A STUDY OF THE PSYCHOLOGICAL AND PHYSIOLOGICAL EFFECTS OF CAFFEINE ON HUMAN HEALTH

PDE
Submitted to the Faculty of the UNION GRADUATE SCHOOL

in partial fulfillment of the requirements for the degree of DOCTOR OF PHILOSOPHY in HUMAN NUTRITION AND PUBLIC HEALTH SCIENCE

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Prepared for a Graduation Committee Meeting on May 29, 1989
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CHAPTER 1
INTRODUCTION

To begin to have a new consciousness about caffeine so that we can become aware of how this drug can affect our physiology and psychology is a problem. The reasons for this are certainly complicated, but we can start by considering a factor dominating all of our lives—our "habits." When we become aware of and take responsibility to change our habits, we are taking a first step in the process of awakening. The result must not only be an improvement in the quality of our lives, but the world itself will be changed for the better.

The use and abuse of caffeine is a major public "habit" and may be as important a factor as heredity and environment in the etiology of physiological and psychological disorders. To recognize this, we must know that we are creatures of habit. Most people are caffeine consumers because from birth this food-drug is set before us, if not offered directly, along with orange juice, cereal, dessert, and cigarettes.

The current literature unequivocally demonstrates that caffeine not only affects our physiology, but has a profound effect on our psychology as well. Caffeine is a potent central nervous system stimulant and much of its "psychological" activity may be related to this action of the drug. Its effects on the nervous system are obviously adverse at high doses. It may not be obvious that at lower doses, when used in moderation, it may have beneficial effects. For example, its possible
therapeutic use in hyperkinetic children certainly would seem advantageous when compared to the current treatment with more powerful stimulants which have concomitant adverse reactions, i.e., asthma, upper respiratory problems, colds, and flu. Also, with the intense day-to-day pressures imposed and accepted by many of us, is there any harm in "relaxing" with a hot cup of tea or coffee? On the other hand, caffeine is a drug which is subject to abuse. The fact that it is a drug with a potentially powerful effect escapes most of us who think of coffee as a relatively harmless beverage. Recently published studies and reports of personal observations have shown without a doubt that caffeine abuse (caffeinism) may result in a syndrome which resembles and may be confused or confounded with true psychotic states. This may lead to misdiagnosis and mistreatment. A question arises from the varied reports of caffeine consumption in psychiatric populations. Does caffeine stimulate psychosis or does psychosis stimulate caffeine consumption?

These are not trivial findings because of the ready availability of caffeine and the psychological problems which we are experiencing in this era. This thesis reviews some of the knowledge of caffeine's effects with the hope that we will all be more educated and more careful in the use of this commonly ingested and abused drug.

The physiological action of caffeine is briefly reviewed, as psychological and physiological effects must go hand-in-hand. In addition to its central nervous system effects, caffeine has significant effects on the cardiovascular system, gastric acid secretion, and
catecholamine (adrenaline) release. In large doses, caffeine has been shown to be a mutagen in animals, plants, and bacteria, and has been shown to exhibit teratogenic properties in various animal species. In addition, the elusive cause of restless legs syndrome is believed to be due in some cases to caffeine.

The results of the small research study consists of three kinds of observations resulting from consumption of caffeine beverage during a two-week period: (1) perceived psychological effects via administration of a questionnaire; (2) effects on adrenal function determined by a medical examination; and (3) physical-chemical measurements of urine, an indication of the anabolic effect of caffeine according to a theory of Dr. E. Revici.

The growing knowledge of the detrimental effects of caffeine and its abuses have led to a plethora of articles attempting to raise the level of awareness of the medical and scientific community in this regard.

In an editorial in *Connecticut Medicine* (1979), the caffeine-hype is condemned. Four billion gallons of caffeine-containing soft drinks are produced each year, using caffeine from decaffeinated coffee beverages. Thus, caffeine is taken from the elderly and given to the young. The symptoms of caffeinism are evident at very low doses in some susceptible persons. The abuse of caffeine is now a public health problem in children. Agitation, restlessness, quality of sleep lessened, and hyperkinesis may result from overindulgence in cola and other caffeine-containing beverages. A recent study (Gross, 1975) in New Haven
on hyperkinetic children revealed a high consumption of caffeinated beverages among these afflicted children. The increasing sales of decaffeinated coffee suggests that the public is becoming more aware of the dangers of excess caffeine.

Dr. Reus, of the Langley-Porter Neuropsychiatric Institute, reports in *Primary Care* (1979) that the behavioral effects of caffeine are now well known. Doctors should be aware that many drugs can cause emotional and/or psychological changes which are difficult to differentiate from real stress-related psychological effects. Thus, incorrect diagnoses and treatments may often be incurred in such situations.

Dr. R. P. Grancher (1980), who is concerned with research on the physiological and psychological effects of caffeine, noted a publication by DeFreitas in which psychiatric patients had improved symptoms when decaffeinated coffee replaced regular coffee. Dr. Grancher considers this of "immediate clinical importance." He urges that the effects of caffeine in psychiatric patients (indeed, in all psychological disturbances) be clarified, as he puts it. He notes also the relationship of smoking and caffeine consumption. Smoking increases caffeine metabolism, thereby shortening and diminishing its effect. This may result in increased ingestion. Also, caffeine has been shown to interact with anti-psychotic drugs, *in vitro*, a precipitate being formed. Further investigation of these effects is also recommended.

A very interesting editorial in the *Journal of Clinical Toxicology* (1978), addresses the problem of volatile disorders. The editor states
that caffeine is among those abused drugs (including narcotics, sedatives, amphetamines) which are used to bring disorders upon ourselves with "volition." That is, some of us are willfully self destructive. This behavior is somewhat associated with a "defect" of the will. We must all become aware of the difficulties and severe problems of overcoming this behavior. Coffee is considered "the most innocent of beverages." As the author notes, a single cup of coffee (100 mg of caffeine) is usually thought of as harmless. However, some "sensitive" persons may develop "behavior toxicity indistinguishable from cocaine amphetamine bummer." As is now well known, the psychological effects include sleeping problems, irritability (over-reacting to a stimulus), nervousness, headache, and withdrawal symptoms characterized by headaches and shakiness.

In the same vein, Dr. James P. Henry, of U.S.C. School of Medicine, in an article in Aviation Space Medicine (1978), discusses the concept of self-imposed stress, what he calls the "noradrenaline addict." These types, typified by the James Bond model, must self induce an excitatory state to enliven their existence. This is often accomplished by caffeine (in addition to smoking and drinking). Caffeine is a "drug of abuse." Five cups a day are sufficient to induce a habit. Caffeine results in adrenal stimulation or overstimulation (spurred on, stirred up, roused to action on a higher level). Withdrawal results in a depression of adrenal function, and the typical symptomatology of caffeine withdrawal, which I mention so often, headaches, irritability, and depression (dejection; a
sinking of spirits). A study of Johns Hopkins graduates (by Thomas) showed that the graduates who showed depression, followed up in later life, were heavy caffeine and tobacco users. He suggested that increased awareness of nervousness, anger, and anxiety leads to more use of caffeine (cigarettes and alcohol) in an effort to alleviate these feelings.
Physiological and Pharmacological Effects

J. Murdoch Ritchie, in Goodman and Gilman's text on pharmacology (Ritchie, 1975) described the pharmacological effects of caffeine. The largest sources of caffeine are from the plants used to make coffee, tea, cocoa, and kola (the basis of cola beverages), although it is also found in Latin America as mate and guarana.

Caffeine particularly has a profound effect on the central nervous system, but it also affects, to a lesser degree, the heart muscle, gastric secretion and diuresis. Interestingly, caffeine is ingested daily by a vast number of people and is unique in that it is a potent drug considered to be part of our normal diet.

Caffeine stimulates the central nervous system first at the higher levels, the cortex and medulla, and finally the spinal cord at higher doses. Mild cortex stimulation appears to be beneficial because it raises glucose, resulting in more clear thinking and less fatigue. Caffeine has been shown to improve attention in a study which simulated night driving (Leinart, 1966). The onset of the effect of caffeine occurs within one hour and lasts for three to four hours (Baker, 1972).

The equivalent of one or two cups of coffee (150 to 250 mg of coffee) is sufficient to induce adverse effects. The occurrence of
hyperesthesia, an unpleasant sensory sensation, can be stimulated by large doses of caffeine.

The medullary, respiratory, vasomotor, and vagal centers are stimulated by caffeine. This effect is due to an increased sensitization to carbon dioxide, but needs large doses to elicit this effect, 150 to 250 mg parenterally. The spinal cord is stimulated at higher doses and convulsions and death may result. More than 10 grams are needed for such toxicity to occur in man (Ritchie, 1975).

Stimulation of the central nervous system is followed by depression (Klein and Salzman, 1975), although the effect is small at low doses, e.g., a single cup of coffee. After two hours, Klein reported that males (but not females) showed a lower central nervous system stimulation compared to placebo. The post stimulation "let down" with caffeine results in fatigue and lethargy and the constant stimulation caused by chronic caffeine dosing could be disastrous (Abrams, 1977; Dowell, 1965).

Children, because of their small size, are more susceptible to caffeine. One report noted that hyperactivity and insomnia observed in children could be attributed to excess caffeine intake from cola drinks (Consumer Research, 1973). According to Dr. Page, "There is no doubt that children should be kept from using coffee and the popular caffeine-containing soft drinks" (Abrams, 1977).

Caffeine's effect on the cardiovascular system is less profound than its central nervous system action. Its direct stimulatory effect on the heart may be neutralized by its central vagus stimulation. The direct
effect predominates at very large doses with tachycardia and, eventually, with resulting arrhythmias. Caffeine has the ability to potentiate ionotropic responses to B-adrenergic agonists and glucogon (Ritchie et al., 1975).

Although caffeine dilates blood vessels by a direct action, its central effect is one of constriction. At higher doses, the dilating effect is apparent (Peach, 1972; Poisner, 1973).

Similarly, because its direct and central effects are antagonistic, the resultant effect of caffeine on blood pressure is unpredictable. The net effect is usually of less than 10 mm of Hg in blood pressure (Ritchie et al., 1975). Caffeine's purported efficacy in hypertensive or migraine headaches may be due to a decrease in blood flow as a result of the increased cerebral resistance (Ritchie et al., 1975).

Caffeine also stimulates releases of catecholamines from the adrenal medulla and norepinephrine is released from nerve endings in the isolated heart (Bellett et al., 1971).

One of the many physiological effects of caffeine is an increase of the metabolic rate (Acheson, 1980). The increase is probably due to release of catecholamines (adrenaline). Dr. Bellett has shown that caffeine increases the free fatty acid content of the blood and increases the urinary secretion of catecholamines, although only at controlled times, post prandically and in absence of sugar. Dr. Acheson showed that free fatty acid levels doubled with 8 mg/kg of caffeine (equivalent to 5-6 cups of coffee). At half this dose (4 mg/kg), the same increase was
noted in both obese and normal persons. The increased metabolism is thought to be due to the increase of the readily available fatty acids, a source of energy. If caffeine was given with meals, the effect was synergistic. Thus, the extra energy boost noted with caffeine is probably related to the adrenal stimulation and increased free fatty acid availability. The rise in free fatty acids items limited with food intake, especially available carbohydrates.

Auditory reaction time was decreased and auditory vigilance increased when caffeine was given to 12 volunteers at doses of 75 to 300 mg (Clubley, 1979). Subjects also felt more alert, but no differences in short term memory or arithmetic performance were observed. The auditory vigilance test consisted of repetitive short length tones. The arithmetic test consisted of the calculation of simple sums. The auditory reaction time was the total time required to press a switch. Significant subject variability was observed with regard to reaction time. The effect of caffeine based on this test may be due to both "peripheral (muscular work) and central stimulation."

It has been shown that prolonged augmentation of gastric secretion results from caffeine administration and that ulcer patients have sustained elevation of acid as opposed to normals (Ritchie et al., 1975).

A dose of approximately 10 g or more taken orally can be fatal (Gleason et al., 1969). The toxic effects are due to central nervous system and circulatory system stimulation and include some well recognized prominent symptoms in addition to those which can result at
high doses or in hypersensitive persons: Insomnia, restlessness, excitement, tinnitus, flashes of light, quivering muscles, tachycardia, extrasystoles, and even low grade fever and mild delirium have been observed.

Harrie (1970) described a patient whose constant headaches were due to excessive caffeine consumption. He stated, "I suspect that the condition is much more common than supposed and could well be one of the more frequent causes of chronic recurrent headache." Headaches can also be precipitated by caffeine withdrawal, especially by those who have the "habit".

Caffeine's effects are more apparent in children than adults. A study by Dr. Judith Rappaport and colleagues (1981), of the National Institutes of Mental Health, concerned the effect of caffeine in boys and male college students. The young boys were more affected by caffeine than the college men. These effects included increased "motor activity, speech rate, and decreased reaction time." Adverse effects of caffeine were more obvious in children and for those adults who habitually drank little caffeine.

The boys were approximately 11 years old and the men 22 years old on the average. The adults were either low (26 mg/day) or high (565 mg/day) caffeine users. The children averaged 125 mg a day. Side effects and psychological effects were measured using a questionnaire after consumption of a caffeine beverage or placebo beverage. Motor activity was measured electronically. Other measures of caffeine effects included
"speech communication tasks," memory, reaction time, "sustained attention measure," and skin conductance.

This study confirmed previous investigations which showed that performance measured in adults was not affected by caffeine very much. Children, however, showed significant effects and also had more side reactions. The effect of caffeine on "feeling nervous and jittery" was clearly closely related in children. Children were less variable in their response to caffeine than the adults in this study.

Low caffeine users had more severe subjective "psychological" effects than high caffeine users. Even high users had the jitters and nervousness at high doses.

Kupiets and Winsberg (1977) used a test which showed discrimination to psychostimulant drugs for children with reading difficulty. The authors used a cross-over design with 10 boys, giving placebos and caffeine. No effect of caffeine on "attentional" problems was found in this study.

Although caffeine is well absorbed when taken orally, its absorption may be erratic because of its low solubility and because it may cause gastric irritation. Caffeine is principally metabolized with only 10 percent excreted in the urine unchanged (Ritchie et al., 1975).

Caffeine has a physiological half-life of three and a half hours (Parsons and Neims, 1978) to six hours (Aranda et al., 1979). Its physiological effects are observed in less than one hour (Parsons and Neims, 1978). Infants do not metabolize caffeine as well as adults and
thus have a half-life of about four days (Aranda et al., 1975).

Certainly, continuous ingestion of caffeine by infants can be dangerous. If a cup of coffee is consumed by an adult six or seven times a day, it would result in a high steady concentration of caffeine in the blood. As little as four cups a day can result in appreciable omnipresent amounts of caffeine in the body.

Caffeine can accumulate in severe liver disease (Stratland, 1976) when its half-life can increase to 96 hours. If these patients drink coffee, they should be closely monitored.

Caffeine is known to interact with other drugs, resulting in a modified effect. For example, caffeine administered with nardil (a MAO inhibitor) caused headaches and high blood pressure (Pakes, 1979). This potentially dangerous interaction was first noted by Berkowitz et al. (1971) and implicated serotonin in the mechanism.

Caffeine and barbitol are antagonistic, with caffeine (in coffee) reducing the sleeping time induced by barbitol. Decaffeinated coffee had no effect (Aeschbacher et al., 1975). In another study, caffeine resulted in reduced sleeping time, which was counteracted by pentobarbitol in hospitalized patients (Forrest et al., 1972).

**Caffeinism**

Reimann (1967) describes the effects of caffeinism: insomnia, appetite loss, weight loss, irritability, flushing, low fever, and chilliness. Those most susceptible are night people, people whose jobs
keep them up at night, such as truck drivers, waitresses, and theater people.

Caffeine beverages are said to give a "vigorous, energetic feeling," working for 2-3 hours after ingestion. It has been shown to prevent "attention lapses" and to improve the speed at which physical tasks can be performed. However, intellectual performance seems not to be affected (Graham, 1978).

Other symptoms attributed to the habitual excessive ingestion of caffeine are such disturbing effects as agitation, restlessness, and anxiety, sometimes misdiagnosed as anxiety neurosis (Greden, 1974). Caffeinism has been considered by some medical authorities to be a real public health problem. Children are particularly susceptible and the "hyperkinetic" syndrome observed in many children may be at least partially due to habitual caffeine use. Children who consume only cola drinks may be taking in an amount of caffeine equivalent to 8 cups of coffee a day, if their lower weight is taken into account. Particularly, children should not be given caffeine-containing beverages and if symptoms resembling those attributable to caffeine overdosage occur, excess caffeine consumption should certainly be considered as a possible cause.

Gilliland and Andress of the University of Oklahoma (1981) investigated caffeinism in college students. Caffeinism is expressed by anxiety, depression, and other psychophysiological factors. Through a survey, they identified abstainers, low, moderate, and high caffeine
consumers. They then compared caffeine consumption to performance. High consumption of coffee was 5 or more cups per day. (The average of the high consumer group was 8 cups/day.) The high user group showed more evidence of anxiety and depression. Men seemed less affected than women. Academic scores were also adversely affected in the high user group. The moderate and high consumer group showed similar traits, which were significantly different from the caffeine abstainers.

**Behavioral Effects**

Caffeine's stimulating activity on the central nervous system, as well as other body organs, results in certain physiological effects, which may be considered to be behaviorally-oriented. Caffeine produces more rapid, clearer flow of thought, allays drowsiness and fatigue, increases the capability of a greater sustained intellectual effort, and more perfect association of ideas. It also causes a keener appreciation of sensory stimuli and reaction time is diminished. Motor activity is increased: typists, for example, work faster with fewer errors. Tasks requiring delicate muscular coordination and accurate timing may, however, be adversely affected. All of this occurs at doses of 150 to 250 mg of caffeine (approximately two cups of coffee) according to Ritchie (1975).

In 1912, Hollingsworth, who was a psychologist, reported caffeine's effect on mental and motor efficiency in a study sponsored by Coca-Cola. In nine double-blind tests, he found beneficial effects for both mental
and motor performance at doses of 65 to 130 mg of caffeine. At a dose of 300 mg of caffeine, the results were tremors, poor motor performance, and insomnia. These results have withstood the test of time (Stephenson, 1977).

Goldstein (1965) showed no effect of caffeine on objective measures of performance, although most subjects "felt" more alert and physically active. However, some subjects felt nervous.

Mitchell, Ross, and Hurst showed caffeine to prevent attention lapses in a visual monitoring test which simulated night driving. The effect persisted for the two to three hour experiment (Stephenson, 1977).

A 200 mg dose of caffeine resulted in decreased decision time scores and improved motor time scores in volunteers (Smith et al., 1977). Hand steadiness, however, was impaired. After a caffeine intake of 200 mg, introverts performed less well on a verbal ability test as compared to extroverts when time pressure was applied (Ritchie et al., 1975).

Wayner et al. (1976) reported on the effects of caffeine on schedule dependent and schedule induced behavior in mice. Caffeine (3.125, 6.25, 12.5, 25, 50, and 100 mg/kg) was tested on lever pressing, schedule induced licking, and water consumption of mice. The effect on mice at 80 percent of body weight was different than when mice were allowed to recover the lost weight. At the lower weight, caffeine had little effect except at the highest dose (equivalent to 100 cups of coffee given at once). At their ordinary weight, the mice were more sensitive to caffeine, with all measures enhanced even at the lower dose (equivalent
to approximately three cups of coffee). At high doses, all measures decreased: the mice became tolerant.

Castellano (1976) studied the behavior of mice under two sets of conditions. One involved a natural preference (swimming towards a light - "L") and the other involved an acquired behavior pattern (swimming toward the dark - "D"). A facilitation of learning and consolidation after caffeine dosing was noted in naive mice after the "D" procedure. Natural tendencies were also enhanced by caffeine as noted by improved performance in the "L" procedure. Animals pretrained in the "D" procedure exhibited behavioral disruption after treatment. Animals pretrained in the natural "L" procedure needed very high doses to cause disruption. Amphetamines do not show the results as demonstrated in this paper, whereas other drugs, such as hallucinogens, do show a similar effect. The implication is that the mechanism of caffeine's action may be similar to hallucinogenic drugs.

**Effect on Sleep**

Caffeine is known to cause insomnia because of its central nervous system stimulating activity. In fact, its major therapeutic use is to allay sleep and drowsiness, being the only OTC (over-the-counter) stimulant approved by the FDA (Federal Food and Drug Administration). Several studies investigating this action in some detail have been published.
Karacan (1976) found that caffeine given half an hour before sleep adversely affected the sleeping patterns in normal subjects. The effect is dose related. Caffeine's effect simulates clinical insomnia and gave the same response as coffee containing an equivalent amount of caffeine. Decaffeinated coffee showed no effect on sleep.

Dorfman and Jarvick (1970) showed a dose-response effect on caffeine on the self estimation of sleep latency (which was increased) and quality (which was decreased). This was a double-blind study in which 60, 120, and 250 mgs. of caffeine was administered one hour before bedtime.

Mikkelsen (1978) notes that caffeine seems to inhibit deeper stages of sleep as opposed to disturbances of the REM (Rapid Eye Movement) stage. Other studies show contradictory evidence, REM being affected by caffeine, leaving the situation to be resolved.

The tolerance developed to caffeine's effect on sleep by coffee drinkers has been documented by Colton (Stephenson, 1977). Non-coffee drinkers were more sensitive to coffee's insomnic effect, whereas coffee drinkers were relatively insensitive in this regard. Non-coffee drinkers experienced disturbed sleep patterns and delayed onset of sleep.

Mueller-Limmroth (Stephenson, 1977) showed that the quality of the first three hours of sleep was impaired by the ingestion of coffee before retiring. This is approximately equal to the half-life of caffeine in the body.

Goldstein did extensive work on the effect of coffee and showed that coffee drinkers slept more soundly when they took placebos, as opposed to
caffeine in coffee. If 150 to 200 mgs. of caffeine were taken before bedtime, there was an increased sleep latency which was less pronounced in persons who were heavy ingestors of caffeine (Goldstein et al., 1965).

These studies show that caffeine has a profound effect on sleep. Heavy and continued use of caffeine results in tolerance so that heavy users have less sleep disturbance or need more to obtain its stimulating effect.

The Caffeine Personality

Several studies have been designed to see if an association between a "personality" type and caffeine consumption exists, i.e., "what kind of person drinks coffee?" Also, how do various "types" respond to caffeine.

One hundred ninety-nine (199) females from a non-coed college were given a personality test, self-rated, and no significant differences were found between coffee and non-coffee drinkers (Primavera, 1975). (There were differences between smokers and non-smokers, however.)

People considered to be "low impulsives" performed less well and "high impulsives" were aided by morning coffee; but the opposite occurred when coffee was taken at night (Revelle et al., 1975). The authors of this study suggest that the effect could be due to the different circadian rhythms of extroverts and introverts with regard to impulsivity and caffeine's stimulant effect. The decreased performance is considered to be a consequence of "overarousal." Caffeine has been said to have effects on arousal and anxiety. It was shown that stress is also a
factor affecting the observed activity of caffeine, with reduced performance and effectiveness when stress is increased.

Eysenck and Folkard (1980) disagree with the above findings, pointing out discrepancies and incorrect assumptions. For example, the times at which the coffee and tests were administered did not coincide with the circadian rhythms of introverts and extroverts as observed in the authors' experience and published studies. Also the analysis was unidimensional, based on an impulsive component only. This seems to be an oversimplification. The cross-over design also may have introduced complications caused by a carry over effect. Caffeine is known to induce anxiety and has arousal effects. These are related to measures of neurosis and, perhaps, should not have been neglected in Revelle's analysis.

**Smoking and Coffee**

It has been established that coffee consumption and cigarette smoking are correlated; they go hand-in-hand. Marshall performed a test where smokers were given 0, 1, 2, or 3 cups of coffee while working on a crossword puzzle (Marshall, 1980). The more coffee they drank, the more they smoked. The experiment was repeated, testing "no beverage, water, postum, decaffeinated, and regular coffee." Drinking coffee, both caffeinated and decaffeinated, was associated with increased cigarette consumption. When no beverage or water was given, smoking was less. Kozlowski, in 1976, showed that more nicotine was taken with the
caffeinated coffee and was not related to the caffeine concentration. Therefore, smoking seems to be related directly to caffeine and not to the liquid consumption. The author suggests that coffee consumption be reduced for those who wish to stop smoking.

Marshall thought that the association of smoking and coffee consumption could be explained on the basis of physiological rather than psychological effects. He reasoned that change in urine acidity caused by coffee could affect the excretion of nicotine and caffeine might affect the metabolism of nicotine. Coffee makes the urine acid and nicotine is excreted more rapidly under these conditions. Smokers were given water, coffee, coffee plus sodium bicarbonate (an alkalizing agent) and coffee plus ascorbic acid. The urine acidity had no effect on cigarette use. There was increased smoking with both bicarbonate and ascorbic acid. This author suggests that smoking with coffee is a conditioned reflex.

**Psychological Effects**

Caffeine in excess has been reported to induce hallucinatory and psychotic states in high doses in some people (Mullin, 1978). The case of a man who hallucinated after taking in 1000 mgs. of caffeine in a short time internally during a dog sled race has been reported. She tells of a 31 year old truck driver who said he was being attacked by bright shiny bugs and flies which were trying to bite him. He worked in a cola factory and drank 120 ounces a day (10 cans). The day before the
attacked, he had consumed 20-25 cans, equivalent to more than 1000 mgs. of caffeine. This man recovered from his hallucinatory, psychotic attack in 2 days. Similar reports of caffeine's effect at high doses have been reported previously. As early as 1914, Orendorff reported a case of excess cola consumption in which an individual showed eccentric and stubborn behavior with periods of exhilaration and depression. In 1936, a psychosis which included symptoms of delirium, confusion, and manic-depressive character was reported as a result of an overdose of caffeine.

As pointed out by Rippere in the British journal, The Lancet, coffee can "cause and exacerbate pre-existing psychological states. Nevertheless, coffee is still given to psychiatric patients and little effort is made to give decaffeinated coffee."

Reimann (1967) noted that symptoms of a psychoneurotic woman disappeared when coffee intake was reduced. She presented with an irregular fever, insomnia, anorexia, and irritability, having consumed large amounts of coffee.

Mikkelsen (1978) noted caffeine's involvement in schizophrenic like states similar to those observed by Greden in anxiety neurosis symptoms of patients who consumed large quantities of caffeine (coffee). One case cited was of a white male in a catatonic state who threatened his mother after having gone on a coffee jag over injustices caused to him by his mother. He felt that the patient developed paranoid delusions which were, at least in part, due to the coffee. A 30 year old white single
female exhibited paranoid and auditory hallucinations. An anxiety state had resulted in increased coffee consumption. In the hospital, she noted the correlation of these strange feelings with coffee consumption. Other examples of psychotic behavior, as noted in the literature, are described in this report. Forty years ago a case of psychosis was reported in which a 24-year old female took 60 gr. (about 4 g.) of caffeine. Manic symptoms developed. Mikkelsen theorizes that adrenal cyclase which is increased by caffeine may be a receptor for dopamine. If this system is abnormal in schizophrenics, caffeine may further sensitize the patient. Certainly, coffee should be considered as a factor in this disease.

Habituation, Addiction, and Tolerance

Caffeine and coffee consumption have been investigated with regard to the degree that this habit results in tolerance and withdrawal effects. These studies look beyond the obvious social implications and psychic dependence (Ritchie, et al., 1975) of coffee consumption which may be related to the "first cup of coffee to wake me up" or "the coffee break" or to its association with smoking. Coffee, milk, sugar, cigarettes, and sugar with chemicals certainly poison the body and brain and create toxicity. In the latter case, it is of interest that coffee drinkers were shown to take more nicotine when deprived of coffee; a substitution of one toxic allergen for the other (Kozlowski, 1976).

Caffeine has not only been considered habit forming, but also addicting. Crothers considered morphinism and caffeinism to be similar,
with caffeine causing loss of self-control, spells of agitation, and depression as well as psychotic behavior (Stephenson, 1977). Ritchie mentions a report by Colton that tolerance can develop for the diuretic salivary stimulation and sleep disturbance effects of caffeine.

Cola consumption in amounts of 48 to 111 ounces per day (144 to 333 mgs. of caffeine per day) was reported to have caused physical effects on withdrawal (Diamond and Pfiffering, 1974). The resultant effects were depression, nervousness, decreased alertness, sleeping difficulty, frequent mood changes, and various other behavioral difficulties which were attributed to caffeine withdrawal.

In an oft-quoted study, Kozlowski observed that habitual coffee drinkers will drink more coffee if it contains less caffeine. He supplied coffee containing either 25, 40, or 100 mgs. of caffeine to experimental subjects, keeping at least some caffeine in the coffee to prevent possible severe withdrawal symptoms which include, according to Kozlowski, headache, fatigue, and irritability. The test took place in two settings: a university dining room, where an urn was supplied, and in an area where school teachers had their coffee breaks. The average number of cups consumed, according to caffeine content, is shown in the table below:
Table 1
Average Number of Cups Consumed, According to Caffeine and Content

<table>
<thead>
<tr>
<th></th>
<th>Caffeine 100 mg</th>
<th>Caffeine 50 mg</th>
<th>Caffeine 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urn in university</td>
<td>4.2</td>
<td>5.0</td>
<td>4.5</td>
</tr>
<tr>
<td>School teachers</td>
<td>2.6</td>
<td>3.0</td>
<td>3.1</td>
</tr>
</tbody>
</table>

The subjects also reported feeling better as more coffee was consumed. This study suggests that the taximolecular levels of caffeine dropped, so craving for the "fix" and withdrawal syndrome symptoms arose.

One of the most frequently observed symptoms of caffeine withdrawal from regular users is headache. This effect is paradoxical in that caffeine is also used to ameliorate headache pain (British Medical Journal, 1977).

Greden (1980) reported that approximately 11% of psychiatric patients experienced headaches when caffeine was withdrawn. The headaches usually start about 18 hours after the last caffeine dose and are characterized by painful throbbing with the worst pain 3-6 hours later. These headaches, according to Greden, can last for a day or more, often occurring on weekends, because of the changes in habits which occur at these times, for these patients. This is how a vicious cycle can begin with caffeine. Thus, coffee or caffeine-containing drugs can
relieve the headache, and the caffeine habit continues and is perpetuated.

Indeed, headache is one of the chief symptoms observed as a result of caffeine withdrawal in those who ingest relatively large quantities of caffeine on a regular basis. Dr. Greden has done considerable research in this area (1980). He tested people who experienced caffeine withdrawal headache and found that they showed more anxiety and depression, as evidenced by psychological tests. These people also feel less healthy and take more caffeine and anti-anxiety drugs compared to persons who do not experience the withdrawal headache. Dr. Greden notes that a large caffeine intake results in a certain tolerance to caffeine's effects. He also points out that 22% of psychiatric patients ingest 750 mgs. or more of caffeine daily. In this report, 28% of 152 persons tested had caffeine withdrawal headaches. This group considered their health not as good as others and scored worse on State-Trait Anxiety Index scores. They also fared worse on the Beck Depression scores, particularly with regard to sadness, guilt, pessimism, failure, and expectation of punishment.

The persons who experienced the withdrawal headaches took in more caffeine, an average greater than 600 mg/day. They perceived that the caffeine gave them energy and cleared their thoughts, although they agreed that it could have deleterious effects. Thirty-eight (38) percent of those with caffeine withdrawal headaches thought that caffeine helped their headache, as compared to 7% in the group who did not experience the
headaches. A case history of a 32-year old housewife was presented. She reduced her caffeine intake because the headaches she experienced were relieved with a caffeine-containing pill, creating the cycle. The recommended treatment is to stop the cycle using intermittent withdrawal. People do not really appreciate that all of this can be caused by caffeine intake and thus are reluctant to stop their caffeine intake. Once the cycle is interrupted, any problems, such as headaches, can be treated symptomatically.

Harrie reported a case of a patient who experienced constant headaches for a period of time exceeding two years. When a psychiatrist found that tension was not the cause, the medical diagnosis was too much "serenity." This woman was so psychologically habituated to caffeine that she even suffered after having coffee passed off as decaffeinated. Thus, paradoxically, the caffeine headache can occur in some from drinking coffee as well as in others during the withdrawal.

The 24-hour fasting during Jewish high holidays (Yom Kippur) often results in headaches. Other symptoms include a lethargy in the morning, nausea, and occasional vomiting (Shorofsky, 1977). These symptoms were found to be relieved by caffeine or salicylates, suggesting that the adverse effects of fasting might be due to withdrawal.

Although the occurrence of headaches when caffeine is withdrawn is well documented, the effects of caffeine do not seem to be adaptive; tolerance is not obvious (Graham, 1978). That is, the physiological
effects of caffeine are evident in heavy caffeine users as well as abstainers.

Abrams (1977) says, "There is no doubt that a certain degree of psychic dependence, that is habituation, develops from the use of xanthine beverages."

A questionnaire completed by more than 200 young housewives showed that the perceived effects of caffeine depended on previous use (Goldstein et al., 1969). The heavy coffee drinkers had few sleep disturbances and less evidence of nervousness after their morning coffee, as compared to non-drinkers. If the morning coffee was stopped, the habitual coffee drinkers experience nervousness, headache, and irritation. The non-coffee drinkers reacted negatively to coffee, experiencing effects opposite to the coffee drinkers. An experiment was devised to verify the results of the questionnaire involving 18 housewives, non-coffee drinkers, and 38 who drank five or more cups per day. The results confirmed those obtained from the questionnaire previously administered (Goldstein et al., 1969). This experiment was double-blind and placebo-controlled and caffeine was administered in coffee at 0, 150, and 300 mg. Coffee drinkers showed a dose-response effect, whereas non-coffee drinkers showed signs such as nervousness, jitters, and upset stomachs at all doses of caffeine, but not on placebo.

An interesting case of caffeine withdrawal was reported by Dr. C. Gibson of M.I.T. in the New England Journal of Medicine (1981). According to Dr. Gibson, the amount of MHPG, a norepinephrine metabolite,
is "used to classify patients with affective disorders and to predict therapeutic response to antidepressant drugs..." A patient who drank 10-15 cups of coffee per day showed the highest levels of MHPG ever observed by the author, after elimination of coffee (3 to 4 times that observed in normals). The patient also had withdrawal symptoms which "included headache and anxiety." This increase probably is a result of "sympathetic activation," perhaps a rebound effect or compensatory action.

Ritchie (1975) says that tolerance and physiological dependence on caffeine beverages does occur to some extent but he feels that this does not present a problem. He says that coffee or tea drinking are socially acceptable and are apparently not harmful when practiced in moderation.

However, it does appear that, at least in some persons, excess consumption of caffeine can result in severe physiological dependence and withdrawal effects and is a problem to be reckoned with.

The addiction liability of caffeine and its relation to the mechanism of addiction has been studied in quite some detail in both human and animal models. This interest in caffeine stems not only because of its wide use but because of its profound pharmacological activity.

Caffeine is a phosphodiesterase inhibitor and induces a morphine-like withdrawal syndrome in "opiate-naive" rats as shown in a study by Butt and co-workers (1979). This effect is related to caffeine's ability to inhibit cyclic AMP (cAMP) phosphodiesterase in rat
brain homogenates. (The activity is not related to CGMP phosphodiesterase.) Naloxone, a narcotic antagonist, results in withdrawal symptoms when given to narcotic (morphine) addicts. Similar symptoms occur when naloxone is given to chronic caffeine users (methylxanthines, in general). In fact, withdrawal symptoms caused by naloxone in addicts are greatly increased in the presence of caffeine. The methylxanthines appear to act by inhibiting the hydrolysis of phosphodiesterase of cyclic AMP. Caffeine was given subcutaneously to opiate-naive rats one hour before naloxone was given. The animals were observed for 15 minutes after the naloxone, with particular emphasis on behavioral excitation effects. Opiate dependence is characterized by increased cAMP activity, which is related to the abstinence syndrome.

Collier and co-workers (1981) have been active in research elucidating the mechanism of addiction. They hypothesize that opiate dependence is due to a "hypertrophy of a neuronal cAMP in compensation for the inhibition by the opiate of an adenylate cyclase." They show that there is a relationship between caffeine consumption and opiate addiction. Also, opiates may be used as an antidote for theophylline and caffeine poisoning. The withdrawal symptoms from caffeine are very much like that of morphine. They cannot be differentiated in opiate-naive animals. The typical experiment is to give the narcotic antagonist, naloxone, after administration of the "addicting" drug. With some caffeine derivatives, the time for withdrawal symptoms to occur after administration of naloxone is much shorter than that observed with
morphine. They have tested this theory of opium dependence and the hypertrophy of neuronal cAMP, which is inhibited by opiates. If this is true, phosphodiesterase inhibitors, such as caffeine, in conjunction with opiates, should increase withdrawal symptoms. Opiates are stronger than caffeine and, if given together, opiates predominate. However, if the caffeine is administered to opiate dependent animals, the withdrawal effects caused by naloxone are increased.

If rats are left on their own, they seek more morphine when given methylxanthines. The methylxanthines counteract the effects of opiates but synergize the dependence. The authors of this report state that the relationship of methylxanthines to opiates is intimate and paradoxical. The inhibition by caffeine of phosphodiesterase increases cAMP which antagonizes the opiates and synergizes antagonists such as naloxone. They postulate the increased cAMP causes the release of endogenous opiates which inhibit adenylate cyclase. Therefore, phosphodiesterase inhibitors (which increases cAMP) enhance the opiate dependence. When opiate dependent rats are withdrawn, cAMP is increased. The inhibition of neuronal adenylate cyclase by opiates results in hypertrophy of cAMP. Caffeine increases the induction of opiate dependence. In relation to caffeine's role in opiate addiction, the authors state, "Since caffeine is arguably the most widely taken drug in the world, we believe these possibilities demand serious study."

Dr. E. M. Boyd (1965), in an article in the Canadian Journal of Physiology and Pharmacology, observed the effects caused by the caffeine:
Dr. Boyd noted withdrawal symptoms which lasted one week. These included decreased locomotor activity (1/2), proteinuria, glycosuria, and lowered body temperature.

Deneau and co-workers (1969) used a test where monkeys were able to self-administrate drugs to demonstrate drug dependence. If a dependency occurs, the monkey voluntarily takes more drug. A drug which is "psychotoxic" is considered addictive with abuse potential. In this report, caffeine (in addition to the usual narcotics such as morphine) was shown to produce a "psychological dependence." However, caffeine did not produce psychotoxic effects. The monkey has been shown to be a very good model for humans for such drugs. Most of the drugs which cause physiological dependence are central nervous system depressants, although some stimulants also fall into this class. The authors define physiological dependence as the "voluntary initiation and maintenance of self-administration of drugs." If the drug is desired, the monkey can press a lever (in this experimental set-up) and the drug is delivered through an intravenous indwelling catheter. A second lever did not deliver the drug. With caffeine, self-administration was sporadic but was increased by automatically injected priming doses. No toxicity was observed during the experiment or after withdrawal. It should be noted that the monkeys make their own decisions and that these animals had not been pre-treated to induce dependence (in marked contrast to parallel types of studies with cocaine).
Vitiello and Woods (1977) describe an experiment in which rats received caffeine injections for 12 consecutive days. The rats then avoided a solution which they had associated with the absence of caffeine. The authors call this a "physiological withdrawal." Similar behavior had been previously demonstrated in morphine addicted rats. In the present experiment, rats were given various doses of caffeine and saline controls by injection. After 12 days, the saline group was divided into two groups, half being given saline and the others given caffeine. The rats on caffeine were also divided into two groups, one group given saline and the other the same dose of caffeine they had been given on the previous 12 days. Then, on the 13th day, the rats were given water with saccharine rather than their usual plain water. The rats which (1) were on saline during the 12 days and saline on the 13th day or (2) on caffeine during the 12 days and caffeine during the 13th day consumed the saccharine water in preference to the plain water. They had not been changed and preferred the sweeter water. Those which were switched from saline to caffeine or caffeine to saline on the 13th day avoided the saccharine water according to the caffeine dosage, i.e., the larger the dose, the greater the avoidance. This aversion showed that caffeine can cause a dependence. A change in caffeine dose in one day was sufficient to cause an aversion to the associated drink in this conditioning experiment (taste acuity change, catecholamines, hypothalamic effects).
The effect of naloxone of precipitating withdrawal symptoms in morphine addicted monkeys was duplicated by caffeine in a study by Aceto et al. (1978). The addicted monkeys were more severely affected by the typical, usual effects of caffeine than non-addicted animals. This result is again theorized to be due to cAMP phosphodiesterase inhibition. Morphine withdrawal results in increased cAMP which can be inactivated by phosphodiesterase. The symptoms, which were intensified by caffeine, include "avoiding contact, vocalizing, crawling or rolling, restlessness, tremors, wretching, vomiting, and coughing.

Although many people become dependent on caffeine and exhibit symptoms of caffeinism at low doses (8 cups or more a day is considered to be very harmful), a certain tolerance has been observed, after constant use, to diuretic and salivation effects (Foxx and Rubincoff, 1979). Also, drinkers of coffee have less sleep disturbance reactions. It has been also reported that coffee consumption is increased in time to compensate for the diminished effects due to tolerance.

Foxx and Rubincoff (1979) applied a method for the gradual withdrawal of caffeine which had previously been used for coffee. Three persons were chosen for the study on the basis of a questionnaire describing previous habits with regard to caffeine consumption. These persons drank eight or more brewed cups of coffee, had symptoms associated with coffee drinking, and wanted to cut down consumption. During a baseline period, an assessment of caffeine intake was made. The objective of the experiment was to decrease the consumption gradually to
a specified target value in four phases. A small monetary incentive was included as part of the program.

The subjects recorded daily consumption, including activities associated with drinking the beverage. Graphs were made each day of total consumption. These were handed in at the end of each phase. Follow-up contacts were made at the end of the study to check consumption following the withdrawal regimen. During the study, subjects were monitored by people who agreed to check on the veracity of the subjects. These monitors were contacted by the authors to see if, indeed, habits had changed and to verify the reports. Each subject showed a significant decrease in caffeine consumption, which was maintained or decreased over almost a one-year period. Subject one consumed 1000 mgs. of caffeine at the start, which was decreased to 300 mgs. after the withdrawal regimen. The second subject showed similar results, whereas the third subject did less well. Subject three decreased his caffeine intake from almost 2200 to 300 mg, but went up to 500 mgs. during the follow-up.

All subjects reported lessened psychological effects, i.e., lessened irritability, tenseness, and "hyper" feeling. Thus, this approach can be considered as a possibly useful approach in reducing the intake of caffeine among habitual users.

Among other methods to break the coffee habit is a relaxation technique reported by Hyner (1979), in which he used reinforcement cards. This resulted in decreased tachycardia and eventual discontinuance of
caffeine tablets by habitual users. This technique resulted in both decreased tea and coffee consumption.

Just how much is too much coffee? That depends upon the individual, but obvious physiological effects are considered to occur after one or two cups of coffee, and certainly after intake of 250 mgs. of caffeine. Table 2 (Graham, 1988) shows the amount of caffeine typically found in various beverages and OTC (over-the-counter) drugs. The moderately high intake of 650 mgs. per day taken by 1/4 of the adult population is certainly enough to elicit adverse physiological and psychological effects.

**TABLE 2. CAFFEINE FOUND IN VARIOUS SOURCES**

<table>
<thead>
<tr>
<th>Beverage</th>
<th>Caffeine Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ground coffee</td>
<td>85 mg</td>
</tr>
<tr>
<td>Instant coffee</td>
<td>60 mg</td>
</tr>
<tr>
<td>Decaffeinated coffee</td>
<td>3 mg</td>
</tr>
<tr>
<td>Instant tea</td>
<td>30 mg</td>
</tr>
<tr>
<td>Cocoa</td>
<td>6-42 mg</td>
</tr>
<tr>
<td>Cola (8 oz.)</td>
<td>32 mg</td>
</tr>
<tr>
<td>Cold and allergy tablets</td>
<td>15-30 mg/tablet</td>
</tr>
<tr>
<td>Headache tablets</td>
<td>32 mg/tablet</td>
</tr>
<tr>
<td>Stay-awake tablets</td>
<td>100-200 mg</td>
</tr>
</tbody>
</table>
Anxiety and Caffeine

A particularly disturbing symptom of caffeinism has recently been observed to be more prevalent than previously supposed in the development of psychotic symptoms, indistinguishable from anxiety neurosis, according to Dr. John Greden of the University of Michigan. That caffeine can produce an effect of this sort was reported in the literature as early as 1936 by McManamy and Schube (Navin, 1980; Stephenson, 1977). They described the psychotic state of a woman who had just ingested 10 cups of coffee, equivalent to about 1 gm (1000 mg) of caffeine, over the course of several hours. Pierce also had reported delirium and tremulousness in adults when large amounts of caffeine were taken (Stephenson, 1977). It is known that, even in smaller amounts, "dangerous sensory and motor disturbances" can occur.

Dr. Greden reported several case studies of patients in whom symptoms which were "indistinguishable from anxiety neurosis" were caused from excessive doses of caffeine (1974, 1976). According to this researcher, these symptoms included "nervousness, irritability, tremulousness, occasional muscle twitching, insomnia, sensory disturbances, tachypnea, palpitations, flushing, arrhythmias, diuresis, and GI disturbances." He also noted that when caffeine was withdrawn, symptoms such as anxiety and headaches occurred. He made a special point to note that psychiatrists should be aware of this syndrome and consider caffeine intake when diagnosing psychiatric patients. Thus, if a diagnosis of anxiety neurosis is made, caffeine intake should be
carefully monitored to eliminate caffeine as a possible instigating factor. Although 1 billion kg (more than 2 billion pounds) of coffee are consumed annually in this country, caffeine intake has not been a usual part of the information on the patient's record. According to Greden, as little as 50-200 mgs. of caffeine can induce the effect in susceptible persons.

Withdrawal symptoms have been documented in other studies. Greden notes the study by Goldstein (previously noted) in which withdrawal symptoms of heavy coffee drinkers who were deprived of their daily morning coffee included irritability, less efficiency on the job, nervousness, lethargy, restlessness, and headache.

Three cases were described by Dr. Greden. One case involved a nurse who drank 10-12 cups of coffee a day and reported headaches, breathlessness, PVC/s, and lightheadedness. Examination revealed no overt illness; she was normal except for these symptoms, which disappeared 36 hours after withdrawal of coffee.

A 37-year old army lieutenant colonel had suffered for two years with anxiety, dizziness, tremulousness, apprehension, restlessness, and diarrhea, having chronic difficulty in falling asleep. He drank 8-14 cups of coffee each day, blaming the habit and his symptoms on the pressure put on him by a very demanding boss. His total caffeine intake was 1200 mg/day, including cola and cocoa drinks. The symptoms were relieved when his caffeine intake was reduced.
Another army officer who drank 10-15 cups of coffee a day in addition to tea and cola as well as consuming caffeine-containing analgesics (1500 mgs. of caffeine per day) had severe tension headaches which disappeared after his caffeine intake was reduced.

These symptoms of excess caffeine usage are not new. The previous literature had reported anxiety, vertigo, instability, agitation, weakness, and headaches, as well as psychotic episodes as a result of caffeine abuse. Dr. Greden points out that if patients do not respond to psychopharmacological or hypnotic agents, then caffeine abuse may be the cause of these symptoms. Particularly, this should be considered in the diagnosis of "hyperkinetic" children.

The effects described by Greden have since been corroborated and verified in various reports in the literature. Molde (1975) tells of a prisoner who drank 50 cups of coffee a day! He showed "severe anxiety symptoms" which did not remit when drugs such as tranquilizers and other antipsychotic agents were administered. Reduction in caffeine intake caused the symptoms to disappear. Excess drinking of coffee by prisoners is not uncommon and may initiate a vicious cycle: a bored person drinking more coffee resulting in caffeinism which may result in more consumption.

MacCullum (1979) reported the case of a young 28-year old housewife from a professional family who drank more than 20 cups of coffee each day. She had "palpitations, persistent anxiety, attacks of cold sweat, shortness of breath, and tingling of extremities," and was in a state of
panic. In an unsuccessful effort to relieve these symptoms, she was put on a regimen of benzodiazepines for more than six weeks. The symptoms only disappeared three weeks after coffee was eliminated. Again, as Dr. Greden also has recommended, Dr. MacCullum suggests inquiries about caffeine habits with the answer coming by "simply asking a few questions."

An article by Hire (1978) showed a strong correlation between coffee drinking and anxiety, although no correlation of tea or cola consumption and anxiety was noted.

The intake of caffeine (coffee, etc.) has been correlated with the degree of mental illness in psychiatric patients. It is not clear if the caffeine intake intensifies the psychiatric disorder or whether those with more severe problems tend to drink more coffee. In any event, in another study by Dr. Greden and associates (1978), 83 hospitalized psychiatric patients were interviewed and showed an association of symptoms with high caffeine intake. This may provide an explanation of some problems which have been experienced in diagnosing outpatient disorders. Eighteen of the 83 patients (22 percent) were high caffeine consumers (750 mgs. or more).

These high caffeine users had higher scores on various psychiatric tests which measure anxiety and depression compared to those whose caffeine intake was lower. The high users also had more clinical symptoms, used more drugs such as sedatives, hypnotics and tranquilizers, and reported that their general health was less good than the low users.
Three groups of caffeine users were identified in this population, categorized as low, intermediate and high users. The low users took in between 0 and 249 mg/day, the intermediate users 250-749 mg/day, and the high users 750 mgs. or more per day. There were no special differences between the groups based on demographic information such as age, sex, race, marital status, and religion. In addition to the increased anxiety and depression in the high user group (1/2 of these showed severe depression), they also reported feeling more tired, blue, and tense. They were less rested, happy, and content. As reported in other studies, the high caffeine users had less trouble sleeping when taking caffeine. Greden feels this is due to a tolerance or, perhaps, a difference in the metabolic handling of caffeine by these patients. The high users group also smoked more and drank more alcohol. (Many alcoholics substitute coffee for alcohol in Alcoholics Anonymous.)

The exaggerated symptoms described above are the same as those of caffeinism, although the depressive effect is unexpected. Caffeine is used to counter depression due to its stimulating effect.

In an attempt to explain the above effects, Greden notes that caffeine "modifies catecholamine levels, inhibits phosphodiesterase breakdown of cAMP and sensitizes catecholamine receptor sites." He notes the work of Cobb in which a group of unemployed workers who had a greater norepinephrine (a catecholamine) release when stressed than when not under stress, and he concludes that these biochemical effects may be involved in the induction of anxiety/depression by caffeine. Dr. Greden
considers caffeine to be a psychotropic drug and 25 percent of the population may take more than 500 mgs. per day, a large physiologically active dose. He describes three cases in which caffeinism may be misdiagnosed as an anxiety syndrome.

Dr. Greden concludes that caffeine is found among a fairly large percentage of hospitalized patients with psychiatric symptoms. Caffeine should not be used as part of psychiatric treatment routines, e.g., to reduce drowsiness from psychotropic medications as has been occasionally suggested.

A case of delirium induced by caffeine under stress was reported by Stillner (1978). A man involved in an Alaskan dog sled race went 48 hours without sleep in an effort to win the race. He took 1000 mgs. of caffeine within three hours, after which he hallucinated, became tremulous, had buzzing his ears, and experienced dizziness. These symptoms disappeared with time and he reported his experience after the race. This corroborates other reports of the effects of excessive use of caffeine.

Caffeine withdrawal can also cause anxiety symptoms. White and co-workers (1980) reported in *Science* that muscle tension and anxiety were evident among college students (who were regular coffee drinkers) when they abstained from caffeine. This was a double blind study in which grapefruit juice, with and without caffeine, was administered after 3-7 hours abstinence from caffeine. Electromyographic (EMG) readings in high coffee drinkers before caffeine was to be given was higher, showing
increased muscle tension. After coffee or placebo was taken, the EMG was not increased. Psychological tests were administered and no difference in anxiety was observed between high and low caffeine users or between the placebo and treatment group. However, there was a strong correlation between coffee consumption history and anxiety scores. The authors conclude that caffeine withdrawal symptoms include increased anxiety and muscle tension to go along with reports of headache, drowsiness, lethargy, and irritability.

Dr. John Neil and associates (1978) reported on the possible complication of caffeinism in diagnosing psychiatric patients. He suggests that self-medication may confound behaviors of patients. Caffeine has been considered the most popular "psychotropic" drug in North America and coffee and tea drinking are not usually in the records of psychiatric patients. In this experiment, hypersomnic patients with various diagnoses and caffeine consumption participated. The authors conclude that "self medication with large doses of caffeine is a likely response to the anergia and hypersomnia experienced during certain types of depression." This may lead to diagnostic confusion and a complicated course of therapy. Mixed depressive states may be caused by excess caffeine consumption and Dr. Neil et al. suggest, also, that unipolar II depressives may use more caffeine as they become depressed.

Caffeine, in these patients, provides only transitory relief as it is not a true antidepressant. Caffeine also may render anxiolytic and antipsychotic medications less effective.
Psychological Disorders and the Psychiatric Population

Dr. Greden says, "... caffeinism can be found among those who have psychiatric problems." Symptoms of excessive caffeine consumption are similar to anxiety neurosis (Avery, 1980) and include nervousness, irritability, recurrent headache, twitching, and gastrointestinal disturbance among other symptoms (Greden, 1974). This is a known effect of caffeine and Greden adds, "... all medications including caffeine have a potential for abuse and many individuals clearly ingest symptom-producing doses daily."

According to a survey, one of four Canadian adults took more than 250 mgs. of caffeine/day, enough to bring on severe caffeine effects. Psychiatric patients are particularly susceptible to caffeine according to Bezchlibnyke and Jeffries (1981). Coffee drinkers show anxiety and get higher depression scores on psychological tests. Schizophrenia is worsened with caffeine. Hostility, suspiciousness, anxiety, and irritability were reduced in schizophrenics as shown by DeFrietas and Schwartz (1979). Coffee drinking and use of tranquilizers are highly correlated. They recommend that coffee and tea not be served to psychiatric patients. Identification of drugs which may interact with caffeine should be routine. The authors feel that to institute such changes may be difficult and considerable education is necessary to effect changes in the coffee "habit" among patients, physicians, and administrators of psychiatric institutions.
Rodby and Mallory of Sonoma State Hospital in California (1977) reported a study involving 15 aggressive females, ages 18 to 30, in their institution. They attacked others and caused disturbances, in general. They drank 4 to 15 cups of coffee a day, an average of 7.1 cups. Decaffeinated coffee was substituted for the regular coffee. After eight weeks, the average coffee consumption was reduced to two cups a day. The number of disturbing episodes was reduced from 15 to 6.3 per day during the last two weeks. Decaffeinated coffee was continued after the study was completed.

As previously noted, one of the most well known effects of caffeine, indeed marketed for this effect, is its ability to ward off sleep, to help one stay awake. Of interest is the fact that a common symptom of psychiatric patients is sleep disturbance "... and, psychiatric patients drink lots of coffee" (Navin and Wilson, 1980). This unfortunate occurrence results in a certain amount of confusion when diagnosing and treating psychiatric patients. According to Navin and Wilson, the time patients spend in hospitals is increased because of such unrecognized effects and that, in fact, patients may be given medication to counteract the caffeine-induced sleep disturbances, resulting in unnecessary overmedication.

Brezenova, in 1974, published results of a study on 82 psychiatric patients, comparing the effects on sleep patterns of coffee and decaffeinated coffee. He noted previous studies in which 300 mgs, of
caffeine resulted in less sleep, longer latency (time to fall asleep) and easier arousal once asleep, in a group of volunteers.

Karacan (1976) had showed that REM occurred earlier than usual in the sleep cycle, and that deeper stages of sleep, stages III and IV, occurred later in the night compared to normal sleep patterns. The effects were dose related; the more caffeine, the stronger the sleep disturbance. Tolerance can develop with habitual caffeine use, heavy coffee drinkers having been shown to have less caffeine induced adverse effects on sleep than those who took smaller amounts. When these heavy users were deprived, the caffeine effects were similar to non-users.

In his study, Brezenova tested 82 patients in a small facility. Most of the patients were schizophrenic or depressives. The study was blinded; the coffee served by the kitchen staff was either caffeinated or decaffeinated, unknown to the patient and floor-staff population. Paradoxically, when regular coffee was served, there was a greater tendency to sleep quietly; and patients had more trouble sleeping or returning to sleep once awakened when taking decaffeinated coffee. Also, when decaffeinated coffee was served, there was an increase in the dispensing of medication within the institution. In fact, there was less nervousness when coffee was served. A possible clue to this result was that more decaffeinated coffee was consumed than caffeinated coffee, suggesting that the need for caffeine was involved; the patients were looking for more caffeine. The results could be explained by "withdrawal syndrome symptoms." The increased restlessness and difficulty in
sleeping could be due to the withdrawal of caffeine from these patients who were used to having their caffeinated coffee.

Winstead (1976) studied the caffeine habits and psychological traits, particularly anxiety of psychiatric patients in a military setting. One hundred and thirty-five (135) patients were included in the study and were given the State-Trait Anxiety Inventory Test and the Minnesota Multiphasic Personality Inventory (MMPI) test. Thirty-four (34) patients drank five or more cups of coffee on each of two or more days and were considered high coffee users. The high users tended to be older, single, divorced, or separated. The high users had more incidence of psychosis, depression, and neurosis. There was significantly higher anxiety among these high users, but none was diagnosed as having anxiety-neurosis. There was a tendency towards anxiety symptoms upon caffeine withdrawal in the high user group. According to Winstead, it is not clear which is "cause and effect" with regard to these findings. Is caffeine causing the effects or is increased caffeine consumption a result of the disease? In any event, schizophrenic and psychotic patients should not be given any coffee. It increases anxiety, can neutralize the effect of sedatives, and interfere with the action of other anti-psychotic drugs.

The effects of caffeine in chronic psychiatric patients were described by DeFreitas. Fourteen (14) males, ages 22-56 years, of whom 11 were schizophrenic, were included in the study. They were first given decaffeinated coffee for three weeks, followed by regular coffee. Two
psychiatric rating scales, Nurses Observation Scale for In-Patient Evaluation (NOSIE) and Pupil Behavior Rating Scale (PBRS), were used to evaluate the patients. Overall, the patients improved when on decaffeinated coffee. Anxiety and tension were reduced when patients who chronically drank coffee were given decaffeinated coffee, although a temporary worsening was sometimes seen at first.

Some of the factors and scale items which were improved with decaffeinated coffee were suspiciousness, anxiety, tension, hostility, excitement, and somatic concern on the BPRS scale and patient's assets, social competence, personal neatness, irritability, manifest psychosis, and retardation factors on the NOSIE scale.

That psychiatric patients drink more coffee has been repeatedly documented. Granacher (1980) concurs that such patients drink huge amounts of coffee. He also notes that smoking is correlated with coffee consumption. Metabolizing enzymes are induced by these substances which would increase the metabolism of other substances, including drugs; this is a factor to be seriously considered for such patients.

**Psychiatric Patients—Interaction with Drugs and Treatment**

Kulhanek et al. (1978) has reported that coffee drinking by psychiatric patients can have effects other than those directly induced pharmacologically. Caffeine can physically interact with and affect the action of some antipsychotic drugs. Caffeine is used therapeutically in schizophrenic patients, e.g. based on its central nervous system action.
Mikkelson (1978) told of two schizophrenics whose symptoms were lessened on coffee or tea. When drugs such as phenothiazines, fluphenazine, and butyrophenone drops are mixed with caffeine-containing beverages such as coffee or tea, a precipitation reaction occurs. This reaction occurs with pure caffeine benzoate or caffeine salicylate but not caffeine HCl, as reported by Kulhanek (1978).

In an article by Hirsch (1981), this precipitation was noted with elixir of CPZ, haloperidol, fluphenazine, dropnidol, promethazine, promazine, and prochlorperazine. Trifuoperazine and propranolol did not form precipitates.

In a recent article in The Lancet, Bowen (19 ) notes that in addition to the above effects, caffeine may act as a pharmacological antagonist to some psychotropic drugs as well as enhancing their metabolism. He tested blood levels of various drugs in patients who did and did not take coffee and found no difference as a result of caffeine intake. Apparently, these interactions are not evident in vivo, i.e., in the body.

Caffeine's Effect in Attention Deficit Disorder (ADD) and Hyperkinetic Children

Hyperkinetic (hyperactive) children have been shown to respond to central nervous system stimulants resulting in improved attention, concentration, and decreased activity. Side effects are usually disturbing with the more powerful drugs (i.e., methylphenidate) and include insomnia, anorexia, nervousness, weight loss, and abdominal pain.
Sympathomimetic drugs, for example, have a positive effect in many Attention Deficit Disorder (ADD) hyperkinetic children. Side effects are observed in about one of eight children so treated and included anorexia, nervousness, irritability, insomnia, and stomachache or abdominal pain. Schnackenberg (1973) reported in the *American Journal of Psychiatry* that positive effects were seen when two cups of coffee were taken rather than the usual drugs, dextroamphetamine and methylphenidate (MP). The children said that the coffee made them feel better; it "calms me down." Both teachers and parents evaluated the children; the teachers not knowing when children were off treatment. A rating scale for hyperkinesis devised by Davids was used. The score, when the children were on MP, was 17.2; when children were off the drug without coffee, the score was 25.9; and the score was 16.87 when coffee was used without drug.

The children were on the coffee regimen for an average of 6.2 months. No side effects were observed and 200-300 mgs. of caffeine appeared to work well (2-3 cups of coffee). The conclusion was that caffeine, considered a safer alternative, works as well as MP with less side effects and less cost. Also, the long term effects of MP have yet to be established.

This study was repeated, supposedly in a more rigid well-controlled manner by Garfinkel et al. (1975), using MBD children as the subjects. Garfinkel's study was double blind, comparing the effects of MP, caffeine, and a placebo on the behavior of the children. Eighteen
children with MBD who had the following characteristics were tested: hyperactive, short attention span, impulsive, affective disturbance, and poor school performance. They were all boys with an IQ greater than or equal to 90. The first two weeks of the study no medication was given; then six weeks of medication was given (except weekends); then there was a week of no medication. All drugs (160 mgs. caffeine, MP, and placebo) were added to decaffeinated coffee taken twice a day. The Connors Teacher Rating Scale was used to evaluate the children's behavior. This measures five factors: aggressiveness, inattentiveness, anxiety, sociability, and hyperactivity. MP did better than caffeine on all of these factors. Also, MP was better on a matching test, the Kazan Matching Familiar Figures Test. MP was particularly better on the aggressiveness and hyperactive factors. Caffeine, however, showed no side effects at the dose of 160 mg.

These children were more aggressive than hyperactive. The condition has been considered to be due in part to catecholamine "deficits in dopaminergic pathways," chemical mediators of nervous activity. The author of the article notes that caffeine does not exert its physiological effect in this matter and this fact may account for its lack of effect in his study. Finally, it is of interest that this study, which showed caffeine ineffective in this condition, was sponsored by General Foods, the largest coffee marketer in this country.

Firestone and associates (1978), in a study funded by the Ontario Mental Health Foundation, showed a significant improvement with
methylphenidate as rated by mothers and teachers on tests of impulsivity and motor control. No significant improvement was noted with caffeine, although some children showed a slight improvement. Side effects with both drugs were minimal. Each of 21 hyperactive children received 500 mgs. of caffeine, and 20 mgs. of methylphenidate. This was a carefully controlled study consisting of 17 boys and four girls. In 1978, Firestone did a study comparing 300 mgs. of caffeine with placebo in a double-blind crossover design. In this study, subjective ratings by teachers and parents as well as a reaction time task showed caffeine to be better than placebo although the difference was not statistically significant. Firestone concludes, on the basis of the most recent study, that caffeine is not a meaningful alternative as a treatment for hyperkinetic children.

Gross (1975) published an article on this subject in the journal, Psychosomatics. He compared placebo, caffeine, Ritalin (MP), dextroamphetamine, and imipramine (an antidepressant drug). This study was not double blind and the experimental design was deficient; drugs were given to the children in one order. Gross reported that caffeine actually made the children worse rather than better. Among the 25 children in the study, none were improved on the caffeine and more were "wound up, noisy, loud, jumpy, and silly." The other drugs showed some improvement based on observations of mothers and teachers.

Caffeine did not show activity in 26 minimal brain dysfunction children based on six psychological ratings compared to placebo and
methylphenidate or dextroamphetamine. Caffeine showed cardiovascular side effects and weight loss (Arnold, 1978).

In another report on hyperkinetic children, coffee was found to be slightly less effective than thioridazine and obviously less effective than dextroamphetamine.

In 1977, Reichard and Elder published an article on caffeine's effect on reaction time in hyperkinetic children. It is noted that some of the other drugs used in this condition may inhibit growth and it was concluded that caffeine has potential use in the treatment of these children. Although the stimulants which are used, paradoxically, seem to slow down the children, it may actually be working by increasing their attention span. David's Hyperkinetic Scale was used on the children. They also tested simple reaction time and choice reaction time. Initially, no drug was given (a fruit drink), followed by a drink with about 165 mgs. of caffeine.

Caffeine increased the accuracy of stimulus identification and processing of decreased lapse of attention in the hyperkinetic group. This is what might be expected based on caffeine's known effects on such tasks in normals. Many hyperkinetic, in general, children have a slower reaction time, are less able to maintain attention, and have a lower rate of correct responses on a vigilance performance task as compared to normal children. The worse the condition of the children, the more improvement as a result of caffeine was seen. Thus, it worked better for the hyperkinetic children than for the normals. The authors hypothesized
that caffeine "filters out irrelevant material"; there are fewer
attention lapses.

At higher doses of caffeine, about 300 mgs. or more, side effects
were noted such as "hand tremors and unsteadiness." This result was seen
in both hyperkinetic and normal children. MP was given to three children
after the completion of this test and they showed faster reaction time
than controls, but the results were not more accurate. The author
suggests that caffeine may be a potentially valuable therapy in the
treatment of hyperkinetic children.

The authors note that other studies have shown methylphenidate was
more effective than caffeine in controlling certain aspects of clinical
behavior (impulsivity and hyperactivity). This result does not
contradict those obtained in the study; they are compatible.

The use of caffeine in the treatment of hyperkinetic children
remains unresolved at this time.

Restless Legs, Anxiety, and Caffeinism

Restless legs is a syndrome which may be associated with
anxious-depressed as well as other clinical states. Dr. Lutz (1978), in
an article, suggests that this syndrome is primarily caused by caffeine.
Anxiety is not a causative factor. Caffeine stimulates the nervous
system and has a direct contractile effect on striated muscle. This is
reflected in anxiety, depression, insomnia and the heightened
proprioceptive awareness may result in restless legs. This manifestation
consists of nervousness and movement of legs as a result of a distressing creeping sensation. Its symptoms are most obvious at night when the patient is trying to be still and results in insomnia. Dr. Lutz describes cases of this disorder in detail and cites examples, all of which were alleviated when caffeine was removed from the diet. This condition has been attributed to many causes, including psychiatric disturbances, e.g., restless legs is a frequent symptom of hysteria, anxiety, depression in periods of stress, "normal" persons are also afflicted. All of these states are associated with high central nervous system arousal. Also, restless legs syndrome was first described in England at the time when coffee and tea first were introduced in the country. But, there were many changes and other introductions at that same time. Thus, diagnosis of the restless legs syndrome, as has also been observed in certain psychological disorders, may simply be the result of overdosage of ubiquitous caffeine.

Recent studies have shown that IgE mediated immune mechanisms do not explain many food reactions (American Academy of Allergy, 1980; Kniker and Rodriguez, 1985).

Another area of harmful caffeine effect are those related to early pregnancy. Hughes and Goldstein indicated that there are possible adverse fetal effects of exposure to caffeine during the first 4 months of pregnancy. At birth the infant showed evidence of early arrested cerebral maturation and paraplegia.
Caffeine and Genetics

Propanolol and caffeine are known to cross the placental barrier and will produce pharmacological effects in the fetus. In general, caffeine is a smooth muscle relaxant and vasodilator. However, it appears to exert a constrictor effect on human cerebral vasculature. Thus, it is reasonable to speculate that the synergistic effect of caffeine and ergotamine could result in a more pronounced vasoconstriction of the cerebral vessels. The present case suggests the need for caution in the use of combined vasoconstrictive agents for the treatment of migraines during pregnancy. Therapy with ergotomine combined with caffeine or beta blocker agents increased risk for malformation with a vaso-occlusive aetiology.

Case Study. A caucasian female, product of a first pregnancy, unremarkable family history, however, mother treated for migraines during pregnancy with ergotamine and caffeine. Infant was breech, clinically microencephalic, paraplegic, sensation absent in knees and thighs, etc. Spinal cord lesion.

The co-occurrence of the brain abnormality and cord lesion could be accounted for by a vascular disruptive mechanism. It is significant that the infant was exposed to ergotamine, caffeine, and propanolol during the first 14-20 weeks of gestation.

With a review of the literature, we see the wide effects of caffeine on humans and animals. Now it is necessary to choose specific problems and to select appropriate research methodology.
Bronchogenic carcinoma is closely associated with cigarette smoking although additional environmental or individual factors might regulate a person's susceptibility to that disease. To further define such risk factors, the prevalence of the genetic debrisoquine 4-hydroxylation deficiency was determined before therapeutic intervention in 270 lung cancer patients. Nineteen homozygous carriers of this defect (poor metabolizers) were found (7.0%, 95% confidence limits 4.3%-10.8%), a number being lower than 30 out of 270 reference patients (11.1%, 95% confidence limits 7.8%-15.5%). The odds ratio of 0.81 was of marginal statistical significance (P = 0.067). Subdividing the collective according to histology revealed a trend towards underrepresentation of poor metabolizers especially among patients with adenocarcinoma (1 out of 37, P = 0.086) and among young patients not older than 50 years (none out of 32, P = 0.028). All poor metabolizers (PMs) in the cancer group were smokers. In 18 patients the phenotype assignment was confirmed by a second test several weeks after surgical or other treatment. In 220 of the lung cancer patients the N-acetyltransferase polymorphism was evaluated by means of the molar ratio of 5-acetylamino-6-formylamino-3-methyluracil and 1-methyloxanthine in urine after ingestion of caffeine (coffee). There were 111 (50.5%) slow acetylators and 109 (49.5%) fast acetylators. A statistically significant clustering of either phenotype after stratification according to histology, or debrisoquine hydroxilator status was lacking. Moreover, there was no difference in the ratio of both phenotypes as compared to the reference collective of 245 patients.
(53.5% slow and 46.5% fast acetylators). As a third genetic host factor the ABO blood group frequencies were evaluated in 283 lung cancer patients. The frequency ratio of A/O was significantly higher as compared to 41,423 blood donors (odds ratio 1.37, 95% confidence limits 1.02-1.84, P less than 0.05). A/O tended to be especially high in young patients not older than 50 years. The ratio B/O in bronchial cancer was significantly higher than expected. The results suggest that the debrisoquine hydroxilator status might have an impact on an individual's susceptibility to lung cancer. This association is either a weak one and/or is restricted to certain histological cancer types or to patients with certain characteristics. The acetylator phenotype could not be established as a risk factor, whereas ABO blood groups seem to influence lung cancer susceptibility.

SOS-inducing activity of UV or chemical mutagens (AF-2, 4NQO, and MNNG) was strongly suppressed by instant coffee in Salmonella typhimurium (TA1535/pSK1002). As decaffeinated instant coffee showed a similarly strong suppressive effect, it would seem that caffeine, a known inhibitor of SOS responses, is not responsible for the effect observed. The suppression was also shown by freshly brewed coffee extracts. However, the suppression was absent in green coffee-bean extracts. These results suggest that coffee contains some substance(s) which, apart from caffeine, suppresses SOS-inducing activity of UV or chemical mutagens and that the suppressive substance(s) are produced by roasting coffee beans.
The intent of this study was to investigate the role of inheritance in the determination of susceptibility to methylxanthine-induced behavioral changes. Two strains of inbred mice, SWR and CBA, which differ significantly in their response to caffeine- and theophylline-induced stimulation of locomotor activity, were used in classical genetic crosses to produce reciprocal F1 hybrids, reciprocal backcross progeny F2 progeny. Theophylline dose response curves in the reciprocal F1 hybrid strains were identical to each other and to their methylxanthine-responsive (CBA) parent. These results indicated that theophylline responsiveness behaved as a simple autosomal dominant trait. Behavioral responses of these F1 hybrid strains to caffeine showed the same maximal enhancement of locomotor activity as their CBA progenitor at a dose 10 mg/kg IP, but locomotor activity stimulation also occurred at 32 mg/kg IP, a dose which inhibited their CBA parent. These data suggest that the genes specifying caffeine responsiveness differ from those encoding theophylline responsiveness. For both caffeine and theophylline, behavioral phenotypes and their expected frequencies of occurrence among backcross and F2 progeny differed significantly from the segregation ratios expected for a trait determined by a single gene. These non-Mendelian segregation ratios suggest that locomotor activity stimulation by both of these methylxanthines is polygenically determined. It was anticipated that the same genetically encoded neurochemical mechanism would underlie the difference in behavioral response to the two methylxanthines. However, no significant correlation between caffeine-
induced and theophylline-induced stimulation of locomotor activity was observed among progeny derived from backcrosses of F1 self-crosses.

I have presented some diverse papers which illustrated several problems with caffeine use. A study of caffeine metabolites revealed two kinds of interethnic variation, one pertaining to the well-known acetylation polymorphism affecting the secondary metabolism of the parent drug; the other consisted of a difference in paraxanthine excretion which might indicate an ethnic difference in renal function. Older data on the pharmacokinetics of the antihistaminic drug diphenhydramine also suggested interethnic variables in the fate of the drug which do not necessarily involve metabolizing capacity. In short, pharmacokinetic factors other than metabolism may make additional contributions to ethnic differences in drug response. Studies of taste and smell are not only models of receptor variability but they may be used to reveal underlying biochemical differences. Furthermore, a polymorphism in tasting ability constituted an epidemiological risk factor for thyroid disease which was greater enhanced in the presence of an appropriate human leukocyte antigen (HLA, histocompatibility gene). It is clear that the HLA complex will have to be increasingly considered in relation to pharmacological responses. Variabilities of superoxide dismutase and of various enzymes involved in heme production were described briefly because of their inherent or historical interest. In each case, however, the occurrence of variants was confined to small population groups as an expression of
founder effects and regional polymorphism. Several other instances of ethnic differences in drug response were merely cited.

Interest has recently grown in the possible role of chromosomal fragile sites as factors predisposing to chromosome rearrangements characteristic of specific human cancers. Data from two series of experiments relating to this hypothesis are presented. First, the effects of caffeine and theophylline on expression of the fragile X and common fragile sites was studied in lymphocytes from three subjects. Caffeine and theophylline did not enhance fragile X expression under the conditions employed, but did greatly enhance expression of the common fragile sites. Second, three patients with acute nonlymphocytic leukemia-M4 and inv(16)(p13q22) in leukemic cells were tested for the presence of fra(16)(q22) in normal cells. The fragile site was not seen in any of the patients in this study.
CHAPTER 3
RESEARCH METHODOLOGY OF THE SELECTED PROBLEM

General

Caffeine is probably the most widely used drug in the world. Its ubiquitous use is accepted because caffeine is usually thought of as benign or at least exhilarating. In fact, caffeine is not innocuous. It is a potent drug, and excessive or sustained use can lead to adverse physiological and psychological effects. Studies of these effects have been reported in the medical and scientific literature for many years as presented in Chapter 2 of this study. Some of these reports are anecdotal. More recently, many scientific, controlled studies have been published. As the potential for the adverse effects of caffeine become more apparent, more effort is being devoted to document its activity.

Perceived psychological effects are difficult to quantify or calculate. Goldstein (1969) has published several studies in which reactions to caffeinated and decaffeinated coffee were assessed in both caffeine and non-caffeine users via extensive questionnaires. The reactions depended on previous caffeine habituation and use. Heavy users had less effects on sleep, irritability, and nervousness.

Caffeine ingestion stimulates many bodily responses, some of which are opposite in direction. For example, after ingesting caffeine, the heart rate is initially decreased, and then increased about an hour after intake.
In some persons, the drug may also promote increases in serum lipids and glucose, probably through catecholamine mediation. However, in individuals disposed to hypoglycemia, a rapid elevation in blood glucose prompts an insulin response, which may then lower the blood glucose to comfortable levels about two or three hours following intake of caffeine. (Ritchie, 1975)

Subjects with high levels of caffeine ingestion may, in part, enjoy the effects of the drug which is stimulating their otherwise under-functioning adrenal glands.

Previous experimental work has shown that caffeine increases the output of epinephrine and norepinephrine from the adrenal glands (Ritchie, 1975). In the present study, this effect of caffeine was measured by physical examination and urine sodium levels in the experimental subjects.

Another objective of the study was to verify the effects of caffeine as an anabolic agent. According to Dr. Emanuel Revici, certain physical-chemical properties of urine are indicators of the anabolic or catabolic effect of drugs and nutrients.

**Research Design**

Caffeine is a potent pharmacologic and psychotropic agent. Many studies in both animals and humans have been performed in order to quantify and characterize its physiological and psychological effects.

The research presented in this dissertation consists of two kinds of observations resulting from consumption of a caffeine beverage during a second week: (1) effects on adrenal function determined by a medical
examination; and (2) physical-chemical measurements of urine, an
indication of the anabolic effect of caffeine according to a theory
proposed by Dr. E. Revici. In addition, perceived psychological effects
of caffeine were studied by means of a questionnaire and daily diary.

Research Methods

Subjects

A. One group of subject volunteers had been drinking the equivalent
of at least three cups of coffee per day (approximately 150 mg. of
caffeine from all sources, including tea, caffeinated soda, and
chocolate). This level of caffeine consumption was for at least one
year. Eleven such subjects completed both the first week of
decaffeinated tea and the second week of return to the caffeinated tea
beverage. Six other chronic caffeine users who started the study dropped
out during the first week. The policy was to advise these subjects who
were uncomfortable that they, in fact, were drinking decaffeinated tea.
Those who dropped out returned to their usual caffeinated beverages.
These subjects ranged in age from 25 to 75 years.

B. A second group of subject volunteers who had a history of no
caffeine consumption, ingested no caffeine. Six such subjects completed
both the first week of caffeinated tea and the second week of
decaffeinated tea. Five other non-caffeine subjects who started the
study dropped out during the first week. They stopped because they were
uncomfortable. These subjects ranged in age from 25–65 years.
The tea bags given to all subjects were identical in appearance and flavor. Tetley tea manufactures a standard caffeinated tea and a decaffeinated with the same appearance and flavor. The subjects were never informed as to which tea they were issued.

The subjects were instructed to steep the tea by placing the bag in a cup and pouring boiling water over the tea bag, filling the cup. The tea bag was to be removed after three minutes.

Two separate studies were conducted:

In Study A, eleven (11) chronic caffeine users brewed and drank five cups of decaffeinated tea per day for one week. They returned at the end of Week 1 and were re-examined via the Ragland Postural Blood Pressure Test (Burch and de Pasquale, 1962) and had their urine analyzed via the Koenigsburg Test (Brooks, 1925) for Urinary Sodium-Chloride Excretion and the Revici Anabolic/Catabolic Index (1961). They were then given thirty-five tea bags from which to brew five cups of caffeinated tea per day for a second week. At the end of this week, the blood pressure and urine measurements were recorded.

In Study B, six (6) non-caffeine users brewed and drank five cups per day of caffeinated tea during the first week and were switched to decaffeinated tea during the second week.

**Adrenal Function**

In addition to the data supplied by the diary, subjects were given a physical-medical examination to assess adrenal function prior to and after each week of the study. According to Goodman and Gilman, caffeine
stimulates "the release of catecholamines from the adrenal medulla."
Caffeine also releases catecholamines due to a central action and by
affecting C-AMP.

Adrenal function was tested via the:
1. Ragland Blood Pressure Test
2. Koenigsburg Urinary Sodium and Chloride Excretion

Various responses were observed for 17 subjects during a two week
period. Each subject participated in one week of caffeine intake (150 mg
daily) from tea and one week of consumption of an otherwise identical
non-caffeinated tea.

A Medical Evaluation Which Focused on Adrenal Gland Status

The tests for adrenal function included the following:

1. Ragland Blood Pressure
2. Koenigsburg Test for Urinary Sodium-Chloride Excretion.

Ragland Postural Blood Pressure Test: Method and Physiologic Basis
(Burch and de Pasquale, 1962):

This test is a means of evaluating adrenal activity. It detects
diminished adrenal function.

**Method:** The difference of the systolic blood pressure measured with
the patient in the supine position and in the erect, or standing,
position, is an indication of adrenal function. The patient lies supine
for four minutes. The blood pressure is taken in this position and
immediately after the patient stands up.
Upon arising from the supine position and standing erect, the normal subject has a rise, or elevation, of the systolic blood pressure. The systolic pressure usually rises approximately 5-10 mm mercury, since the cardiovascular system must pump blood to the head against the force of gravity, higher blood pressure is required.

When diminished adrenal function is present, the systolic blood pressure taken in the erect, or standing, position may actually fall. The degree of lowering of the erect blood pressure gives some indication of the magnitude of diminished adrenal function.

Adrenal glands have a major role in controlling the tone of the splanchnic veins. These veins do not have valves and are dependent upon nerve function.

**Koenigsburg Test for Urinary Sodium-Chloride Excretion (Brooks, 1925):**

The adrenal gland produces aldosterone, which instructs the kidneys to retain sodium. If adrenal gland function is diminished, aldosterone production is decreased and salt is spilled into the urine.

**Method:** The Koenigsburg Test is a titration procedure. Ten drops of urine are placed in a test tube. One drop of 10 percent potassium chromate solution is added to the urine. 0.74 percent silver nitrate solution is added dropwise until the color of the solution turns brick red. The number of drops required for subjects with normal adrenal function is about 25. Excessive sodium and chloride in the urine will require more silver nitrate reagent to turn the solution brick red.
Psychological Effects

In addition to keeping a daily diary, subjects were requested to answer a questionnaire prior to, and after each week of the study, as follows:*

1. Did you feel stimulated?
2. Did you feel tired?
3. Did you drink more coffee, tea, or cola than usual?
4. Did you feel alert?
5. Did you have headaches?
6. Were you nervous or anxious?
7. Did you have:
   a. insomnia?
   b. difficulty falling asleep?
   c. Difficulty staying asleep?
8. Did you have stomachaches?
9. Did you feel depressed?
10. Did you feel "good" (a feeling of well-being?)
11. How was your appetite?
12. Did you notice anything different from usual? (Non-smokers only). If "yes," explain.
13. Did you notice anything different from usual? (Smokers only)
    If "yes," explain.
14. For smokers only: Cigarette use per day - ___ cigarettes.

* See Appendix for the actual form used.
Urine Measurements (Revici Anabolic/Catabolic Index)

Urine samples were analyzed prior to the study and after each of the two study weeks to determine specific gravity, surface tension* and pH. These results were combined to form an index to describe the catabolic/anabolic effect of the drug.

According to Dr. E. Revici, the best indication of catabolic/anabolic effect is measured by a composite index of the urine measurements as follows:

\[
\text{Index} = 1 = 2(74 - \text{s.t.}) + \text{pH} + \text{last two digits of s.g.}
\]

\[
\begin{align*}
\text{pH} = \text{alkaline} & = 5 \\
\text{pH} = \text{neutral} & = 10 \\
\text{pH} = \text{acid} & = 20
\end{align*}
\]

For example, if s.t. = 70, pH = acid and s.g. = 1.016, the index is

\[
2(74-70) + 20 + 16 = 44 \text{ (see Discussion).}
\]

Having outlined the research methodology, it is now necessary to review the results and discuss the projects.

Statistical Methods

Three statistical procedures are used in this experiment—correlated t-tests, t-tests for independent groups, and Pearson Correlation Coefficients:

*Revici urotensiometer.
1. Correlated t-tests are used when the same subjects are compared on two occasions, e.g., "Pre" test status and then at the end of week 1. The t-ratio comparing the two means is used as a measure of significance based on a pre-determined significance level.

2. The t-tests for independent groups are utilized when two independent groups are compared, i.e., caffeine group versus no-caffeine group. The t-ratio indicates whether the two means are statistically different.

3. The Pearson correlation coefficient indicates the amount of linear relationship between two variables, with the coefficient ranging between +1.0 and -1.0 with 0 indicating no relationship between the two variables. For example, this coefficient was used to indicate the degree of relationship between BP and sodium secretion.

The level of significance in behavioral research is usually set at .05. A one-time test is presented to indicate possible trends.
CHAPTER 4
RESULTS AND DISCUSSION

Previous experimental work has shown that caffeine increases the output of epinephrine and norepinephrine from the adrenal glands (Goodman and Gilman, 1975). In the present study, this effect of caffeine was measured by physical examination and urine sodium levels in the experimental subjects.

Various responses were observed for 17 subjects during a two-week period. Most subjects participated in a week of caffeine intake (175 mg daily) from a caffeine tea, and a week of consumption of an otherwise identical non-caffeinated tea.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Days in Study</th>
<th>Reason for Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>27</td>
<td>F</td>
<td>6</td>
<td>Irritable</td>
</tr>
<tr>
<td>8</td>
<td>32</td>
<td>M</td>
<td>7</td>
<td>Stomach upset</td>
</tr>
<tr>
<td>9</td>
<td>37</td>
<td>M</td>
<td>6</td>
<td>Overstimulated</td>
</tr>
<tr>
<td>10</td>
<td>29</td>
<td>F</td>
<td>7</td>
<td>Irritable</td>
</tr>
<tr>
<td>11</td>
<td>41</td>
<td>M</td>
<td>7</td>
<td>Headache</td>
</tr>
</tbody>
</table>

Non-caffeine participants 7, 8, 9, 10, and 11 dropped out, as follows:
These five subjects dropped out since they were uncomfortable. Even though we explained to them that the caffeine week was nearing its end and that the next week would be the converse; namely, the decaffeinated tea, they were still reluctant. Some were fearful that they might continue to receive some caffeine despite our explanation. It is of interest that the desire to avoid caffeine was so strong in these subjects.

Each participant in the caffeine experiment completed daily diary sheets which are represented in Appendix B. Dr. Feldman and I were very specific and exacting in our instructions for patient compliance. An example was that each patient was interviewed on a nearly daily basis by phone and once a week in the office. We would ask them, "Have you complied exactly?" Six non-caffeine users and eleven (11) caffeine users maintained the strict research protocols to the end. All of the N.C.'s from all sources of caffeine, including chocolate, beverages, and medicines. There were at least 13 of the caffeine-consuming participants (chronic caffeine users) were disqualified during the experiment because of non-compliance. Of the non-caffeine participants, five withdrew by day six or seven (the later stages of the experiment) and eleven by the third day.

Comparisons of the amount of sodium and chloride in the urine serve as an indirect reflection of aldosterone level and thus, indirectly, adrenal function.
MEDICAL EXAMINATIONS

BLOOD PRESSURE, SODIUM SECRETION, AND ADRENAL STATUS

CAFFEINE CONSUMERS

Blood Pressure

**Introduction**

During the pre-test examination, C-1 had a supine blood pressure of 110/70, which fell to 80/50 when rapidly standing erect. The important data is the change between the systolic blood pressure (the upper-higher number) when standing versus lying down (supine). Since in the normal subject the systolic pressure should rise when standing erect, the usual difference between standing minus supine is a positive number. Since C-1 had a drop of systolic reading from 110 to 80, we generate a -30, which is the mathematical data placed in Table 4. This table, BLOOD PRESSURE, SODIUM SECRETION, AND ADRENAL STATUS OF CAFFEINE CONSUMERS AFTER WEEK 1, summarizes the presentation of all blood pressure data.

Since we compared the blood pressure when standing erect with that of the supine position, a negative value reflects a fallen blood pressure upon standing. The more negative the number, the greater the drop in blood pressure and thus the greater abnormal or weakened adrenal function.
TABLE 4. BLOOD PRESSURE, SODIUM SECRETION, AND ADRENAL STATUS OF CAFFEINE CONSUMERS. WEEK 1 THESE SUBJECTS RECEIVED NO CAFFEINE, WHILE WEEK 2 THEY CONSUMED 5 CUPS OF CAFFEINATED TEA DAILY.

<table>
<thead>
<tr>
<th>Subject Code</th>
<th>Blood Pressure Standing minus Supine</th>
<th>Sodium Secretion</th>
<th>Adrenal Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&quot;Pre&quot; End of Wk 1 End of Wk 2</td>
<td>&quot;Pre&quot; End of Wk 1 End of Wk 2</td>
<td>&quot;Pre&quot; End of Wk 1 End of Wk 2</td>
</tr>
<tr>
<td>C-1</td>
<td>-30 -14 -8</td>
<td>60 52 48</td>
<td>Severely Improved; Still Low</td>
</tr>
<tr>
<td>C-2</td>
<td>-2 0 3</td>
<td>28 26 31</td>
<td>Normal About same Almost same</td>
</tr>
<tr>
<td>C-3</td>
<td>-4 -9 42</td>
<td>27 32 25</td>
<td>Mildly Slightly About same Low</td>
</tr>
<tr>
<td>C-4</td>
<td>-20 -40 -10</td>
<td>58 65 34</td>
<td>Severely Mildly Worse Better than Pre</td>
</tr>
<tr>
<td>C-5</td>
<td>-12 -25 -19</td>
<td>48 56 51</td>
<td>Mildly Slightly About same Low</td>
</tr>
<tr>
<td>C-6</td>
<td>-22 -16 -10</td>
<td>41 35 29</td>
<td>Severely Slightly About same Better</td>
</tr>
<tr>
<td>C-7</td>
<td>-2 -5 6</td>
<td>29 31 32</td>
<td>Slightly Almost same About same Low</td>
</tr>
<tr>
<td>C-8</td>
<td>-6 -9 -12</td>
<td>35 27 37</td>
<td>Slightly About same About same</td>
</tr>
<tr>
<td>C-9</td>
<td>-10 -6 -4</td>
<td>30 26 28</td>
<td>Slightly About same About same</td>
</tr>
<tr>
<td>C-10</td>
<td>-20 -5 -16</td>
<td>62 45 53</td>
<td>Severely Improved Back to Pre Status</td>
</tr>
<tr>
<td>C-11</td>
<td>-5 0 -2</td>
<td>32 28 33</td>
<td>Mildly Improved Mildly Low</td>
</tr>
</tbody>
</table>

Mean -132.99 -129.00 -88.00 450.00 422.95 400.99

T-Test

T-Test
Comparison of Means

Results: Each individual's score was added to produce a sum divided by the number of subjects, producing a mean value. The comparison of these means for the "Pre," End of Week 1 and End of Week 2 are shown in Table 5. The statistical analysis is illustrated in detail as the CORRELATED T-TEST COMPARING THE MEANS OF BLOOD PRESSURE OF CAFFEINE CONSUMERS (Table 5).

Two findings which were of interest although not statistically significant at the .05 level were: 1) the difference between the blood pressure End of Week 2 versus the "Pre" blood pressure and 2) the blood pressure Week 2 versus the blood pressure End of Week 1.

The mean for the blood pressure "Pre" was -12.09 with a standard deviation of 9.51. The mean for blood pressure after Week 2 was -8.00 with a standard deviation of 6.245. The mean difference score was -4.09 with a T-ratio of -1.57, thus the probability was equal to .147 for a 2-tail test of significance. Similarly, the mean for blood pressure End of Week 1 was -11.72 while at the End of Week 2, it was 8.00. The mean difference score was -3.72 with a T-ratio of -1.17, thus the probability was equal to .271 for a 2-tail test of significance or .136 for a 1-tail test of significance.

Comment: Since the blood pressure means at End of Week 1 versus End of Week 2 were less negative, this reflects a slight improvement in blood pressure readings. This improvement indicates better adrenal function. Reintroducing caffeine after a week of abstinence improved adrenal
### Table 5. Correlated T-Test Comparing the Means of Blood Pressure and Sodium Secretion of Caffeine Consumers "Pre" versus Week 1, "Pre" versus Week 2, and Week 1 versus Week 2.

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BP WK1</td>
<td></td>
<td>-11.7273</td>
<td>11.884</td>
<td>3.583</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP WK2</td>
<td></td>
<td>-8.0000</td>
<td>6.245</td>
<td>1.883</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP WK2</td>
<td></td>
<td>-8.0000</td>
<td>6.245</td>
<td>1.883</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SS &quot;Pre&quot;</td>
<td>11</td>
<td>40.9091</td>
<td>13.736</td>
<td>4.142</td>
<td>2.4545</td>
<td>7.515</td>
<td>2.266</td>
<td>.851</td>
<td>.001</td>
<td>1.08</td>
<td>10</td>
<td>.304</td>
<td>.152</td>
</tr>
<tr>
<td>SS WK1</td>
<td></td>
<td>38.4545</td>
<td>13.779</td>
<td>4.155</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SS &quot;Pre&quot;</td>
<td>11</td>
<td>-40.9091</td>
<td>13.736</td>
<td>4.142</td>
<td>4.4545</td>
<td>8.756</td>
<td>2.640</td>
<td>.773</td>
<td>.005</td>
<td>-1.59</td>
<td>10</td>
<td>.122</td>
<td>.061</td>
</tr>
<tr>
<td>SS WK2</td>
<td></td>
<td>-36.4545</td>
<td>9.720</td>
<td>2.931</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SS WK2</td>
<td></td>
<td>36.4545</td>
<td>9.720</td>
<td>2.931</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
function. Also when comparing adrenal status End of Week 2 with the adrenal status "Pre," there was a slight but not significant improvement.

Since caffeine abstinence seemed to improve adrenal function slightly, one could hypothesize that the adrenals had a rest period. The striking improvement after caffeine is reintroduced evidently shows that caffeine has the ability to strengthen the adrenal function. Since the subjects had weakened adrenal function in the "Pre" state, we can only conjecture that after more than one week back on the caffeine, they might in time return to the pre-adrenal ("Pre") state. See Table 6 depicting THE COMPARISONS OF BLOOD PRESSURES OF CAFFEINE USERS END OF WEEK 2 (BACK ON CAFFEINE) VERSUS STATUS "PRE" (NORMAL CAFFEINE STATE).

Comparison of Subjects to Themselves

Results: Each subject's blood pressure "Pre" versus End of Week 2 was tabulated and the difference computed as seen in Table 6.

When comparing each person's data across time as computed to averaging all subjects, we noted that six subjects had differences of -4 to +6 where an improvement would generate a positive number (C-2, C-3, C-7, C-9, C-10, C-11). Three subjects had improved readings of +10 to +22 (C-1, C-4, C-6). Two subjects had numbers of -6 or -7, which was a worsened adrenal state.

Comments: Those subjects that improved the most (C-1, C-4, C-6) showed the most aberrant negative blood pressure readings in the "Pre"
TABLE 6. COMPARISONS OF BLOOD PRESSURES OF CAFFEINE USERS END OF WEEK 2 (BACK ON CAFFEINE) VERSUS STATUS "PRE" (NORMAL CAFFEINE STATE).

### About the Same Week 2 versus "Pre"

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Week 2</th>
<th>Difference Week 2 vs. &quot;Pre&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-2</td>
<td>-2</td>
<td>-3</td>
<td>-1</td>
</tr>
<tr>
<td>C-3</td>
<td>-4</td>
<td>+2</td>
<td>+6</td>
</tr>
<tr>
<td>C-7</td>
<td>-4</td>
<td>-6</td>
<td>-4</td>
</tr>
<tr>
<td>C-9</td>
<td>-10</td>
<td>-4</td>
<td>+6</td>
</tr>
<tr>
<td>C-10</td>
<td>-20</td>
<td>-16</td>
<td>+4</td>
</tr>
<tr>
<td>C-11</td>
<td>-5</td>
<td>-2</td>
<td>+3</td>
</tr>
</tbody>
</table>

### Improved Week 2 versus "Pre"

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Week 2</th>
<th>Difference Week 2 vs. &quot;Pre&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-1</td>
<td>-30</td>
<td>-8</td>
<td>+22</td>
</tr>
<tr>
<td>C-4</td>
<td>-20</td>
<td>-10</td>
<td>+10</td>
</tr>
<tr>
<td>C-6</td>
<td>-22</td>
<td>-10</td>
<td>+12</td>
</tr>
</tbody>
</table>

### Adrenals Worse Week 2 versus "Pre"

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Week 2</th>
<th>Difference Week 2 vs. &quot;Pre&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-5</td>
<td>-12</td>
<td>-19</td>
<td>-7</td>
</tr>
<tr>
<td>C-8</td>
<td>-6</td>
<td>-12</td>
<td>-6</td>
</tr>
</tbody>
</table>
state. The two subjects (C-5, C-8) who were worse had no specific profile in the "Pre" state.

Each subject's blood pressure was also analyzed as THE COMPARISONS OF BLOOD PRESSURE OF CAFFEINE USERS END OF WEEK 1 (OFF CAFFEINE) VERSUS END OF WEEK 2 (BACK ON CAFFEINE) (Table 7).

Results: Similar results to Table 6 were found when comparing End of Week 1 versus End of Week 2. Eight subjects (C-1, C-2, C-5, C-6, C-7, C-8, C-9, C-11) had a difference of -3 to +6. Two had improved from +11 to +30 (C-3, C-4). One subject worsened (C-10) with a difference of -11.

Comments: Thus, reintroduction of caffeine in chronic caffeine users, in general, showed very little change. Eight subjects were about the same, three were improved, and one was worse. Thus, the chronic caffeine group showed little change via the reintroduction of caffeine.

Sodium Secretion

Introduction

During the pre-test examination, C-1 required 60 drops of 0.74 silver nitrate solution added drop-wise until the color of the solution turned brick red. The number of drops required is proportional to the quantity of sodium and chloride in the urine. The same method of drop titration was used on each urine sample so that the number of drops is proportional to the sodium and chloride of all subject titrations. Please note that 60 drops is a very high reading and represents a high amount of spillage of sodium and chloride into the urine. Table 4, BLOOD
TABLE 7. COMPARISONS OF BLOOD PRESSURES OF CAFFEINE USERS END OF WEEK 1 (OFF CAFFEINE) VERSUS END OF WEEK 2 (BACK ON CAFFEINE).

### About the Same End of Week 1 versus End of Week 2

<table>
<thead>
<tr>
<th></th>
<th>End of Week 1</th>
<th>End of Week 2</th>
<th>Difference End Week 2 vs. End Week 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-1</td>
<td>-14</td>
<td>-8</td>
<td>46</td>
</tr>
<tr>
<td>C-2</td>
<td>-0</td>
<td>-3</td>
<td>-3</td>
</tr>
<tr>
<td>C-5</td>
<td>-25</td>
<td>-19</td>
<td>6</td>
</tr>
<tr>
<td>C-6</td>
<td>-16</td>
<td>-10</td>
<td>6</td>
</tr>
<tr>
<td>C-7</td>
<td>-5</td>
<td>-6</td>
<td>-1</td>
</tr>
<tr>
<td>C-8</td>
<td>-9</td>
<td>-12</td>
<td>-3</td>
</tr>
<tr>
<td>C-9</td>
<td>-6</td>
<td>-4</td>
<td>2</td>
</tr>
<tr>
<td>C-11</td>
<td>0</td>
<td>-2</td>
<td>-2</td>
</tr>
</tbody>
</table>

### Improved End of Week 1 versus End of Week 2

<table>
<thead>
<tr>
<th></th>
<th>End of Week 1</th>
<th>End of Week 2</th>
<th>Difference End Week 2 vs. End Week 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-3</td>
<td>-9</td>
<td>+2</td>
<td>+11</td>
</tr>
<tr>
<td>C-4</td>
<td>-40</td>
<td>-10</td>
<td>+30</td>
</tr>
</tbody>
</table>

### Work End of Week 1 versus End of Week 2

<table>
<thead>
<tr>
<th></th>
<th>End of Week 1</th>
<th>End of Week 2</th>
<th>Difference End Week 2 vs. End Week 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-10</td>
<td>-5</td>
<td>-16</td>
<td>-11</td>
</tr>
</tbody>
</table>
PRESSURE, SODIUM SECRETION, AND ADRENAL STATUS OF CAFFEINE CONSUMERS, summarizes the presentation of all sodium secretion data. THE CORRELATED T-TEST, shown in Table 5, COMPARING THE MEANS OF SODIUM SECRETION OF CAFFEINE CONSUMERS is a statistical evaluation of significance of the results.

**Results:** The only significant correlated T-test numbers were sodium secretions End of Week 2 versus the "Pre" test. End of Week 2 had fewer drops of solution and thus, less sodium secretion. The mean "Pre" was 40.90 with a standard deviation of 13.73. The mean End of Week 2 was 36.45 with a standard deviation of 9.72. The mean difference score was 4.45 with a T-ratio of 1.59. The probability was equal to .122 for a 2-tail test of significance of .061 for a 1-tail test of significance.

**Comments:** Thus the analysis of adrenal function via sodium secretion yielded results very similar to the blood pressure data. Figure 1, SODIUM SECRETION OF CAFFEINE CONSUMERS, shows the bar representation of data in Table 6.
FIGURE 1. SODIUM SECRETION OF CAFFEINE CONSUMERS - BAR REPRESENTATION OF DATA IN TABLE 4.
TABLE 8. BLOOD PRESSURE, SODIUM SECRETION, AND ADRENAL STATUS OF NON-CAFFEINE CONSUMERS. WEEK 1 THESE SUBJECTS RECEIVED 5 CUPS OF CAFFEINATED TEA DAILY, WHILE WEEK 2 THEY CONSUMED NO CAFFEINE.

<table>
<thead>
<tr>
<th>Subject Code</th>
<th>Blood Pressure Standing Minus Supine</th>
<th>Sodium Secretion</th>
<th>Adrenal Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&quot;Pre&quot;</td>
<td>End of Wk 1</td>
<td>End of Wk 2</td>
</tr>
<tr>
<td>NC-1</td>
<td>+14</td>
<td>0</td>
<td>-2</td>
</tr>
<tr>
<td>NC-2</td>
<td>0</td>
<td>+20</td>
<td>+20</td>
</tr>
<tr>
<td>NC-3</td>
<td>+10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NC-4</td>
<td>-4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NC-5</td>
<td>-4</td>
<td>0</td>
<td>-10</td>
</tr>
<tr>
<td>NC-6</td>
<td>+10</td>
<td>0</td>
<td>+10</td>
</tr>
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</table>

<p>| | | | | | | |</p>
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<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>26</td>
<td>22</td>
<td>18</td>
<td>143</td>
<td>159</td>
<td>165</td>
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<tr>
<td>Mean</td>
<td>4.33</td>
<td>3.66</td>
<td>3.00</td>
<td>23.83</td>
<td>26.5</td>
<td>27.5</td>
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</tbody>
</table>

T-Test

T-Test
Table 9. Correlated T-Test Comparing the Means of Blood Pressure and Sodium Secretion of Non-Caffeine Consumers "Pre" Versus Week 1, "Pre" Versus Week 2, and Week 1 Versus Week 2.

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>BP WK1</td>
<td></td>
<td>3.6667</td>
<td>8.042</td>
<td>3.283</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP &quot;Pre&quot;</td>
<td>6</td>
<td>4.333</td>
<td>7.941</td>
<td>3.242</td>
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<td>12.628</td>
<td>5.155</td>
<td>.082</td>
<td>.878</td>
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<td>5</td>
<td>.806</td>
<td>.403</td>
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<td>3.0000</td>
<td>10.488</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP WK1</td>
<td>6</td>
<td>3.6667</td>
<td>8.042</td>
<td>3.283</td>
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<td>6.408</td>
<td>2.616</td>
<td>.792</td>
<td>.030</td>
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<td>.809</td>
<td>.405</td>
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<tr>
<td>BP WK2</td>
<td></td>
<td>3.0000</td>
<td>10.488</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SS &quot;Pre&quot;</td>
<td>6</td>
<td>23.8333</td>
<td>5.037</td>
<td>2.056</td>
<td>-2.6667</td>
<td>5.279</td>
<td>2.155</td>
<td>.150</td>
<td>.776</td>
<td>-1.24</td>
<td>5</td>
<td>.271</td>
<td>.136</td>
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<tr>
<td>SS WK1</td>
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<td>26.5000</td>
<td>2.510</td>
<td>1.025</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>SS &quot;Pre&quot;</td>
<td>6</td>
<td>23.8333</td>
<td>5.037</td>
<td>2.056</td>
<td>-3.6667</td>
<td>5.645</td>
<td>2.305</td>
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<td>.731</td>
<td>-1.59</td>
<td>5</td>
<td>.172</td>
<td>.086</td>
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<tr>
<td>SS WK2</td>
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<td>27.5000</td>
<td>3.619</td>
<td>1.478</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SS WK1</td>
<td>6</td>
<td>26.5000</td>
<td>2.510</td>
<td>1.025</td>
<td>-1.0000</td>
<td>2.757</td>
<td>1.125</td>
<td>.649</td>
<td>.163</td>
<td>-0.89</td>
<td>5</td>
<td>.415</td>
<td>.208</td>
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<tr>
<td>SS WK2</td>
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<td>27.5000</td>
<td>3.619</td>
<td>1.478</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
While the mean for the "Pre" blood pressure was 4.33 with a standard deviation of 7.94 after Week 1, it was 3.66 with a standard deviation of 8.04. The mean difference score was .66 with a T-ratio of .13 based on 5 degrees of freedom. The probability was equal to .902 for a 2-tail test of significance or .457 for a 1-tail test of significance. Thus, there was not a significant difference between these two means. Similarly, the mean difference score comparing "Pre" to Week 2 and Week 1 to Week 2 showed no significant difference.

Comments: Evidently, the introduction and the subsequent cessation of caffeine did not affect the blood pressure of the non-caffeine subjects in any statistically significant manner. It is also apparent that the levels of caffeine present to the non-caffeine consumer for the one week of time did not significantly affect the Ragland blood pressure findings at the end of that week.

**Sodium Secretion**

**Introduction**

During the pre-test examination, NC-1 required 23 drops of 0.74 silver nitrate solution added drop-wise until the color of the solution turned brick red. The number of drops required is proportional to the quantity of sodium and chloride in the urine. The same method of drop titration was used on each urine sample so that the number of drops is proportional to the sodium and chloride of all subject titrations. Please note that 23 drops is a very low reading and represents a normal
amount of sodium and chloride in the urine. NC-1 had normal adrenal status in the pre-test condition.

Table 4, the CORRELATED T-TEST COMPARING THE MEANS OF SODIUM SECRETION "PRE" VERSUS WEEK 1, "PRE" VERSUS WEEK 2, AND WEEK 1 VERSUS WEEK 2 is a statistical evaluation of significance.

Results: The only significant statistical difference was the comparison of sodium secretion End of Week 2 when compared to "Pre."

The "Pre" mean was 23.83 with a standard deviation of 5.02. The mean End of Week 2 was 27.30. The mean difference score was -3.66 with a T-ratio of 1.59; probability was equal to .172 for a 2-tail test of significance of .086 for a 1-tail test of significance.

Sodium secretion of the NC group showed higher values (greater sodium secretion) at the End of Week 1 and Week 2 although the "Pre" to Week 2 period had greater statistical meaning. Thus, the caffeine during Week 1 weakened adrenal function but at the End of Week 2, it was even worse.

The five cups of tea a day for one week did affect adrenal function if measured by sodium secretion. The weakened adrenal function was actually more evident at the end of the second week. We have no hypothesis as to why this occurred.
COMPARISON ACROSS SUBJECT GROUPS – CAFFEINE SUBJECTS VERSUS NON-CAFFEINE SUBJECTS

Blood Pressure

The number representing the difference between standing minus supine systolic pressure as numerically listed in Table 4 is put into a bar chart, Figure 2, with three test numbers for each subject, namely "Pre" test, Week 1, and Week 2. For example, C-1, who had a -30 standing minus supine on a "Pre" test condition has a black bar down to the -30 on the vertical scale in this bar chart. The blood pressure reading at the End of Week 1 was a -14 and is shown by the less black second bar which declines down to the -14 on the scale. The End of Week 2 blood pressure of -8 is likewise depicted by the third downward bar.

Comment: This graphic bar display shows that most of the caffeine subjects had negative bars. Thus, the caffeine group tends to have weakened adrenal function.

In the NC group, five out of seven had positive numbers during the "Pre" test (NC-1, +14; NC-3, +10; NC-6, +10; and NC-2, a zero reading). Two subjects had negative numbers but only slightly so (NC-4, -4; and NC-5, -4). The most negative number in the NC group was NC-5, with -10 at the end of the second week. Figure 3, BLOOD PRESSURES OF NON-CAFFEINE CONSUMERS – BAR REPRESENTATION, illustrates this data in graphic form.

The most striking data for the non-caffeinated subjects are the blood pressure status in the "Pre" state, whereby the most negative
FIGURE 2. BLOOD PRESSURES OF CAFFEINE CONSUMERS - BAR REPRESENTATION OF DATA IN TABLE 4.
FIGURE 3. BLOOD PRESSURES OF NON-CAFFEINE CONSUMERS - BAR REPRESENTATION OF DATA IN TABLE 8.
reading was -4 (NC-4, NC-5). The mean "Pre" blood pressure was 4.33, compared to -12 for the caffeine-consumer group.

**Sodium Secretion**

The sodium secretion by many of the non-caffeine subjects at the "Pre" level was much lower than for the chronic caffeine users. The highest value of the NC group was 33; of the C group, none had sodium secretion less than 27, and 6 had a number of 35 or higher. Figure 4, *SODIUM SECRETION OF NON-CAFFEINE CONSUMERS*, graphically shows the sodium secretion levels of this group.

**A Combined Adrenal Score Integrating Blood Pressure and Sodium Secretion Data**

**Introduction**

The bars in Figure 5, *MEDICAL INDEX, WEIGHTED COMBINATION OF BLOOD PRESSURE AND SODIUM SECRETION DATA*, represents a comparison of "Pre" to End of Week 1 (black bars) and End of Week 1 compared to End of Week 2 (lighter bars).

Caffeine subjects C-1 through C-11 and non-caffeine subjects NC-1 through NC-6 are displayed on the same sheet. Note the NC data is to the far right.

In order to combine the Ragland Postural Blood Pressure data with the Koenigsburg Urinary Sodium Excretion for each subject at each test sampling, the Ragland value was mathematically weighted as 3 and the Koenigsburg Urinary Sodium Excretion as 1. This was an arbitrary
FIGURE 4. SODIUM SECRETION OF NON-CAFFEINE CONSUMERS - BAR REPRESENTATION OF DATA IN TABLE 8.
FIGURE 5. MEDICAL INDEX, WEIGHTED COMBINATION OF BLOOD PRESSURE AND SODIUM SECRETATION DATA. BARS REPRESENT COMPARISON OF "PRE" TO END OF WEEK 1 (BLACK BARS) AND END OF WEEK 1 COMPARED TO END OF WEEK 2 (LIGHTER BARS)
formula. This bar graph (Figure 5) visually compares the "Pre" condition to Week 1 and Week 1 with Week 2.

The mathematical combining of these indicators gave a positive bar graph of approximately 19. In other words, C-1 had an improvement in adrenal function from the "Pre" to the End of Week 1. The second bar for C-1 with a value of 7 reflects an End of Week 2 blood pressure of -8 with a sodium secretion of 48. The -8 was 6 better than -14 and the 48 was 4 better than the 52.

Comparison Across Subject Groups - Medical Index Adrenal Score - Caffeine Subjects versus Non-Caffeine Subjects

When comparing the medical index changes, "Pre" to Week 1 and Week 1 to Week 2 of the C group versus the NC group, there was less change of the NC's from week to week as compared with the C's.

ANABOLIC/CATABOLIC INDEX

Introduction

The composite index of urine data is presented in Table 10, ANABOLIC/CATABOLIC INDEX OF CAFFEINE AND NON-CAFFEINE CONSUMERS "PRE," END OF WEEK 1 AND END OF WEEK 2. This reflects the body's status with regard to its anabolic or catabolic mode. A decline in the index number reflects movement in the anabolic direction. Conversely, an increase in the index is a movement in the catabolic direction.
TABLE 10. ANABOLIC/CATABOLIC INDEX OF CAFFEINE AND NON-CAFFEINE CONSUMERS "PRE," END OF WEEK 1, AND END OF WEEK 2.

<table>
<thead>
<tr>
<th>Subject Code</th>
<th>Surface Tension (2-(74-ST))</th>
<th>pH</th>
<th>Specific Grav. (Last 2 Digits)</th>
<th>AC/Index</th>
<th>Index</th>
<th>Index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st &quot;Pre&quot;</td>
<td>2nd &quot;Pre&quot;</td>
<td>3rd &quot;Pre&quot;</td>
<td>4th &quot;Pre&quot;</td>
<td>5th Wk 1</td>
<td>6th Wk 2</td>
</tr>
<tr>
<td>C-1</td>
<td>16</td>
<td>10</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>C-2</td>
<td>14</td>
<td>8</td>
<td>12</td>
<td>10</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>C-3</td>
<td>12</td>
<td>26</td>
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<td>10</td>
<td>10</td>
<td>5</td>
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<td>C-4</td>
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<td>12</td>
<td>10</td>
<td>10</td>
<td>5</td>
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<td>C-5</td>
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<td>22</td>
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<td>5</td>
</tr>
<tr>
<td>C-6</td>
<td>12</td>
<td>10</td>
<td>14</td>
<td>10</td>
<td>10</td>
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<td>C-8</td>
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<td>8</td>
<td>14</td>
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<td>5</td>
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<tr>
<td>C-9</td>
<td>18</td>
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<td>12</td>
<td>10</td>
<td>10</td>
<td>5</td>
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<td>18</td>
<td>16</td>
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<td>10</td>
<td>10</td>
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<td>C-11</td>
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</tr>
<tr>
<td>NC-1</td>
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<td>0</td>
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<td>NC-3</td>
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<td>5</td>
<td>5</td>
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<td>NC-4</td>
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<td>NC-5</td>
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<td>AVERAGE INDEX (NC)</td>
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</table>
CAFFEINE SUBJECTS

**Results:** The **CORRELATED T-TEST COMPARING THE ANABOLIC/CATABOLIC INDEX OF NON-CAFFEINE CONSUMERS "PRE" VERSUS WEEK 1, "PRE" VERSUS WEEK 2, AND WEEK 1 VERSUS WEEK 2** data, Table 11, showed significant differences between Week 1 compared to Week 2 and Week 2 compared to "Pre."

The mean anabolic/catabolic index for the End of Week 2 was 40 with a standard deviation of 5.72. The mean anabolic/catabolic index at the End of Week 1 was 45.7 with a standard deviation of 12.28. The difference between the means was 5.72 with a T-ratio of 1.54; 2-tail probability was .156 and 1-tail probability was .078. This significantly different fall is in the anabolic direction, which would be expected by the reintroduction of caffeine. It is also of interest that the index was significantly less at the end of Week 2 as compared to the precondition. The mean "Pre" was 43.4 with a standard deviation of 10.90. The difference between the means was -3.36 with a T-ratio value of 3.02. The probability was equal to .013 for a 2-tail test of significance or .007 for a 1-tail test of significance.

**Comments:** Evidently, the abstinence from coffee during Week 1 increased the anabolic/catabolic index but not by a statistically significant amount. However, reintroduction of the coffee did significantly lower the index reflecting a true anabolic effect.
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<td>3.287</td>
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<td>13.441</td>
<td>4.053</td>
<td>.332</td>
<td>.318</td>
<td>-.58</td>
<td>10</td>
<td>.573</td>
<td>.287</td>
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<tr>
<td>AC &quot;Pre&quot;</td>
<td>11</td>
<td>43.3636</td>
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</tr>
<tr>
<td>AC WK1</td>
<td>11</td>
<td>45.7273</td>
<td>12.281</td>
<td>3.703</td>
<td>5.7273</td>
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<td>3.730</td>
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<td>.243</td>
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<td>.078</td>
</tr>
<tr>
<td>AC WK2</td>
<td>11</td>
<td>40.0000</td>
<td>9.675</td>
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</tbody>
</table>
NON-CAFFEINE SUBJECTS

The CORRELATED T-TEST COMPARING THE ANABOLIC/CATABOLIC INDEX "PRE" VERSUS WEEK 1, "PRE" VERSUS WEEK 2, AND WEEK 1 VERSUS WEEK 2 (Table 12) compared statistical evaluation of significance.

Comments: Although the Revici Anabolic/Catabolic Index moved in the expected direction for the caffeine subjects, the data was inconclusive for the non-caffeine group. This area requires further investigation.

PSYCHOLOGICAL EFFECTS

Introduction

Each subject was requested to answer a questionnaire prior to the study, after Week 1 and after Week 2. A sample of Plate II follows.

The focus was upon changes from the "Pre" condition to Week 1 mode and from the Week 1 mode to the Week 2 mode. The caffeine subjects had five bags per day of decaffeinated tea for Week 1 and upon re-examination at the end of Week 1, they were then given five caffeinated tea bags per day for seven days.

The responses to the questions 1-11 were grouped into three categories. The MOOD INDEX included questions 1, 2, 4, 6, 9, and 10; and the SLEEP INDEX included 7a, 7b, and 7c. The PSYCHOLOGICAL INDEX included questions 5, 8, and 11.

Since some questions were negative parameters, such as "Did you feel tired," the responses to such a question were reversed in sign in the
<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of Cases</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Standard Error</th>
<th>(Difference) Mean</th>
<th>Standard Deviation</th>
<th>Standard Error</th>
<th>Corr.</th>
<th>2-Tail T Value</th>
<th>Degrees of Freedom</th>
<th>2-Tail Prob.</th>
<th>1-Tail Prob.</th>
</tr>
</thead>
<tbody>
<tr>
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<td>6</td>
<td>37.6667</td>
<td>7.421</td>
<td>3.029</td>
<td>2.6667</td>
<td>12.925</td>
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<td>.583</td>
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tabulations. For example, "Did you feel tired?" the subjects responds, "less." This "less tired" is actually a double negative or more energetic. The inversions of sign were also required for question 6, "Were you nervous or anxious?" and question 9, "Did you feel depressed?" For the PHYSIOLOGICAL INDEX, question 5, "Did you have headaches?" was reversed and "Did you have stomach aches?" was reversed. Improvements which were toward better health or better feelings were depicted with a rising bar.

MOOD

CAFFEINE SUBJECTS

We began the analysis of Figure 6 by focusing upon the heavy black bars for each subject which represents the comparison (or difference) between the End of Week 1 and the "Pre" state.

During the week when the chronic caffeine subjects were given decaffeinated tea (Week 1), there was no clear-cut pattern of mood change. Whereas four reported negative or "worse" mood responses (C-1, -5; C-4, -4; C-6, -1; C-10, -4), four reported positive or improved mood changes (C-3, +2; C-7, +2; C-8, +1; C-9, +2). The other three had no alteration of mood (C-2, C-5, C-11).

Comment: Evidently the mood-related reactions to caffeine abstinence show no single directional pattern.
FIGURE 6. MOOD, PSYCHOLOGICAL EFFECTS VIA QUESTIONNAIRE. COMPARISON OF END OF WEEK 1 TO "PRE" (BLACK BAR) AND END OF WEEK 2 TO END OF WEEK 1 (LIGHTER BAR). CAFFEINE SUBJECTS.
We analyzed Figure 7 by focusing upon the lighter bars which represent the comparison (or difference) between the End of Week 2 and the End of Week 1.

In the chronic caffeine group, caffeine was reintroduced during Week 2. For most subjects (eight subjects) this reintroduction did move them toward "more" stimulated, "less" tired, "more" alert, and "less" depressed. Keep in mind that this was compared to a prior point in time, namely, the week the subjects received decaffeinated tea and this does not necessarily reflect a better state of health. The mood data, as shown by the lighter bars, revealed (C-1, +5; C-2, +4; C-4, +6; C-5, +6; C-6, +3; C-7, +3; C-9, +4; C-10, +6). On the other hand, two subjects had negative mood changes (C-3, -5; C-8, -3); C-11 had no change.

Comment: Although the mood effects of one week of abstinence were both negative and positive, the reintroduction of caffeine did move mood changes in the positive direction. This is not to conclude that caffeine is a healthy or desirable mood elevator, but rather relates to the short-term effect of a one-week abstinence. What might be an interesting future study would be analyzing three weeks of caffeine abstinence and the effect on mood.

NON-CAFFEINE SUBJECTS

Each non-caffeine subject answered a questionnaire in the same manner as the caffeine consumer subjects. The NC subjects were given five tea bags of caffeinated tea per day during Week 1. Upon
FIGURE 7. HOOO, PSYCHOLOGICAL EFFECTS VIA QUESTIONNAIRE. COMPARISON OF END OF WEEK 1 (LIGHTER BARS) - CAFFEINE SUBJECTS TO END OF WEEK 1 (DARKER BARS) - NO-CAFFEINE SUBJECTS.
re-examination at the End of Week 1, they were then given five tea bags per day for seven days of decaffeinated tea. Focusing upon the comparison of End of Week 1 to "Pre" depicted by the heavy black bars in Figure 8 showed that the introduction of caffeine to the non-caffeine user created both positive and negative mood changes without a clear pattern.

Comment: Thus, the caffeine must interact with each person's biochemistry in a unique way. When correlating adrenal status with mood change, it was of interest to note that the three NC group subjects with improved mood all had normal adrenal function. Perhaps, caffeine can stimulate the normal adrenal function. Perhaps, caffeine can stimulate the normal adrenal to produce positive mood in the short-run (in this study for one week).

Analysis of the comparison of End of Week 2 to End of Week 1 (lighter bars) (Figure 9) showed that return to the caffeine-free state in Week 2 resulted in negative mood changes for four subjects (NC-3, -1; Nc-4, -2; NC-5, -2; NC-6, -2).

Comment: Even though the caffeine had been ingested for one week (Week 1), it began to affect mood.

SLEEP

Introduction

The SLEEP INDEX represents the three questions 7a, 7b, and 7c; depicting insomnia, difficulty falling sleep, and difficulty staying
FIGURE 8. MOOD, PSYCHOLOGICAL EFFECTS VIA QUESTIONNAIRE. COMPARISON OF END OF WEEK 1 TO "PRE" (BLACK BAR). NON-CAFFEINE SUBJECTS.
FIGURE 9. MOOD, PSYCHOLOGICAL EFFECTS VIA QUESTIONNAIRE. COMPARISON OF END OF WEEK 2 TO END OF WEEK 1 (LIGHTER BAR). NON-CAFFEINE SUBJECTS
asleep. The bar graph (Figure 10) represents the changes between the End of Week 1 and "Pre" and the End of Week 2 and the End of Week 1. The numerical sign is inverted so that a positive response such as "less" insomnia is depicted with a positive bar.

CAFFEINE SUBJECTS

**Results:** Three C subjects had sleep problems during Week 1 (C-1, -4; C-4, -6; C-11, -4). Two had improvement in sleep (C-7, +2; and C-8, +6). Six had no sleep changes (C-2, C-3, C-5, C-6, C-9, C-10).

In Week 2, two had worse sleep (C-2, -2; and C-8, -2). Two had better sleep (C-4, +6; and C-11, +6). Seven others had no change (C-2, C-3, C-5, C-6, C-7, C-9, C-10).

**Comment:** The sleep effects showed no clear pattern at the End of Week 1 compared to "Pre." It was of interest that many subjects had no alteration of sleep function. Also, there was relatively little effect on sleep when the caffeine was reintroduced.

NON-CAFFEINE SUBJECTS

The comparison of End of Week 1 to "Pre" (black bars) and also End of Week 2 to End of Week 1 (lighter bars) is shown in Figure 11. Four subjects had no change in sleep status comparing End of Week 1 to "Pre" (NC-1, NC-2, NC-5, and NC-6). Two had sleep problems during Week 1 compared to "Pre" (NC-3, -2; and NC-4, -6). In the comparison of Week 2
FIGURE 10. SLEEP INDEX. SLEEP EFFECTS VIA QUESTIONNAIRE. COMPARISON OF END OF WEEK 1 TO "PRE" (BLACK BAR) AND END OF WEEK 2 TO END OF WEEK 1 (LIGHTER BAR). CAFFEINE SUBJECTS
FIGURE 11. SLEEP INDEX. SLEEP EFFECTS VIA QUESTIONNAIRE. COMPARISON OF END OF WEEK 1 TO "PRE" (BLACK BAR) AND END OF WEEK 2 TO END OF WEEK 1 (LIGHTER BAR). NON-CAFFEINE SUBJECTS
to Week 1, three subjects had sleep problems (NC-3, -2; NC-4, -6; NC-5, -2) and three subjects had no change (NC-1, NC-2, and NC-6).

The NC group had caffeine during Week 1 and decaffeinated tea during Week 2.

Comment: For the most part, caffeine produced little change in the sleep function in the NC group. It is of interest that one subject (NC-4), who had the most sleep problems, started the study with somewhat weakened adrenal function.

PHYSIOLOGICAL EFFECTS

Introduction

Questions 5, 8, and 11 comprise the components of this index. Please note that questions 5 and 8 were plotted in the positive direction such that having "less" headache or "less" stomach ache would actually be a positive, healthful sign and therefore is depicted with a bar in the positive direction. As with Figure 7 (Mood), this represents the comparison of the End of Week 1 to the "Pre" status and the End of Week 2 status with the End of Week 1 status (Figure 12).

CAFFEINE SUBJECTS

Results: Five of the eleven had improvements in their physiological indicators of +2 at the End of Week 1 (C-3, C-6, C-7, C-8, and C-9). Four had no change (C-1, C-2, C-5, C-10) and two had physiological changes in the negative direction (C-4, -2; and C-11, -4).
FIGURE 12. PHYSIOLOGICAL INDEX. PHYSIOLOGICAL EFFECTS VIA QUESTIONNAIRE. COMPARISON OF END OF WEEK 1 TO "PRE" (BLACK BAR) AND END OF WEEK 2 TO END OF WEEK 1 (LIGHTER BAR). CAFFEINE SUBJECTS
At the End of Week 2, two had worse of negative physiological changes (C-8, C-10) of -2 each. One had a marked positive C-4, +4. All of the others had no change (C-1, C-2, C-3, C-5, C-7, C-9, C-11).

Comment: Many of the C group subjects had improvement in physiological indicators during Week 1 without caffeine. Such symptoms as stomach aches and headaches were diminished or improved on the schedule which included decaffeinated tea. For most subjects, the reintroduction of caffeine seemed to produce little change as compared to their prior status.

NON-CAFFEINE SUBJECTS

Analysis of the End of Week 1 to "Pre" (black bar) (Figure 13) revealed: four had negative physiological changes (NC-1, -2; NC-2, -2; NC-3, -4; NC-4, -4). Two had no change (NC-5 and NC-6). Comparing End of Week 2 status with End of Week 1 status (lighter bar) (Figure 13): four had negative physiological changes (NC-1, -4; NC-4, -2; NC-5, -2; NC-6, -2). One had positive physiological changes (NC-3, +2).

Comment: The NC group tended to respond to caffeine with headache or stomach ache. The NC group had physiological reactions both to the caffeine mode and to the non-caffeine mode.
Figure 13. Physiological Index. Physiological effects via questionnaire. Comparison of end of week 1 to "pre" (black bar) and end of week 2 to end of week 1 (lighter bar). Non-caffeine subjects.
Conclusions

A. Adrenal Gland Function

1. Chronic caffeine users tended to have diminished adrenal gland function.

2. Caffeine may be taken to stimulate underactive (or even normal) adrenal glands in order to raise the blood sugar level.

3. The temporary energy improvement tends to weaken the adrenal glands so that a higher dose of caffeine is needed to achieve the same energy effect.

4. a) After months of caffeine stimulation to the adrenals, their function becomes suboptimal. The majority of caffeine users in this sample presented with weakened adrenals as shown by the abnormal readings of the Ragland Postural Blood Pressure and the Koenigsburg Urinary Sodium Excretion.

b) Conversely, the majority of the NC group subjects presented with normal adrenal function.

5. Adrenal status was determined by Ragland Postural Blood Pressure and Koenigsburg Urinary Sodium Excretion. The results of these two tests were consistent and in agreement. These two indicators correlated closely, where diminished standing blood
pressure was seen, there was a higher spillage of sodium into
the urine. These two indicators serve as a mathematical
indicator of adrenal strength or weakness.

6. In chronic caffeine subjects, abstinence and reintroduction
seemed to improve adrenal function.

B. Anabolic Effect*

7. In chronic caffeine subjects, the reintroduction of caffeine
after one week abstinence significantly lowered the Anabolic/
Catabolic Index at the End of Week 2. This index change was in
the negative direction which reflects an anabolic process.

C. Psychological Effects

8. Mood Effects -- In the chronic caffeine-user group, one week of
abstinence produced both positive and negative mood changes.
There was no discernible pattern, however, reintroduction of
caffeine did lead to mood changes in the "positive direction."
Introduction of caffeine to non-caffeine subjects was also
associated with both positive and negative mood alterations.
Although there was no consistent pattern, the three NC subjects
with normal adrenals all showed positive mood changes.

*This theory is still the subject of debate and has not yet gained
wide scientific support.) For literature review, see Dr. E. Revici,
1961.
Cessation of caffeine after one week by the NC subjects was followed by a preponderance of mood changes in the "negative direction."

9. **Sleep Effects** -- The chronic caffeine users had no clear pattern of sleep alteration during Week 1 or Week 2. Also, most of the NC group showed little sleep changes.

D. **Physiological Effects**

10. In the C group, the preponderant response to abstinence of caffeine was an improvement in the physiological indicators. Reintroduction produced little change by the end of Week 2. There was a strong tendency for the NC group to respond to caffeine with physiological changes such as headache and stomachache.

E. **Comparison of Caffeine Group (C Group) to Non-Caffeine (NC Group)**

11. NC Group -- The introduction of caffeine to the non-user produced varied reactions although subjects with normal adrenals had positive mood changes. Cessation led to negative mood changes in the majority of NC subjects. There was little change in sleep pattern during either week. Physiological changes such as headaches or stomachaches occurred during the caffeine-use week. The majority also had physiological changes during Week 2.
12. C Group -- The most consistent effects of caffeine abstinence were diminished stomachache and/or headache. This was quantified via numerical changes toward higher numbers which reflected healthful or positive changes. Abstinence showed no overall pattern of mood change. Reintroduction of caffeine was associated with mood changes in the positive direction. Neither Week 1 nor Week 2 produced a clear pattern of sleep changes; there was only very slight effect on sleep during Week 2. However, a week may not be adequate time for complete withdrawal from caffeine's stimulatory effects. No situations were found in the literature to corroborate these observations.

Discussion

One of caffeine's major effects is to stimulate the adrenal glands to secrete epinephrine and norepinephrine, resulting in an immediate boost of energy. However, in time, the adrenals may become exhausted.

In our society, the stress of day-to-day living has a tendency to "wear out" our adrenal glands. This diminished activity results in fatigue. In order to revive adrenal function, many people ingest moderate to high quantities of caffeine. This is an external stimulant. In time, this stimulation wears out the glands, thus the immediate benefit is at the cost of eventual exhaustion.

In day-to-day clinical practice, many patients come to the doctor's office complaining of fatigue. The degree of this symptom varies from
"mild" to "severe." An example of "severe" fatigue is a feeling of being tired and drained of energy, even upon awakening from a restful sleep. At the other end of the spectrum is a diminished ability to work efficiently at the end of the day.

Occasionally, the fatigue is a result of anemia, depression, malabsorption, a toxic state, or a hypothyroid condition. However, it is our observation that most of the time fatigue is a result of diminished adrenal function or adrenal exhaustion. The level of adrenal function can be ascertained by appropriate physical examination and laboratory testing.

In this study, the results of the physical examination and urine sodium excretion evaluation showed that chronic users of caffeine can be differentiated from non-users based on tests which reflected changes in adrenal function during the two test weeks.

In the active nutritional practice of Dr. Martin Feldman, who has served as the scientific monitor, a recent review of medical records showed that more than 65 percent of new patients complaining of fatigue as a major medical symptom were drinking three or more cups of coffee or tea daily. Many patients reported increased intake of coffee and tea as their day-to-day fatigue became more severe. Upon interview they reported the necessity of coffee, tea, chocolate, or certain soft drink beverages to "boost" their energy. It is very likely that caffeine's ability to stimulate adrenal gland activity accounts for the popularity of caffeine beverages in our society.
However, the daily use of caffeine over a period of months leads to diminished adrenal function. The caffeine does, in fact, increase energy but at a price. Also, most patients report the need to drink more caffeine for a similar effect as time passes.

**Recommendations**

The main point of this study is to educate the public at-large as to the physiology of why they like their caffeinated beverages so much and the long-term damage to their body which results. For the great majority, it is to obtain more energy by stimulating their underactive adrenals.

Fortunately, there are available non-drug nutritional programs which have the ability to repair or rebalance weakening adrenal glands toward normal. Such a program consists of lifestyle changes, the avoidance of adrenal stimulants (caffeine in any form) and the consumption of specific nutrients.

1. Vitamin B₅ (Pantothenic Acid) in the range of 300-800 mg/day
2. Vitamin C (Ascorbic Acid) in the range of 2000-10,000 mg/day
3. Herbal Licorice Root in the range of 50-150 mg/day
4. Bovine Adrenal Gland processed to remove any hormonal activity and purified to remove possible toxins
5. L-Arginine in the range of 500-1,000 mg/day
6. B₂ (Riboflavin) in the range of 1-3 mg/day
7. B₃ (Niacin) in the range of 12-36 mg/day
8. B₆ HCl (Pyridoxine Hydrochloride) in the range of 10-50 mg/day.

The lifestyle changes should include diminishing stressors and learning strategies which might diminish anxiety. Some of the many avenues would include meditation, biofeedback, yoga, subliminal stress reduction tapes, excessive stress management counseling.

It is my hope that a larger and more sophisticated experiment will evolve from this work. That experiment should be done in a prison or in an experiment with people's whose diet, behavior, and lifestyle can be controlled and carefully monitored. With proper funding and research facilities, a more comprehensive analysis can be made available to the scientific community and to the public.
BIBLIOGRAPHY


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*Connecticut Medicine, 43*, (1979), 331. Caffeinated drinks, a public health problem.


Crawford, L. V. (1976). A double-blind study of subcutaneous food testing sponsored by the Food Committee of the American Academy of Allergy. *Journal of Allergy and Clinical Immunology*, 57.


APPENDICES
APPENDIX B

CAFFEINE STUDY
Daily Diary

Name: __________________________ Day __________ of Week ________

At the end of each day, check off on the following chart any changes between this week and last week that you are experiencing in energy, sleep, etc. Add any comments.

1. Energy:
   Comments: □ less □ same □ more

2. a) Concentration:
   Comments: □ poorer □ same □ better
   b) Attention span:
   Comments: □ shorter □ same □ longer

3. a) Nervousness:
   Comments: □ less □ same □ more
   b) Depression:
   Comments: □ less □ same □ more
   c) Mood:
   Comments: □ less □ same □ more

4. Irritability
   Comments: □ less □ same □ more

5. Muscular strength:
   Comments: □ less □ same □ more

6. Sense of well-being
   Comments: □ less □ same □ more

7. Falling asleep:
   Comments: □ more difficult □ same □ easier

8. Endurance:
   Comments: □ less □ same □ more

9. Headaches:
   Comments: □ worse □ same □ improved

10. Appetite:
    Comments: □ poorer □ same □ improved

11. For smokers:
    cigarette use:
    Comments: □ less □ same □ more
APPENDIX C

CAFFEINE STUDY QUESTIONNAIRE
Plate I

Name: ___________________________ Sex: ______ Age: ______

To be answered prior to study

1. Approximately how many cups of CAFFEINATED coffee do you drink per day?
   - 1
   - 2
   - 3-5
   - more than 5

2. Approximately how many cups of CAFFEINATED tea do you drink per day?
   (Note that HERBAL teas are NOT CAFFEINATED)
   - 1
   - 2
   - 3-5
   - more than 5

3. How many ounces of CAFFEINATED sodas do you drink per day? (Include beverages containing cola)

4. Do you have trouble falling asleep?  
   - No
   - Yes

5. Once you fall asleep, do you sleep soundly?  
   - No
   - Yes

6. Do you have headaches?
   - Never
   - Seldom
   - About once a month
   - About once a week
   - Almost every day

7. Do you feel irritable?
   - Never
   - Seldom
   - Occasionally
   - Frequently

8. Do you take over-the-counter analgesics (pain-killers)?  
   - No
   - Yes

   If “Yes,” what brand?

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<th>Occasionally</th>
<th>Frequently</th>
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<td>10. Do you feel tired?</td>
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<td>11. Do you feel overstimulated (hyper)?</td>
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<tr>
<td>12. Do you have heart palpitations?</td>
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<tr>
<td>13. Do you have stomach upsets?</td>
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14. Do you smoke cigarettes?  
   - No
   - Yes

   If you do smoke, approximately how many cigarettes per day?
APPENDIX C

CAFFEINE STUDY QUESTIONNAIRE

Plate I

Name: ____________________________ Sex: ____ Age: _____

To be answered prior to study

1. Approximately how many cups of CAFFEINATED coffee do you drink per day?
   - 1
   - 2
   - 3-5
   - more than 5

2. Approximately how many cups of CAFFEINATED tea do you drink per day?
   (Note that HERBAL teas are NOT CAFFEINATED)
   - 1
   - 2
   - 3-5
   - more than 5

3. How many ounces of CAFFEINATED sodas do you drink per day? (Include beverages containing cola)

4. Do you have trouble falling asleep?  
   - No
   - Yes

5. Once you fall asleep, do you sleep soundly?  
   - No
   - Yes

6. Do you have headaches?
   - Never
   - Seldom
   - About once a month
   - About once a week
   - Almost every day

7. Do you feel irritable?
   - Never
   - Seldom
   - Occasionally
   - Frequently

8. Do you take over-the-counter analgesics (pain-killers)?  
   - No
   - Yes
   If "Yes," what brand? ____________________________

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<th>Never</th>
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<td>10. Do you feel tired?</td>
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<td>11. Do you feel overstimulated (hyper)?</td>
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<td>12. Do you have heart palpitations?</td>
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<td>13. Do you have stomach upsets?</td>
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<td>14. Do you smoke cigarettes?</td>
<td>No</td>
<td>Yes</td>
<td>If you do smoke, approximately how many cigarettes per day?</td>
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CAFFEINE STUDY QUESTIONNAIRE  
Part II

Name: _______________________________  Week: ____________
To be filled out AFTER Week One and Week Two of the study.
Answer the following according to how you usually felt during the previous week.

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<th>More</th>
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<tbody>
<tr>
<td>1. Did you feel stimulated?</td>
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<td>2. Did you feel tired?</td>
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<td>3. Did you drink more coffee, tea, or cola than usual?</td>
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<td>4. Did you feel alert?</td>
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<td>5. Did you have headaches?</td>
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<td>6. Were you nervous or anxious?</td>
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<td>7. Did you have a) insomnia?</td>
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<tr>
<td>b) difficulty falling asleep?</td>
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<tr>
<td>c) difficulty staying asleep?</td>
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<td>8. Did you have stomachaches?</td>
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<td>9. Did you feel depressed?</td>
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<tr>
<td>10. Did you feel &quot;good&quot; (a feeling of well-being)?</td>
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<td>11. How was your appetite?</td>
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<td>12. Did you notice anything different from usual?</td>
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<td>If yes, explain.</td>
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<td>13. For smokers only: Did you notice anything different from usual?</td>
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<td>If yes, explain.</td>
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<td>14. For smokers only: Cigarette use per day: ___________________ cigarettes</td>
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NONSIMKERS ONLY
Appendix D

PEARSON CORRELATION COEFFICIENTS BETWEEN BLOOD PRESSURE AND SODIUM SECRETION FOR "PRE," WEEK 1, AND WEEK 2, CAFFEINE SUBJECTS.

Introduction

The Pearson Correlation shows the degree of linear relationship between two variables. A POSITIVE correlation would indicate that the two sets of scores varied together, while a NEGATIVE correlation signifies an inverse relationship.

Of the 15 non-redundant Pearson Correlation coefficients, 14 of the 15 correlations are significant (.10 or less). There are positive correlations between blood pressure at "Pre," Week 1 and Week 2 and between sodium secretion at "Pre," Week 1 and Week 2. There are negative correlations between blood pressure and sodium secretion, the only exception being the correlation between sodium secretion at Week 2 and blood pressure at Week 1: this correlation is negative, but does not reach the desired level of significance.

Using the .10 level for a 1-tail test for the three-measure blood pressure and sodium secretion taken at the "Pre," Week 1 and Week 2 periods shows from Appendix D, PEARSON CORRELATION COEFFICIENTS BETWEEN BLOOD PRESSURE AND SODIUM SECRETION FOR "PRE," WEEK 1, AND WEEK 2, CAFFEINE SUBJECTS, the following specific data: For the chronic caffeine subjects, a POSITIVE correlation between blood pressure "Pre" and blood pressure Week 1 (.506, p=.056). This correlation indicates the values tended to vary together, i.e., subjects who had high scores at "Pre" tended to have high scores at Week 1 and low scores were paired with low scores. There was a significant BLOOD PRESSURE "Pre" and Sodium Secretion "Pre" (-.864, p=.001), i.e., high scorers on blood pressure "Pre" were paired with low scorers on Sodium secretion "Pre" and vice versa.

Comment: The most striking correlation was the very linear negative correlation between each caffeine subject's blood pressure and sodium secretion. In other words, as the blood pressure became less negative (more positive), the sodium secretion values diminished (less sodium was spilled).
<table>
<thead>
<tr>
<th></th>
<th>BP &quot;PRE&quot;</th>
<th>BP WK1</th>
<th>BP WK2</th>
<th>SS &quot;PRE&quot;</th>
<th>SS WK1</th>
<th>SS WK2</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP &quot;PRE&quot;</td>
<td>1.0000 (0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>p = .</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP WK1</td>
<td>.5062 (11)</td>
<td>1.0000</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>p = .056</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>BP WK2</td>
<td>.4646 (11)</td>
<td>.4568 (11)</td>
<td>1.0000</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SS &quot;PRE&quot;</td>
<td>-.8641 (11)</td>
<td>-.5708 (11)</td>
<td>-.6784 (11)</td>
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<tr>
<td>SS WK1</td>
<td>-.6802 (11)</td>
<td>-.8515 (11)</td>
<td>-.5810 (11)</td>
<td>.8508 (11)</td>
<td>1.0000</td>
<td></td>
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<tr>
<td></td>
<td>p = .011</td>
<td>p = .000</td>
<td>p = .030</td>
<td>p = .000</td>
<td>p = .</td>
<td></td>
</tr>
<tr>
<td>SS WK2</td>
<td>-.5132 (11)</td>
<td>-.1899 (11)</td>
<td>-.7908 (11)</td>
<td>.7733 (11)</td>
<td>.5904 (11)</td>
<td>1.0000</td>
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</table>

**TABLE D1. PEARSON CORRELATION COEFFICIENTS BETWEEN BLOOD PRESSURE AND SODIUM SECRETION FOR "PRE," WEEK 1, AND WEEK 2. CAFFEINE SUBJECTS.**
Appendix E

PEARSON CORRELATION COEFFICIENTS BETWEEN BLOOD PRESSURE AND SODIUM SECRETION FOR "PRE," WEEK 1, AND WEEK 2. NON-CAFFEINE SUBJECTS.

Appendix E, THE PEARSON CORRELATION COEFFICIENTS BETWEEN BLOOD PRESSURE AND SODIUM SECRETION FOR "PRE," WEEK 1, AND WEEK 2 for non-caffeine user subjects, displays 15 non-redundant Pearson Correlation coefficients and of the 15 correlations, five are significant at the .10 level or less. These include positive correlations between blood pressure at Week 1 and Week 2 and sodium secretion at Week 1 and Week 2, and negative correlations between blood pressure at Week 1 and sodium secretion at Week 1; blood pressure at Week 2, and sodium secretion at Week 2.

The significant Pearson Correlation coefficients for the NC group relates blood pressure inversely to sodium secretion as illustrated in Appendix E.

Comment: One of the major findings of this entire experiment is the high degree of correlation or agreement when measuring adrenal gland status via both blood pressure and sodium secretion. Although the numbers move in opposite directions, nevertheless they are measuring the identical physiological strength or weakness.
<table>
<thead>
<tr>
<th></th>
<th>BP &quot;Pre&quot;</th>
<th>BP WK1</th>
<th>BP WK2</th>
<th>SS &quot;Pre&quot;</th>
<th>SS WK1</th>
<th>SS WK2</th>
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<tr>
<td>BP &quot;Pre&quot;</td>
<td>1.0000</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>(0)</td>
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<td></td>
</tr>
<tr>
<td>p</td>
<td>.42</td>
<td></td>
<td></td>
<td>.03</td>
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<tr>
<td>BP WK1</td>
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<td>1.0000</td>
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<tr>
<td>p</td>
<td>.326</td>
<td></td>
<td></td>
<td>.36</td>
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<td>.7920</td>
<td>1.0000</td>
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</tr>
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<td>(6)</td>
<td>(0)</td>
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<tr>
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<td>SS &quot;Pre&quot;</td>
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<td>.1761</td>
<td>.2084</td>
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<td>(6)</td>
<td>(0)</td>
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<tr>
<td>p</td>
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<td>.369</td>
<td>.346</td>
<td>.17</td>
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<td>SS WK1</td>
<td>-.0502</td>
<td>-.9017</td>
<td>-.8585</td>
<td>.1503</td>
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<td>(6)</td>
<td>(6)</td>
<td>(6)</td>
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<td>p</td>
<td>.462</td>
<td>.007</td>
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<td>SS WK2</td>
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<td>-.3594</td>
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<td>.6495</td>
<td>1.0000</td>
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<td>(6)</td>
<td>(6)</td>
<td>(6)</td>
<td>(6)</td>
<td>(0)</td>
</tr>
<tr>
<td>p</td>
<td>.176</td>
<td>.248</td>
<td>.026</td>
<td>.366</td>
<td>.081</td>
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APPENDIX F

Table F1 shows a t-test for independent groups, comparing caffeine and non-caffeine subjects at "Pre" status. For blood pressure (BP) at "Pre" status, the caffeine groups have a mean of -12.0909, which is significantly lower (t-ratio = -3.59) than the non-caffeine group (4.3333). For sodium secretion, the caffeine group had a mean of 40.9091, which is a significantly higher t-ratio (2.90) than the non-caffeine group (23.8333).

The mean of the BP of the caffeine group at -12.00 reflects an average drop in BP from supine to erect, which indicates a diminished adrenal function. The NC subject group, with a BP mean of 4.3, reflected much better adrenal function. This difference had a 2-tail probability of .003. Similarly, the sodium secretion (SS) mean for the C subjects "Pre" (40.91) versus 23.83 for the NC subjects. The higher mean reflects sodium secretion which indicates diminished adrenal function.

The mood effects in the caffeine subjects during week one were related to the abstinence from caffeine. In the non-caffeine subject group during week 1 the mood effects were from the introduction of caffeine. Comparing mood data of caffeine subjects versus non-caffeine subjects was difficult since the experimental design actually had two separate independent sub-studies.

Table F2 displays a t-test for independent groups, comparing the caffeine group at week one with the non-caffeine group at week two, as previously explained. For BP, the caffeine group had a mean equal to -11.7273, which is significantly lower43 than the non-caffeine group (3.0000, t-ratio equal to
Table F1

Comparison of Caffeine and Non-Caffeine Subjects at "Pre" Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of Cases</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Standard Error</th>
<th>T-Value</th>
<th>Degrees of Freedom</th>
<th>2-Tail Probability</th>
<th>1-Tail Probability</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NC</td>
<td>6</td>
<td>4.3333</td>
<td>7.941</td>
<td>3.242</td>
<td>-0.30</td>
<td>15</td>
<td></td>
<td></td>
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<tr>
<td>SS &quot;Pre&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>11</td>
<td>40.9091</td>
<td>13.736</td>
<td>4.142</td>
<td>2.90</td>
<td>15</td>
<td>.011</td>
<td>.006</td>
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<tr>
<td>NC</td>
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<td>23.8333</td>
<td>5.037</td>
<td>2.056</td>
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</table>
Table F2
Comparison of Caffeine Group End of Week One
with Non-Caffeine Group End of Week Two

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of Cases</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Standard Error</th>
<th>T-Value</th>
<th>Degrees of Freedom</th>
<th>2-Tail Probability</th>
<th>1-Tail Probability</th>
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<tbody>
<tr>
<td>Blood Pressure</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C - Week 1</td>
<td>11</td>
<td>-11.7273</td>
<td>11.884</td>
<td>3.584</td>
<td>-2.54</td>
<td>15</td>
<td>.023</td>
<td>.012</td>
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<td>NC - Week 2</td>
<td>6</td>
<td>3.0000</td>
<td>10.488</td>
<td>4.282</td>
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<td>15</td>
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<td>Sodium Secretion</td>
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<td>C - Week 1</td>
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<td>.38.4545</td>
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<td>1.80</td>
<td>15</td>
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<td>1.80</td>
<td>15</td>
<td>.079</td>
<td>.040</td>
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</tbody>
</table>
-2.54). For SS, the caffeine group had a mean which was significantly higher than the non-caffeine group, but only for a 1-tail test.

When the caffeine subjects were deprived of caffeine items, their BP at the end of week 1 was -11.72, which reflected adrenal under-activity; whereas the non-caffeine subjects at the end of week 2 (their abstinence week) had BP mean of 3.00. This difference was significant at the .023 level. The sodium secretion caffeine subjects at the end of week 1 was 30.45 as compared with the non-caffeine subjects at the end of week 2 with a mean of 27.50. This was not significant since the probability level was .019 for a 2-tail tests.

Since the caffeine subjects were removed from caffeine during week 1 and the non-caffeine subjects were taken off their one week of caffeine after week 1 (no caffeine during week 2), it is of interest to compare caffeine subjects during week 1 (stopped caffeine) with non-caffeine subjects during week 2 (stopped caffeine).

Another aspect comparing the caffeine subjects to non-caffeine subjects was the comparison of their BP and sodium secretion data in the "Pre" test. These two indications reflect adrenal status prior to the experimental condition.