Coffee & Tea-The Artificial Stressors A Review of the Negative Physiological & Psychological Effects of the Xanthines

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ABSTRACT

Evidence is reviewed to show that the physiological and possibly psychological effects of the xanthines are similar to those of the "fight or flight" reaction with the implication being that the caffeine and theophylline in tea, coffee, and various xanthin-containing beverages and drugs induce the same changes in the body as stress. A number of "at risk" populations are identified who should best avoid any xanthine consumption. The issue of the "safe" dose is discussed and the position is taken that, given the great individual variation in sensitivity and the large number of factors affecting the toxicity of the xanthines, caution is suggested in recommending any one "safe" dose.

INTRODUCTION

Caffeine and theophylline are perhaps the most widely used drugs in society today. Although their role in heart disease and some types of cancer is still being debated, there is much clearer evidence for the xanthines' effects upon cardiovascular and neural systems. The present paper will review the negative effects of caffeine and theophylline with particular focus on their effects on psychological and physiological functioning and the implications these effects hold for researchers, physicians, and clinicians. Evidence will be presented to suggest that drinking a cup of coffee or tea is equivalent to drinking a little cup of stress, as the physiological and perhaps psychological effects of the xanthines are very similar to those induced by stress.

Before reviewing the various effects of the xanthines, it might be helpful to the reader to describe briefly one case of caffeinism, the syndrome which occurs subsequent to excessive (relative to the individual tolerance) caffeine consumption. Though a number of reports of caffeinism exist in the literature, this case is cited in order to emphasize a number of psychological effects inconsistent with healthy day-to-day functioning. In late summer, the subject (a 33-year-old female) began experiencing heart palpitations, severe tightness in the back of the neck, constriction of the throat,

uncontrollable racing thoughts, impulsivity, anxiety, muscle twitches, and headaches. A routine visit to a physician had revealed borderline high blood pressure. There were also episodes of severe depression which appeared to have no basis in the events of the subject's life, but which were subsequently recognized as occurring when the patient's regular supply of diet soft drink was interrupted. General loss of self-esteem, motivation, and lethargy accompanied these periodic depressive episodes. A similar constellation of symptoms some years previously had sent the subject to a general practitioner whose conclusion had been that the various symptoms were psychosomatic. The subject drank only one cup of coffee a day in the morning, so caffeine was originally discounted as the cause of the various adverse symptoms. With the exception of the birth control pill, no other medications were being taken, but the subject reported drinking five or six ten-ounce cans of Diet Pepsi a day. The intake of caffeine in every form was immediately suspended. The following day during the early afternoon, an excruciating headache, worse than any the subject had ever experienced, began. The headache was accompanied by general irritability, difficulty in concentrating, lethargy, a runny nose (rhinorrhea), severe tightness in the throat, and depression. All of these symptoms continued for several days. The tightness in the throat and the headache were the longest lasting though they became milder and milder day by day. Caffeine consumption was not resumed and the subject no longer experienced any of the initial symptoms. Within a month, the previously borderline high blood pressure had returned to normal.

Though all the symptoms mentioned as occurring in this patient are cited as minor effects of the xanthines in various medical drug reference manuals which suggest that they be treated only if they persist, the subject described herein reported that the symptoms were highly disruptive and interfered with normal mental and physical functioning both at work and at home.

Biotransformation & Bioavailability of Caffeine

The absorption of caffeine taken orally is rapid and appears in all tissues within 5 minutes. In humans peak blood plasma levels are reached at about 30 minutes after oral administration (Gilbert, 1976 a). Caffeine is almost entirely transformed in humans and little appears to be excreted via the urine. Controversy exists as to whether caffeine is accumulated. Recent reports indicate that the caffeine metabolism and storage rates of habitual and nonhabitual users may differ. Evidence also suggests that it may take about seven days to decaffeinate the blood of habitual coffee drinkers. Caffeine's plasma half life for humans appears to range from 2.5 to 4.5 hours with 12 to 22 % being metabolized per hour (Gilbert, 1976 a). The theophylline found in tea is metabolized at only about 15 % per hour.

Dosage & the Xanthines

Before reviewing the negative physiological and psychological effects of the xanthines, it is necessary to point out that one of the unique characteristics of the caffeine

literature is the wide inter-and intrasubject variation in the behavioral effects of caffeine. Even when habitual caffeine consumption was controlled for, Goldstein et al. (1965) found tremendous individual variation in response and attributed this to individual differences which "must reflect, for the most part, intrinsic differences in sensitivity of sites of action in the brain."

Due to these tremendous individual differences, the following discussion will, for the most part, refrain from relating dosage to effects.

The Detrimental Physiological Effects of the Xanthines

The symptoms of the subject previously described are characteristic of the symptoms occurring in different combinations in persons suffering from caffeinism or in those ingesting large doses of caffeine or theophylline. These symptoms include insomnia, irritability, cardiac palpitation, tremor, convulsions, flushing, anorexia, diuresis and dehydration from diuresis, fever, albuminuria, epigastric discomfort, anxiety, nervousness and agitation, headaches, tachypnea, reflex hyperexcitability, muscle twitches, muscular leg pains and general muscle pains, diarrhea, dizziness, hyperglycemia, diaphoresis (Roller, 1981), and hyperesthesia (Ritchie, 1970 ; Truitt, 1971).

At very high doses (@ 1,000 mg. or more) abdominal cramping, vomiting, extreme anxiety, tremulousness, impaired memory (Stillner et al., 1978), altered levels of consciousness, vertigo, and sensory disturbances may occur. The effects of the xanthines can interact with a number of factors including age, sex, individual sensitivity, smoking, diabetes, renal dysfunction, drug intake, birth control pill usage, diurnal and seasonal rhythms, and stress. Both the young and the old react to much smaller doses. Relative to the sex of the consumer, men (at least those in their early 20's) have been reported to be somewhat less susceptible to the deleterious effects of caffeine (Gilliland & Andress, 1981). This may, however, be due to weight differences rather than sex per se. There is also a very wide range of individual sensitivity. There is some suggestion in the literature that there may be a correlation between personality type (Revelle et al., 1980) and susceptibility to caffeine. Possibly those who are ordinarily excitable and attuned to a high state of arousal are the most adversely affected by caffeine. Cigarette smokers metabolize caffeine much more quickly than non-smokers perhaps due to their increased liver aryl hydrocarbon hydroxylase activity (Parsons & Neims, 1978). Darragh et al. (1981) have speculated that at least some of the symptoms commonly ascribed to nicotine withdrawal may be due, in part, to caffeine overload. The high correlation between consumption of coffee and consumption of cigarettes has been a consistent finding (Gilbert, 1976 a ; Greden et al., 1978). Like the young and the aged, diabetics and those with kidney and liver dysfunction are adversely affected by very small doses of the xanthines. Caffeine and theophylline may interfere with blood-glucose regulation by insulin in diabetics. Conversely, diabetics may consume caffeine and theophylline-containing beverages in order to correct the hypoglycemia produced by excessive insulin administration (Gilbert, 1976 a). The monoamine oxidase [one of

the two enzymes responsible for degrading the catecholamines (DA & NE)] inhibitors (including pargyline, iproniazid, tranylcypramine, and phenylisopropylhydrazine), tricyclic anti-depressants, various antibiotics, and other drugs may work to increase the toxicity of caffeine (Neil et al., 1978) and presumably the other xanthines as well. There also appears to be an interaction with time of day (Revelle et al., 1980) and season. The effects of caffeine, at least in terms of its causation of the restless-leg-syndrome, have been found to be greatest in spring and, to a lesser extent, late summer and early fall (Lutz, 1978). As will be discussed later, stress appears to increase the toxicity of caffeine (Stillner et al., 1978).

The Effects of Abstinence from Caffeine

Not only is there a now well defined set of symptoms occurring due to an excess of caffeine and other xanthines, but a specific set of symptoms has also been found to occur in excessive caffeine consumers following abstinence from caffeine. These symptoms include anxiety, muscle tension (White et al., 1980), an increase in reaction times (White et al., 1980), irritability, drowsiness, lethargy, malaise, inability to work effectively, impaired motor performance, nervousness, restlessness, feelings of discontent, mental depression, and headache. The latter symptom, the caffeine withdrawal headache, has been well documented (Dreisbach & Pfeiffer, 1943 ; Greden et al., 1980 ; Miller, 1960). Some eighteen hours after the last caffeine dose, a headache begins with feelings of fullness. This usually starts in the early afternoon and reaches its peak three to six hours later. The origin is usually at the back of the head, and it is intensified by bending over or by straining, by relaxation, and by exercise (Greden et al., 1980). The headache is often accompanied by rhinorrhea, mental depression, drowsiness and yawning, and disinclination to work. Persons who have experienced both migraines and the caffeine withdrawal headache report that the two are quite different (Dreisbach & Pfeiffer, 1943) ; and cases have even been reported where a distinct migraine may occur in the middle of a caffeine withdrawal headache (Dreisbach & Pfeiffer, 1943).

It should be noted that not all coffee drinkers who abstain will experience the caffeine withdrawal headache. Goldstein & Kaizer (1969 a) suggest that the people most likely to be afflicted are those who drink coffee because "it gives a lift" or "because I wake up." Those who drink coffee in the morning to relax appear to be the least likely to experience the withdrawal headache.

The Effects of Abstinence from Theophylline

The effects of abstinence from theophylline have not been well documented. However, due to theophylline's strong effect on the cardiovascular system and lesser effects on the brain, researchers may find that lethargy may be the predominant symptom of abstinence from moderate amounts of theophylline with only minor changes occurring in mood and mental functioning. Abstinence from very large doses may have the same type of effect as abstinence from moderate doses of caffeine.

The Psychological Effects of Caffeine

As will be discussed later in the review of the neuropharmacology of caffeine, caffeine affects transmission in the dopamine (DA) and norepinephrine (NE) pathways. If one knew only about the neuropharmacological effects of caffeine and the fact that the NE pathways are involved in emergency responses, euphoria and depression, and anxiety and tension, and that the DA pathways were concerned with emotions, pituitary released hormones, and somehow in schizophrenia, there might be certain predictions one could make about its behavioral consequences. For instance, if schizophrenic symptoms are relieved by blocking the DA pathways, we might predict that caffeine would exacerbate schizophrenic symptoms. Freitas & Schwartz (1979) have indeed reported this to be the case. They found that schizophrenics improved when caffeine consumption was decreased and that this was reversed when coffee was re-introduced. This has particularly serious implications for institutionalized schizophrenics who because of the extreme thirst induced by anticholinergic drugs or because of boredom, may drink large quantities of caffeine containing beverages (Stephenson, 1977). Whereas schizophrenics may deteriorate with caffeine consumption, unipolar depressives have been found to self-medicate with caffeine (Neil et al., 1978). In non-schizophrenic populations, psychotic episodes have been reportedly induced by high caffeine doses (McManamy & Schube, 1936 ; Mikkelson, 1978). These episodes abated after caffeine was withdrawn.

Furlong (1975) studied the charts of patients at the Clarke Institute who were consuming ten or more cups of coffee daily. These patients had frequent reports in their charts of behavioral disorders in childhood, impulsivity, school histories of failure, and learning disabilities. Of eighty-three hospitalized adult psychiatric patients, twenty-two percent were reported to be high caffeine consumers (750 mg. or more per day). Those with the highest caffeine consumption were also those with higher scores on the State-Trait Anxiety Index and Beck Depression Scale. High consumers of caffeine have also reported greater use of sedative-hypnotics and minor tranquilizers (Greden et al., 1978). In a study by Winstead (1976), it was found that of a study of 135 psychiatric patients, those with the highest caffeine consumption (five or more cups a day) were significantly more likely to be diagnosed as psychotic. Greden (1974) and Molde (1975) found that patients with severe anxiety symptoms were relieved of these symptoms by abstinence from caffeine. Stillner et al. (1978) describe delirium and tremulousness produced in an adult consuming the equivalent of ten cups of coffee over a period of several hours.

Among college students, it was found that high caffeine consumption was associated with high anxiety levels, more depression, and lower grades (Gilliland & Andress, 1981). In a group of severely retarded aggressive inpatients who had a high caffeine intake, substitution of decaffeinated coffee brought about such large improvements in behavior that caffeine was permanently eliminated from their diets (Podboy & Mallory, 1977).

Of paticular interest are findings reported at a recent meeting of the World Federa-

tion of Neurology by Dr. Roy Mathew of Vanderbilt Medical School. This study measured changes in blood flow in the brains of 24 normal, healthy subjects given 250 mg. and 500 mg. of caffeine orally. With blood flow being monitored through the use of a radioisotope of Xenon gas, it was found that within 30 minutes after consumption, both doses of caffeine had reduced blood flow in all areas of the brain by about 20 to 25 %. Though the effects of this reduction in blood flow in normals has yet to be clarified, the implications may be clearer for patients with atherosclerosis who may already have cognitive impairment due to reduced blood flow in the brain. This effect of caffeine may also reduce the effectiveness of therapeutic drugs used in epilepsy and various forms of mental illness.

The Psychological Effects of Theophylline

Though theophylline does not appear to affect the brain to the same extent as caffeine, there are reports in the medical literature of affective disorders induced or exacerbated by the drug. Due to its effect on smooth muscle, theophylline is used as the primary ingredient of the majority of bronchodilators for asthma, emphysema, and chronic bronchitis. Wasser et al. (1981) report the case of a 58-year-old black woman with severe asthma who was hospitalized for evaluation of bizarre behavior (periods of mutism, unresponsiveness, flailing of limbs, posturing on all four extremities, intense emotional lability, incessant crying) following medication with 300 mg. to 500 mg. four times daily of theophylline. She had no history of neurologic or psychiatric illness. The abnormal behavior, tremor, and tachycardia declined systematically with the gradual withdrawal of the theophylline.

Murphy et al. (1980) report two cases of severe depression in patients being treated for bronchospasm with theophylline. A 19-year-old asthmatic girl with a previously stable personality became unaccountably depressed and irritable following administration of 225 mg. of theophylline twice daily. The affective symptoms disappeared upon withdrawal of the drug and reappeared when treatment was instigated again. The other case (Murphy et al., 1980) was an 11-year-old asthmatic with eczema and dyslexia. On a dosage of 225 mg. twice daily of theophylline, the subject became acutely depressed, had frequent episodes of crying, and on one occasion admitted to "wanting to take all the tablets and finish everything." No exogenous cause could be identified, and after theophylline was stopped, her depression disappeared immediately.

These cases illustrate two important points relevant to the present paper. The first is that theophylline, at least in high doses, can operate upon the affective areas of the brain. Whether similar though milder disorders occur with more moderate doses has, to the knowledge of the author, yet to be investigated.

The second point is the paradoxical effect of theophylline. In the adult subject, a bipolar disorder was evident, while depression was the primary symptom of the eleven-and nineteen-year old asthmatics. This paradoxical effect has also been reported for caffeine.

The Pharmacology and Neuropharmacology of the Xanthines and the Relationship to Stress

In times of stress the hypothalamus secretes corticotropin-releasing factors (CRF) which cause the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH). This ACTH circulates in the blood and reaches the adrenal cortex which is then stimulated to produce mineralocorticoids which regulate levels of minerals such as sodium, potassium, and chloride, and glucocorticoids which promote the conversion of stored proteins and fats to glucose. In addition, stress causes the hypothalamus to act by way of the sympathetic nervous system to stimulate the production of epinephrine (adrenaline) and norepinephrine (noradrenaline) by the adrenal medulla. Norepinephrine and epinephrine function to elevate blood pressure, increase cardiac output, elevate the basal metabolic rate, cause bronchial dilation and intestinal inhibition, produce glycogenolysis, hyperglycemia, CNS excitability, lipolysis, neutrophilia, and eosinopenia (Forsham, 1963). Another function of epinephrine and norepinephrine is to stimulate the anterior pituitary to secrete more ACTH.

The xanthines' effects upon the CNS are thought to be due to the inhibition of phosphodiesterase (Truitt, 1971 ; Ritchie, 1970 ;White et al., 1980). Phosphodiesterase is responsible for the breakdown of cyclic AMP (cyclic adenosine monophosphate) which is the second messenger of the brain whose levels are increased by the presence of norepinephrine (NE) or dopamine (DA) at the synapse (Iverson, 1979). When NE binds to the postsynaptic receptor, the enzyme adenylate cyclase is automatically switched on and begins to rapidly convert adenosine triphosphate (ATP) into cyclic AMP. Cyclic AMP then acts on the biochemical machinery of the cell to initiate the physiological (or psychological) response characteristic of the transmitter (Iverson, 1979).

Phosphodiesterase breaks down this cyclic AMP thus terminating the behavioral manifestations. Since cyclic AMP is the second messenger responsible for the behavioral effects of pathways involving dopamine (DA) and norepinephrine (NE), it might be useful to review the behavioral and physiological functions of these pathways.

As mentioned earlier, norepinephrine is the transmitter of the sympathetic nerves of the nervous system and thus mediates emergency responses such as acceleration of the heart, dilation of the bronchi, and elevation of blood pressure. The ventral NE pathway has terminals in the pleasure centers of the lateral hypothalamus and may subserve such affective behaviors as euphoria and depression. The dorsal NE pathway to the cerebral cortex may be associated with the control of alertness. Other NE pathways with cell bodies in the brain stem send axons down the lateral sympathetic column of the spinal cord. These spinal cord pathways may mediate emotional influences on muscle tone in such conditions as anxiety and tension (Snyder, 1980).

Dopamine (DA), is the transmitter in the corpus striatum where it is concerned with motor behavior. Blockade of DA action in other brain regions probably accounts for the therapeutic value of anti-schizophrenic drugs. Though the DA pathways are still poorly understood, they are believed to be involved in emotional behavior. DA cells in the arcuate nucleus of the hypothalamus with terminals in the median eminence

probably regulate the release of hypothalamic hormones which then act on the pituitary gland to regulate the release of pituitary hormones (Snyder, 1980). The net affect of the xanthines is thus to sensitize the postsynaptic catecholamine receptors by inhibiting the breakdown of cyclic AMP. Due to this sensitization of catecholamine receptors, it is not surprising that many of the sympathetically mediated symptoms occurring subsequent to stress have also been documented as occurring subsequent to xanthine ingestion. These include increases in the force of contraction of the heart, in heart rate, and in cardiac output. Other cardiovascular effects of the xanthines are the elevation of plasma free fatty acids (Graham, 1978), coronary dilation, an increase in blood pressure (Robertson et al., 1978), and peripheral vasodilation except in the brain where caffeine causes a marked decrease in cerebral blood flow (Bunker, 1979). There is also an increase in blood flow through the lungs due to the relaxation of arterial smooth muscles. In addition, the xanthines cause a measurable increase in the basal metabolic rate and an increase in body temperature (Friedman, 1944). They may also reduce the competence of the esophageal sphincter resulting in reflux and symptoms of heartburn (Bunker & McWilliams, 1979).

The xanthines' respiratory effects include the stimulation of oxygen consumption, as previously mentioned, an increased blood flow to the lungs, and an increased air supply to the lungs. There appears to be a direct effect upon the medullary respiratory center as well.

Gastrointestinal effects of the xanthines include coffee's stimulation of gastric acid secretion (Bunker & McWilliams, 1979), diarrhea due to phasic contraction of smooth muscle, and the inhibition of peristaltic activity in the stomach.

The xanthines act upon the nervous system by contracting skeletal muscles thus resulting in muscle twitches and muscle contraction. This is thought to be the basis of the restless-leg-syndrome (Lutz, 1978). As little as 225 mg. (a dose equivalent to 10 mg. of amphetamine sulphate) of caffeine was found to result in an 80 % increase in urinary adrenaline excretion and a 19 % increase in urinary noradrenaline excretion (Levi, 1967). In young volunteers, a 250 mg. dose increased plasma adrenaline levels by 200 % (Robertson et al., 1978).

It should be noted that all of these effects are the same as those of the "fight or flight" reaction which occurs in times of stress or fear. Research with human populations is needed to clarify the relationship, but all the evidence reviewed in this paper would appear to suggest that caffeine and theophylline in large doses produce physiological and possibly psychological changes equivalent to those produced by moderate to severe stress. The effects of acute, chronic stress upon the body predispose the individual to disease and any number of problems including hypertension (Kaplan, 1978), strokes, heart failure, liver and kidney disease, and possibly cancer. Though to the author's knowledge, no research has investigated the xanthines as the equivalent of stress in humans, there is some evidence from animal studies to support this relationship. Psychosocially stressed male mice develop hypertension, cardiovascular damage, chronic interstitial nephritis, increased levels of plasma renin, noradrenaline,

corticosterone, and adrenal-catecholamine synthetic enzymes, and die prematurely. Henry & Stephens (1980) found that caffeine added to the diets of stressed mice enhanced the stimulation of the neuroendocrine system resulting in further increases in plasma renin, corticosterone levels, blood pressure, and adrenal weight. These effects together with accelerated mortality and increased pathology resulted in the conclusion by Henry & Stephens that chronic consumption of caffeinated liquids adds to the risks of psychosocial stress.

Watson et al. (1980) found that caffeine administered to stress-susceptible pigs triggered the porcine stress syndrome in seven of the eight of those genetically predisposed. Evidence exists that the effects of caffeine are intensified during stressful situations (Stillner et al., 1978). Whether this effect is additive or synergistic is as yet unknown, but in some people, the consequences of a combination of the two in conjunction with heredity may be severe. There is even some evidence that caffeine consumpton may increase in times of stress (Furlong, 1975 ; Mikkelson, 1978). Though no explanation has been offered for this, it may be related to the mood elevating effects mediated by dopamine and norepinephrine pathways in the brain. The author is familiar with several anecdotal cases of this kind where a severe stressor was followed by increased coffee consumption, and the subsequent development of a physical ailment. The possible relationship between stress, increased caffeine consumption, and the development of disease in humans would appear to deserve investigative research. Though better controlled studies are needed, the finding of Minton et al. (1979) that 65 % of the women with benign breast disease who eliminated all methylxanthines from their diet experienced complete resolution within six months adds some support to the suggested relationship.

The Sources of Caffeine

The xanthines are potentially dangerous due to the fact that ingestion of any one of them can affect the toxicity of the others. Though there are six major xanthines (aminophylline, caffeine, dyphlline, oxtriphylline, theobromine, and theophylline), our discussion centers on caffeine and theophylline as these are the most common methylxanthines found in beverages and drugs. Though they all share common effects, the most common xanthines (caffeine, theophylline, and theobromine) differ in the intensity of their effects on the various systems of the body. Caffeine has the greatest affect on the CNS, theophylline has its greatest effect on the cardiovascular system, and theobromine has no effect on the CNS but is the most powerful diuretic (Miller, 1960).

Tables 1-12 list the xanthine content of many common food and drug products in North America. Though information on the theophylline content of tea and its relative effects in combination with caffeine are lacking, tea does contain both caffeine and theophylline. As can be seen from Table 1, the caffeine content of tea differs with the length of brewing time and the type of tea with green tea containing less caffeine. Iced tea, which is often consumed in large quantities by children and adults during the summer, contains caffeine equal to that found in many colas and soft drinks. Tea

drinkers wishing to cut down on their caffeine consumption can do so by shortening brewing time and using green or instant tea.

As with tea, the caffeine content of coffee varies with the method of preparation (Table 2). Automatic drip contains the highest levels of caffeine, followed by percolated, instant and finally decaffeinated. Gilbert (1976 a) has warned, however, that some types of coffee, such as espresso can contain as much as 333 mg. of caffeine per cup. Gilbert (1976 b) also found that home brewed coffee may be generally weaker than the coffee served in restaurants and institutions.

Cocoa products (Table 3) contain both caffeine and theobromine. A small chocolate bar contains approximately 25 mg. of caffeine and a chocolate drink can contain anywhere from 6 to 142 mg. Milk chocolate has been reported to contain around 6 mg. per 10 oz. serving while Ovaltine has only trace amounts.

Table 4 lists the caffeine content of many of the leading colas and soft drinks in the U. S. and Canada. As can be seen, the standard size of cola and soft drink cans differs between the two countries ; Canada uses 280 ml. (9.3 oz.) cans while the U. S. uses 360

Table 1 Caffeine content of tea

TEA, TYPE	AMOUNT OF CAFFEINE PER 5 OZ./150 ML. SERVING
Brewed 1 min.	9-33 mg.
Brewed 3 min.	20-46 mg.
Brewed 5 min.	20-50 mg.
Black	50 mg.
Green	30 mg.
Iced Tea (12 oz./360 ml. cans)	22-36 mg.
Instant	30 mg.

Table 2 Caffeine content of various types of coffee.

COFFEE, TYPE	AMOUNT OF CAFFEINE PER 5 oz./150 ml. SERVING
Automatic drip	110-150*mg.
Percolated	64-124 mg.
Instant	40-108 mg.
Decaffeinated, brewed	2-3 mg.
Decaffeinated, instant	——

* Some types of coffee, such as espresso can contain as much as 333 mg. per cup (Gilbert, 1976 a)

Table 3 Caffeine content of cocoa products.

COCOA PRODUCT	CAFFEINE CONTENT	SIZE OF SERVING
Chocolate bar	25 mg.	small bar
Chocolate drink	6-142 mg.	6 oz./180 mg.
Milk Chocolate	6 mg.	10 oz./300 mg.
Ovaltine	traces	——

ml. (12 oz.) cans. No information could be found on whether the caffeine content of drinks in cans differed from soda fountain drinks. Another difference between the two countries is the fact that in Canada caffeine is found only in cola beverages, while in the U. S. it can be found in non-cola drinks such as Mello Yellow, Mountain Dew, and Sunkist Orange. As a recent Consumer Reports article noted, the amount of caffeine added to soft drinks and colas is added at the discretion of the manufacturers as long

Table 4 Caffeine content of the leading soft drinks.

PRODUCT	CANADA 280 ml, cans (@ 9.3 oz.)	U. S. 360 ml. cans (12 oz.)	MILLIGRAMS PER 100 ml. CANADA	U. S.	REFERENCE
Coca cola	–	34 mg.	–	9.44	Consumer Reports
	–	64 mg.	–	17.97	Bunker, 1979
	28 mg.	–	10	–	Coca Cola Canada
Cragmont Cola	–	traces	–	+	Consumer Reports
Diet Coke	33.4 mg.	–	12	–	Coca Cola Canada
	–	+	–	+	
Diet Dr. Pepper	–	54.2 mg.	–	15.06	Bunker, 1979
	–	37 mg.	–	10.3	Dr. Pepper Canada
	not manuf	–	–	–	
Diet Mr. Pipp	not manuf	52 mg.	–	14.4	Consumer Reports
Diet Pepsi	27.6 mg.	–	9.86	–	Pepsi Cola Co.
	–	34 mg.	–	9.4	Consumer Reports
Diet RC	–	33 mg.	–	9.17	Bunker, 1979
Diet Rite	–	31.7 mg.	–	8.81	Bunker, 1979
	–	34.0 mg.	–	9.4	Consumer Reports
	27.9	–	9.9	–	RC Cola Canada
Dr. Pepper	–	38 mg.	–	10.5	Consumer Reports
	–	60.9 mg.	–	16.9	Bunker, 1979
	33.6 mg.	–	12.0	–	Dr. Pepper Canada
Mello Yello	–	51 mg.	–	14.16	Consumer Reports
	0	–	0	–	Coca Cola Canada
Mountain Dew	0	–	0	–	Pepsi Canada
	–	54 mg.	–	15.19	Bunker, 1979
Mr. Pipp	not manuf	33 mg.	–	9.16	Consumer Reports
Pepsi	30.6 mg.	–	10.91	–	Pepsi Canada
	–	43.1 mg.	–	11.98	Bunker, 1979
	–	37 mg.	–	10.3	Consumer Reports
Pepsi Light (Pepsi Free)	–	traces	–	+	
	traces	–	+	–	Pepsi Canada
RC Cola	–	33.7 mg.	–	9.36	Bunker, 1979
	–	36.0 mg.	–	10.0	Consumer Reports
	27.9 mg.	–	9.9	–	RC Cola Canada
Shasta Cola	not manuf	42 mg.	–	11.66	Consumer Reports
Sunkist Orange	–	42 mg.	–	11.66	Consumer Reports
Tab	28.0 mg.	–	10.0	–	Coca Cola Canada
	–	49.2 mg.	–	13.72	Bunker, 1979
	–	44.0 mg.	–	12.2	Consumer Reports

as it does not exceed the upper limit set by the government.

Listed in Table 5 are many of the popular North American drinks which do not contain caffeine. As noted previously, non-cola drinks in Canada have no caffeine added.

All major over-the-counter stimulant/stay-awake preparations have caffeine as either their primary or sole ingredient (Table 6). It is clearly possible to ingest very large amounts of caffeine through use of these preparations.

Another source of relatively large amounts of caffeine are the appetite suppressants (Table 7). Achor & Extein (1981) recently reported several cases of the exacerbation of mania and the precipitation of affective illness by appetite suppressants. All three patients had histories of minor affective disorders (postpartum dysphoria ; mood irritability & impulsivity ; bipolar affective disorder) which had not required hospitalization until diet aids exacerbated them. Though caffeine fatalities are rare, one such

Table 5 List of some of the soft drinks which contain NO caffeine

PRODUCT	CAFFEINE CONTENT
Diet Seven-Up	0
Diet Sunkist Orange	0
Fanta Orange	0
Fresca	0
Ginger Ale	0
Hires Root Beer	0
Mello Yellow	0 (Canada only)
Mountain Dew	0 (Canada only)
Patio Orange	0
Pepsi Free	0 (traces only)
RC 100	0
Seven-Up	0
Sprite	0
Teem	0
Caffeine-Free Diet Coke	0

Table 6 Caffeine content of nonprescription stimulant products.

PRODUCT	MANUFACTURER	CAFFEINE CONTENT
Amostat tablets	(North American)	100 mg.
Caffedrine	(Thompson)	250 mg.
Double-E Alertness Capsules	(Keystone)	180 mg.
NoDoz Tablets	(Bristol-Myers)	100 mg.
Prolamine Capsules	(Thompson)	140 mg.
Quick-Pep Tablets	(Thompson)	150 mg.
Tirend Tablets	(Norcliff-Thayer)	100 mg.
Verb T. D. Capsules	(American Pharm)	200 mg.
Vivarin Tablets	(J. B. Williams)	200 mg.
Wakoz	(Jeffrey Martin)	200 mg.

SOURCE : *Handbook of Nonprescription Drugs*, 1977

case following ingestion of over-the-counter appetite suppressants by a 19-year-old female has been reported (McGee, 1980).

As can be seen from Table 8, a large number of nonprescription analgesics contain caffeine. The caffeine content ranges from 15 mg. to 100 mg. Walker (1977) has questioned the value of caffeine in mixtures for relief of pain and headache except in

Table 7 Caffeine content of some nonprescription appetite suppressants.

PRODUCT	MANUFACTURER	CAFFEINE CONTENT
Anorexin Capsules	(Thompson)	100 mg.
Appedrine Tablets	(Thompson)	100 mg.
Dexatrim Capsules	(Thompson)	200 mg.
Odrinex Tablets	(Fox)	50 mg.
Prolamine Capsules	(Thompson)	140 mg.
Spantrol Capsules	(North American)	150 mg.(anhydrous)

SOURCE : *Handbook of Nonprescription Drugs*, 1977

Table 8 Caffeine content of some nonprescription analgesics.

PRODUCT	MANUFACTURER	CAFFEINE CONTENT
Anacin	(Whitehall)	32.5 mg.
Anodynos	(Buffington)	+
A. S. A. Compound	(Lily)	32.5 mg.
BC Tablets	(Block)	16.0 mg. Tablet
Powder		33 mg. Powder
Bromo-Seltzer	(Warner-Lambert)	32.5 mg./capful
Capron Capsules	(Vitarine)	32 mg.
Comeback	(Norcliff-Thayer)	100 mg.
Cope	(Glenbrook)	32 mg.
Dolor	(Geriatric Pharm.)	30 mg.
Duradyne	(O'Neal, Jones & Feldman)	15 mg.
Emagrin	(Otis Clapp)	+
Empirin Compound	(Burroughs Wellcome)	32 mg.
Excedrin	(Bristol-Myers)	64.8 mg.
Goody's Headache Powder	(Goody's)	32.5 mg.
Maranox	(Dent)	15 mg.
Medache	(Organon)	32 mg.
Nilain	(A. V. P.)	32.5 mg.
PAC	(Upjohn)	32 mg.
Panodynes Analgesic	(Keystone)	16.2 mg.
S-A-C	(Lannett)	30 mg.
Sal-Fayne Capsules	(Smith, Miller, Patch)	32 mg.
S. P. C.	(North American)	16.25 mg
Stanback Tablets	(Stanback)	16 mg. Tablet
Powder		32 mg. Powder
Trigesic	(Squibb)	30 mg.
Vanquish Caplet	(Glenbrook)	33 mg.

SOURCE : *Handbook of Nonprescription Drugs*, 1977

those cases where vascular headaches are involved.

Table 9 lists the major menstrual products containing caffeine with the caffeine content ranging from 16.2 mg. to 100 mg. per tablet. In these types of preparations caffeine is probably meant to serve the dual functions of an analgesic and a diuretic. The possibility exists that some of the symptoms of the premenstrual syndrome may be either caused or exacerbated by this type of caffeine-containing product.

Cold remedies can be another source of caffeine though they may not contain as much caffeine as the appetite suppressants, premenstrual medications, and stimulants. Values in this category range from 15 mg. to 30 mg.

Table 11 lists the major caffeine-containing U. S. prescription drugs[1)] as listed in the 1982 *Physicians' Desk Reference*. These products are prescribed for a range of different problems including tension headache, vascular headaches, fatigue, etc. Caffeine content ranges from 30 mg. to 100 mg. per tablet.

Table 9 Caffeine content of some nonprescription menstrual products.

PRODUCT	MANUFACTURER	CAFFEINE CONTENT
Aqua-Ban	(Thompson)	100 mg.
Femcaps Capsules	(Buffington)	+
Femicin	(Norcliff-Thayer)	65 mg.
Flowaway Water 100's	(DeWitt)	20 mg.
Midol	(Glenbrook)	32.4 mg.
Odrinil	(Fox)	extract, 16.2 mg.
Pre-Mens Forte	(Blair)	100 mg.

SOURCE : *Handbook of Nonprescription Drugs*, 1977

Table 10 Caffeine content of nonprescription cold and allergy products.

PRODUCT	MANUFACTURER	CAFFEINE CONTENT
Andodynos Forte	(Buffington)	+
BC All Clear	(Block)	32 mg.
Cenagesic	(Central)	15 mg.
Coricidin	(Schering)	30 mg.
Coryban-D	(Pfipharmecs)	30 mg.
Dristan Tablets	(Whitehall)	+
Duadacin	(Hoechst-Roussel)	30 mg.
Duradyne-Forte	(O'Neal, Jones, Feldman)	30 mg.
Euphenex	(O'Neal, Jones, Feldman)	15 mg.
Fendol	(Buffington)	+
Hista-Compound No. 5	(North American)	32.5 mg.
Midran Decongestant	(Columbia Medical)	32.5 mg.
Neo-Synephrine	(Winthrop)	15 mg.
Pyrroxate	(Upjohn)	32.5 mg.
Sinarest	(Pharmacraft)	30 mg.
Super Anahist	(Warner-Lambert)	+
Triaminicin	(Dorsey)	30 mg.
Valihist	(Otis Clapp)	+

SOURCE : *Handbook of Nonprescription Drugs*, 1977

Table 11 Caffeine content of various prescription drugs.

PRODUCT	MANUFACTURER	CAFFEINE CONTENT
A. P. C. w/Butalbital	(Purepac)	+
A. P. C. w/Codeine	(Burroughs Wellcome)	32 mg.
Apectol Tablets	(Legere)	40 mg.
Buff-A Comp Tablets	(Mayrand)	40 mg.
Butalbital w/APC	(Premo)	+
Cafamine T. D. Capsule	(Legere)	75 mg.
Cafergot	(Sandoz)	100 mg.
Cafergot P-B	(Sandoz)	100 mg.
Cetased, Improved	(Wesley)	40 mg. (USP)
Efed II	(Alto)	125 mg.
Emprazil Tablets	(Burroughs Wellcome)	30 mg.
Emprazil-C	(Burroughs Wellcome)	30 mg.
Esgic Tablet & Cap.	(Gilbert)	40 mg. (USP)
Excedrin	(Bristol-Myers)	65 mg.
Fiorinal	(Sandoz)	40 mg. (USP)
Fiorinal w/Codeine	(Sandoz)	40 mg. (USP)
G-1 Capsules	(Hauck)	40 mg.
Medigesic Plus Cap.	(U. S Chemical)	40 mg.
Migral Tablets	(Burrough Wellcome)	50 mg.
Milgaralam Capsules	(Lambda)	100 mg.
NoDoz	(Bristol-Myers)	100 mg.
Pacaps	(LaSalle)	40 mg.
Repan Tablets	(Everett)	40 mg. (Anhydrous)
Rogesic Capsules	(Rotex)	40 mg.
SK-65 Compound Cap.	(Smith, King & French)	32.4 mg.
Soma Compound	(Wallace)	32 mg.
Soma Compound w/codeine	(Wallace)	32 mg.
Synalgos Capsules	(Ives)	30 mg.
Synalgos-DC	(Ives)	30 mg.
T-Gesic	(Williams)	40 mg.
Vanquish	(Glenbrook)	33 mg.

SOURCE : *Physicians' Desk Reference*, 1982

The final important source of the xanthines are drugs used in the treatment of asthma. Table 12 lists the amounts of theophylline found in major over-the-counter asthma products. As mentioned earlier, ingestion of any one of the xanthines can affect the toxicity of the others, therefore, in determining a person's intake, this type of product should be taken into consideration. In addition to these nonprescription asthma products, the majority of prescription bronchodilator products contain some form of theophylline or another of the lesser known xanthines. These drugs are administered in the form of injections, oral doses, and suppositories. Drug reference manuals for physicians are very specific about warning that patients using these bronchodilator products should avoid the ingestion of other xanthine products.

Table 12 Theophylline content of some nonprescription asthma products.

PRODUCT	MANUFACTURER	THEOPHYLLINE CONTENT
Asma-Lief	(Columbia Medical)	130 mg.
Bronitin	(Whitehall)	130 mg.
Bronkaid	(Breon)	100 mg. (anhydrous)
Bronkotabs	(Breon)	100 mg.
Phedral	(North American)	129.6 mg.
Primatene M	(Whitehall)	130 mg.
Primatene P	(Whitehall)	130 mg.
Tedral	(Warner-Chilcott)	130 mg./tablet (anh) 32.5 mg/5 ml elixir 65 mg./5 ml suspen.
Thalfed	(Beecham Labs)	120 mg. (hydrous)
Verequad	(Knoll)	130 mg./tablet 65 mg./5 ml (as calcium salicylate)

SOURCE : *Handbook of Nonprescription Drugs*, 1977

At Risk Xanthine Consumers

The widespread psychological and physiological effects of the xanthines put a number of populations at risk. Caffeine's interference with blood-glucose regulation (Gilbert, 1976 a) by insulin contraindicates caffeine in any form for diabetics. There has been found to be a decreased tolerance to caffeine and theophylline accompanying normal aging (Stephenson, 1977) ; this combined with the reduced effectiveness of tissues and organs of the body and the reduced ability to adapt to stress should discourage xanthine intake in this group. Whereas adult nonsmokers with uncomplicated asthma may have a theophylline half-life of 7 to 9 hours, elderly adults with chronic obstructive pulmonary disease, corpulmonale, or other causes of heart failure or liver pathology may have a theophylline half-life lasting 24 hours or longer (USPDI, 1981). Another clear contraindication is the use of caffeine in glaucoma patients. Graeber (1968) found that 300 mg. of caffeine can raise the intraocular pressure by a considerable amount when the glaucoma is unregulated. The rise in blood pressure and the abnormal contraction of the heart produced by the xanthines' effect on the pituitary and subsequently the sympathetic nervous system would appear to discourage its use by heart patients and those with high blood pressure. Liver (including alcoholics),kidney, and gastrointestinal patients are also likely to be adversely affected by caffeine. Those with pulmonary edema or concurrent infection also have slower clearance rates of theophylline as do patients taking certain antibiotics (erythromycin, troleandomycin, clindamycin, linomycin). Another factor which has been found to affect the elimination of caffeine is the use of oral contraceptive steroids. Patwardhan et al. (1980) found that steroid contraceptives impaired the elimination of caffeine. The clearance rates in women not using this type of contraceptive were the same as those found in men.

As reviewed earlier, the xanthines exacerbate schizophrenic and psychotic symp-

toms as well as various affective disorders. In large doses they may even precipitate psychotic episodes in otherwise normal people. Thus, caffeine and theophylline might well be eliminated from the diet of patients of this type. People under extreme stress are also likely to have their condition exacerbated by excess amounts of the xanthines; therefore, those undergoing any type of extreme psychological or physiological stress might best avoid consumption of xanthine-containing products.

Another population and one more difficult to describe is made up of those who are xanthine-sensitive. The characteristics of this group have yet to be clearly defined but may include those who become nervous easily and who are normally "high strung" and emotional. There is some evidence to suggest that females are more affected by caffeine (Gilliland & Andress, 1981) and the female who becomes nervous easily, is under a lot of stress, and who generally leads a fast-paced existence might also eliminate or drastically reduce the caffeine in her diet for relief of stress related symptoms.

The last population and the one which may be the greatest at risk psychologically are the children. As with the cases of theophylline induced depression mentioned earlier, caffeine has been found to be paradoxical with it having a calming effect on certain hyperactive children. This has not been found to be true of all hyperactive children, however, and the evidence has unfortunately been used to play down the adverse effects caffeine may have on them. Neumann (1979) mentions a survey conducted of "hyperkinetic" children in New Haven, Connecticut which found all such children to be consumers of caffeinated drinks. A recent study by Elkins et al. (1981) comparing amphetamines and caffeine found that caffeine increased motor activity in prepubertal males. Silver (1971) has reported the disappearance of tachycardia (heart palpitations) in one child and of insomnia in another when colas were withdrawn from their diets. Far more research is needed, but undoubtedly the same individual CNS differences in sensitivity exist in children as in adults. This sensitivity combined with the fact that for a child the same effects are produced by half the adult dose bring into question the advisability of allowing children to drink coffee, large amounts of xanthine-containing beverages, and consume large amounts of chocolate. The parents of children being treated for asthma should be particularly careful and eliminate all xanthines from their child's diet if the child is using bronchodilators containing theophylline. While caffeine may relieve hyperactivity in some, it may even induce it in others. Pediatricians have expressed concern over the caffeinism in children and teenagers as manifested in the symptoms of restlessness, irritability, sleeplessness, and nervousness (Manber, 1976). Children and teenagers experiencing these symptoms will undoubtedly be experiencing the depression as well, and the caffeine consumption of suicidal children might well deserve investigation.

An added warning may come from the research finding that theophylline, theobromine, and caffeine affect the anterior pituitary and thyroid function of rats by causing the release of hypothalamic somatostatin which inhibits Growth Hormone (GH) and Thyroid Stimulating Hormone (TSH) secretion (Spindel et al., 1980).

It is not only the children and infants who may be adversely affected by caffeine, but neonates as well. The Surgeon General of the United States recently warned that pregnant women should eliminate caffeine from their diets as caffeine has been found to cross the placental barrier (Horning et al., 1973) and can adversely affect the unborn child. Though the way in which the xanthines may affect the fetus have yet to be clearly determined, the study of the effects of caffeine on the GH and TSH hormones cited above and the following study suggest two possibilities.

Enslen et al. (1980) have demonstrated that the first generation of rats whose mothers had had caffeine added to their diets showed increases in paradoxical sleep and markedly reduced dopamine levels in the locus coeruleus. Though dopamine levels were reduced, noradrenaline levels remained unchanged. These effects were less pronounced in the second generation.

Mothers breast-feeding their infants should also avoid coffee, tea, and other xanthine-containing products as caffeine and theophylline are secreted in their milk.

The half-life of theophylline in infants (0 to 6 months) is more than 24 hours. In a study of theophylline clearance by age, Grygiel & Birkett (1980) found that premature neonates eliminate unchanged theophylline and caffeine in their urine, indicating the absence of oxidative pathways for theophylline metabolism. Another study by Brazier et al. (1980) found that theophylline given to premature neonates was converted to caffeine. This metabolic pathway is the inverse of adults in whom caffeine is demethylated to give theophylline.

Banner & Czajka (1980) describe caffeine overdose in three full-term neonates following the administration of large doses of caffeine and benzoate sodium for respiratory depression. The infants exhibited one or more of the following symptoms : tachypnea, fine tremor of the extremities, opisthotonus, tonic-clonic movements, and nonpurposeful jaw and lip movements. These symptoms suggested neonatal seizures and prompted therapy with anticonvulsants. Though these symptoms were caused by rather large doses (36 to 136 mg/kg) administered directly to the infants, less severe but similar symptoms may possibly be induced by large amounts of xanthines crossing the placenta or reaching the infant in the mother's milk.

Given the widespread psychological and physiological effects of caffeine, it would appear to be advisable to take advantage of the recent proliferation of caffeineless beverages and eliminate caffeine from children's diets altogether.

What is a High Dose of the Xanthines?

Given all these adverse effects, what would be considered a"safe" dose. For the "at risk" populations mentioned above, the answer may be a dosage of 0 mg. For normal healthy adults, the answer is far less clear. The great individual variations in sensitivity seriously cloud the issue. As a starting point, let us cite the conclusion of Gilbert (1976 a) that a person ingesting upwards of 600 mg. of caffeine a day [ie. 2 cups of espresso, or 4 cups of some institutional automatic drip, or 6 cups or some instant coffees, or 3 Vivarins] is possibly more likely than normal to die of heart disease,

ulcers of the stomach and duodenum, and carcinomas, especially of the kidneys and urinary tract. They are also more likely than normal to experience headaches, insomnia, difficulty in and dysphoria on waking, and a constellation of symptoms indistinguishable from anxiety (Gilbert, 1976 a). As is evident from the case cited at the beginning of the article, individual sensitivity may cause the individual to experience a constellation of adverse symptoms at doses of around 300 mg., the equivalent of one cup of coffee, a headache remedy, and a premenstrual medication. At the extreme end of the continuum are those allergic to caffeine. In these people, symptoms can be so severe as to incapacitate patients for several years (Finn & Cohen, 1978). Due to this wide variation in sensitivity and the large number of factors (stress, age, sex, health, medications, season, etc.) affecting the strength of the xanthines, care should be taken in recommending a "safe" dose as the "safe" dose for one person may induce borderline psychosis and high blood pressure in another.

Recommendations for Physicians, Clinicians, and Researchers

The suggestion of the present paper is that the xanthines affect the individual in much the same way as either physiological or psychological stress. The similarity between the two may result in a diagnosis of psychosomatic disease when an excess of or abstinence from caffeine or possibly theophylline is the actual cause. Physicians, psychiatrists, and clinicians should determine the amount of caffeine and theophylline consumed in all forms as a matter of course. Those cases especially likely to be related to caffeine are those with daily morning headaches, those that report that coffee is good for their headache, those who develop a headache following abstinence from caffeine, those that get relief from caffeine containing analgesics, and those with coronary and various psychophysiological symptoms. The clinician should remember that the depression, loss of esteem, and lethargy caused by abstinence and the uncontrollable thoughts, impulsiveness, compulsive behavior, and even psychosis, caused by caffeine excess can closely mimic naturally occurring states. As Greden et al. (1980) have suggested, once caffeine has been determined as the source of the negative symptoms, the person should be educated as to the cause and should be fully educated as to the sources of the caffeine and the other xanthines, their effects on the body, the consequences of continued use, and the various unpleasant symptoms which may accompany withdrawal. The person should also be counseled to avoid caffeine containing analgesics.

Psychophysiologists doing research in arousal, skin conductance, heart rate, etc. may want to control for xanthine intake. In the second testing of the skin conductance of some subjects, this author found considerable increases when decreases would have been expected due to habituation to the task. Questioning revealed that the subjects had drunk a cup of coffee just before the second testing and had had none before the first one (both sessions were at the same time of day).

Another pitfall which researchers, both in medicine and psychology, must avoid is the paradoxical effects of caffeine and theophylline in different individuals. The

xanthines clearly arouse some while they may cause depression in others. There is thus a pressing necessity to delineate more clearly the characteristics of these two groups of individuals. Uncontrolled for, this factor can seriously impede our understanding of both the affects of the xanthines and other types of drugs as well. The relationship this paradoxical effect holds to individual sensitivity is yet unclear. It is clear, however, that caffeine's effects do not vary linearly (Victor et al., 1981).

Yet another factor capable of confounding results at the time of subject selection is something which Goldstein encountered in his research. He found that many abstainers from caffeine were either reluctant or refused to participate in his study (Goldstein & Kaizer, 1969 a). These abstainers may very well be those who have discovered that they are particularly sensitive to caffeine's negative effects and thus avoid it. Excluding this group from study will seriously affect the generalization of results.

Conclusions

Caffeine is a drug. The body develops a need for it, and abstinence from it is followed by a number of adverse psychological and physiological symptoms including mental depression, feelings of discontent, anxiety, irritability, lethargy, inability to work, nervousness, restlessness, headache, increased muscle tension, and increased reaction times (slower responding). Though research is needed to confirm the exact relationship, caffeine and theophylline appear to have almost the identical effect on the body as that of stress. Certainly the effects on the sympathetic nervous system mimic those of a stimulus inducing the "fight or flight" reaction. Greater investigation is needed to determine if chronic xanthine consumption may predispose the body to various diseases in the same way as prolonged stress.

The psychological and physiological effects of caffeine reviewed suggest that certain populations including patients with hyperthyroidism, glaucoma patients, heart patients, patients being treated with certain antibiotics, hypertensive patients, diabetics, alcoholics ; liver, kidney, lung, and gastrointestinal patients ; the elderly ; and children should avoid caffeine altogether. It was also recommended that persons under stress and certain xanthine-sensitive individuals greatly curtail their intake of caffeine and theophylline. Though more research is needed, women taking certain types of birth control pills may also wish to reduce their xanthine intake. The caffeine-sensitive population may possibly contain more females, but the exact character of this group has yet to be determined. It has also been suggested that individuals who have recently quit smoking may lessen the nicotine withdrawal symptoms by curtailing their consumption of caffeine containing products.

The issue of the "safe" dosage of caffeine was discussed and the conclusion was reached that great caution should be taken in specifying an exact dose as factors such as stress, age, sex, drug treatment, etc. can interact with individual sensitivity to make one person's "safe" dose another's ticket to psychosis.

The recommendation was made that physicians and clinicians determine the caffeine intake from all sources as a matter of routine.

Based on the evidence presented in this paper, it is not difficult to understand why the majority of the countries with the highest mortality rates from heart disease and renal cancer also happen to be those with the highest xanthine consumption (Gilbert, 1976 a).

FOOTNOTES

1) It should be noted that product names differ considerably in Canada and this list should not be used as a reference list for Canadians.

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