i.e., in rabbit #1 the increase from 36.0 to 39.0 represents a 3/36 or about a 8% change of the measured red cell concentration). Something radically altering the quiescent state is occurring. The flipping over situation was construed as a "stress situation". Indeed, it may be so to an animal so labile as the rabbit. The fact that many rabbits urinated and defecated immediately after lends further credence to the assumption that they were undergoing some fearful and stressful process and a subsequent sympathetic discharge. However, the fact remains

that the increase may be due primarily to the change in posture and position or to exercise that the rabbit was subjected to. Kaltreider and Meneely⁴³ demonstrated a significant increase in the hematocrit due to a decrease in plasma volume resulting from severe exercise in man. Fawcett and Wynn⁴⁴ noted further that a change in posture from the horizontal to the vertical caused a reduction in plasma volume and a concomitant increase in hematocrit in human subjects. Control rabbits, consisting of rabbits who were not flipped over, did not show any fluctuation in their hematocrits beyond 0.5 percentage points in any of the readings taken. While the blood collected at the marginal ear veins represents blood flow in the ears and not total-body flow it is analogous to drawing blood from one of the antecubital veins and measuring the hematocrit from that sample. Both do not represent the total body picture but rather the blood picture at that site. To determine whether either of the above factors were involved in the significant change in the hematocrit, the following experiment was undertaken.

2. AUDITORY STIMULATION

METHOD

Twenty of the rabbits were subjected to various frequencies of noise emanating from a sonifier. Each rabbit was individually placed in a restraining box which allowed very little room for movement but had an opening to allow the head to protrude. The box was placed so that the rabbits' ears were directly applied to the source of the noise. Hematocrit readings were taken in the same way described above-prior to, just after, and at variable periods after the noise stimulus.

RESULTS

Eight of the 20 rabbits responded to the auditory stimulus by first straightening out their ears and laying them straight on their heads (a sign of fear³⁷) and then shaking their heads in an attempt to get them into the box and away from the noise. This would continue for as long as the auditory stimulus was applied, never more than 10 seconds. The hematocrits of these 8 rabbits increased between 2.0 and 3.5 percentage points after the noise was heard and returned to and remained at the pre-stress level about 3 minutes after the noise ceased.

The remaining 12 rabbits seemed to be unaffected by the noise and acted as though nothing in their environment had changed. Furthermore, all their hematocrit readings did not show any increase and were found to be within 0.5 percentage points of each other. Table 2 shows an example of these results:

TABLE 2 - Noise and Hematocrit

<u>RABBIT #5 (reacted to sound)</u>		<u>RABBIT #14 (did not react)</u>	
Pre-Noise Hct.	34.0	Pre-Noise Hct.	37.5
	34.5		37.0
"Noise Hct."	37.0	"Noise Hct."	37.5
	37.0		37.5
5 Min. Post Hct.	34.5	5 Min. Post Hct.	37.0
	34.5		37.5
30 Min. Post Hct.	34.0	30 Min. Post Hct.	37.0
	34.5		37.0

DISCUSSION

The placement of rabbits in a restraining box eliminated the possibility that the hematocrit change was due to a change in posture or position. The squirming which 8 of these animals showed while hearing the noise indicated that they were able to move only slightly and not enough

to change position. Furthermore, the limited motion allowed did not permit the animals to be exercised and probably reduced this factor to a bare minimum. It would therefore seem that the remaining factor, namely fear and stress, played the greatest role in causing the observed hematocrit changes.

It should be noted that 12 of the animals did not respond to the auditory stimulus by a recognizable sign and also did not show the increased hematocrits seen above. The most likely explanation was that these animals did not hear the noise and consequently did not react either physically or hematologically. Jonas⁴⁵ attributes this most likely to middle ear disease, a very common entity among laboratory rabbits.

Since it appeared that the most likely factors causing the increased hematocrit was fear and stress, the next step was to discover the reason or reasons for this rise.

3. RADIO-IODINATED (I^{131}) SERUM ALBUMIN

METHOD

Radio-iodinated (I^{131}) serum albumin was used to tag rabbit serum albumin in order to trace the changes which were occurring in the plasma while the hematocrit was being altered. If the plasma alone were the cause of the increased hematocrit, it could accomplish this either by shifting preferentially to other locations and being trapped there ("plasma trapping") or by rapidly shifting some of its water. A significant increase in the specific activity of the plasma would be indicative of this rapid shift in plasma water.

All rabbits at some point had their plasma tagged with 10 microcuries of radio-iodinated (I^{131}) human serum albumin by an injection in one of their marginal ear veins. From that point on, all of the remaining blood samples were drawn from the opposite ear.

To minimize the uptake of radioactive iodine by the thyroid gland, 1 to 2 ml of Lugol's Solution was administered 2 days before injection and continued for one week thereafter. The rabbits were again subjected to the flipping over "stress situation" and hematocrits drawn and read before, just after and considerably after the flipping. After the blood was drawn into the microhematocrit tube, centrifuged and the hematocrit determined, the tagged plasma was separated from the cells and part of the former delivered into a precisely calibrated 20 lambda pipette. Plasma from this pipette was then delivered into a 3 ml test tube filled with 1 ml of water. The 20 lambda pipette was rinsed 3 times and the radioactivity of the 3 ml test tube was determined on the Picker Spectroscaler. These tests were run for 3 days on 10 rabbits. Control readings were registered from rabbits who had been tagged with radioactive iodine but were not subjected to the "stress situation".

RESULTS

The results of 2 of the rabbits who were flipped over and 1 of the control rabbits is shown in Table 3.

From the data shown in this table it is clear that while the hematocrit rose immediately after the flipping episode this was not accompanied by a statistically significant rise or fall in the radioactive counts. The radioactive counts were well within the 2 standard

TABLE 3 - RADIOACTIVE IODINE STUDIES

	Day 1		Day 2		Day 3	
	Hct.	Radio.	Hct.	Radio	Hct.	Radio
Pre-stress	38.0	7218 ± 170	39.0	4721 ± 138	38.0	3172 ± 112
	38.5	7254 ± 170	39.0	4770 ± 138	38.0	3083 ± 112
Stress	40.5	7198 ± 170	42.0	4796 ± 138	41.0	3115 ± 112
	40.5	7261 ± 170	42.5	4738 ± 138	41.5	3158 ± 112
5-Min. Post	38.5	7185 ± 170	39.5	4801 ± 138	38.5	3189 ± 112
	38.0	7201 ± 170	39.0	4734 ± 138	38.5	3117 ± 112
30-Min. Post	38.0	7232 ± 170	39.0	4718 ± 138	38.5	3194 ± 112
	38.0	7273 ± 170	39.0	4752 ± 138	38.0	3137 ± 112
Background:		148 counts/min.	103 cts/min.		134 cts./min.	
<u>RABBIT #18</u>						
Pre-stress	36.0	6427 ± 160	36.5	3601 ± 120	36.0	2289 ± 94
	36.0	6503 ± 160	36.5	3655 ± 120	36.0	2323 ± 94
Stress	38.5	6512 ± 160	39.0	3653 ± 120	39.0	2278 ± 94
	39.0	6458 ± 160	39.0	3680 ± 120	39.0	2333 ± 94
5-Min. Post.	36.0	6488 ± 160	36.5	3629 ± 120	36.5	2303 ± 94
	36.5	6439 ± 160	36.0	3697 ± 120	36.5	2261 ± 94
30-Min. Post	36.0	6499 ± 160	36.5	3664 ± 120	36.0	2318 ± 94
	36.0	6431 ± 160	36.5	3705 ± 120	36.5	2341 ± 94
Background:		148 cts/min.	103 cts/min.		135 cts/min.	
<u>CONTROL #1</u>						
Time 0	43.0	5921 ± 144	42.5	3465 ± 128	43.0	2223 ± 94
	43.0	5878 ± 144	42.0	3391 ± 128	42.5	2175 ± 94
Time 10 Min.	43.0	5937 ± 144	42.0	3432 ± 128	43.0	2237 ± 94
	43.0	5942 ± 144	42.0	3478 ± 128	43.0	2274 ± 94
Time 15 Min.	43.5	5907 ± 144	42.0	3492 ± 128	43.0	2236 ± 94
	43.0	5863 ± 144	42.5	3413 ± 128	42.5	2192 ± 94
Time 45 Min.	43.5	5927 ± 144	42.5	3470 ± 128	43.0	2240 ± 94
	43.5	5950 ± 144	42.5	3404 ± 128	43.0	2202 ± 94
Background:		148 cts/Min.	103 cts/Min		135 cts/Min.	

deviations as compared to those readings both before and after the "stress situation". It can also be seen that all of the radioactive readings of the control rabbit were all within 2 standard deviations of each other.

DISCUSSION

A significant increase in radioactive counts after the "stress situation" would have been indicative of a loss of plasma water from the vascular space and, consequently, a model simulating Stress Polycythemia. The results did not prove this to be the case. The fact that the radioactive count was not significantly different from the previous or later readings in the calm state is compatible with a "shift in the plasma". However, this cannot be said with certainty because the increase in hematocrit may be due to extrusion of red cells into the circulation from blood depots and normally sequestering regions.

Despite the fact that this phenomenon did not seem to be akin to the known mechanism of Stress Polycythemia, it was decided to continue to see what factors might be influential.

4. IRON⁵⁹ STUDIES

To distinguish between the two remaining mechanisms-temporary increase in circulating red blood cells and "plasma trapping" - is virtually impossible with the current means available. Nevertheless, it is believed that older red blood cells are often squeezed out preferentially and it was decided to investigate this as a possible mechanism.

If red cell sequestration or volume change was a factor, it might be age red cell age (population) - specific. Thus, pulse labeling of red cells at a specific age with changes in specific activity during

stress could represent the egress or gain of age-related red cells.

METHOD

Twelve rabbits were injected with 8 microcuries of Fe^{59}Cl , and again hematocrit and radioactive readings were taken before, immediately after, and a longer time after the "stress situation". These readings were taken 18 days and 39 days after the injection of the Fe^{59} . Control readings consisted of those injected rabbits in the calm state throughout.

RESULTS

The results for 2 rabbits and 1 control are recorded in Table 4. These results are indicative of all those in the study.

DISCUSSION

The data in Table 4 shows that despite the increased hematocrit there was no significant change in the radioactive counts for either the young or the old red blood cells. Burnell⁴⁶ et. al. showed that the average red blood cell of the rabbit reaches senescence around the fortieth day, but despite the general belief that old red blood cells are squeezed out of sequestered areas preferentially, this does not seem to be the mechanism for the phenomena described above. The values obtained from the Fe^{59} counts during the 18th day after injection would seem to indicate that young red blood cells, likewise, do not contribute anything significant to the resultant increased hematocrit.

The above studies suggest that the most probable mechanism for the observed hematocrit rise is a shift in the plasma or preferential "plasma trapping". It has long been realized that capillary blood contains a higher proportion of plasma than venous blood and therefore, has

TABLE 4 - Fe⁵⁹ STUDIES

	<u>18 Days After Fe⁵⁹</u>		<u>39 Days After Fe⁵⁹</u>	
	<u>Hct.</u>	<u>Radio.</u>	<u>Hct.</u>	<u>Radio</u>
<u>Rabbit #Fe1</u>				
Pre-Stress	44.0	567 ± 48	45.0	437 ± 42
	44.0	544 ± 48	45.5	421 ± 42
Stress	46.5	563 ± 48	48.0	412 ± 42
	46.5	562 ± 48	47.5	436 ± 42
5-Min. Post	44.0	531 ± 48	45.0	425 ± 42
	44.5	539 ± 48	45.0	440 ± 42
30-Min. Post	44.0	548 ± 48	45.0	415 ± 42
	44.0	564 ± 48	45.0	407 ± 42
Background		14 counts/Min		17 counts/Min.
<u>Rabbit #Fe2</u>				
Pre-Stress	45.0	464 ± 42	45.5	380 ± 38
	45.0	465 ± 42	45.5	374 ± 38
Stress	47.5	468 ± 42	48.0	383 ± 38
	47.5	469 ± 42	48.5	358 ± 38
5-Min. Post	45.0	457 ± 42	46.0	364 ± 38
	44.5	480 ± 42	46.0	353 ± 38
30-Min. Post	45.0	476 ± 42	45.5	387 ± 38
	45.0	483 ± 42	45.5	370 ± 38
Background		14 counts/min.		17 counts/min.
<u>Rabbit - Control #1</u>				
Time 0	48.5	469 ± 42	46.0	400 ± 40
	48.0	435 ± 42	46.5	387 ± 40
Time 10 min.	48.0	504 ± 42	46.0	427 ± 40
	48.0	479 ± 42	46.5	393 ± 40
Time 15 min.	48.5	495 ± 42	46.5	376 ± 40
	48.5	501 ± 42	46.5	401 ± 40
Time 45 min.	48.0	462 ± 42	46.0	400 ± 40
	48.0	481 ± 42	46.0	382 ± 40
Background		14 counts/min.		17 counts/min.

a lower hematocrit.⁴⁷ The experiments seem to indicate that during the "stress situation" there is a further sequestration of plasma in capillaries which may have become temporarily closed or had their circulation slowed. This was the same conclusion which Hahn et al⁴⁸ arrived at in studying the effects of epinephrine on the venous hematocrit value in dogs. The possibility that catecholamines might be the mediator of the increased hematocrit in the animal model was then explored.

5. CATECHOLAMINES

The importance of catecholamines and their role in fear, anger, and the preparation in facing emergencies was first described by Cannon.² He stated that both the secretion of adrenalin and the activation of the sympathetic division of the autonomic nervous system prepared the animal for "flight or fright". More recent and detailed studies indicate that norepinephrine secretion is increased by emotional stresses with which the individual is familiar, whereas epinephrine secretion rises when the individual faces situations in which he does not know what to expect.⁴⁹ Both epinephrine and norepinephrine are known to alter the hematocrit in physiologic quantities and so a study was undertaken to examine their effects in the rabbit.

a) EPINEPHRINE

Epinephrine, the emergency hormone of the sympathetic nervous system, is released from the adrenal medulla. Several investigators have previously administered exogenous epinephrine to man and animals to alter the vascular state. Kaltreider et al⁵⁰ administered 1 cc of a 1/1,000 solution of epinephrine to several men. He noted an increase in hematocrit

and attributed this to hemoconcentration secondary to vasoconstriction in the skin and splanchnic areas. We now know that any vasoconstriction by epinephrine is overshadowed by its vasodilator properties on muscle. In referring to one of his previous papers,⁴³ Kaltreider noticed that "there is a striking similarity between the effect of severe exercise on the blood volume and the response of the blood to epinephrine. In both circumstances there is a hemoconcentration. . ."

Davis⁵¹ produced an experimental polycythemia in rabbits by injecting them with 0.1 mgm to 0.3 mgm of epinephrine hydrochloride for 12 to 18 days. The resulting polycythemia was attributed to local hypoxia of the bone marrow secondary to the vasoconstriction action of epinephrine. This was later refuted by Parson⁵² who felt that the increased hematocrit was due to a redistribution of cells and plasma within the vascular system.

METHOD

Epinephrine in doses ranging from 0.20 cc to 1.00 cc of a 1/1,000 solution were injected subcutaneously into 10 rabbits. The epinephrine was injected for 15 consecutive days and almost daily recordings of any changes in the hematocrit were noted from between 1 minute to 60 minutes after injection. These rabbits were not flipped over and were allowed to remain in their normal quiescent state. Control rabbits consisted of those in a quiet state but without epinephrine injected.

RESULTS

The results with epinephrine injection showed that there was no noticeable change in hematocrit values. Table 5 documents representative data.

TABLE 5 - EPINEPHRINE AND THE HEMATOCRIT

	<u>Day 3</u>	<u>Day 8</u>	<u>Day 15</u>
	<u>Hct.</u>	<u>Hct.</u>	<u>Hct.</u>
<u>Rabbit #E1</u>			
Pre-injection	36.5 36.0	38.0 38.0	37.5 37.0
1-Min. Post	36.0 36.0	38.5 38.0	37.5 37.5
5-Min. Post	36.5 36.5	38.0 38.0	37.0 37.0
15-Min. Post	36.5 37.0	38.5 38.5	37.5 38.0
30-Min. Post	36.5 36.0	38.0 38.0	38.0 37.5
45-Min. Post	36.0 36.5	38.0 38.0	37.5 38.0
60-Min. Post	36.5 36.5	38.0 38.5	37.5 37.5

Dosage to rabbit #E1 was 0.5 cc of a 1/1,000 solution of epinephrine for 15 consecutive days.

DISCUSSION

Epinephrine is now known to definitely cause a loss of protein-free fluid to the tissues and, therefore, increase the hematocrit.⁵³ The failure to get a response in the rabbit with such large doses may be due to the unphysiological means of administration, poor absorption from the site of injection, or failure to reach the proper receptors. It is also possible that a transient increase in the hematocrit was missed because sampling was not done at the proper time.

The measured hematocrit values varied from 36.0 to 38.5 during the 15 days of the trials. This variance was no greater than that observed in control rabbits. Evidence for an increased hematocrit from epinephrine was, therefore, not noted from the above studies. It is possible that the expected results were nullified by other physiological effects of epinephrine, specifically those on the kidney. Large doses of epinephrine are known to decrease the filtration fraction by stopping blood flow through some nephrons. The drug can also include antidiuresis through stimulating release of ADH. Perhaps these factors combined to nullify the hemoconcentration known to occur in man.

b) NOREPINEPHRINE

The main function of norepinephrine in the body appears to be the maintenance of normal sympathetic tone and adjustment of circulatory dynamics. This is achieved primarily by its widespread vasoconstrictor properties. Finnerty⁵⁴ et al noted the following during Levophed infusions in man: An average 15% decrease in plasma volume, no change in red cell mass, and an average increase of 8% in the hematocrit. They felt that an increased hydrostatic capillary pressure was the most likely explanation for the decrease in plasma volume. This was felt to be due to an increased venous pressure secondary to venoconstriction. Decreased vascular volumes were also noted in the dog following administration of norepinephrine by Rose and Freis⁵⁵.

Since regional vasoconstriction is an important part of the reflex adjustment to the "stress" of exercise or emotion and since the actions of norepinephrine reproduce very closely those of the stimulated sympathetic nerves in stress situations, it was decided to observe its

effects on the rabbit hematocrit.

METHOD

Eight rabbits were injected intravenously with from 0.1 mg to 0.6 mg. of norepinephrine for 2 days. They had previously been injected with radio-iodinated (I^{131}) serum albumin and Fe^{59} to trace the movement of the plasma and red blood cells. Hematocrit and radioactive readings were taken before injection and at various times after. The rabbits were in a calm state throughout. Controls consisted of rabbits in a quiescent state without norepinephrine.

RESULTS

The rabbits showed no significant fluctuations in either hematocrit or radioactive counts. Table 6 traces the values of one rabbit, which is indicative of the course of the others.

TABLE 6 - NOREPINEPHRINE AND THE HEMATOCRIT

<u>RABBIT #N3</u>	<u>DAY 1</u>			<u>DAY 2</u>		
	<u>Hct.</u>	<u>I^{131}</u>	<u>Fe^{59}</u>	<u>Hct.</u>	<u>I^{131}</u>	<u>Fe^{59}</u>
Pre-Injection	40.0	2732 ± 104	367 ± 38	40.5	1805 ± 84	358 ± 38
	40.0	2771 ± 104	384 ± 38	40.5	1804 ± 84	383 ± 38
.5 Min. Post	40.0	2801 ± 104	360 ± 38	41.0	1787 ± 84	370 ± 38
	39.5	2793 ± 104	391 ± 38	40.5	1794 ± 84	401 ± 38
1 Min. Post	39.5	2816 ± 104	402 ± 38	41.0	1822 ± 84	393 ± 38
	40.0	2757 ± 104	372 ± 38	41.0	1760 ± 84	367 ± 38
2 Min. Post	40.0	2720 ± 104	349 ± 38	40.5	1789 ± 84	377 ± 38
	39.5	2780 ± 104	377 ± 38	40.5	1839 ± 84	399 ± 38
3 Min. Post	40.0	2820 ± 104	397 ± 38	40.5	1810 ± 84	360 ± 38
	40.0	2743 ± 104	399 ± 38	41.0	1799 ± 84	384 ± 38
Background		93 cts/Min.	12 cts/Min.		90 Cts/Min.	15 cts/Min.

DISCUSSION

Mention has already been made of the fact that 2 groups of investigators felt the increased hematocrit from norepinephrine infusion was due to a hemoconcentration phenomenon. This hypothesis was further substantiated by a report by Brunjes et al⁵⁶ citing a case of pheochromocytoma associated with a diminished blood volume. This was postulated to result from diminished plasma volume produced by circulating vasoconstrictors and secondary reduction of red-cell mass.

Despite such impressive evidence, there is no sign that such is the case with rabbits in the present experimental situation. In addition, there is no report in the literature to confirm or deny this type of work in the rabbit. The dosage for the rabbit was established by scaling down proportionately the amount for men. Since the administration was intravenously there is little doubt that the substance entered the body. The most likely explanations are that the norepinephrine didn't reach the proper receptors or that the timing of the blood samples was off. The latter seems unlikely since readings were taken from 20 seconds to 10 minutes after injection, and one would have expected to discover a significant rise in at least one of the 80 trials recorded.

The evidence involving norepinephrine was so strong from other studies that it was decided to stress the animals in a situation where it was depleted.

6. RESERPINE

Reserpine is a rauwolfia preparation which depletes stores of norepinephrine, dopamine, and serotonin from many organs, including brain, heart, blood vessels, and the adrenal medulla. The drug not

only causes a release of these amines but also blocks their uptake by interfering with the "amine pump". In order to examine the effects of reserpine on the "stress situation", the following experiment was initiated.

METHOD

Bertler et al⁵⁷ was able to severely deplete the norepinephrine pool of the adrenal medulla of rabbits by administering 5 mg/kg of reserpine daily. Six rabbits were subjected to the "stress situation" and when it was noted that their hematocrits increased, they were then started on 5 mg/kg of reserpine daily for 10 days. At the end of this time they were again subjected to the "stress situation" and hematocrit readings noted. Both radio-iodinated (I^{131}) serum albumin and Fe^{59} Cl had been previously injected to follow the course of both the cells and the plasma. Two weeks after the last dose of reserpine had been administered another trial was run (day 25).

RESULTS

Table 7 shows the results obtained with one of the rabbits. Like all other previous tests and tables, the results were similar in all the other rabbits.

TABLE 7 - RESERPINE AND HEMATOCRIT

RABBIT #R1	DAY 1		DAY 11				DAY 25	
	Hct.	Fe^{59} Count	Hct.	I^{131} Count	Fe^{59} Cnt.	Hct.	Fe Count	
Pre-stress	34.0	399 ± 40	35.0	2749 ± 104	337 ± 36	35.5	273 ± 32	
	34.0	358 ± 40	35.0	2703 ± 104	349 ± 36	35.0	259 ± 32	
Stress	36.5	414 ± 40	35.0	2767 ± 104	361 ± 36	37.0	289 ± 32	
	36.5	381 ± 40	35.5	2731 ± 104	373 ± 36	37.0	260 ± 32	
5 Min. Post	34.5	386 ± 40	35.5	2782 ± 104	385 ± 36	35.5	301 ± 32	
	34.0	423 ± 40	35.0	2712 ± 102	355 ± 36	35.5	291 ± 32	
30 Min. Post	34.0	374 ± 40	35.0	2721 ± 102	395 ± 36	35.5	272 ± 32	
	34.5	393 ± 40	35.0	2740 ± 102	367 ± 36	35.5	287 ± 32	
Background	13 cts/Min.		110 cts/Min.		9 cts/Min.	18 cts./Min.		

DISCUSSION

Reserpine has affected the hematocrit response of the rabbits to the "stress situation". It is known that there must be a pool of norepinephrine available for proper functioning of the sympathetic endings. Axelrod et al⁵⁸ showed that H³-norepinephrine taken up by the pool is actually released by sympathetic nerve stimulation and appears in the venous effluent blood. Inhibition of the effects of peripheral adrenergic nerve activity is due to depletion of norepinephrine from sympathetic postganglionic fibers. This has been shown to occur quite readily after the administration of reserpine as contrasted to tissue levels of norepinephrine, which are reduced less readily and completely. The possibility that this is causing the animal not to respond to the "stress situation", as it did in two other trials when reserpine was not present, must be strongly considered.

Nevertheless, other explanations exist and currently these cannot be ruled out entirely. The first is that reserpine depletes the catecholamine stores of the brain, and the possibility that the response might be centrally mediated must be kept in mind. Second, reserpine is known to cause a secondary release of histamine, a known vasodilator agent which might have its own effects. Reserpine also causes the depletion of amines and other substances, whose structure and function we know little or nothing about and which might affect the results obtained. And lastly, reserpine decreases the stores of norepinephrine in the myocardium as well, and this leads to a decrease in cardiac output and secondary effects on the kidney and entire vascular system.

CONCLUSION

In summary, when rabbits were subjected to being flipped over in the air 3 times by the scruff of their necks or having shrill noises piped into their ears, one of the ways they responded was to increase their hematocrit. It is hypothesized that this represents a response to one of the "stress situations" described above. The rapidity with which the blood change occurred is quite consistent with the participation of a neurochemical transmitter. While both epinephrine and norepinephrine have been known to cause alterations of the blood volumes, it was not possible to show that either had a hematologic effect in rabbits. However, depletion of norepinephrine by reserpine resulted in a failure of the rabbit to respond to the "stress situation" in the way it had done before.

The actual mechanism whereby the hematocrit changes was not uncovered. Inasmuch as it could not be shown that the change was due to a hemoconcentration phenomenon with the loss of plasma, this does not serve as a model for Stress Polycythemia. Nevertheless, it has been shown here for the first time that rabbits respond to certain threatening situations by raising their hematocrits and that this rise is capable of being altered.

- | | | | |
|---|-------------------------------------|---|-------------------------------------|
| 1. Are you happiest when you get involved in some project that calls for rapid action? | Yes ? No
: : :
: : :
: : : | 25. Are your feelings rather easily hurt?..... | Yes ? No
: : :
: : :
: : : |
| 2. Do you sometimes feel happy, sometimes depressed, without any apparent reason? | Yes ? No
: : :
: : :
: : : | 26. Do you like to have many social engagements? | Yes ? No
: : :
: : :
: : : |
| 3. Does your mind often wander while you are trying to concentrate? | Yes ? No
: : :
: : :
: : : | 27. Would you rate yourself as a tense or "highly-strung" individual? | Yes ? No
: : :
: : :
: : : |
| 4. Do you usually take the initiative in making new friends? | Yes ? No
: : :
: : :
: : : | 28. Do you generally prefer to take the lead in group activities? | Yes ? No
: : :
: : :
: : : |
| 5. Are you inclined to be quick and sure in your actions? | Yes ? No
: : :
: : :
: : : | 29. Do you often experience periods of loneliness? | Yes ? No
: : :
: : :
: : : |
| 6. Are you frequently "lost in thought" even when supposed to be taking part in a conversation? | Yes ? No
: : :
: : :
: : : | 30. Are you inclined to be shy in the presence of the opposite sex? | Yes ? No
: : :
: : :
: : : |
| 7. Are you sometimes bubbling over with energy and sometimes very sluggish? | Yes ? No
: : :
: : :
: : : | 31. Do you like to indulge in a reverie (daydreaming)? | Yes ? No
: : :
: : :
: : : |
| 8. Would you rate yourself as a lively individual? | Yes ? No
: : :
: : :
: : : | 32. Do you nearly always have a "ready answer" for remarks directed at you? | Yes ? No
: : :
: : :
: : : |
| 9. Would you be very unhappy if you were prevented from making numerous social contacts? | Yes ? No
: : :
: : :
: : : | 33. Do you spend much time in thinking over good times you have had in the past? | Yes ? No
: : :
: : :
: : : |
| 10. Are you inclined to be moody? | Yes ? No
: : :
: : :
: : : | 34. Would you rate yourself as a happy-go-lucky individual? | Yes ? No
: : :
: : :
: : : |
| 11. Do you have frequent ups and downs in mood, either with or without apparent cause? | Yes ? No
: : :
: : :
: : : | 35. Have you often felt listless and tired for no good reason? | Yes ? No
: : :
: : :
: : : |
| 12. Do you prefer action to planning for action? | Yes ? No
: : :
: : :
: : : | 36. Are you inclined to keep quiet when out in a social group? | Yes ? No
: : :
: : :
: : : |
| 13. Are your daydreams frequently about things that can never come true? | Yes ? No
: : :
: : :
: : : | 37. After a critical moment is over, do you usually think of something you should have done but failed to do? | Yes ? No
: : :
: : :
: : : |
| 14. Are you inclined to keep in the background on social occasions? | Yes ? No
: : :
: : :
: : : | 38. Can you usually let yourself go and have a hilariously good time at a gay party? | Yes ? No
: : :
: : :
: : : |
| 15. Are you inclined to ponder over your past? | Yes ? No
: : :
: : :
: : : | 39. Do ideas run through your head so that you cannot sleep? | Yes ? No
: : :
: : :
: : : |
| 16. Is it difficult to "lose yourself" even at a lively party? | Yes ? No
: : :
: : :
: : : | 40. Do you like work that requires considerable attention? | Yes ? No
: : :
: : :
: : : |
| 17. Do you ever feel "just miserable" for no good reason at all? | Yes ? No
: : :
: : :
: : : | 41. Have you ever been bothered by having a useless thought come into your mind repeatedly? | Yes ? No
: : :
: : :
: : : |
| 18. Are you inclined to be overconscientious? | Yes ? No
: : :
: : :
: : : | 42. Are you inclined to take your work casually, that is as a matter of course? | Yes ? No
: : :
: : :
: : : |
| 19. Do you often find that you have made up your mind too late? | Yes ? No
: : :
: : :
: : : | 43. Are you touchy on various subjects? | Yes ? No
: : :
: : :
: : : |
| 20. Do you like to mix socially with people? | Yes ? No
: : :
: : :
: : : | 44. Do other people regard you as a lively individual? | Yes ? No
: : :
: : :
: : : |
| 21. Have you often lost sleep over your worries? | Yes ? No
: : :
: : :
: : : | 45. Do you often feel disgruntled? | Yes ? No
: : :
: : :
: : : |
| 22. Are you inclined to limit your acquaintances to a select few? | Yes ? No
: : :
: : :
: : : | 46. Would you rate yourself as a talkative individual? | Yes ? No
: : :
: : :
: : : |
| 23. Are you often troubled about feelings of guilt? | Yes ? No
: : :
: : :
: : : | 47. Do you have periods of such great restlessness that you cannot sit long in a chair? | Yes ? No
: : :
: : :
: : : |
| 24. Do you ever take your work as if it were a matter of life or death? | Yes ? No
: : :
: : :
: : : | 48. Do you like to play pranks upon others? | Yes ? No
: : :
: : :
: : : |

Read each question carefully. Answer YES if you think it is true about you. Answer NO if you think it is not true about you.

APPENDIX IITAYLOR MANIFEST ANXIETY SCALE

- ___ 1. I do not tire quickly.
- ___ 2. I am often sick to my stomach.
- ___ 3. I am about as nervous as other people.
- ___ 4. I have very few headaches.
- ___ 5. I work under a great deal of strain.
- ___ 6. I cannot keep my mind on one thing.
- ___ 7. I worry over money and business.
- ___ 8. I frequently notice my hand shakes when I try to do something.
- ___ 9. I blush as often as others.
- ___ 10. I have diarrhea ("the runs") once a month or more.
- ___ 11. I worry quite a bit over possible troubles.
- ___ 12. I practically never blush.
- ___ 13. I am often afraid that I am going to blush.
- ___ 14. I have nightmares every few nights.
- ___ 15. My hands and feet are usually warm enough.
- ___ 16. I sweat very easily even on cool days.
- ___ 17. When embarrassed I often break out in a sweat which is very annoying.
- ___ 18. I do not often notice my heart pounding and I am seldom short of breath.
- ___ 19. I feel hungry almost all the time.
- ___ 20. Often my bowels don't move for several days at a time.
- ___ 21. I have a great deal of stomach trouble.
- ___ 22. At times I lose sleep over worry.
- ___ 23. My sleep is restless and disturbed.
- ___ 24. I often dream about things I don't like to tell other people.
- ___ 25. I am easily embarrassed.

- ___ 26. My feelings are hurt easier than most people.
- ___ 27. I often find myself worrying about something.
- ___ 28. I wish I could be as happy as others.
- ___ 29. I am usually calm and not easily upset.
- ___ 30. I cry easily.
- ___ 31. I feel anxious about something or someone almost all of the time.
- ___ 32. I am happy most of the time.
- ___ 33. It makes me nervous to have to wait.
- ___ 34. At times I am so restless that I cannot sit in a chair for very long.
- ___ 35. Sometimes I become so excited that I find it hard to get to sleep.
- ___ 36. I have often felt that I faced so many difficulties I could not overcome them.
- ___ 37. At times I have been worried beyond reason about something that really did not matter.
- ___ 38. I do not have as many fears as my friends.
- ___ 39. I have been afraid of things or people that I know could not hurt me.
- ___ 40. I certainly feel useless at times.
- ___ 41. I find it hard to keep my mind on a task or job.
- ___ 42. I am more self-conscious than most people.
- ___ 43. I am the kind of person who takes things hard.
- ___ 44. I am a very nervous person.
- ___ 45. Life is often a strain for me.
- ___ 46. At times I think I am no good at all.
- ___ 47. I am not at all confident of myself.
- ___ 48. At times I feel that I am going to crack up.
- ___ 49. I don't like to face a difficulty or make an important decision.
- ___ 50. I am very confident of myself.

OTHER EVENTS

Heavy alcohol intake

EMPLOYMENT HISTORY

Changed jobs Severe Stresses at work Retired

FAMILY EVENTS

Remarried Mother died Moved

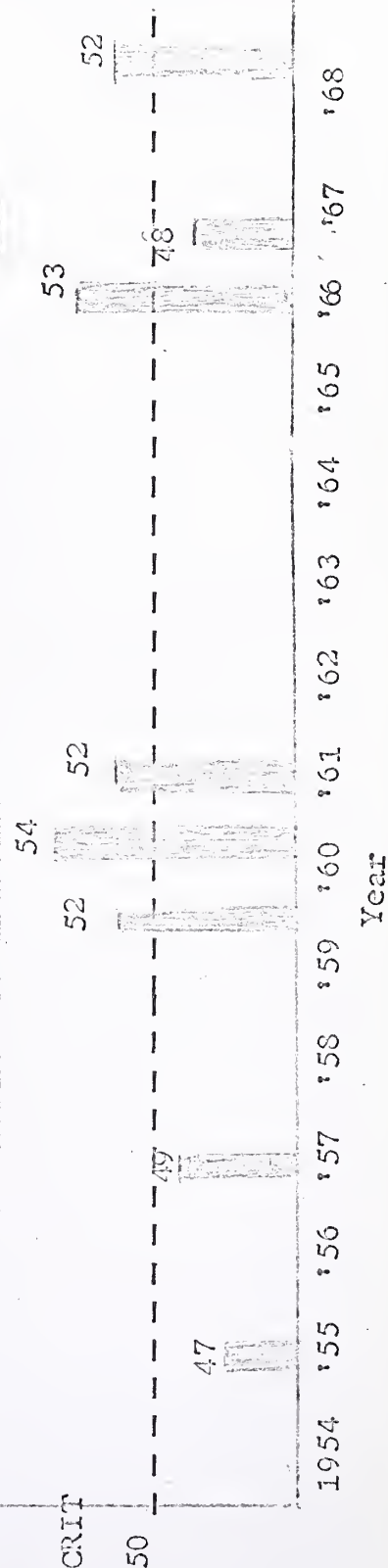
PSYCHIATRIC HISTORY

Under psychiatric care Day of mental confusion and amnesia Insomnia

MEDICAL HISTORY

First told of hypertension Acute prostatitis attack Gouty arthritis attack STRESS POLYCYTHEMIA DIAGNOSED

HEMATOCRIT



OTHER EVENTS

∞ Automobile accident

EMPLOYMENT HISTORY

Started as policeman

Promoted to detective

Promoted to lieutenant

FAMILY EVENTS

Feuding with wife started

Daughter born

Moved into new home

Wife threatened separation for first time

Sister died

PSYCHIATRIC HISTORY

Tinnitus & vertigo

Insomnia

MEDICAL HISTORY

Varicose veins stripped

Severe epigastric pains

Hemorrhoidectomy

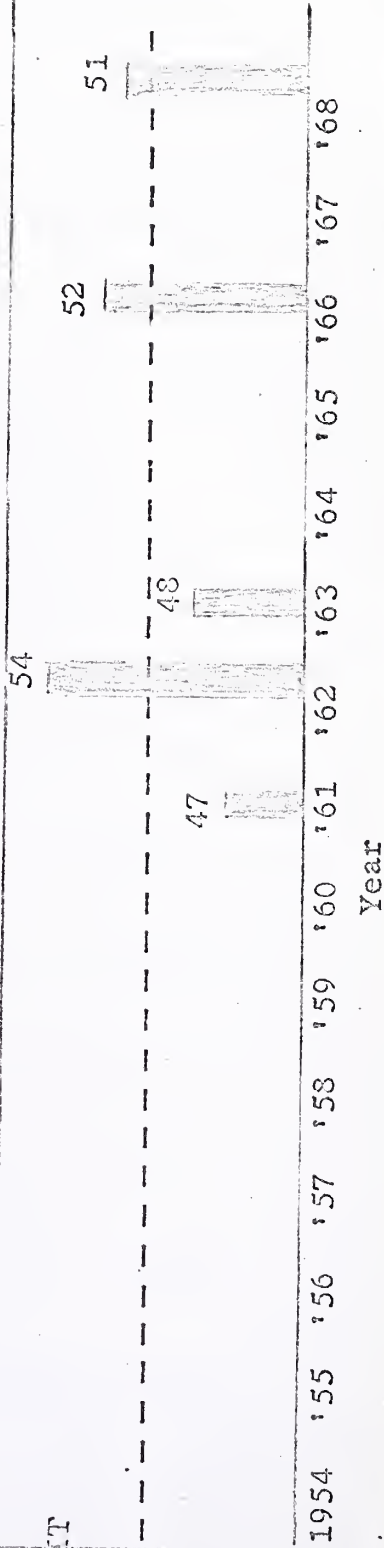
First told of hypertension

Duodenal ulcer diagnosed

STRESS POLYCYTHEMIA DIAGNOSED

HEMATOCRIT

50



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