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Caffeine Use Before, During and After Pregnancy
and Associated Effects in the Offspring

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Thesis presented to the Faculty of Graduate Studies of
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requirements for the degree of Master of Arts in Psychology.

Ottawa, August, 1983

The undersigned hereby recommend to the Faculty of
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Abstract

Caffeine consumption by both the male and female may have adverse effects on the offspring. The purpose of this study was to investigate maternal caffeine habits before, during, and after pregnancy as well as paternal caffeine intake before pregnancy, and to explore the effects of reported caffeine use on mother and child. The sample of subjects consisted of 286 women from the Ottawa area, who were a subsample of 623 volunteers involved in the Ottawa Prospective Prenatal Study investigating the effects of soft drug use during pregnancy. By means of a questionnaire, data on maternal use of tea, coffee, cola-drinks, chocolate bars and drinks, and medication were collected in a retrospective manner for before, during and after pregnancy. Information regarding variables such as cup or portion size, method of preparation, strength and use of decaffeinated products was requested. Paternal caffeine consumption before pregnancy was estimated from typical intake of caffeinated or decaffeinated coffee. Fifty-three samples of coffee and tea as consumed by the mother were analysed for caffeine concentration in an effort to establish appropriate values for determining the amount of caffeine in cups as described. As part of the Ottawa Prospective Prenatal Study, information regarding maternal use of alcohol and

tobacco before and during pregnancy was available as well as data on infant characteristics and maternal socioeconomic status, age, weight, parity, gravida and medical history.

Caffeine use by both males and females is common. During pregnancy fewer women but still a majority continue to consume caffeine but usually at lower intake levels. After pregnancy, caffeine consumption tends to persist at reduced levels for several months and then to resume prepregnancy patterns. Heavier maternal caffeine intake of more than 300 mg daily during pregnancy was associated with lowered birth weight and head circumference of the infant after accounting for maternal nicotine use. No relationship was apparent between maternal caffeine use and the incidence of caesarian sections, breech births, miscarriage, premature births or infant apnea.

In conclusion, the results indicate that heavy caffeine use is not common during pregnancy but that intake levels of over 300 mg daily may be associated with reductions in infant birth weight and head circumference.

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Introduction

Caffeine is one of the world's most widely used drugs. Research has shown that more than 90 percent of adults in Ontario consume caffeine daily (Gilbert, 1976). Its long-standing use in the common beverages of tea, coffee and soft-drinks promotes an acceptance in the typical North American diet. Potential risks associated with caffeine consumption are difficult to ascertain because of problems in assessment of intake and separation from the effects attributable to the strongly correlated habits of alcohol use and smoking (Kuzma & Kissinger, 1981). Nevertheless, the need is pressing to evaluate caffeine's role in human health and reproduction. In spite of the difficulties associated with caffeine research, the somewhat ambiguous results of animal and human studies prompted the United States Food and Drug Administration, in November, 1980, to issue a warning to pregnant women to avoid or limit consumption of caffeine-containing products.

The present study concentrates on the use of caffeine before, during and after pregnancy and associated effects in the fetus and neonate, while recognizing the influence of other concomitant variables such as maternal alcohol and nicotine use, maternal age, weight and socio-economic class.

The multiple dietary sources of caffeine are first

considered followed by an investigation into the prevalence of caffeine use, changing habits in pregnancy and caffeine's association with other drug habits. General physiological and psychological effects of caffeine are outlined as well as caffeine's possible modes of action.

In order to study potential exposure to caffeine the absorption, distribution, metabolism and excretion of caffeine in man, in the pregnant woman, the fetus, the neonate and the breast-fed infant are investigated. Although the importance of caffeine laboratory studies with animals is recognized, the difficulties with extrapolating to the human condition are emphasized and a brief summary of major reproductive effects of varying doses of caffeine with animals is outlined. Most of the caffeine research with humans has been recent and the reproductive findings are reported in a comprehensive manner with an attempt to look for consistencies across human and animal studies. Evidence suggesting male-mediated effects of caffeine use in reproduction is discussed. Although caffeine's potential for provoking mutagenesis and teratogenesis is noted, the outcome variables of major concern in the present study are infant apnea, birth weight, gestation, and incidence of miscarriage.

Dietary Sources of Caffeine

Caffeine is present in coffee, tea, cocoa, soft-drinks, chocolate and some medications (see Table 1). Assessment of an individual's caffeine intake presents methodological problems because of variation in the caffeine content of dietary sources due to brand, portion or cup size, method of preparation, preferred strength and use of decaffeinated products. Many studies have approximated daily caffeine intake by multiplying the number of cups of coffee consumed daily by the average amount of caffeine in a cup of coffee. Although a positive correlation exists between coffee intake and caffeine intake (Gilbert, 1976), the tremendous variation of caffeine in tea and coffee and the contribution of other caffeine-containing products must be considered in calculation of caffeine intake. Emphasis needs to shift from beverage consumption to caffeine consumption before definitive statements can be made about the effects of caffeine.

Caffeine in coffee. Caffeine content in a cup of regular coffee has been estimated to vary from 14 to 333 mg (Gilbert, Marshman, & Schwieder, 1976). Decaffeinated coffee contains usually from one to two mg per cup (Gilbert et al., 1976). Different cup sizes, methods of preparation, products and preferred strengths influence the amount of caffeine found in coffee.

Table 1

Caffeine Content in mg of Various Portions of Dietary Sources

Coffee

Instant

regular M=66 (29-117) (Gilbert et al., 1976)
 $\bar{X}$ =59 (40-108) (Burg, 1975)

decaffeinated M= 1 (1- 2) (Gilbert et al., 1976)
 $\bar{X}$ = 3 (2- 5) (Burg, 1975)

Percolated M=74 (39-168) (Gilbert et al., 1976)
 $\bar{X}$ =83 (64-124) (Burg, 1975)

Drip M=112(56-176) (Gilbert et al., 1976)

Tea

regular M=27 (8- 91) (Gilbert et al., 1976)

leaf $\bar{X}$ =41 (30- 48) (Burg, 1975)

instant $\bar{X}$ =28 (24- 31) (Burg, 1975)

green (15- 21) (Canadian Consumer, 1981)

herbal none (Canadian Consumer, 1981)

Caffeinated (33- 52) (Consumer Reports, 1981)

Soft-drinks (21-45.4) (Gilbert et al., 1976)

Chocolate Bars 20 per 30g (Gilbert, 1981)

Chocolate Drinks $\bar{X}$ =10 (1- 20) (Consumer Reports, 1976)

Caffeine in Medication

Cold/Allergy (15- 32) (Consumer Reports, 1982)

Pain relievers (32-100) (Consumer Reports, 1982)

Stimulants, diuretics

weight-control aids (100-300) (Consumer Reports, 1981)

In home-prepared coffee samples, a range of 140 to 285 ml in cup size was reported by Gilbert et al. (1976) yet many studies have not considered this source of variation (Burg, 1975).

Preparation of coffee by filter, percolation or instant method affects caffeine content. Gilbert (1976) explains that with drip or filter preparation, water is passed over the ground beans only once dissolving about 20 percent of the bean and almost all the caffeine. In percolated coffee, water repeatedly passes through the grind, extracting up to 30 percent of the bean, and adding bitterness but not more caffeine to the brew. To counteract the bitterness, a reduced proportion of bean may be employed and thus the caffeine content of percolated coffee is also dependent on tolerance of a bitter taste. Hydrolyzing the coffee bean for instant coffees results in retention of 48 percent of the bean but only about one-half is actually caffeine. Again, less instant coffee is typically used to offset the bitter taste and therefore caffeine concentration tends to be lower.

Plant variety also exerts an influence. Increasingly, the lower quality but more strongly caffeinated robusta bean from Africa and Indonesia is replacing the Arabica bean from Central and South America because of lower cost and higher

crop yield. The robusta bean's primary use is in instant and blended coffees and may lead to greater caffeine concentrations in these preparations (Gilbert, 1981).

Burg (1975) on the basis of over 2000 laboratory samples of coffee, prepared according to manufacturers' directions, suggested a standard average for caffeine content of coffee in a 150 ml cup, of 85 mg for drip or percolated brew and 60 mg for instant coffee. These figures have been used in many studies to compute caffeine intake from coffee.

However, when ranges of caffeine content in cups of coffee are considered, use of a standard average becomes questionable. Burg's (1975) published ranges of 64 to 124 mg per cup of ground coffee and 40 to 108 mg for instant coffee are indications of product variation. Greater ranges are possible if coffee is not prepared according to instructions.

Indeed Gilbert et al. (1976) with analyses of 46 home-prepared samples of coffee found more variability but generally less caffeine per cup than had been previously reported in laboratory prepared samples. The discrepancy might be due to relaxation of manufacturers' instructions in the home and/or to additions of milk or cream which would decrease the caffeine concentration and caffeine content per cup. If women during their reproductive years drink home-prepared rather than commercially prepared coffee, they may

consume less caffeine than assumed.

These data suggest a need to determine more accurately caffeine intake. If incorrect average caffeine values are used to assess caffeine consumption, the error is greatly compounded with heavy users and can, as Gilbert et al. (1976) suggest, lead to the establishment of meaningless risk levels of consumption. Their concern on the basis of the lower caffeine content of home-prepared samples is that drug effects may be attributed falsely to higher levels of intake.

Although a more precise measurement of caffeine intake is needed, practical limitations do exist. If some accuracy must be sacrificed, recognition of possible ranges of exposure is essential.

Caffeine in tea. Tea not only contains caffeine but also the related compounds, theobromine and theophylline, but the main physiological effects of tea are thought to depend on its caffeine content (Martinek & Wolman, 1955). Although tea leaves generally contain more caffeine by weight than coffee beans, proportionately more beans are required to make a cup of coffee and average caffeine concentration in coffee in Canada is approximately two or three times that of tea (Gilbert, 1976).

The caffeine content in cups of tea also varies widely

depending on cup size, brand, type of tea leaves and strength. Burg (1975) found an average value of 30 mg of caffeine per cup of tea and cautiously recommends this as a standard.

However, in varying cup sizes of 115 to 300 ml, a range of 8 to 91 mg and a median of 27 mg of caffeine have been found in 37 home-prepared samples of tea (Gilbert et al, 1976). Burg (1975) also found with a 150 ml cup, caffeine values ranging from 24 to 48 mg, demonstrating product variation. The Canadian Consumer (1981) reports a range of 15 to 21 mg in green tea, 28 to 47 mg in regular black tea and no caffeine in herbal teas. The variation in values for each type of tea is attributed to steeping time which lasted between one and five minutes. Reports indicate that all caffeine is removed from tea leaves into the beverage after steeping for one-half hour (Fox & Cameron, 1970).

As with coffee, attempts to assess caffeine intake from tea should involve recognition of various determinants of caffeine concentration in a cup of tea.

Caffeine in soft-drinks. In both Canada and the United States, cola beverages are required to contain at least a trace of caffeine (Consumer Reports, 1981). However only a small proportion of caffeine in cola-drinks comes from its natural source the kola nut. More than 95 percent of the caffeine present in cola-drinks and 100 percent of the

caffeine in non-cola soft-drinks such as Mountain Dew are added by the manufacturer (Consumer Reports, 1981).

Although considerable variation of caffeine content exists among cola and other caffeine-containing soft-drinks, Gilbert et al. (1976) note a typical value of 40 mg per serving which they emphasize, is in excess of the average caffeine content of a cup of tea. For a 12 oz serving, Consumer Reports (1981) found a range of 33 to 52 mg of caffeine in 14 soft-drinks known to contain caffeine and Gilbert (1976) published manufacturers' reports ranging from 21 to 45.4 mg for 10 caffeine-containing varieties.

Caffeine concentration in soft-drinks is changing and determination of caffeine content may be difficult, but, nevertheless, the soft-drink contribution to caffeine intake should be recognized.

Caffeine in cocoa and chocolate. Cocoa and chocolate contain more theobromine than caffeine. The caffeine content of chocolate drink mixes has been found to vary from one to 20 mg per serving with an average of 10 mg (Consumer Reports, 1976). The standard 30 g chocolate bar contains about 20 mg of caffeine (Gilbert, 1981). It is unlikely that chocolate contributes in a significant way to a caffeine risk level unless consumed frequently or in addition to other caffeine-containing substances.

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Caffeine in medications. Almost 2000 over-the-counter (OTC) drugs contain caffeine (Consumer Reports, 1982). Typical uses for caffeine-containing medication include headache, pain relief, weight control, drowsiness, water loss, colds and allergy (Soyka, 1981). A standard dose for most cold remedies contains about 30 mg of caffeine but pain relievers may have up to 130 mg and stimulants, diuretics and weight-control aids typically contain 100 to 300 mg of caffeine for standard doses (Consumer Reports, 1981). Regular use every four hours of a diuretic and two or three cups of coffee a day could easily lead to a daily caffeine intake of about 800 mg. Of particular concern here is the practice of prescribing diuretics for women in late pregnancy which would increase the maternal and fetal burden of caffeine.

Caffeine Use

History and origin. Caffeine has had a long history of use as a stimulant. Paleolithic man is believed to have prepared beverages from caffeine-containing plants (Rall, 1980). The popularity of coffee made from the seeds of *coffea arabica* and *coffea robusta* spread from its origins in Arabia to Ethiopia, Turkey, then to Africa and Europe and finally to North and South America. Tea from the leaves of *Thea sinensis* originated in China, cocoa from the seeds of *Theobroma cacao* in Mexico, and cola-drinks from the nuts of the *cola acuminata* tree in West Africa (Graham, 1978; Consumer Reports, 1981).

Extent of use. Approximately 1.8 million metric tons of coffee and 4.5 million metric tons of tea are produced each year. Total annual caffeine consumption equally shared by tea and coffee is estimated at 80,000 metric tons (Gilbert, 1981). Considering the world population of 4.4 billion, the average daily caffeine consumption is almost 50 mg per person. Based on imported levels of coffee and tea, an estimate of our national average adult caffeine consumption per day is about 200 mg of caffeine from coffee and 100 mg from tea (Gilbert, 1981).

However these data are based on production and importation figures not on reports of tea and coffee intake

and do not give a clear picture of caffeine consumption.

Graham (1978) reports that, in his opinion, the most reliable estimates of caffeine intake were made in 1977 by the GRAS (generally recommended as safe) Survey Committee of the National Academy of Sciences. Their approach involved a comprehensive menu census including various caffeine sources and portion size data which was incorporated into an estimated daily intake of caffeine. Table 2 in modified form illustrates the results.

Use and trends in Canada. In Ontario, research suggests that more than 90 percent of adults drink a caffeinated beverage daily and that more than 25 percent drink five or more cups of tea or coffee or both daily (Gilbert, 1976). Coffee accounts for 60 percent of all caffeine consumed in Canada, tea for 30 percent and cola drinks, chocolate products and medicine, 10 percent (Gilbert, 1981). Coffee consumption has remained stable over the last 20 years. Although the use of brewed and instant coffees has been approximately equal, popularity of ground coffee is increasing. About 15 percent of coffee used is decaffeinated. Tea has traditionally been more popular in Eastern Canada and British Columbia but overall intake is on the decline (Gilbert, 1981).

Gilbert (1981) discusses the variation of coffee and tea intake with age and sex. While tea consumption

Table 2

Estimated Daily Intake Of Caffeine

Age	Total	Users Only		
	Person-Days Surveyed	Mean Intake (mg/Day)	Mean Intake (mg/Day)	% Of Total Person-Days
6-11mos	1274	4.2	77	6
12-24mos	2548	15	49	30
2-5 yrs	12628	29	70	41
6-17yrs	40726	43	101	43
18 + yrs	114618	186	227	82
pregnant	1078	144	193	74

increases with age, coffee use peaks between the ages of 40 and 49 years. Trends indicate that more older people are drinking coffee and coffee consumption is decreasing with men but increasing with women. Statistics also indicate that females drink more tea than males and thus, despite declining overall tea intake in Canada, as described earlier, female caffeine consumption in this country probably is increasing (Gilbert, 1981).

Use during pregnancy. In an American study, the average number of drug preparations ingested during pregnancy, labour and delivery, was found to be 10.3 with a range of 3 to 29. The most commonly ingested medications were analgesics, antihistamines, diuretics and caffeine containing drugs (Horning, Butler, Nowlin & Hill, 1975). The use of caffeine by pregnant women has been surveyed. Graham (1978) reports that in an American survey by a GRAS Committee, 74 percent of pregnant women consumed caffeine from various sources with an overall average of 186 mg per day and a users' average of 227 mg per day (see Table 2). A similar proportion of 77 percent with a sample of more than 5000 pregnant women in California was found by Kuzma and Sokol (1982). In another study of 156 mothers, 95 percent of the women ingested caffeine during their pregnancies in coffee, tea, colas, analgesics and antihistaminic

preparations with a greater proportion consuming coffee than tea (Hill, Craig, Chaney, Tennyson & McCulley, 1977). The larger proportion of women reporting caffeine use may be a function of the smaller sample size and/or the inclusion of medications as a caffeine source.

Martin (1982) reports that almost 15 percent of women in the prime child bearing years of 20 to 35 drink more than six cups of coffee daily but gives no reference or indication of the sample involved. Her statement may be based on a large demographic survey described by van dan Berg (1977) which revealed that 13 percent of the pregnant women drank more than six cups of coffee daily. More recent large surveys, by Rosenberg, Mitchell, Shapiro and Slone (1982) and Linn, Schoenbaum, Monson, Rosner, Stubblefield and Ryan (1982) revealed smaller proportions of heavy caffeine users among pregnant women. In the former case, 11 percent, and the latter case, five percent consumed the equivalent, as the authors describe, of four or more cups of coffee daily. In the Linn (1982) study, only one percent apparently consumed more than the equivalent of seven cups of coffee daily. It is interesting to note that the subjects in these latter two studies lived in the Eastern United States or Toronto whereas the subjects in van dan Berg's (1977) study lived in California. Perhaps regional influences affect caffeine use as was demonstrated in

Western and Eastern Canada (Gilbert, 1981). Decline in heavy consumption of caffeine during pregnancy may also have occurred in the interim between the data collection of the two sets of studies.

The relationship of caffeine use to other risk factors.

Gilbert (1976) reports positive correlations between both coffee consumption and smoking, and smoking and alcohol use. Coffee use tends to increase with alcohol use up to 40 ml of alcohol daily and then declines with greater alcohol consumption. It is not clear whether 40 ml refers to absolute alcohol levels but the implication is moderate use. If absolute alcohol, the 40 ml approximates two shots of liquor or two beer. A large, prospective American study, initiated in 1974, of 12000 women examined primarily patterns of alcohol and cigarette use during pregnancy but also published data on their relationship to maternal caffeine consumption (Kuzma & Kissinger, 1981). Their data indicate that caffeine use increases with smoking across all categories of alcohol use. Alcohol and caffeine consumption is positively correlated when considered alone but a different pattern of use emerges when categories of tobacco use are considered. For non-smokers, the data are consistent with Gilbert's (1976) findings: women tend to consume more caffeine with increasing alcohol use up to a

exert its action.

The kidneys bear the burden of excreting water soluble drugs whether biotransformed or not. However renal function of the neonate is immature: the glomerular filtration rate and active tubular secretion rate is lower than in adults (Finnegan & Fehr, 1980). Also the neonatal capability to excrete water and electrolytes and maintain acid-base balance is not fully developed.

Most metabolic pathways in the neonate are inactive or only slightly functional (Finnegan & Fehr, 1980). Horning et al. (1975) demonstrated that the neonate can metabolize caffeine only after the first few days of life because of a lack of necessary enzymes (Morris & Weinstein, 1981). In urine samples collected from neonates one to three days after birth and from mothers after delivery, caffeine was found unchanged in both samples. However caffeine comprised more than 85 percent of the methylated xanthines and urates in neonatal urine compared to 26 percent or less in maternal, evidence of extensive demethylation in the adult but not the neonate. The caffeine burden is increased in the neonate by the metabolism of theophylline to caffeine, a biotransformation that occurs in the opposite direction in adults (Bada, Khanna, Somani & Tin, 1979; Bory, Baltassat, Porthault, Beghenod, Frederich & Aranda, 1979; Brazier & Salle, 1981).

throughout pregnancy and of those who changed their pattern, more increased their intake than decreased (Hook, 1976).

The potential interactive effects of caffeine, nicotine and alcohol are discussed later in the section on drug interactions.

Socioeconomic status is an important factor to consider in relation to caffeine use and effects yet no reference in the literature can be found that examines the association.

Caffeine use and drug dependence. A large proportion of the adult population of North America and many other parts of the world may be physically dependent on caffeine (Gilbert, 1976). Drug dependence may involve any combination of tolerance, physical dependence and compulsive abuse (Goldstein, Aronow & Kalman, 1974). Mild physical dependence and a small degree of tolerance develop with regular use of more than 350 mg of caffeine daily (Gilbert, 1981).

Caffeine tolerance develops as users become less nervous and experience less insomnia with continued use. The tendency to seek additional stimulation with more caffeine develops easily because the initial stimulatory effects occur rapidly but then dissipate within a few hours with an accompanying period of behavioural and mental depression if the caffeine dose has been high (Goldstein et

al., 1974).

Interruption of regular intake of more than 350 mg of caffeine daily elicits a caffeine withdrawal syndrome characterized by a reduction of alertness and activity, an increase in drowsiness and irritability, and a psychic craving typical of compulsive abuse (Goldstein, Kaizer & Whitby, 1969). Withdrawal reactions from any drug have often been expected to resemble withdrawal from central nervous system depressants (Finnegan & Fehr, 1980). Kalant (1973), however, describes withdrawal reactions to the stimulant, amphetamine as depression, prolonged sleep and voracious appetite, and Finnegan and Fehr (1980) suggest that these effects, which are consistent with Goldstein's (1969) findings are typical withdrawal reactions to stimulant drugs such as caffeine.

Neonatal reactions of extreme drowsiness for up to four days after birth with maternal use of amphetamines throughout pregnancy are reported by Finnegan and Fehr (1980). A caffeine neonatal withdrawal reaction has never been described. However the slow fetal clearance of caffeine (Aranda, Sitar, Parsons, Loughnan & Neims, 1976) increases exposure and enhances the possibility of drug dependence. If the fetus develops a dependency on the maternal supply of caffeine, withdrawal symptoms may occur as caffeine is eliminated from the neonatal system. Some

evidence exists to indicate that neonatal apnea might be an indication of caffeine withdrawal (Aranda, 1976). Neonatal apnea is defined as cessation of breathing of greater than 10, 20, or 30 seconds duration with or without bradycardis and/or cyanosis (Aranda & Turmen, 1979). Caffeine clearance in non breast-fed neonates is coincident with the usual onset of apnea at two to three days (Aranda, 1976). In addition, Aranda, Gorman, Bergsteinsson and Gunn (1977) have found that caffeine is an effective treatment for apnea in preterm infants and the neonate.

The evidence suggests that maternal physical dependence on caffeine can lead to fetal dependence and subsequent withdrawal difficulties for the neonate perhaps manifested in part as apnea.

General Physiological and Psychological Effects

Caffeine is a powerful central nervous system stimulant. The general physiological effects of consuming caffeine have been investigated mainly from a behavioural point of view. The cortex is most sensitive and is affected first by the presence of caffeine followed by the medulla and finally the spinal cord if caffeine concentration is high (Julien, 1981).

The myocardium is stimulated directly by caffeine but this effect may not result in an increased heart rate since caffeine's stimulation of the vagal nerve acts to decrease the heart rate. Similarly, although caffeine dilates the coronary, pulmonary and general systemic blood vessels by direct action on the vascular musculature, its action on the medullary vasomotor centre promotes blood vessel constriction (Goldstein et al., 1974).

In addition, caffeine increases the metabolic rate by about ten percent, relaxes the smooth muscles of the bronchi, strengthens skeletal muscle contraction, exerts a diuretic effect of the kidney, stimulates the respiratory centre, and increases gastric secretion (Goldstein et al., 1974).

Moderate intake of 150 to 200 mg of caffeine results in increased mental alertness, decreased drowsiness and fatigue, heightened sensory perception, increased motor

activity and quicker reflex actions (Goldstein et al., 1974). Larger doses of 300 to 500 mg produce nervousness, restlessness, insomnia, headache, tense and trembling muscles, upset stomach and unpleasant sensory disturbances (Goldstein et al., 1974). Intestinal irritation and vomiting occur with very large doses and fatal doses are rare (Vandenbroucke, 1981). The fatal oral dose for adults is considered to be about ten grams (Gilbert, 1981).

Implications of these effects for reproductive hazards are not known. Caffeine's action to relax muscle fibre may induce complications during labour and delivery if the contractions of the uterine muscles are weakened. The stimulation of the respiratory centre may lead to fetal dependence on caffeine as a respiratory stimulant (Aranda, 1976) and may be responsible for apnea upon withdrawal.

Chemical Structure of Caffeine

Caffeine is an alkaloid of molecular weight 194.19 and structurally identified as 1,3,7-trimethylxanthine. Two other naturally occurring methylated xanthines are theophylline (1,3-dimethylxanthine) found in tea, and theobromine (3,7-dimethylxanthine) found in tea and cocoa (Graham, 1978).

Caffeine is structurally similar to the purines, adenine and guanine, which comprise two of the four symbols of the genetic code. The configurations of purine, adenine and guanine are drawn in Figure 1, taken from Gilbert (1976), as well as caffeine, theobromine, theophylline, and caffeine's major metabolites, paraxanthine and 1-methylxanthine.

Figure 1

Configurations of Purine and 8 Purine Derivatives

from Gilbert (1976)

Fig. 1 - Formulae of purine and eight purine derivatives including adenine and guanine, which are involved in genetic coding, xanthine, and five methylxanthines of which three, caffeine, theobromine, and theophylline, occur in beverages, and two, paraxanthine and 1-methylxanthine are reported metabolites of caffeine in human urine

Teratogenesis

Teratology at one time referred to the study of congenital malformations that were visible at birth and that were induced by exogenous agents during gestation. However a more recent broader definition includes morphological, biochemical and behavioural anomalies that arise from drug exposure in utero and that are detected at birth or later.

Teratogenic potential depends on the chemical and pharmacological nature of the drug and its access to the fetus, the sensitivity of different tissues, the time of its actions, the level and duration of its dosage and the genetic constitution of the fetus. The use of other drugs can potentiate, interact, attenuate or have no effect on the action of caffeine. The presence of caffeine, itself, can result in enzyme induction or inhibition which can alter plasma concentration and change effects (Finnegan & Fehr, 1980).

A teratogenic dose produces at one extreme, temporary impairment and at the other, fetal death. Although with most drugs, the teratogenic zone is narrow and is described by a steep dose-effect curve (Finnegan & Fehr, 1980), caffeine's zone has not been determined.

Unfortunately in the case of caffeine, teratogenic determinants and effects are not clearly known. However, considering its extensive tissue distribution, its metabolic

its inactive end-product and thereby increase cyclic AMP levels (Gilbert, 1976). However, Snyder (1981) suggests instead that caffeine acts to prevent adenosine binding. Adenosine depresses nerve cell firing in the brain by inhibiting the release of neurotransmitters. Caffeine, structurally related to adenosine, may bind instead of adenosine to receptors on neuronal membranes and allow the neurons to fire more readily and simultaneously raise cyclic adenosine levels. Intracellular levels of cyclic AMP have been found to be inversely related to cell division (Abell & Monahan, 1973; Timson, 1977). Increased levels of cyclic AMP can alter both mitosis and meiosis and the hormone balances in the mother and fetus (Finnegan & Fehr, 1980; Abell & Monahan, 1973). In the female caffeine abstainer, cyclic AMP levels decline for most of gestation but do rise in late pregnancy. Caffeine use during pregnancy elevates cyclic AMP levels throughout gestation and the effects of this disturbance are not clearly known (Weathersbee & Lodge, 1977).

Caffeine may act to either directly (Gilbert, 1976) or indirectly (Berridge, 1975) increase the availability of calcium ions. Calcium increases the contractile state of muscle fibres and, in this way, caffeine could affect neuromuscular activity. In addition, calcium is known to

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Metabolism of caffeine increases steadily in infancy until the infant reaches an adult functioning level by about eight months (Aldridge & Neims, 1979). Warszawski, Ben-Zvi, Gorodischer, Arnaud and Braćco (1982) also confirm with young dogs, increasing metabolism with increasing age.

Thus the neonate is at a disadvantage in the metabolism and excretion of caffeine.

In the breast-fed infant. Under normal conditions, human breast milk is more acid than plasma and thus more amenable to accepting alkaline drugs such as caffeine resulting in possibly higher concentrations of caffeine in breast milk than in plasma (Finnegan & Fehr, 1980).

Caffeine levels of 3.2 to 8.6 ug per ml have been found in human breast milk (Horning et al., 1975) but the dose an infant consumes is very small (Berlin, 1981). After

Absorption and Distribution

To assist with the interpretation of caffeine doses, in mg/kg, and caffeine concentrations, in ug/ml, as presented in the following sections, approximate values are illustrated in Table 3 modified from Gilbert (1976)

Absorption of caffeine is directly related to pH (Soyka, 1981) and independent of type of beverage consumed or time of day (Oser & Ford, 1981; Marks & Kelly, 1973). Caffeine is rapidly absorbed from the gastrointestinal tract and reaches all tissues of the body within five minutes (Gilbert, 1976). Peak blood levels are reached within about 60 minutes (Soyka, 1981; Gilbert, 1981; Timson, 1977) although considerable variation of absorption rates and plasma levels exists among individuals. After administration of 250 mg of caffeine to nine healthy adults, peak plasma levels ranged from four to 26 ug per ml and were reached by five subjects at 30 minutes, three at 60 minutes and one at 120 minutes (Robertson, Frolich, Carr, Watson, Hollified, Shand & Oates, 1978).

The distribution of caffeine in different tissues was shown to be in approximate proportion to their water content and in the same concentration as plasma (Axelrod & Reichen-thal, 1953; Soyka, 1981). Caffeine moves freely into the human ovary and testes (Goldstein & Warren, 1962) and into uterine secretion, the blastocyst, fetal tissue, amniotic

Table 3

Selected Caffeine Concentrations and Doses

Modified from Gilbert (1976)

Selected Caffeine Concentrations

<u>Concentration</u> <u>----(ug/ml)----</u>	<u>Source, Equivalent or Use</u>
0.8	Found in plasma of human newborn
1	Average level of exposure of most cells of many humans
6	Approximate peak plasma concentration 30 after a strong cup of coffee
144	Typical concentration in tea
360	Typical concentration in coffee
500	Minimum concentration causing chromosome breaks in human cells

Selected Caffeine Doses

<u>Dose</u> <u>(mg/kg)</u>	<u>Route</u>	<u>Species</u>	<u>Source or Effect</u>
2.4	Oral	Human	Typical cup of tea (27 mg)
1.1	Oral	Human	Typical cup of coffee (74 mg)
2.5	Oral	Human	Strong cup of coffee (176 mg)
2.9	Oral	Human	Reduced fatigue effects

fluid, cord blood and breast milk (Soyka, 1981). The concentration of caffeine was similar in the cerebrospinal fluid indicating easy passage over the blood-brain barrier (Arnaud, Bracco & Welsch, 1982; Somani, Khanna & Bada, 1980).

Parsons and Neims (1981) examined the cord plasma of 15 healthy full term infants and found caffeine in all the samples. Studies have revealed mean concentrations of caffeine in cord blood ranging from .8 to 1.6 ug per ml (Gilbert, 1976; Parsons & Neims, 1981; Soyka, 1981). Analysis of 15 amniotic fluid samples revealed a median value of .5 ug per ml (Horning et al, 1975).

The high lipid solubility, non-ionized state and low molecular weight of caffeine are thought to facilitate placental transfer (Morris & Weinstein, 1981; Finnegan & Fehr, 1980). Diffusion also depends on placental blood flow, and strength and presence of caffeine binding to plasma proteins (Finnegan & Fehr, 1980). Caffeine is 75 to 85 percent unbound (Morris & Weinstein, 1981) and is therefore free to diffuse. As pregnancy develops, the trophoblastic epithelium thins and the rate of diffusion should increase (Finnegan & Fehr, 1980).

Metabolism and Excretion

In the non-pregnant human adult. Caffeine is metabolized in the liver first to paraxanthine (1-7 dimethylxanthine) and then to monomethylxanthine forms of 1-methylxanthine and 7-methylxanthine with only a negligible amount excreted unchanged (Axelrod & Reichenholz, 1953; Horning et al., 1975; Arnaud & Welsch, 1981). It is important to recognize that the presence of methylxanthines cannot only be attributed to caffeine intake. Purine compounds abound in organisms and their food and methylxanthines can be produced and excreted indigenously (Gilbert, 1976).

The mean metabolic half-life of caffeine in healthy non-pregnant non-smoking adults is reported as six hours and as 3.5 hours in healthy non-pregnant smokers (Parsons & Neims, 1978). This discrepancy could be due to metabolism of tobacco products resulting in increased drug-metabolizing enzymes available to act on caffeine (Gilbert, 1976). Other drugs affect the metabolism of caffeine, such as the inducer, 3-methylcholanthrene and other methylxanthine inhibitors (Morris & Weinstein, 1981).

Accumulation of caffeine does occur with repeated consumption of caffeine-containing substances throughout the day. Although metabolites of caffeine and only traces of caffeine itself are excreted in human urine, considerable

renal concentration of caffeine may occur (Gilbert, 1976). Axelrod and Reichenenthal (1953) reported no day to day accumulation because of the rapidity of caffeine metabolism, but a more recent study indicates that blood clearance of caffeine in habitual coffee drinkers may take up to seven days and that metabolism of caffeine may differ between habitual and lighter users of the drug (Warren, 1969).

In the pregnant human. During pregnancy, decreased drug binding, due to hypoalbuminemia and substitution of endogenous material at binding sites, may occur leading to greater concentration of free caffeine in plasma and tissues (Finnegan & Fehr, 1980). In addition, caffeine biotransformation is handicapped during pregnancy by a decrease in oxidative and reductive pathways. Although reasons for this are not clear, Finnegan and Fehr (1980) suggest that an increased level of progesterone metabolites might inhibit caffeine hydroxylases in the maternal liver (see also Aldridge, Bailey & Neims, 1981; Patwardhan, Desmond & Johnson, 1979).

Metabolism by oxidation, reduction or hydrolysis renders a drug more water-soluble and thereby promotes excretion in urine or feces. Thus delay of caffeine biotransformation in turn causes a delay in drug excretion and an increase in drug exposure and risk of toxicity

(Finnegan & Fehr, 1980).

Researchers have reported a prolongation in elimination of caffeine during pregnancy particularly in the later stage and that this returns to normal after delivery (Neims, Bailey & Aldridge, 1979; Parsons & Pelletier, 1982; Parsons, Aranda & Neims, 1976; Knutti, Rothweiler & Schlatter, 1981). By mid-pregnancy, the clearance rate is half of that of a non-pregnant healthy woman and, by late pregnancy, the rate is decreased to one-third (Aldridge et al., 1981). Parsons and Neims (1978) found that, in the last two weeks of pregnancy, the mean metabolic half-life of caffeine in non-smokers was 21.5 hours and 9.6 hours in smokers. Soyka (1981) reports a half-life of 20 hours in late pregnancy. This third trimester impaired elimination can result in elevated exposure of the fetus to caffeine if the woman does not decrease her intake (Parsons & Neims, 1981).

Although the delay in elimination occurs after the time of maximal risk of morphological fetal injury in the first trimester, the increased exposure in the second and third trimesters coincides with general growth and the development of genital tissue, the nervous system and teeth.

In the fetus. No studies have been published on a placental role in the metabolism of caffeine (Morris & Weinstein, 1981). However the fetus does not have the ability to metabolize caffeine (Horning et al, 1975) because

of lack of enzymes (Morris & Weinstein, 1981) and must therefore rely on maternal circulation or elimination into the amniotic fluid. In the fetus, most of the blood from the umbilical vein passes into the liver and then a much higher proportion, compared to an infant, passes to the brain. Gali, Spano and Szyska (1975) indicate that caffeine appears to accumulate in fetal rat brain tissue. Caffeine can alter the metabolism of neurotransmitters and thus may affect fetal brain function (Groisser, Rosso & Winick, 1982). The consequences of human fetal exposure to elevated levels of caffeine at a critical period in brain development in terms of subsequent behavioural abnormalities has not yet been studied.

In the neonate. In the neonate the total body water is proportionately higher than the 60 percent body weight in adults: 85 percent of body weight in premature infants and 70 percent in full term infants (Finnegan & Fehr, 1980). Caffeine's distribution in tissues in proportion to water content (Axelrod & Reichenthal, 1953) may thus be extensive.

Plasma protein-binding of drugs can be considerably less in the neonate as compared with the adult because of reduced plasma proteins and protein binding of endogenous substances. The consequence for the neonate is that more caffeine is in a free form to cross cellular membranes and

exert its action.

The kidneys bear the burden of excreting water soluble drugs whether biotransformed or not. However renal function of the neonate is immature: the glomerular filtration rate and active tubular secretion rate is lower than in adults (Finnegan & Fehr, 1980). Also the neonatal capability to excrete water and electrolytes and maintain acid-base balance is not fully developed.

Most metabolic pathways in the neonate are inactive or only slightly functional (Finnegan & Fehr, 1980). Horning et al. (1975) demonstrated that the neonate can metabolize caffeine only after the first few days of life because of a lack of necessary enzymes (Morris & Weinstein, 1981). In urine samples collected from neonates one to three days after birth and from mothers after delivery, caffeine was found unchanged in both samples. However caffeine comprised more than 85 percent of the methylated xanthines and urates in neonatal urine compared to 26 percent or less in maternal, evidence of extensive demethylation in the adult but not the neonate. The caffeine burden is increased in the neonate by the metabolism of theophylline to caffeine, a biotransformation that occurs in the opposite direction in adults (Bada, Khanna, Somani & Tin, 1979; Bory, Baltassat, Porthault, Beghenod, Frederick & Aranda, 1979; Brazier & Salle, 1981).

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maternal consumption of 150 mg of caffeine, the infant receives 1.5 mg in a litre of breast milk if ingested within one hour of caffeine intake (Tyrala & Dodson, 1977). A litre of milk is approximately the amount that a three week old baby would drink in a 24 hour period (Fried, personal communication, 1982).

However the plasma membrane is most permeable during the colostrum phase of secretion occurring for the first week after birth (Finnegan & Fehr, 1980). Thus the neonate may be exposed to higher levels of caffeine in the first few days of life. If the mother continues to take caffeine while breast-feeding, the neonate continues to be exposed and because of the difficulty with infant caffeine metabolism may be subject to a cumulative effect.

Overview of Animal Studies with Caffeine

The study of the effects of caffeine in the animal laboratory allows control of factors that are impossible to manipulate with humans and difficult to manage statistically. Genetic and environmental factors are more controlled and caffeine's highly correlated habits in humans of alcohol and smoking are not involved. In this way, it is hoped, the pure effects of caffeine use will emerge.

However limitations do exist to inferences about the human condition drawn from the results of animal studies. Perhaps the pure effects of caffeine do not occur with humans because of other factors such as drug interactions.

Generalizing from animal experiments to humans presents many difficulties. Different animal species react differently to drug treatments. Consideration of similarities in rate and pathway of drug metabolism, dose access to fetal tissues, and time of exposure and extrapolating dose response is essential before inferences relating to humans are drawn from animal research (Heinonen, Slone & Shapiro, 1977).

Modes of caffeine administration in animals have been diverse. Parenteral administration or intubation of caffeine results in much higher peak plasma concentrations than would occur if the same amount of caffeine was taken gradually over a 24 hour period in food or drinking water.

(Palm, Arnold, Rachwall, Leytcek, Teague & Kensler, 1978).

Doses administered to animals have often been far in excess of heavy caffeine use by humans. Adverse effects may be due to direct action of caffeine on embryonic or fetal tissue or an indirect action through maternal or placental tissue. With the high doses administered in some animal experiments, the health of the pregnant animal is impaired which could result in reproductive disorder. Burg (1975) suggests that one to five mg per kg would be an appropriate experimental dose for animals to relate clinically to the average 150 ml cup containing 83 mg of caffeine.

The question of dose equivalents is unresolved. Weathersbee and Lodge (1977) feel that investigators, when extrapolating from animals to humans, have erred in using uncorrected body weight instead of dose equivalents based on metabolic body weight. Dose levels of caffeine are typically described in terms of milligrams per kilogram of body weight. Although such description is meaningful for research inferences within species, Gilbert (1976) cautions application between species. Drug effects are related not only to body weight but to basal metabolic rate. Gilbert suggests that doses for interspecies comparisons be related instead to surface area because of its connection with the basal metabolic rate which in many species is about 1000

kcal per metre squared of surface area. Interspecies lethal doses for rats, cats and humans are the same when such a correction is made (Gilbert, 1976). Animal surface area in square metres is approximately $.07$ multiplied by body weight (in kg) ^{$3/4$} . The presence of the constant, $.07$, prompts simplification to use of a metabolic weight equated as body weight ^{$3/4$} . The metabolic weight of a $.2$ kg rat and a 70 kg man are $.3$ kg and 24.2 kg respectively (Mitoma, Sorich & Neubauer, 1968). Thus dose equivalents extrapolating from lighter to heavier species are lower when based on metabolic weight rather than body weight. Caution must be exercised in interpreting the results of animal experiments so that a higher level of safety than actually exists is not accepted.

Unlike most experimental animals that are bred in a controlled manner, man is not uniform genetically nor in his exposure to environmental elements nor in his state of health. Patwardhan, Desmond and Johnson (1979) have reported delays in metabolism of caffeine with liver disease and Goldstein and Kaiser (1969) suggest that genetic variation may be manifested in subjects' refusal to participate in caffeine studies because of allergy or drug sensitivity.

The metabolic pathway of caffeine in man with paraxanthine metabolizing to 1-methylxanthine has not been

demonstrated in animals (Burg, 1975). In the rat, for example, each demethylation pathway is of similar qualitative importance and 42 percent of rat urinary caffeine metabolites are trimethyl derivatives compared with four percent in the human (Arnaud & Welsch, 1981). Palm et al. (1978) report that the rate of caffeine elimination in rats is about twice as fast as in man.

With the difference in the rate and pathway of metabolism, the genetic and environmental variation in man, and the dilemma of dose equivalence, animal research cannot provide answers to the human condition but it can help to direct the questions.

Mutagenesis

Caffeine's structural similarity to uric acid and the two purine DNA pairs, adenine and guanine has prompted investigation into potential mutagenic effects. Caffeine induces chromosomal abnormalities in bacteria (Demerec, Bertani & Flint, 1951), fungi (Fries, 1950), plants (Kihlman & Levan, 1949) *Drosophila* (Andrew, 1959) and in mammalian cells in vitro (Kuhlmann, Fromme, Heege & Ostertag, 1968). Human cells in culture when exposed to caffeine at concentrations of about 200 ug per ml manifest chromosomal breaks related in a direct linear fashion to caffeine concentration (Kuhlmann et al., 1968). Kuhlmann et al. (1968) report that caffeine-induced chromatid breakage with human cells in vitro occurs only during DNA synthesis. If also true, in vivo, caffeine would exert little genetic damage in non-dividing tissue. Thus females would have little genetic consequence of caffeine consumption after birth because of the absence of DNA replication of ova. However, in males, genetic effects could accumulate with caffeine use and induce mutagenic damage (Kuhlmann et al., 1968). In addition, caffeine could exert genetic damage on developing germinal cells in the fetus (Finnegan & Fehr, 1980). Chromosome damage of the germ cells may lead to miscarriage, premature birth or stillbirths, or congenital malformations (Finnegan & Fehr, 1980), outcomes that have

been related to caffeine use.

However, at concentrations of one ug per ml, which is approximately the body water concentration of a regular coffee drinker consuming about 250 mg caffeine daily (Goldstein et al, 1974) there was a negligible increment in chromosomal breakage (Ostertag, Duisberg & Sturman, 1965).

Consideration of a threshold level of mutagenicity is of concern when large doses are used in animal experiments. The increased mutation rate observed in *Drosophila* (Andrew, 1959) was only five-fold despite a very high caffeine dose, a result not repeated in another laboratory (Adler, 1970). The potent mutagenic effects on *Escherichia coli* and other micro-organisms both when acting alone and in combination with other mutagens (Timson, 1977) seem to be associated with inhibition of DNA repair processes and are observed only at caffeine concentrations much in excess of human use of caffeine (Rall, 1980).

Timson (1977) concludes that caffeine is definitely mutagenic in micro-organisms, mildly mutagenic in *Drosophila*, and likely not mutagenic in mammals with normal dietary caffeine intake. He attributes lack of mutagenicity in humans to caffeine's more rapid metabolism, antimitotic activity which would threaten the survival of a caffeine-mutated cell, and human resistance through long exposure.

However, because of delayed metabolism in pregnancy and lack of metabolism in the fetus, and caffeine's demonstrated ability to alter both cell divisionary processes (Abell & Monahan, 1973), the problem of mutagenesis is not clearly resolved.

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A teratogenic dose produces at one extreme, temporary impairment and at the other, fetal death. Although with most drugs, the teratogenic zone is narrow and is described by a steep dose-effect curve (Finnegan & Fehr, 1980), caffeine's zone has not been determined.

Unfortunately in the case of caffeine, teratogenic determinants and effects are not clearly known. However, considering its extensive tissue distribution, its metabolic

impairment in the fetus and pregnant woman, its renal burden and accumulative nature, caffeine requires definition with respect to teratogenic potential.

Animals. The following review of animal studies will not be extensive due to difficulties of extrapolating to the human condition as discussed previously. The studies selected provide a description of the main effects on the offspring of caffeine administered in varying doses and by different methods to the pregnant animal.

Although early reports on the teratogenic effects of caffeine in animals were negative, subsequent studies found that high single doses over 100 mg per kg daily, of injected or intubated caffeine, provoked embryonic deaths and malformations, consisting of cleft palate, limb-reduction deformities and subcutaneous hematomas in mice (Nishimura & Nakai, 1960; Fujii & Nishimura, 1969) and rats (Leuschner & Schwerdtfeger, 1969). These effects have not been consistent across species (Collins, 1979) nor with lower doses (Gilbert & Pistey, 1973)

One interesting study by Fujii and Nishimura (1974) demonstrated that the caffeine-induced malformations in mice offspring were significantly decreased by the use of catecholamine blocking agents. This study has implications for human reproduction because of the increased level of catecholamines found during pregnancy after ingestion of 220 mg of caffeine (Bellet, Roman, Decostro, Kim & Kershbaum, 1969). Weathersbee and Lodge (1977) suggest that catecholamine increase produces a rise in maternal blood

pressure and results in vasoconstriction of the placental and uterine vasculature which impairs fetal oxygenation. This explanation might account for decreased placental weights found in caffeine-treated rats (Weathersbee & Lodge, 1977).

In animal studies, when doses administered or modes of administration were more similar to human use, congenital malformations were not observed but other signs of reproductive disorder were in evidence. Fujii and Nishimura (1972) demonstrated a decrease in fetal weight, litter size and an increase in fetal resorptions when rats were fed, not injected or intubated, with 180 mg per kg daily throughout gestation. Gilbert and Pistey (1973) injected rats every six hours with caffeine doses of 20 mg, 40 mg, 80 mg per kg per day and found a dose-related increase in number of resorptions and decrease in birth weight in the offspring but no developmental malformations.

With lower doses of caffeine (10 mg/kg/day) equivalent to levels considered at risk for humans (Weathersbee, Olsen & Lodge, 1977), fed to rats in their drinking water throughout pregnancy and lactation, progressive growth reductions in offspring were apparent with successive pregnancies but no malformations or litter size effects were in evidence (Dunlop & Court, 1981). In the fifth pregnancy,

severe fetal growth retardation was apparent and neonatal mortality was 44 percent, suggestive of a cumulative effect in caffeine-treated mothers. The authors are hesitant to attribute the results to a direct action by caffeine. Although decreasing neonatal weights were in evidence, all caffeine-consuming dams gained weight. However stress and reduction in maternal potential weight gain may play an intermediary role. The study is important in its simulation of ingestion patterns in humans and points to potential direct or indirect consequences of prolonged caffeine use.

Butcher, Wooten and Vorhees (1980) administered brewed coffee as drinking water to rats and found a lowered birth weight effect but no other apparent reproductive anomalies. Nolen (1981) and Palm et al. (1978) also demonstrated that malformations did not occur in rat offspring with oral administration of 30 mg or less of caffeine per kg daily. Unlike other studies which do not mention the health of the pregnant animal (Gilbert & Pistey, 1973), Palm et al. (1978) note that administration of 30 mg per kg daily of freshly brewed coffee to rats did not interfere with the normal behaviour, growth, pattern of eating and drinking or reproductive performance of the subjects. In the two latter studies, no birth weight effect or increased incidence of resorptions was noted but delayed ossification was apparent and was thought to be a result of retardation in bone

calcium deposition. This finding may have some basis in the caffeine-related disturbance reported earlier of intracellular calcium levels.

The mode of administration and dose of caffeine are critical in provoking teratogenesis. Single high caffeine doses (>100 mg/kg) administered parenterally, or by intubation appear to induce malformations; administration of high doses (180 mg/kg/day) of caffeine in food can reduce birth weight and increase the number of resorptions; lower caffeine doses (<50 mg/kg/day) have been shown in some studies to reduce birth weight and increase the number of resorptions but in other studies to have no apparent adverse effect other than delayed bone calcification.

Humans. Critical periods in embryonic age exist for drug-induced morphological teratogenesis in humans.

During the first few weeks after conception, the preimplantation period, environmental factors usually do not influence the embryo. If damage does occur, the result is usually severe, leading often to death of the embryo (Finnegan & Fehr, 1980).

Days 13 to 56 of gestation comprise the period of organogenesis. The type of malformation produced depends on the state of development at the time of drug exposure. The sensitivity periods in humans for nervous system tissue is 15 to 25 days, for heart tissue 20 to 40 days, and for limb tissue 24 to 46 days (Eriksson, Catz & Yaffe, 1973).

All organs continue to mature after the first trimester but extensive development occurs with the genitals, teeth and nervous system. Fetal exposure to drugs during the second and third trimesters may lead to central nervous system effects that are not apparent in the neonate but are manifested later in life.

In humans, several large studies have shown no relationship between caffeine consumption and congenital malformations. Heinonen et al. (1977) found no increase in the number of malformed children with 5773 mothers who had consumed caffeine during the first four months of pregnancy. However the authors express caution with interpreting no

linkage between caffeine and malformations since most of the women consumed caffeine and were thus classified as users in the analysis. A dose response relationship, or threshold effect might exist but not be apparent with this methodology.

In a retrospective study of 2030 malformed infants, Rosenberg et al. (1982) found no association between maternal caffeine consumption during pregnancy and the occurrence of any one of six specific birth defects when caffeine habits were compared with those of a control group comprised of 712 other malformed children. In this study, only a small proportion of the women were considered as heavy caffeine users and therefore the effects of heavy caffeine consumption could not be evaluated. Another handicap of the study is that, although no differences were observed among the seven groups of malformed infants with respect to maternal caffeine use during pregnancy, a question remains as to whether maternal caffeine use contributes toward non-specific malformations. Computation of milligrams of caffeine ingested was based on caffeinated coffee, tea and cola but did not consider cup size, method of preparation or strength of beverage.

In Boston, between 1977 and 1980, 12,205 non-diabetic, non-asthmatic women were interviewed within a few days of delivery to gain information about their medical history and soft drug use during pregnancy. Linn (1982) and coworkers collected caffeine information for the first trimester of pregnancy only and found no relationship with maternal caffeine consumption and congenital malformations of the infants. In this study, as in the previous report, only a very small proportion of the women reported heavy caffeine use as described previously. Other limitations of the study involve assessment of caffeine intake. Women were asked to report the number of cups of coffee or tea consumed daily: no differentiation among coffee, tea or decaffeinated beverages was made; no allowance for method of preparation, cup size or strength was employed; no inclusion of other caffeine-containing substances in intake questions decreased the accuracy of the caffeine intake assessment and changed the implication of the "no coffee or tea" group from no caffeine intake to undefined caffeine intake.

The previous three studies were handicapped in examining potential effects of heavy caffeine use because of either methodology or the small number reporting heavy use. However one retrospective Belgian study by Borlee, Leshat, Bouckaert and Misson (1978) found that heavy coffee consumption during pregnancy of eight or more cups of coffee

daily was associated with an increase in incidence of malformations among infants. From a sample of 202 malformed infants, 23.2 percent had mothers who typically consumed eight or more cups of coffee daily whereas only 12.9 percent of the 175 control mothers drank in the heavy category. Among the 44 mothers of malformed infants who were heavy coffee drinkers, 16 or 36.4 percent were smokers; among the 21 mothers of normal infants who were heavy coffee drinkers, 10 or 47.6 percent were smokers. Although the authors conclude that no association exists in this study between heavy coffee drinking and smoking, it would be erroneous to conclude that smoking was not related to the incidence of malformations because a smaller proportion of mothers of malformed infants might have smoked more heavily than the mothers of the normal group. Medications were not taken more often by the mothers of malformed infants compared with mothers of the normal infants but heavy coffee drinkers took more medication than moderate coffee drinkers. A shorter gestation was observed with heavy coffee drinking mothers (36.2 weeks) of malformed infants compared with the other mothers of malformed infants (37.6 weeks) but this gestational effect was not pronounced when heavy coffee drinking mothers of the control infants (38.5 weeks) were compared with the lighter coffee drinking mothers of the

control sample (38 weeks). This study by Borlee et al. is widely quoted because their finding of an association between malformations and maternal caffeine use is unique. Among the congenital malformations in the study group were cleft palate and limb abnormalities, two results reported in animal offspring after high maternal doses of caffeine (Fujii & Nishimura, 1969). Caffeine intake in the Belgian study was based on the number of cups of coffee consumed which may not be appropriate but the incidence of heavy use in Belgium appears to be greater which provides an opportunity of studying more readily its effects. Gilbert (1976) quotes a 1971 per capita coffee consumption ratio of 1.78 to 1.00 when comparing Belgium to Canada. However the retrospective manner of the investigation involves selection of a group of subjects with malformations, a disorder which has a very low incidence in the general population. Such specific selection increases the likelihood of finding adverse associations.

The results of research with humans suggest that congenital malformations are not associated with typical caffeine use, as reported, during pregnancy. It is possible that with heavy caffeine use of 600 mg or more daily, an increase in malformations would be in evidence as in Borlee's study (1980) but as is apparent in several large studies, very few pregnant women report drinking this much

coffee in Canada and the United States.

Consistent with the animal literature, at doses typical of human use during pregnancy, reproductive disorders other than structural malformations have been reported in mothers and infants.

When examining the effect of maternal caffeine use on major indices of child health, such as birth weight, the contribution of other factors must be considered. Contradictory reports describing effects on birth weight, spontaneous abortions, prematurity and stillbirth have been published.

A large study, conducted by Yerushalmy (1971) in the United States from 1960 to 1967, involved 15,000 pregnant women of mixed ethnic backgrounds. Heavy coffee drinking of at least seven cups daily occurred in 13 percent of the women and 65 percent of these women were smokers. Coffee consumption was positively related to prematurity but when prematurity was considered by means of comparing heavy coffee users categorized as smokers or non-smokers, the relationship between coffee use and prematurity appeared to be explained by smoking (van den Burg, 1977). Hogue (1981) analysing the same data but employing the entire sample stratified by smoking status and gestation showed that heavy coffee consumption was related to prematurity and suggests

that caffeine consumption be considered in future research as a factor related to low birth weight.

Weathersbee et al. (1977) in a retrospective study of 800 predominantly Mormon households found that 15 of 16 pregnancies during which the women consumed at least 600 mg of caffeine daily ended unfavourably, eight in spontaneous abortions in the first trimester, five in stillbirth, and two with premature births. In 13 cases where the husband consumed more than 600 mg of caffeine daily and his wife less than 400 mg of caffeine daily, four pregnancies ended with spontaneous abortions, two with stillbirth and two with premature births. In 23 households, where total caffeine intake by both spouses was between 300 and 450 mg of caffeine daily, favourable pregnancy outcomes resulted. The authors suggest that daily caffeine intake of 600 mg or more increases the risk of fetal loss and that the toxicity may be male mediated. Caffeine intake in this study was based on the number of cups of coffee, tea and cola used. Weathersbee notes that Utah in 1971 had the highest birth rate in the United States and the lowest fetal, neonatal and infant death rates while sales of alcohol and cigarettes were approximately half the average for the United States. Although the use of alcohol, tobacco and caffeine are discouraged by Mormons, Weathersbee does not describe the alcohol and tobacco habits of the 16 women: His subsample

may include non-Mormons or caffeine-using Mormons who would also disregard restriction on alcohol and tobacco use. Weathersbee did claim to control loosely for alcohol by observing that none of the heavy caffeine users were heavy beer drinkers but inadequate consideration of the contribution of maternal smoking and alcohol use is apparent.

A prospective study of 5200 pregnant women in Germany found lower birth weight and greater incidence of prematurity and deaths in infants whose mothers were heavy caffeine consumers independent of age, parity, socioeconomic status, body weight, or the use of tobacco or beer. Again heavy coffee users tended to smoke as well (Mau & Netter, 1974: cited in Finnegan & Fehr, 1980).

Kuzma and Sokol (1982) demonstrated a consistently negative dose response relationship of caffeine and birthweight across three categories of smoking in 5093, maternal-infant pairs. Other contributing factors to the birthweight variance in the infants were gestation, prepregnancy weight, weight gain, ethnicity, maternal tobacco, alcohol and illicit drug use, parity and number of previous spontaneous abortions. Neither family income nor mother's education was found associated with birth weight.

Farkas (1978) observed tea habits of Cree Indians in

Quebec as consumption of six to ten large mugs of strong tea daily. The tea was typically steeped over low heat for several hours extracting all the caffeine (Fox & Cameron, 1970). Thus caffeine intake could reach 720 to 1500 mg depending on cup size. Farkas speculates on an association between tea intake and the fact that the infant death rate in the Canadian Indian population is double the national rate. Clearly, before any conclusions can be reached, more research is required to control for other potential contributing factors such as lower socioeconomic status and higher incidence of alcoholism.

In a prospective well-designed study of 1529 pregnant women, Streissguth (1980) examined the effects of heavy maternal caffeine use (≥ 444 mg/day) on pregnancy outcome. Caffeine intake was based on maternal consumption patterns of coffee, tea, cola and chocolate. Streissguth (1980) found that the positive association between heavy caffeine intake and reproductive loss remained after consideration of alcohol and smoking habits. In fact, incidence of prior abortions was found unrelated to either heavy alcohol or heavy nicotine use when examined separately. Caffeine use during pregnancy was also related to a decrease in the incidence of vertex presentations. A twofold increase in breech presentations was evident with daily caffeine intake of at least 444 mg and threefold increase with intake of at

least 592 mg. Maternal smoking and alcohol habits were not related to presentation, and the association between caffeine use and presentation remained when low birth weight and premature babies were excluded from the analysis. As Streissguth notes, breech presentations are related to fetal abnormalities in the form of lower fetal and placental weights, lower Apgar, more congenital anomalies, higher perinatal mortality rates, higher rates of labour complications and later neurologic and motor abnormalities. Heavy maternal caffeine use but not heavy drinking or smoking was associated with cyanosis and acrocyanosis in the neonate at the time of hospital discharge. Cyanosis may be a manifestation of apnea, one of the proposed elements of a caffeine withdrawal syndrome and evaluation at discharge when the baby is usually at least two or three days of age might allow time for withdrawal signs to emerge (Aranda, 1976).

In the large study, referred to previously, by Linn et al. (1982), low birth weight occurred more often among heavy caffeine users but when smoking was taken into account, the association disappeared. The women were all interviewed after delivery and therefore caffeine's potential effects on spontaneous abortion could not be studied. However more of the heavy caffeine users had previously experienced one or

more unfavourable pregnancy outcomes such as stillbirth and spontaneous or induced abortions. The 5.4 percent lost to the sample because of early discharge and the 2.9 percent because of refusal could have included a disproportionately high incidence of mothers who had premature births or stillbirths but whose caffeine habits are unknown. Heavy coffee drinking was associated with less toxemia, slightly higher incidence of false labour and premature delivery, premature rupture of membranes, breech birth, transverse lies and other abnormal presentations.

No reference in the literature could be found relating the ponderal index to caffeine use. Villar, Belizan, Spalding and Klein (1982) discuss the ponderal index as a means of detecting those infants who are underweight for their length as a result usually of third trimester growth reduction. Infants who have a normal weight to length ratio will have a normal ponderal index whereas infants with low birth weight for their length will have a low ponderal index. The ponderal index discriminates well between two classes of low birth weight newborns: newborns malnourished in utero have a low ponderal index and newborns exposed to nicotine in utero tend to be small-for-dates infants with normal ponderal indices. (Dalby, 1978) Such an index might give further insight into the manner of caffeine's action.

At the present time, the association between

reproductive anomalies and caffeine use is not clear and the separation of nicotine and caffeine effects is difficult. However some consistency in research with humans and between human and animal studies is evolving. The same adverse reproductive outcomes associated with heavy caffeine use have been reported by several authors: reproductive loss (Weathersbee et al., 1977; Mau & Netter, 1974; Streissguth, 1980; Linn et al., 1982); prematurity (Weathersbee et al., 1977; Linn et al., 1982; Hogue, 1981; Mau & Netter, 1974); unusual birth presentations (Streissguth, 1980; Linn et al., 1982). Although lowered birth was associated with caffeine use in the study by Linn et al. (1982) before controlling for maternal smoking, only one study indicates the persistent association after control (Kuzma & Kissinger, 1982). This finding is of interest because of similar reports in the animal literature. The higher incidence of reproductive loss with heavy caffeine use corroborates the evidence in animal studies pointing to such an association.

Fertility Male-mediated-Effects

Thayer and Kensler (1973b) showed that caffeine can reduce the fertility of male mice when administered in drinking water at doses of 300 ug per ml, a reasonable consumption level for humans. With lower caffeine concentrations, no consistent effect on fertility was noted (Thayer & Kensler, 1973a).

Caffeine has been implicated in reduced male fertility in other studies (Ax & Lodge, 1974). However it is not clear in these studies whether the presence of caffeine in food or drinking water resulted in the animals consuming less food and water. Testicular atrophy and aspermatogenesis are also possible consequences of starvation.

In an experiment with Chinese hamsters, administration of 200 ug per ml of caffeine daily for 60 days had no effect on fertility, embryonic mortality or litter size but did result in marked skewing of the sex ratio in favour of females among the progeny of treated males, a result not in evidence with progeny of caffeine-fed females and untreated males (Weathersbee, Ax & Lodge, 1975). This sex-ratio result is consistent with another report by Kuhlmann et al (1968) in research with *Drosophila*.

In fact, caffeine may have a role in increasing fertility. Caffeine solutions of 2000 ug per ml have

increased the motility and longevity of bovine (Garbers, First, Sullivan & Lard, 1971) and human (Haesungcharern & Chulavatnatol, 1973) spermatozoa. A lower concentration of 30 mg per ml increased only the motility of hamster sperm (Schoenfeld, Amelar & Dubin, 1975).

These findings may account for the change in sex-ratio described earlier. Caffeine's effect on sperm motility is greater for sperms of lower initial motility (Schoenfeld et al, 1975) and thus the slower and heavier female spermatozoa may be particularly energized increasing the possibility that they will fertilize the ovum.

Administration of caffeine to male rats at 50 mg per kg per day for four days followed by mating resulted in increased neonatal mortality of 37 percent. Three males failed to mate and five females with a positive vaginal smear for sperm did not deliver (Soyka & Joffe, 1980). At caffeine doses of 5 mg per kg per day for four days the neonatal mortality rate was 20 percent approximately double that of controls. In a study, described earlier by Weathersbee et al. (1977), including predominantly Mormon households, out of 13 heavy caffeine male users with spouses who consumed less than moderate amounts of caffeine there were four spontaneous abortions, two stillbirths and two premature births. However the small number and lack of

control for other variables reduce the significance of the large proportion.

Caffeine may have an effect on spermatogenesis and oogenesis because of increased levels of cyclic AMP. No alterations of meiotic divisions within the testes have been observed in studies but postmeiotic maturational effects altering the motility and metabolism of the sperm cells and influenced by cyclic AMP might explain the decreases in male fertility in evidence (Adler, 1970; Weathersbee & Lodge, 1977). Caffeine at high doses can inhibit normal oogenesis (Boyd, Dolman & Knight, 1965) and may be due to increased levels of cyclic AMP suppressing the ova's meiosis and resulting in fewer ova (Weathersbee & Lodge, 1977).

Drug-Interactions

Drug interactions refer to changes in the effect of a drug by the previous or concurrent presence of one or more other drugs or substances.

Psychoactive drugs can interact by one drug changing the sensitivity of the central nervous system to another, or by one drug affecting biotransformation or protein binding of another drug and thus altering the proportion of free drug in the system.

Drugs with similar actions tend to potentiate one another. Thus alcohol, a central nervous system depressant might counteract the effects of caffeine whereas nicotine, a central nervous system stimulant might potentiate them.

The prevalence and highly correlated use of both caffeine and alcohol has led to studies on antagonistic effects. However, the exact nature of the interaction between the two drugs is still not clear (Gilbert, 1976).

Studies examining the effects of maternal tobacco use have often failed to consider the additive or synergistic effect of concurrent caffeine use. More than 45 studies of over 500,000 births have confirmed that tobacco smoking during pregnancy is associated with a decrease in birth weight (Finnegan & Fehr, 1980). The dose-related effect is independent of race, parity, maternal size and weight gain, socioeconomic status and sex of child. The lowered birth

weight is not explained by shorter gestation and the infants are considered small-for-date not preterm. The incidence of spontaneous abortion, fetal and neonatal death is increased in a dose-related manner to smoking of the mother; increased maternal exposure to tobacco is associated with abruptio placenta, placenta previa, bleeding, premature and prolonged rupture of the membranes and premature delivery; association between the sudden infant death syndrome and maternal smoking both during and after smoking has been demonstrated. Causes for these events have been suggested but no firm conclusions have been reached. Yerushalmy (1971) argues that attributing causality of these events to maternal smoking is not possible at this time. Indeed, current caffeine concerns, the association between caffeine and tobacco use, the similarity of observed effects, for example lowered birth weight, abortions, prematurity, stillbirths, the similar nature of the central nervous system stimulant, all lead to questions about potentiating effects.

Summary of the Literature Review

Caffeine research is warranted because of its widely distributed and common usage, and its suggested involvement in disease and reproductive disorders. Caffeine is known to cross the placenta, to equilibrate rapidly between maternal plasma and fetus, and to be difficult to metabolize for women in mid to late pregnancy, for the fetus and for the neonate. The delayed elimination results in higher levels of exposure of longer duration.

The animal literature does include reports of the mutagenic and teratogenic effects of caffeine but only at high doses. However using dose equivalents for humans in terms of metabolic weight rather than body weight, brings the teratogenic doses in animals to conceivable heavy caffeine consumption levels for humans. Animal research involving lower caffeine doses has revealed dose-related caffeine effects in the form of lowered birth weight and resorptions in some but not all studies.

Human studies of the effects of caffeine use during pregnancy have been few in number and conflicting in their results. Only one study reports an association between congenital malformations and heavy maternal caffeine use. A decrease in birth weight, and an increased incidence of miscarriages, stillbirths and premature births have been related to caffeine use by some researchers but not by

others. A caffeine withdrawal syndrome has been suggested, with apnea and cyanosis as manifestations.

Although results have not been consistent in human or animal research, many reproductive disorders associated with heavy caffeine are common across studies. Congenital abnormalities, lowered birth weight and reproductive loss have been implicated in animal and human studies; prematurity and unusual birth presentations have been reported in several studies with humans.

Consistent with the animal literature, a threshold effect for reproductive disorder in humans involving a minimal consumption of 400 to 600 mg of caffeine daily seems probable. Considering a risk level for caffeine use underlines the importance of the strong methodological concern expressed by many researchers of valid measurement of human caffeine intake (Hogue, 1981; Linn et al., 1982; Burg, 1975; Gilbert, 1976). In the majority of human studies, the estimate for caffeine intake has been based on caffeine beverage consumption rather than caffeine consumption.

Purpose

The intent of this study was to examine the extent and changing habits of caffeine use before, during and after pregnancy and to explore the relationship of caffeine intake with reproductive events. Typical patterns of consumption for the major caffeine-containing substances were incorporated into a computation of daily caffeine intake which took into account portion size, method of preparation, strength and beverage type where applicable, for each of three years before pregnancy, each of three trimesters and the year following birth. Potential effects of caffeine use were examined with maternal and infant outcomes while recognizing the role of concomitant variables such as maternal alcohol and tobacco use, maternal age, weight, parity, and socioeconomic class. Maternal outcome variables included a history of reproductive loss and premature births, and pregnancy weight gain; infant variables included birth weight, birth length, ponderal index (birth weight/birth length ratio), head circumference, gestation, presentation at birth, Apgar, birth anomalies, and the incidence of apnea as reported by the mother on the questionnaire. Paternal coffee consumption was examined in relation to reproductive disorder and the sex-ratio of the offspring.

Research on risks associated with caffeine use in humans took the form of examination of outcome variables according to different levels of caffeine use. However because the caffeine groups were not alike in all pertinent areas, varying observations could not be attributed with certainty to caffeine use. Even if all measured pertinent factors were controlled in the design, the possibility exists that an unmeasured or unmeasurable characteristic would explain the effect (Lechat, Borlee and Bouchat, 1980). Thus the purpose of this investigation was not to attribute causality of any effect to caffeine use but to examine effects that may occur with a greater likelihood as caffeine consumption increases.

The Ottawa Prospective Prenatal Study

The subjects involved in the present study form a subsample from a large-scale on-going prospective study investigating the effects of maternal soft drug use on the offspring. The complete methodology is described elsewhere (Fried, Watkinson, Grant & Knights, 1980). As part of the larger study, pregnant women in the Ottawa area were interviewed, usually in the women's home, and optimally once in each trimester of pregnancy by trained research assistants. After written consent (see Appendix 1), verbal responses were recorded on a questionnaire designed for maximal recording ease and computer entry (see Appendix 2).

Information was collected in the following areas:

- 1.) Personal information including age, height, weight of mother and father and socioeconomic status.
- 2.) Family health history including reproductive history of mother.
- 3.) Maternal consumption of alcohol in terms of a quantity-frequency index subsequently converted to average ounces of absolute alcohol.
- 4.) Maternal and smoking habits in terms of frequency of use and brand used subsequently converted to mg of nicotine.
- 5.) Maternal marihuana habits and use of other drugs.
- 6.) Maternal nutrition by means of 24 hour dietary recall

subsequently analysed in terms of nutritional adequacy by a computer program designed for this purpose (Watkinson, 1979). Caffeine intake for that day is also computed taking into account various dietary sources and portion sizes.

Information regarding drug use was collected for pre-pregnancy and for each of the three trimesters of pregnancy. At the time of each interview, women were questioned retrospectively about all preceding time frames in an effort to check reliability of self-report.

The hospital at which the mother delivered was informed of her participation in the study and hospital staff notified the study personnel after birth occurs. A research nurse visited the hospital to collect information on the physical status of the newborn (gestation length, birth-weight, length, head circumference, Apgar scores, anomalies, temperature, pulse, etc.) and perinatal events (length of labour, presentation, analgesics and anesthetics used, time and type of birth).

Postnatal Questionnaire

The Sample

A subsample of 365 women, whose babies in the larger study, previously described, were at least one year of age were contacted by telephone to determine interest in answering a multifaceted questionnaire. Only two women declined. Of 365 questionnaires sent, 286 were returned by the previously established cut-off date of May 25, 1983. Two sets of twins were involved. The age criterion of one year was necessary to satisfy requirements for sections of the questionnaire that were unrelated to this investigation. The infants studied were born between 21/2/82 and 12/3/83. The sample of women was predominantly white middle-class and well-educated.

The Questionnaire

An explanatory letter (see Appendix 3) and the questionnaire (see Appendix 4) were mailed to all the women, who agreed to participate in the postnatal portion of the study, with a self-addressed stamped envelope. A small group of women was asked about the length of time required for completion and their general reaction to the questionnaire. Response was favourable and the average time taken to complete the questionnaire was about 30 minutes.

The questionnaire was designed to maximize ease and enjoyment for the mothers and to facilitate computer entry. Guidelines for questionnaire design for survey research were followed (Backstrom & Hurch, 1963).

The questionnaire consists of four sections, namely

- 1.) General Health and Development of Your Child
- 2.) Infant Feeding
- 3.) Lifestyle Habits
- 4.) Home/Family

Caffeine intake questions are contained in the Lifestyle Habits section along with a requested history of other drug use. Maternal and infant outcome variables of interest to this study are in the General Health and Development Section and the Home/Family sections.

The questions relating to caffeine use are described below. Options were provided to respond with "don't know" or "can't remember" codes.

Maternal caffeine use. In the seven time frames of the third, second and first year before pregnancy, the first, second and third trimesters and the year after pregnancy, the women are asked to report their typical use of coffee, tea, cola drinks or Mountain Dew, chocolate bars, chocolate drinks and caffeine-containing medication.

Question 20: Requests typical consumption of coffee in terms of

- a.) frequency of use daily
- b.) size of cup in ounces
- c.) type of coffee (regular or decaffeinated or both)
- d.) method of preparation (instant or freeze-dried, percolated, dripped, other)
- e.) description by others of strength used (strong, medium, weak)

Question 21: Requests typical consumption of tea in terms of

- a.) frequency of use daily
- b.) size of cup in ounces
- c.) type of tea (regular, green, mint, decaffeinated, other)
- d.) description by others of strength used

Question 22: Requests typical consumption of cola drinks or Mountain Dew in terms of

- a.) frequency of use daily
- b.) portion size in ounces
- c.) type (regular, without caffeine)

Question 23: Requests typical consumption of chocolate bars in terms of

- a.) frequency of use per week
- b.) portion size (small: 30g; medium: 45g; large: 60g)

Question 24: Requests typical consumption of chocolate drinks in terms of.

- a.) frequency of use per week
- b.) size of cup in ounces

Question 25: Requests typical consumption of medication in terms of

- a.) number consumed per week of specific types plus an "other" category.

Paternal coffee habits.

Question 26: Requests typical consumption of coffee in the year before pregnancy in terms of

- a.) frequency of use daily
- b.) type (regular, decaffeinated, or both)

Outcome variables. The questions relating to outcome variables are described below:

Question 8: Describes the condition of apnea and requests, if manifested, age of child at first occurrence and details regarding frequency and duration of episodes and treatment.

Question 38: Requests information about previous

miscarriages, if they occurred and in what years.

Question 39: Requests information about previous stillbirths, if they occurred and in what years.

Question 40: Requests information about premature births, if they occurred and in what years.

Rationale. The following points are offered to clarify certain aspects of the questionnaire:

a.) Difficulties arise with the representation of caffeine intake over time in terms of daily caffeine consumption. All daily indicators lose information about fluctuations in use over time but some may be more valid and reliable than others. Recollection of average use over time involves subjective calculations and bias may be introduced by varying inferences about the meaning of the term. A 24 hour dietary record narrows, unnecessarily, assessment of caffeine intake to one day's use which may not be at all representative of regular daily use.

"Typical" use of caffeine-containing substances was requested for many reasons. The typical pattern should be more readily and accurately recalled. Recollection of the typical pattern involves only memory of common practice whereas recollection of an average requires memory of all practices and a calculation. The word typical was thought

to have a more easily understood meaning than the word average for many people. Typical use gives an appraisal of extended exposure of the mother and fetus over time whereas extrapolating from a 24 hour dietary recall is hazardous.

One difficulty with the request for typical use might be variance with respect to degree. For some, total use may be defined by the typical, for others typical use may include only the most common consumption level. However the major sources of caffeine in the diet are coffee and tea and it is felt that these habits tend to be regular, not episodic, and therefore well described by typical use. Intake of other sources of caffeine such as caffeinated soft-drinks and chocolate bars may not be as well defined by typical use because of more sporadic consumption patterns but their contribution, if sporadic, to the computed daily caffeine intake is minimal. On the other hand, if their consumption is regular and frequent, classification of intake on a typical basis should be a valid representation of caffeine intake.

b.) The questions regarding use of caffeine-containing substances were, of necessity, retrospective. The assumption was made that adult coffee or tea drinking, if present, tends to be regular and frequent and thus more memorable. An option was provided to respond with a question mark symbolizing an inability to remember. Absence

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of response unless explained was interpreted as missing information.

c.) The request for information on dates of previous miscarriages was designed and ordered within the questionnaire to have minimal negative impact. The term miscarriage was felt to be less threatening than abortion. For similar reasons, no differentiation was made between spontaneous and therapeutic abortions or IUD (intra-uterine device) miscarriages. Some women may not consider therapeutic abortions as miscarriages and therefore omit the dates in their response.

Study 1: Algorithm for Computation of Caffeine Intake

An appropriate algorithm was necessary to determine the milligrams of caffeine consumed daily by the mother from the information collected on the follow-up questionnaire. Adequate published data were available for computing caffeine intake from chocolate bars and drinks, cola beverages and medications with the maternal reports of portion size and frequency of use. The values of caffeine content for these substances which were utilized in the algorithm are described in Appendix 6D. However caffeine content in tea and coffee varies greatly. To gain information on caffeine content of tea and coffee as consumed by the volunteers, samples of diverse styles of coffee and tea preparation were collected.

The Sample

Fifty-three randomly selected women, all of whom had returned a postnatal questionnaire, were contacted by telephone for consent. All agreed to participate.

Procedure

The women were requested to prepare the cup of coffee or tea as consumed in their regular sized cup, adding milk or cream but not sugar, and to cover and set aside in the refrigerator. An appointment was arranged to pick up the

samples. During the subsequent home visit, the samples were measured and poured into containers supplied by the Department of Health and Welfare. When the beverages were collected, the women were asked to describe the sample and their current coffee or tea use in terms of the questionnaire format (see Appendix 5).

The 37 samples of coffee and 16 samples of tea were analysed for caffeine concentration at the Health Protection Branch of the Department of Health and Welfare by High Performance Liquid Chromatography (Klassen & Stavric, 1983). A summary of the results appears in Appendix 6A. Comparison of the obtained caffeine values with published data (Gilbert et al., 1976; Bunker & McWilliams, 1979; Burg, 1975; Graham, 1978) was necessary either to establish congruency or to suggest advisability of using median caffeine intakes from our sample as standard values for the rest of the group.

The mothers were invited to telephone the office for the results of the coffee or tea analysis if they were interested.

Results

The median caffeine concentration for tea and the range boundaries and median caffeine concentrations for all methods of coffee preparation were lower than published data (see Table 4). Gilbert et al. (1976) collected home-

Table 4

Comparison of caffeine concentrations (ug/ml) of sample
with published data

	Median	Range	$\bar{X}$
Coffee:			
Dripped	303.9 (n=13)	174.5-740.7	379.9
	*621 (n=14)	*218 -753	***988
Percolated	352.7 (n=10)	156.7-587.7	336.9
	*436 (n=11)	*195 -1170	***561 **713
Instant	267.2 (n=10)	83.5-479.5	276.4
	*328 (n=21)	*102 -559	***399 **446
Decaffeinated	5.3 (n=3)	4.3- 8.6	
	*5 (n=3)	*2 - 8	
Tea:			
Regular	142.5 (n=14)	60.3-247.2	151.3
	*144 (n=37)	*43 -400	***280 **270
Green	316.9 (n=1)		**135
Herbal	342.1 (n=1)		
	**0		

*Gilbert et al. (1976)
**Bunker & McWilliams (1979)
***Burg (1975)

prepared samples of coffee and tea as consumed with normal additions such as cream and sugar and found lower caffeine concentrations than samples prepared in the laboratory according to manufacturers' instructions (Burg, 1975; Bunker & McWilliams, 1979). This similarity to the present findings is suggestive of modification in preparation of coffee and tea in the home. Dilution with cream or milk also would contribute to lower caffeine concentrations.

Although the sample tea concentrations and Gilbert's (1976) analysed tea values were alike, the caffeine concentrations of the coffee sample were lower when compared with Gilbert's (1976). In response to adverse caffeine publicity of recent years, mothers may be making an effort to cut down on caffeine intake by reducing the caffeine content in the cup. In addition, the price of coffee in Canada increased to over six dollars per pound in 1977 due to a severe frost in Brazil and may have changed habits of preparation. The lower caffeine content may be a result of frugality. No mention is made in Gilbert's article (1976) about the characteristics of his sample. The women in this sample are predominantly middle-class and well-educated and the possibility exists that a differential method of preparation exists with this group and that they are more susceptible to medical pressures.

Method of coffee preparation. The median caffeine con-

centrations for different methods of coffee preparation varied across the groups with the percolated method yielding the greatest caffeine concentration (352.7 ug/ml) followed by the dripolated method (303.9 ug/ml) and the instant method (267.2 ug/ml). This finding is inconsistent with published data in which the order of decreasing concentration has been drip, percolated and instant. With the recent increased popularity of automatic drip coffee-makers, it is possible that previous instant or percolated coffee users have retained preference for weaker coffee and adjusted the preparation of drip coffee to conform to their tastes.

Within each group, internal variability is high (SDs: Percolated, 134.5; Drip, 181.5; Instant, 144.3) and the range of caffeine concentration is broad (see Table 4). Considerable overlap of caffeine concentrations across groups exists (see Table 4) and a normal distribution of values is not apparent for any group (see Appendix 6B).

Assessed strength. The introduction of a self-reported strength variable was tested for predictive validity. The strength-related questions directed the responder to classify strength according to others' appraisal in an effort to reduce the subjectivity of the responses. Mothers' reports of tea and coffee strength as described by others

account for some variation in caffeine concentrations (instant coffee, $r=.68$; percolated coffee, $r=.47$; drip coffee, $r=.57$; overall coffee, $r=.56$; black regular tea, $r=.45$). Error may exist in the mothers' assessment of others' descriptions of coffee and tea strength. However strength may be assessed not by caffeine concentration but by aroma, colour, taste and other factors (personal communication: Dr. B. Stavric, Health Protection Branch).

Estimated volume. The women were asked (see Appendix 5) to estimate the size of the cup containing the sample of tea or coffee that they had prepared and the volume of coffee or tea was also measured by the interviewer. In this way the reliability of self-reported estimates of volume could be deduced. A few limitations exist with this methodology. The women were asked to estimate the cup size and not the volume of coffee or tea. However the beverage volume was measured. The reason for the cup-size request was greater simplicity for the respondent; the assumption was that women would fill their cups almost to capacity. Without exception, the assumption was found true. Although the measured volumes overall could legitimately be less than the estimated cup size, a ratio of 18:19 existed when the incidence of measured volume as less than estimated volume was compared with the incidence of estimated volume as less than measured volume.

Out of the 53 women questioned regarding cup size, 51 reported the volume in ounces and one did not give an estimate. Thus the reliability estimates were calculated in terms of ounces: 81 percent accuracy within one ounce; 96 percent accuracy within two ounces; 100 percent accuracy within three ounces. The range of volume measurement was 89 to 355 ml (3 to 12 oz); the range of estimated cup size was 89 to 296 ml (3 to 10 oz).

The measured volume of coffee and tea was uncorrelated to strength as assessed by others ($r = -.007$) indicating that in this sample, the amount consumed from one cup was not related to assessed strength. However estimated volume was more related to assessed strength ($r = .17$). Women may inflate their estimate of volume when the assessed strength is greater and/or decrease their estimate when the assessed strength is weaker.

Tea types. One sample each of herbal and green teas was collected. These proved to have the highest caffeine concentrations of all 16 samples of tea. Laboratory preparations have revealed that herbal teas contain no caffeine whereas prepared green teas contain approximately half the caffeine compared with regular tea (Bunker & McWilliams, 1979). The presence of many different types of tea on the market may lead to erroneous classification of

some teas as herbal. In this case, the women claimed to have used Loblaws Bulk Herbal Tea.

The low frequency of exclusive use of herbal or green tea (see Appendix 8B), the potential for categorizing incorrectly a tea as herbal, and the variability of caffeine content for green teas (Bunker & McWilliams, 1979) precluded a correction for these specific tea types in the assessment of an individual's caffeine intake.

Adequacy of predictors. Multiple regression analysis with the analysed caffeine concentrations as the dependent variable (excluding decaffeinated coffee) and employing median caffeine values for different methods of preparation and strength ranked as 1, 2, and 3 for weak, medium and strong coffee revealed a multiple R of .6. The strength predictor accounted for 32 percent of the variance in caffeine concentration; the median caffeine concentrations for methods of preparation added four percent. Similarly, with the analysed caffeine concentrations for tea, the strength predictor accounted for 20 percent of the variance.

In order to determine the reliability of the preparation medians and strength predictors for the caffeine concentration for coffee and the strength predictor for the caffeine concentration for tea, three methods were employed, namely, two directional single cross validation, and sampling correlational distributions from the sample and the

sample after replication. Details regarding the techniques and results can be found in Appendix 6C. Each method of coffee preparation manifested high internal variability and the methods proved not to be a reliable predictor. However the assessed strength of both tea and coffee appeared to be a reliable predictor and was incorporated into a regression equation to predict caffeine concentrations for the remaining sample.

Decaffeinated beverages. Three samples of decaffeinated coffee were collected. The strengths as assessed conformed with the analysed caffeine concentrations (Appendix 6A) and the values were consistent with published data (Table 4). A correction was built into the algorithm to take both the use of decaffeinated coffee and a combination of caffeinated and decaffeinated coffee into account. Decaffeinated tea and soft-drinks were considered as caffeine-free.

Algorithms for computing estimated daily caffeine intake. To compute a general estimate for the milligrams of caffeine ingested daily by one woman, the following steps were employed.

- 1) Milligrams of caffeine ingested daily from coffee = 8.99 (overall sample median caffeine concentration in mg/oz) * (cup size in oz) * 1 (if regular caffeinated) or $.018$ (if

.decaffeinated) or .51 (if combination) * (number of times used daily).

2) Milligrams of caffeine ingested daily from tea = 4.63 (overall sample median caffeine concentration, in mg/oz) * (cup size in oz) * 1 (if regular, herbal, green or combination of these) or 0 (if decaffeinated) * (number of times used daily).

3) Milligrams of caffeine ingested daily from caffeine-containing soft-drinks = 3.3 (standard from published data in mg/oz) * (portion size in oz) * (number of times used daily).

4) Milligrams of caffeine ingested daily from chocolate bars = 20 (if small chocolate bar - in mg) or 30 (if medium chocolate bar - in mg) or 40 (if large chocolate bar - in mg) * (number of times used weekly) * (1/7 to convert to daily use).

5) Milligrams of caffeine ingested daily from chocolate drinks = 1.7 (standard value from published data in mg) * (cup size in oz) * (number of times used weekly) * (1/7 to convert to daily use).

6) Milligrams of caffeine ingested daily from all medications = the sum of [caffeine content in mg for each specific medication * number of times used weekly * 1/7 to convert to daily use].

7) Total milligrams of caffeine consumed daily from all

sources = (1 + 2 + 3 + 4 + 5 + 6).

The second algorithm incorporating an assessed strength predictor involved the substitution of steps one and two of the preceding section with the following.

1) Milligrams of caffeine ingested daily from coffee = (cup size in oz) * 1 (if regular caffeinated) or .018 (if decaffeinated) or .51 (if combination) * (number of times used daily) * .029573199 (correction from ug/ml to mg/oz) * (65.5 + (132.4 * strength rank)).

2) Milligrams of caffeine ingested daily from tea = (cup size in oz) * 1 (if regular, herbal, green or combination of these) or 0 (if decaffeinated) * (number of times used daily) * .029573199 (correction from ug/ml to mg/oz) * (59.9 + (43.3 * strength rank)).

The transformation from the analysed concentrations in ug/ml to mg/oz was necessary to conform with the data as entered on the questionnaire. The other numbers describe the constants and regression coefficients in the multiple regression equations

Discussion

Many difficulties arise in attempts to validly measure an individual's caffeine intake. The variety of sources, caffeine variation among brands and preparation methods, portion sizes, all contribute to the complexity.

This study tried to improve on current methodology by investigating the predictive potential of some sources of caffeine variation. Including portion sizes and dietary sources of caffeine increased measurement accuracy. Strength of beverages as assessed by others also proved to have some predictive validity. However variation in the caffeine concentrations in coffee was not well explained by popular methods of preparation i.e. drip, percolated and instant but rather depended on idiosyncratic practice.

The likelihood is that the estimates of daily caffeine intake computed by the two algorithms correlate highly and that one may be substituted for the other in correlational analyses. However when categories of caffeine use are formed and risk levels are discussed, both estimates are of interest.

Study 2: Investigation of Infant Apnea as Related
to Caffeine Withdrawal

As described in the Introduction, there is a delay in maternal caffeine elimination in the second and third trimester of pregnancy (Aldridge et al., 1981) and slow fetal clearance of caffeine (Horning et al., 1975) which may lead to fetal dependence on caffeine. After birth, the infant may experience the effects of caffeine withdrawal. Because caffeine acts as a respiratory stimulant (Goldstein et al., 1974) part of the withdrawal syndrome may be breathing disturbances such as apnea (Aranda, 1976).

Substudy A: Examination of Infant's Hospital Record

The sample. Hospital records of 10 infants of the larger study's heaviest caffeine users ($x=560$ mg, $SD=455$, $range=370-1850$) as determined by 24 hour dietary recall and 10 randomly selected records of infants whose mothers did not consume caffeine.

Procedure. A letter of introduction was presented to the Medical Research Department at the Ottawa Civic Hospital informing the personnel of my involvement in the research group under the direction of Dr. P.A. Fried (see Appendix 7A). The medical records of the infants born to the mothers

in the two caffeine groups were reviewed in a blind fashion. Perinatal variables were recorded and subsequently compared for differences between the groups.

Results. No substantial differences were noted with reporting of withdrawal signs or apnea.

Discussion. Although one potential source of information regarding possible caffeine withdrawal signs, as described earlier, is the infant's hospital record, none were found with this study. However a major interference in assessing differences involved early discharge from the hospital which would not allow sufficient time for caffeine withdrawal due to the prolonged half-life of three to four days in the neonate. In addition, breast-fed children of caffeine-consuming mothers continue to be exposed and withdrawal may be more gradual.

Thus only apneic episodes as observed and reported by the mother in the questionnaire could be utilized in assessing differences.

Substudy B: Mother's Report

The sample. On the postnatal questionnaire, six women reported observing apnea with their children (see Appendix 4: question 8).

Procedure. The apnea question had been deliberately designed as limited in scope and to gain more detailed information, an interview in the mothers' homes was arranged. Questions for the home interview were developed with an aim to gain information regarding many contributing factors to apnea (see Appendix 7B). Maternal caffeine and other drug habits were unknown to the interviewer until after the data were collected.

Result. Details of the home interviews are described in Appendix 7C. Table 5 includes part of the interview data and maternal drug habits.

No connection was apparent between maternal caffeine intake and infant apnea with this small sample. Five of the six mothers consumed caffeine in their pregnancies but in each case, the caffeine intake was lower than the overall average of 172 mg of caffeine daily. The dietary sources of caffeine varied among the five users: two drank tea only, one drank tea and chocolate drinks, one consumed coffee and caffeinated soft-drinks and one woman drank tea, coffee, chocolate drinks and ate chocolate bars during her pregnancy.

Discussion. The apnea as described by the mothers is not likely associated with maternal caffeine use. The low

levels of maternal caffeine intake and the nature and age of apneic onset belie the manifestation of apnea as part of a caffeine withdrawal syndrome with these infants. One note of interest involves the prevalence of allergies which were reported with three of the six children, with all of the mothers and with three of the fathers. Although this observation may be related to the incidence of apnea, a controlled investigation into the association was beyond the scope of this study.

Table 5.
Apnea Reports as related to maternal drug habits and
allergies

Case Number	Severity		Drug Habits			Allergies		
	a	b	c	d	e	Child	Mother	Father
6		1	.02	0	85		X	
3		2	.1	0	0	X	X	X
1		3	.4	24	112	X	X	X
5		4	.6	0	56		X	X
2		5	.2	0	75	X	X	
4		5	.02	7	102		X	

- a. case numbers consistent with those in Appendix 7B
b. apnea ranked roughly in increasing order of severity
c. in oz absolute alcohol per day
d. in mg nicotine per day
e. in mg caffeine per day

Study 3: Habit Changes and Effects of Parental Caffeine

Use on Offspring

The major undertaking of the present investigation is two-fold:

- 1.) to examine alterations in patterns of caffeine use and related life-style habits before, during and after pregnancy.
- 2.) to investigate the possible relationships between caffeine habits and neonatal variables.

The Sample

The 288 returned postnatal questionnaires (see previous section entitled Postnatal Questionnaire) supplied a sample of 284 mother/child pairs and two mother/twin sets. No significant demographic prenatal differences were detected when the 79 percent who returned the questionnaire were compared with the non-responders by means of the data available with the Ottawa Prospective Prenatal Study.

Procedure

Maternal caffeine intake was estimated by the algorithms described in Study 1. The general estimate of caffeine consumption predicted without the strength

correction was used in the study of habit changes. The two estimates of caffeine intake were highly correlated and thus with the correlational techniques used in the study of habit changes, either estimate would suffice. The means and standard deviations reported may differ between the two estimates but the relative importance of the contributions of the dietary sources under study was considered stable. Both the general and strength-adjusted estimates were considered in the investigation of potential effects on the offspring because of the potential threshold effect of caffeine and the consideration of a legitimate risk level of caffeine consumption. Prepregnancy and pregnancy alcohol and nicotine use was not requested in the postnatal questionnaire but was available from the larger study. Alcohol use daily was calculated in terms of ounces of absolute alcohol from a Quantity-Frequency Index (Jessor, Graves, Hanson & Jessor, 1968). Nicotine use daily was calculated in terms of mg of nicotine by multiplying the number of cigarettes smoked by the amount of nicotine present in the brand and size used.

In order to investigate if caffeine is associated with effects above a critical intake level, caffeine use was categorized. A decision to split the sample at 300 mg of caffeine daily (0 through 300 mg; greater than 300 mg) was made because of the paucity of abstainers and very heavy

users in the sample. This breakdown yielded approximately 10 heavy users: the number in the heavy sample group varied according to time frames and the strength correction. Intake of over 300 mg daily corresponds with a frequently quoted category in the literature of about four or more cups of coffee daily (Linn et al., 1982; Rosenberg et al., 1982) and with researchers who define heavy use as more than 300 mg daily (Kuzma & Sokol, 1982).

A caffeine exposure level taking into account the mother's weight was computed. For each of the trimesters of pregnancy, the mother's weight if available for each month of pregnancy, recorded as part of the Ottawa Prospective Prenatal Study was used to determine caffeine intake per kilogram of body weight. An exposure level was also computed using the mother's prepregnancy weight. Again, a dichotomy was established with an attempt to isolate a small group containing those women most heavily exposed and compare them with the remaining sample. The boundary for the dichotomy was 5 mg/kg and was derived by selecting the previously described division of 300 mg for caffeine intake and dividing by an average prepregnant weight of 60 kg. The division at this point again produced approximately 10 women who were likely to have the heaviest exposure to caffeine.

The fathers' daily caffeine intake from coffee was

estimated by using the median concentration found in the analysed coffee samples (8.99 mg/oz), multiplying by a volume correction (seven ounces was the intermediate volume in a bimodal, six and eight, distribution of volume for maternal samples) and correcting for decaffeinated, or a combination of decaffeinated and regular coffee.

When maternal and paternal caffeine habits were investigated, data for parents of twins were included to form a sample size of 286. The multiple births were excluded from the analysis of potential effects on the infants resulting in a sample of 284 parent/child pairs.

In the larger study, perinatal information was recorded from the hospital records and included birth weight, length, head circumference, gestation, presentation, anomalies, Apgar scores and sex.

Nominal variables. With nominal dependent variables, T-tests were performed with two groups using caffeine as a continuous variable. Caffeine use was also categorized into seven groups and studied in crosstab form with the categorical dependent variables of interest. Chi-square analyses were performed when two sets of categorical variables were compared.

Ordinal variables. Ordinal dependent measures were used as dependent variables in parametric T-test analyses because of their normal distributions and because the

investigations involving these measures was limited in sample size in scope and in intent. Kendall correlation coefficients were computed when the range of categories was small and the probability of tied ranks was high; otherwise Spearman correlation coefficients were used.

Interval-type variables. Pearson product moment correlations were computed between caffeine as a continuous variable and continuous dependent variables of interest. When caffeine use was dichotomized, continuous variables were studied by means of T-tests.

Significance testing. A confidence interval of .95 was used for all hypotheses testing. In the T-test analyses, a confidence interval of .95 was also employed for homogeneity of variances between groups. If considered homogeneous, a pooled variance estimate was used; if not homogeneous a separate variance estimate was used. When studying a dependent variable, different estimates of caffeine intake and exposure resulted in varying sample groups with different variances. For some of these estimates, pooled variances were used while separate variances were required by others leading to rejection and lack of rejection of the null hypothesis with similar differences in the means.

Feed-back to mothers. The mothers will be informed of

the study results. With the larger study, approximately once a year, a letter is mailed to the mothers expressing appreciation for their participation and outlining recent research results.

Results

Characteristics of sample. The sample comprised of 286 mothers and fathers, 284 single births and two sets of twins.

The demographic characteristics of the samples are shown in Table 6. The average family income is \$31,042 (SD: 13521) which is lower than the Statistics Canada 1981 average of \$36,825 for the Ottawa metropolitan area. The mean age of the mothers in the study is 29.0 years (SD: 4.2). Four percent of the mothers did not graduate from high school, 25 percent graduated from high school, 57 percent graduated from university or college, and 13 percent have a post graduate degree. The sample of women was predominantly anglophone (77 percent) with eight percent francophone and the remainder in a mixed or other category.

For approximately one-half of the sample the infant in the mother/child pair was the mother's first child (46 percent) ; the other multipara had from one to seven previous children. The pregnancy under study was the first

Table 6
Maternal and Perinatal Variables
Descriptive Statistics and Correlations
with Caffeine Consumption

Variable	Mean	Range	SD	r with prepregnancy caffeine consumption	r with pregnancy caffeine consumption
Maternal:					
Age (yrs) a	29.0	18-40	4.2	.05	.07
Education	2.8	1-4	.7	-.08	-.12*
Family Income	31,042	2,421- 80,000	13,521	.16**	-.03
Gravida	2.2	1-9	1.3	.02	.19**
Parity	.7	0-7	.9	-.02	.17**
Weight before pregnancy (kg)	58.3	41-102	9.3	.08	.18**
Pregnancy weight gain (kg)	14.6	0-45	5.0	.06	-.08
Perinatal:					
Length of labour (hr)	16.8	1-95	25.9	-.07	-.05
Length of gestation (wk)	39.7	24-43	1.7	.04	.02
Birth weight (g)	3519	670-4840	511	.04	.02
Birth length (cm)	51.4	31-58	2.7	-.02	.002
Head circum- ference (cm)	34.6	22-39	1.7	.02	-.02
Apgar 1 min.	8.1	1-10	1.5	.04	.08
Apgar 5 min.	9.3	1-10	.9	.01	.01

**p< .01

*p< .05

a

Code 1: did not graduate from high school
 Code 2: graduated from high school
 Code 3: graduated from college or university
 Code 4: obtained a post-graduate degree

for 35 percent and ranged from the second to the ninth for the remaining sample.

One hundred and forty-three male infants were born compared with 139 females. The most common type of birth was spontaneous (49 percent) followed by low forceps (24 percent), Caesarian sections (13 percent) and midforceps deliveries (12 percent). Head presentation was usual (85 percent) and the incidence of breech was two percent.

The women in this study who consumed a heavier intake of caffeine prepregnancy tended to have higher family incomes and during pregnancy tended to be more poorly educated, heavier in weight, and to have had more pregnancies and more children.

Relationships among estimates of caffeine intake. The larger study's estimate of caffeine intake, by means of a 24 hour dietary recall correlated significantly with the total estimated caffeine intake in the present study ($r = .52$, $p = .001$).

The estimated individual caffeine intake based on an assessed strength correction correlated highly with the unadjusted estimated in the seven time frames studied (r s: never less than .94).

Caffeine use: Proportion of women. In each of the three years preceding their pregnancies, 99 percent of the women consumed caffeine. For the first, second and third

trimesters of pregnancy, 91, 93 and 93 percent, respectively, reported caffeine intake. In the year following pregnancy, 98 percent of the women claimed caffeine use.

The proportions of women who use each source were very stable over the three prepregnancy years and also over the three trimesters of pregnancy (see Figure 2). Thus an average for the number of women who used each source of caffeine was computed for the prepregnancy years, and for pregnancy. For the period before pregnancy 74 percent used coffee, 63 percent tea, 20 percent caffeinated soft-drinks, 34 percent chocolate bars, 17 percent chocolate drinks and 17 percent caffeinated drugs. For the pregnancy period, 51 percent used coffee, 56 percent tea, 16 percent caffeinated soft-drinks; 32 percent chocolate bars, 20 percent chocolate drinks, and 3 percent caffeinated drugs. In the year after pregnancy, 69 percent consumed coffee, 66 percent tea, 20 percent caffeinated soft-drinks, 30 percent chocolate bars, 17 percent chocolate drinks and 12 percent caffeinated drugs.

It should be emphasized that the respondents who could not remember intake (see Appendix 8F) were excluded from these proportions. The declared abstainers number an average of 3 (1 percent) prepregnancy, 20 (7 percent) during

Figure 2. Distribution of maternal daily use of various sources of caffeine for the seven time frames.

- - total: percent of mothers consuming caffeine.
- ▼ - coffee: percent of caffeine users consuming coffee.
- * - tea: percent of caffeine users consuming tea.
- ▲ - chocolate bars: percent of caffeine users consuming chocolate bars.
- - caffeinated soft-drinks: percent of caffeine users consuming caffeinated soft-drinks.
- - caffeinated drugs: percent of caffeine users consuming caffeinated drugs.
- - chocolate drinks: percent of caffeine users consuming chocolate drinks

pregnancy and 5 (2 percent) in the year following pregnancy.

Caffeine use: Quantity of intake. Distributions for total caffeine intake and for frequency of use for all dietary sources of caffeine are included in Appendix 8A.

The users' means for total caffeine are shown in Figure 3. Again intakes over the prepregnancy years as well as the trimesters are similar allowing the use of averages as reasonable statistical indicators. In the three years before pregnancy, caffeine users had an average daily intake of 173 mg of caffeine (1 - 1134), during pregnancy an average of 108 mg (1 - 867) and after pregnancy 148 mg (1 - 719). Coffee drinkers averaged 156 mg (1 - 1079) before pregnancy, 98 mg (1 - 719) during pregnancy, and 124 mg (1 - 19) after pregnancy. Tea drinkers consume an average of 69 mg (0 - 370) prepregnancy, 63 mg (0 - 370) during pregnancy and 70 mg (0 - 370) after pregnancy. For caffeinated soft-drink users, the prepregnancy average was 29 mg (0 - 119), the pregnancy average 28 mg (0 - 132) and the after pregnancy average 26 mg (0 - 89). Chocolate bar users consumed a consistent average of 6 mg (1 - 30) caffeine over prepregnancy, pregnancy and after pregnancy. Chocolate drink users averaged 5 mg (1 - 47) prepregnancy, 4 mg (1 - 17) during pregnancy and 4 mg (1 - 14) after pregnancy. Users of caffeinated drugs consumed a daily average 17 mg (3 - 23) of caffeine prepregnancy, 46 mg (4 - 450) during

Figure 3. Distribution of mean quantity (mg) of maternal daily use of various sources of caffeine for the seven time frames.

- - total: mean intake of users.
- ▼ - coffee: mean intake of coffee users.
- ★ - tea: mean intake of tea users.
- - soft-drinks: mean intake of soft-drink users.
- - caff. drugs: mean intake of caffeinated drug users.
- ▲ - choc. bars: mean intake of chocolate bar users.
- - choc. drinks: mean intake of chocolate drink users.

pregnancy and 17 mg (4 - 94) in the year after pregnancy.

Mean contributions of various dietary sources to total caffeine intake (see Table 7) are stable over the prepregnancy years with coffee the main contributor followed by tea. During pregnancy coffee's contribution declines but persists as the major element in the caffeine total intake. Tea, caffeinated soft drinks, chocolate bars and chocolate drinks, all contribute more to the total caffeine intake during pregnancy. During the year after pregnancy, habits almost return to prepregnancy contribution levels.

Correlations among dietary sources. Table 8 describes the correlation between sources of caffeine use. The positive association between tea and coffee use is apparent before and during pregnancy but is not consistent in all the time frames. Chocolate bar use is consistently associated in a direct fashion to coffee consumption in the non-pregnant state. Caffeinated soft drink and chocolate drink intake are directly related to tea and coffee use sporadically over the seven time frames.

Changes in caffeine intake. The decline in mean caffeine use during pregnancy (see Figure 3) was further investigated on an individual basis. The absolute difference in caffeine use for each individual was computed between all combinations of time frames. The mean

Table 7

Contributions of Dietary Sources
to Total Caffeine Use (percent)

	3rd year pre	2nd year pre	1st year pre	1st tri	2nd tri	3rd tri	Year after
Coffee	68	68	69	56	55	52	61
Tea	26	26	26	37	39	39	33
Caffeinated soft drinks	3	3	3	5	5	4.5	3.5
Chocolate bars	.7	.7	.7	1	1	2	.8
Chocolate drinks	.3	.4	.4	.8	.7	.6	.3
Caffeinated drugs	1.6	1	2	.7	.8	2	1

Table 8

Pearson Product-Moment Correlations^a
for Various Caffeine Sources for Users in all Time Frames

	Coffee	Tea	Caffeinated soft-drinks	Chocolate bars	Chocolate drinks	Caffeinated drugs
Coffee						
		1: .23**	7: -.30*	1: .46**	4: .36*	
		2: .35**		2: .42**	5: .35*	
		4: .21*		3: .37**	7: .44*	
		6: .23*		7: .43**		
Tea						
			5: .45*		3: .65**	
			7: .34*			

**p < .01

*p < .05

^a

Time frames are represented by:

- 1: 3rd year before pregnancy
- 2: 2nd year before pregnancy
- 3: 1st year before pregnancy
- 4: 1st trimester
- 5: 2nd trimester
- 6: 3rd trimester
- 7: Year after pregnancy

differences are described in the matrix in Table 9. Cluster analysis (see Figure 4) revealed three predominant groups of the three time periods before pregnancy, the three trimesters of pregnancy and the year after pregnancy. The most dissimilar groupings are the three prepregnancy time frames compared with the three trimesters of pregnancy. The average habit change involving the year after pregnancy was similar when compared with prepregnancy and pregnancy.

The proportion of women changing their caffeine habits across all seven time frames is described in Table 10. Across the prepregnancy period and during pregnancy, approximately two-thirds of the women did not change their caffeine consumption and the remainder was split almost equally into those who increased and those who decreased caffeine intake. Sixty-two percent of newly pregnant women decreased while only eight percent increased their intake; conversely 56 percent after pregnancy increased while nine percent decreased their intake ($\chi^2 = 72.5$, $p < .001$).

The decrease in overall mean caffeine intake as well as the number of users persisted throughout pregnancy. The principal source for the decrease was a reduction in the prevalence of use and mean caffeine intake from coffee. Tea users also decreased in number and the quantity of caffeine intake during pregnancy. Although the number of women drinking caffeinated soft-drinks decreased during pregnancy,

Table 9

Means of Absolute Change in Individual Caffeine

Intake between Time Frames

	3rd year pre	2nd year pre	1st year pre	1st tri	2nd tri	3rd tri	Year after
3rd year pre		17	31	83	84	89	67
2nd year pre			21	81	83	88	64
1st year pre				76	77*	82	54
1st tri					19	30	63
2nd tri						14	55
3rd tri							56

Figure 4. Results of cluster analysis of the means of absolute change in individual intake between time frames.

Table 10

Percent of Women with Changing
Caffeine Habits over the Seven Time Frames

	Increase	Decrease
Third - second year before pregnancy	15	11
Second- first year before pregnancy	19	13
First year before pregnancy- 1st trimester	8	62
1st trimester- 2nd trimester	16	13
2nd trimester- 3rd trimester	12	12
• 3rd trimester- year after pregnancy	56	9

the average caffeine intake remained approximately the same. Habit changes during pregnancy were not apparent for chocolate bar or drink use. Although users of caffeinated drugs declined in number during pregnancy, the mean caffeine intake among the users was higher in all three trimesters.

Fathers' coffee habits. The mean overall number of cups for the fathers was 2.8 (SD 2.3; 0 - 13) and the users' mean was 3.4 (SD 2.1). The fathers' overall use in terms of cups of coffee was positively associated with maternal caffeine consumption from coffee except for the second and third trimesters of pregnancy and the total intake in all time frames except for the third trimester (r_s .13 - .3, $p = .001 - .014$)

Changing patterns from 1978 to 1982. Consumption levels of various sources of caffeine according to specific years are described in Table 11. The criterion for assignment to one specific year was the birthdate of the child.

A division between 1979 and 1980 yielded an approximately equal split in sample size. Comparison of the mean caffeine intake levels in the two groups reveals a decrease in intake levels in five of the seven time frames with the two exceptions being the third trimester and the year after pregnancy. A further breakdown into mean caffeine consumption in each of five years, 1978 to 1982

Table 11

Mean Caffeine Intake According to
Specific Years (mg/day)

	% of cases	3rd year pre	2nd year pre	1st year pre	1st tri	2nd tri	3rd tri	Year after
1979	97	178	175	171	108	104	98	144
1982	107	170	169	169	100	95	99	148
1978	81	197	196	180	114	118	117	139
1979	88	169	166	168	104	98	90	146
1980	84	179	184	182	104	98	98	145
1981	80	166	159	159	93	88	98	147

*Year is defined by birthdate of the child

showed general decline in use during the prepregnancy years, consistent decrease in caffeine use during pregnancy and some decline from 1978 to 1981, and a consistent increase in intake from pregnancy to postpregnancy but little change in use from 1978 to 1981 for the period after pregnancy. The small sample size of 8 for 1982 hindered the interpretation for that year and was not considered.

The proportion of women using various sources of caffeine from 1978 to 1982 inclusive was examined. Again the women were grouped according to the birthdates of their children. Although the proportions using each source vary slightly over the years, no directional trend is in evidence other than an increase in tea and chocolate drink users.

Mean caffeine intakes from various sources by users according to the child's birthdate are presented in a series of tables (see Appendix 86). Statistics for the year 1982 are poor indicators because of the small sample size. Similarly for the less popular caffeine sources, the smaller numbers involved hinder the interpretation. No obvious trends over the years studied are observed with the mean caffeine intake of chocolate bars and drinks and caffeinated drugs. With caffeinated soft drinks, a decline in use is apparent in prepregnancy years from 1978 to 1981 inclusive while use during and postpregnancy shows erratic variation. The mean caffeine intake from tea shows no association with

the years studied. During each of the prepregnancy years, the mean caffeine intake from coffee shows a general decline from 1978 to 1981 but was not related to the span in years for during and postpregnancy.

Relationships with other life style habits before and during pregnancy. Correlations of caffeine use before and during each trimester of pregnancy with other life-style habits reveal a strong association with nicotine use for all four time frames and with alcohol use in the first and second trimesters of pregnancy. When all three habits were categorized and correlated, strong associations were apparent before and during each of the trimesters of pregnancy ($p < .01$) with the sole exception of a weaker association between alcohol and nicotine use in the third trimester of pregnancy ($p = .15$). Caffeine intake was categorized into 12 groups (0, > 0 to 50, > 50 to 100, > 100 to 150, > 150 to 200, > 200 to 250, > 250 to 300, > 300 to 350, > 350 to 400, > 400 to 450, > 450 to 500, > 500 mg caffeine daily); alcohol use into four groups (0, .01 to .13, .14 to .85, > .85 oz alcohol daily); nicotine use into three groups (0, .1 to 15.9, > 16 mg nicotine daily). The alcohol and nicotine categories are based on previously published reports (Fried et al., 1980).

Using the alcohol, nicotine and caffeine data as

interval or continuous variables, total caffeine intake and contributions from various sources were correlated with alcohol and nicotine use (see Appendix 8H). The main contributors to the strength of the correlations between caffeine use and the other habits were coffee and tea use. Caffeinated soft-drinks are also highly correlated with nicotine use in the prepregnancy year and the second and third trimester.

When individual coffee habit changes from the prepregnant to the pregnant state were correlated with individual alcohol and nicotine changes, no association was in evidence (r : nicotine and coffee change = $-.1$ $p = .34$; r : alcohol and coffee change = $.04$ $p = .36$). Tea habit changes were not associated with nicotine habit changes (r : nicotine and tea change = $-.01$, $p = .49$) but with alcohol habit changes (r : alcohol and tea change = $-.35$ $p = .007$).

Further investigation of habit changes into pregnancy involved creating specific habit combinations (see Table 12). Across all habit combinations, the greatest proportion of women reduced their alcohol consumption from prepregnancy into pregnancy. Approximately 50 percent reduced nicotine, and 40 percent coffee into pregnancy. Tea however was reduced by only approximately 9 percent and the incongruence of the alcohol and tea proportions is consistent with the previously quoted inverse habit change relationship.

Table 12

Habit Changes into Pregnancy

Percent of women who reduced:

Habit Combinations	N	All habits in combination	Alcohol	Nicotine	Coffee	Tea
Alcohol Nicotine and Coffee	47	31	96	45	49	-
Alcohol Nicotine and Tea	32	5	84	55	-	10
Alcohol and Coffee (no nicotine)	82	27	73	-	35	-
Alcohol and Tea (no nicotine)	104	7	82	-	-	8
Coffee (no nicotine no alcohol)	3	-	-	-	0	-
Tea (no nicotine no alcohol)	3	-	-	-	-	0

*No-one in the study smoked and drank tea or coffee without consuming alcohol and no-one smoked and drank alcohol without consuming coffee or tea.

Comparison of estimates of caffeine intake and exposure.

Both the general and strength-adjusted estimates of caffeine intake (mg) and exposure (mg/kg) were investigated with all outcome variables but only the more discriminating were reported.

Incidence of miscarriages, stillbirths and prematurity.

For pregnancies within the four time frames of the third, second and first years before the study pregnancy and the year following the study pregnancy, 35 miscarriages were reported: 31 unique cases, one woman who miscarried three times once in each of the pre-pregnancy years, one woman who miscarried in the second and first year before pregnancy and another who miscarried in the third and second year before pregnancy. Six premature births were reported but there was no incidence of stillbirths in the seven time frames.

For each time frame of miscarriage or prematurity occurrences, total mean caffeine intake from both estimates as well as mean intake from various sources were compared between the miscarriage/prematurity groups and the remaining sample. The total mean caffeine intake from the general estimate for each time frame is presented in Table 13. Sporadic significant differences occurred between the groups with various sources of caffeine but when weighted averages of the varying samples sizes for the four time frames were

Table 13

Relationship between Total Caffeine Intake in Time Frames
and the Incidence of Miscarriage and Prematurity

<u>X (mg caffeine)</u>				
<u>Miscarriages</u>				
	<u>Caffeine Users</u>		<u>Total Sample</u>	
	<u>miscarriage</u> <u>group</u>	<u>remainder</u> <u>of sample</u>	<u>miscarriage</u> <u>group</u>	<u>remainder</u> <u>of sample</u>
3rd year pre	248 (n=10)	172 (n=258)	248 (n=10)	169 (n=261)
2nd year pre	162 (n=8)	173 (n=263)	144 (n=10)	171 (n=264)
1st year pre	153 (n=13)	172 (n=260)	153 (n=13)	171 (n=262)
Year after	155 (n=2)	148 (n=265)	155 (n=2)	145 (n=270)
<u>Prematurity</u>				
	<u>Caffeine Users</u>		<u>Total Sample</u>	
	<u>prematurity</u> <u>group</u>	<u>remainder</u> <u>of sample</u>	<u>prematurity</u> <u>group</u>	<u>remainder</u> <u>of sample</u>
3rd year pre	165 (n=3)	175 (n=265)	164 (n=3)	172 (n=268)
1st year pre	259 (n=2)	170 (n=271)	258 (n=2)	169 (n=273)
Year after preg	170 (n=1)	148 (n=266)	170 (n=1)	145 (n=271)

computed for the miscarriage and prematurity groups and for the remaining samples, only small differences were apparent (see Table 14) except for drug intake. Noteworthy, however is the consistently greater mean caffeine intake from coffee, tea, caffeinated drugs and total sources for the miscarriage group when compared with the remaining sample. Although the mean caffeine intake from coffee was lower for the prematurity group, the inverse was true for tea consumption.

The mean caffeine intake from caffeinated medication was greater for all time frames when the groups were compared and this increase was apparent with the weighted overall average (see Table 14). The proportion of women using drugs in the miscarriage and prematurity groups was compared to the average number of women using drugs over the three pregnancy periods in the remaining sample. A significantly greater proportion of women in both the miscarriage and prematurity groups when compared with the remaining samples used caffeinated drugs (miscarriage group vs remainder : $\chi^2 = 44.8$, $p < .01$; prematurity group vs remainder : $\chi^2 = 9.6$, $p < .01$)

When the proportion of women using tea and coffee was compared across groups, a significantly greater number of coffee and tea drinkers was found in the group who had miscarried than in the rest of the sample (Tea: $\chi^2 = 5.9$,

Table 14

Relationship between Caffeine
Intake and Incidence of Miscarriage and Prematurity

	mg (mg caffeine)			
	Miscarriages		Prematurity	
	miscarriage group	remainder of sample	prematurity group	remainder of sample
Maternal coffee intake	111	127	94	125
Maternal tea intake	50	44	94	43
Maternal caffeinated medication	23	2	14	2
Total maternal caffeine intake	179	166	197	162
Paternal coffee intake	166	156	151	157

$p(<.02$; Coffee: $\bar{X}^2 = 7.96$, $p(<.01)$.

Alcohol and nicotine data were available for the year before the study pregnancy and were studied in relation to the incidence of miscarriage in that prepregnancy year. The average alcohol consumption for the miscarriage group (0.53 ounces absolute alcohol daily) did not vary significantly from the remainder of the sample (.50 oz absolute alcohol daily) nor did the number of alcohol users across the two groups. The number of smokers was not related to the incidence of miscarriage; the mean nicotine exposure was higher in the miscarriage group (6.6 mg nicotine daily) than the rest of the sample (4.0 mg nicotine daily) ($p = .325$).

Average caffeine use over the three years before pregnancy and average caffeine use during pregnancy were studied in relation to the total number of reported previous miscarriages. Although no dose relationship was noted, four of the six women who experienced three or more previous miscarriages reported higher caffeine intake both prepregnancy ($\bar{X} = 340$ mg, range 226 - 478 compared with users' overall mean of 173 mg) and during pregnancy ($\bar{X} = 220$ mg, range 143 - 299 compared with a users' overall mean of 108 mg). All six women consumed caffeine before and during their pregnancies ($\bar{X}$ before = 250 mg, range = 27 - 478; $\bar{X}$ during = 170 mg, range = 27 - 299).

No association was found with the incidence of coffee or tea use and the occurrence of premature births. When the use of caffeine during pregnancy was related to premature births in the study pregnancies, again no association was observed ($r = .02$).

The mean number of cups of coffee for the fathers of the miscarriages was 3.1 (SD 2.5) which is higher than the remaining sample ($\bar{x} = 2.8$ SD = 2.3). Five mothers reported coffee use by the father but did not know the quantity consumed. Four fathers (13 percent) did not drink coffee according to the mothers' reports. Two fathers drank decaffeinated coffee and one a combination of decaffeinated and regular.

The mean number of cups of coffee for the fathers of the premature babies was 3.3 (SD 2.6) which is also higher than the remaining sample ($\bar{x} = 2.8$ SD = 2.3).

However no association was found between the proportion of fathers drinking coffee or the mean caffeine intake from coffee and the incidence of miscarriage or prematurity.

Sex Ratio of Infants. The sex ratio of infants was studied from the perspective of the fathers' caffeine consumption. The 259 father/single birth pairs were approximately evenly divided with 137 male and 122 female babies. The average paternal caffeine intake did not differ significantly between the two groups ($I = .64$, $p = .52$): the

fathers of male babies consumed an average of 161 mg of caffeine daily; the fathers of female babies, an average of 150 mg daily. Categorizing the fathers intake into six groups (0, > 0 and < 100, > 100 and < 200, > 200 and < 400, > 400 and < 500, > 500) and comparing the offspring ratio revealed no association between heavier paternal caffeine intake and a increased proportion of female infants.

Caesarian sections and breech presentations. A breech presentation often promotes a decision to perform a Caesarian section and therefore the two variables are considered as an interrelated pair.

Caesarian sections occurred with 13 percent of the births under investigation; breech presentation occurred with 1.8 percent.

Total caffeine use in the third trimester was categorized and studied in relation to the incidence of both Caesarian sections and breech presentations. The mothers of the four infants presenting in breech position were all light caffeine users (< 100 & < 100mg of caffeine daily). A general decline occurred in the proportion of Caesarian sections as opposed to other types of birth across categories of increasing caffeine use. The mean caffeine intake of the Caesarian section mothers was less than that

of the control group when third trimester (79 mg daily vs 102 and 80 vs 101 with the strength corrected estimate of caffeine intake) and average over pregnancy (86 mg daily vs 103 and 78 vs 84 with the strength corrected estimate) intakes were considered.

Perinatal variables. The perinatal variables under investigation are length of gestation, length of labour, birth weight, birth length and head circumference, Apgar and birth anomalies. A ponderal index was also computed ((birth weight in kg/birth length in cm) * 100).

Alcohol and nicotine use during pregnancy. When Pearson correlations were computed with the perinatal variables under study, no significant associations were found with alcohol use during pregnancy, and pregnancy nicotine use was only found associated with birth weight and birth length.

Dichotomized caffeine intake (0-300mg; >300mg) for the third trimester and a pregnancy average both strength-adjusted and general, was compared with T-tests for differences in average nicotine and alcohol use over pregnancy. Mean alcohol consumption was consistently though not significantly lower in the heavier caffeine group in each comparison. Mean nicotine use by the heavier caffeine group was consistently higher and significantly in the case of the strength-adjusted caffeine intake average over

pregnancy ($\bar{x}$ = 11.7 mg versus 2.2 mg for the remaining sample; t = 2.87, p = .017).

The strong relationship between nicotine and caffeine use and the association of nicotine use with some of the perinatal variables required attention in the form of statistical control and/or interpretation of an additive or potentiating relationship between caffeine and nicotine exposure.

Apgar 1 and 2. The distribution of Apgar scores was consistent across all categories of caffeine use for Apgar 1 and across categories of caffeine use to 300 mg daily with Apgar 2 at which point, the proportion of perfect scores, (10) was higher with the lighter caffeine users than with heavier users (χ^2 = 2.78, p < .1). The proportion of scores less than 7 did not vary significantly between the two groups.

Length of Labour. No association was found between length of labour and estimates of caffeine intake or caffeine exposure after adjustment for mother's prepregnancy and pregnancy weight.

Gestation. The length of gestation was estimated using the date of the last menstrual period. In cases where this information was not available, anthropometric measurements and ultrasound data were used. Pearson correlations

revealed no significant association between gestation and caffeine, alcohol, or nicotine use during pregnancy.

When caffeine use was dichotomized into heavy versus light or non-users, no differences in gestation were apparent for the two groups.

Corrections of caffeine intake for mothers' prepregnancy and pregnancy weights also resulted in a lack of significant association.

Head circumference. Head circumference was not correlated significantly with caffeine, alcohol or nicotine use during pregnancy nor with mother's weight corrected estimates of caffeine exposure.

When the strength-corrected average caffeine use was grouped the mean head circumference was significantly smaller in the heavier consumption group, 33.5 cm compared with 34.6 cm in the remaining sample ($T = 2.17$, $p = .03$) a difference that did not disappear after adjustment for nicotine intake (Ancova: $F = 5.5$, $p = .019$) and mother's education ($F = 4.14$, $p = .04$). However when the estimate of caffeine exposure based on the mother's prepregnancy weight (mg/kg) was used, this significant association was diffused ($T = 1.6$, $p = .1$).

Within the heavy group, a correlation was performed to investigate a dose relationship. A positive relationship was significant suggesting that heavier caffeine use within

the group was associated with larger head circumferences (Pearson: $r=.66, p=.009$; Spearman: $r=.73, p=.004$).

Birth Length. Pearson correlations did not reveal any significant association between birth length and caffeine or alcohol use during pregnancy. A negative relationship was apparent with average nicotine use during pregnancy ($r = -.10, p = .039$).

When caffeine use was dichotomized, no significant differences in birth length were present.

When the mothers' prepregnancy and pregnancy weights were incorporated into the estimate of caffeine intake no significant associations resulted.

Birth weight. Pearson correlations between birth weight and use of caffeine and alcohol were not significant. Pregnancy nicotine use was negatively related ($r = -.11, p = .026$).

However, when the strength adjusted estimate of average caffeine use over pregnancy was dichotomized, a significant decrease in average birth weight was observed with the heavier users, 3158 g compared with 3537 g for the remaining sample ($T = 2.48, p = .014$). Pearson and Spearman correlations within the heavy group as assessed by the strength adjusted average over pregnancy revealed a positive relationship between caffeine use and birth weight (Pearson:

$r=.64$, $p=.01$; Spearman: $r=.49$, $p=.05$). Within the heavy group, 10 of the 12 women had babies with lower birth weights than the average of the remaining sample and four infants weighted under 3000 g. The range in gestation was 38 to 43 weeks. Estimates of caffeine intake ranged from 301 mg to 632 mg with a mean of 424 mg and a standard deviation of 130. Table 15 describes the major variables of concern for the 12 heavier users as defined by the strength-adjusted estimate of caffeine intake.

The difference in the birth weights between the two groups remained after controlling for nicotine use in pregnancy ($F = 5.09$, $p = .02$) but not after controlling for mother's education ($F = 3.5$, $p = .06$). The average educational level for mothers in the heavy group was 2 compared with 2.8 in the remaining sample ($F = 3.7$, $p = .000$). The codes for education range from 1 to 4 in the direction of more education. Average parity was higher and average family income lower in the heavier caffeine group but neither difference was significant ($p=.33$ and $p=.16$, respectively). Although not statistically significant, third trimester comparisons of dietary intake based on the 24 hour dietary recall record indicate lower average intake for the heavier caffeine group of calories, protein, calcium, vitamin A, thiamin, riboflavin and vitamin C. Average niacin and iron intakes were very similar. The average

Table 15

Description of Heavy Caffeine Users^a

Case #	Daily Caffeine Intake (mg)	Birth Weight	Gestation	Nicotine use during preg. (mg daily)	Mothers' Educ ^b
1	557	2860	40	32.5	3
2	469	3080	40	11	missing
3	337	3175	39	20	1
4	381	3140	39	20	1
5	631	3400	39	60	1
6	313	2630	38	0	2
7	313	2980	41	0	3
8	516	3750	40	4	1
9	313	2610	40	16	3
10	632	3990	43	6	2
11	324	3100	40	17	3
12	301	3184	39	0	2
Remaining Sample (N:248)	86	3537	39.7	2.2	2.8

^a Those women who consume on average during pregnancy more than 300 mg caffeine daily as defined by a strength adjusted estimate

^b

- Code 1: did not graduate from high school
- Code 2: graduated from high school
- Code 3: graduated from college or university
- Code 4: obtained a post-graduate degree

nutrient intake levels for both groups approached or exceeded recommended standards.

Estimates of caffeine exposure based on the mothers' pre-pregnancy and pregnancy weights and expressed as a ratio of mg/kg, similarly were not significantly related to birth weight. However, when the general estimate of caffeine exposure during pregnancy was dichotomized (≤ 5 mg/kg; > 5 mg/kg) and birth weights compared, significant differences were noted. The mean birth weight of the infants for the more heavily exposed caffeine group was 3125 g compared with 3535 g for the infants of the remaining sample ($T=2.46$, $p=.014$). The significant difference between the groups persisted after controlling for average nicotine use during pregnancy ($F=5.35$, $p=.021$). Although not statistically significant, the more heavily exposed group had a lower average family income and educational level. Parity was higher with this group, significantly in the case of average pregnancy exposure ($T=2.46$, $p=.014$) but did not account for the difference in birth weight which remained significant after its control ($F=6.5$, $p=.01$).

Ponderal index. Estimates of caffeine intake and exposure were not correlated significantly with the ponderal index.

When caffeine intake was dichotomized (≤ 300 mg,

)300mg), no significant differences were apparent with the mean ponderal index. The strength-adjusted estimate of average caffeine intake yielded the greatest difference in the means ($T=1.87, p=.06$) with the heavier caffeine group having a lower average ponderal index.

Birth anomalies. Anomalies present at birth were recorded in the delivery room and may include minor malformations, meconium aspiration, or the umbilical cord around the baby's neck.

When caffeine use was dichotomized little difference was evident in the incidence of birth anomalies between the two groups: 42 percent (5 of 12) recorded anomalies in the heavier caffeine group (based on strength-adjusted estimate) compared with 41 percent (97 of 338) in the remaining sample. Of the five anomaly incidences in the heavier caffeine group, three infants had the umbilical cord wrapped around their necks and one of these children also was suctioned for meconium aspiration. With another infant the cord presented first and the fifth anomaly occurrence was a failure to progress in labour because of second stage malposition.

Discussion

A summary of the major findings of the present study is as follows:

- 1.) Caffeine habits change from prepregnancy to pregnancy. Fewer women consume caffeine and those who continue with caffeine intake into pregnancy tend to reduce the amount. Coffee is the major contributor to caffeine intake and is the major source of the decrease in pregnancy.
- 2.) Negative reproductive effects of caffeine use were not apparent at lower ranges of caffeine use. However, women who consumed over 300 mg of caffeine daily during pregnancy gave birth to lighter babies with smaller head circumferences, on an average, than the remaining sample with no significant differences in length.
- 3.) No striking relationship was noted between maternal or paternal caffeine intake and the incidence of prematurity or miscarriage other than an increased number of women in the miscarriage group who consumed coffee or tea in their affected pregnancies.

Confounding variables. In studies of this nature, women are not randomly assigned to groups and thus other factors potentially related to the criterion variables may be disproportionately distributed across the groups under study. The role of these confounding variables must be

recognized and dealt with in the interpretation of research results. One method is to measure and statistically control other variables that are related to the dependent variable and independent variable of interest. Alternatively, other contributing independent variables can be viewed in association with the group membership as designated so that events naturally occurring together are explained together.

The relationship of family income and education to caffeine use before and during pregnancy is interesting. No reference in the literature could be found to describe these relationships. In this study, caffeine use during prepregnancy but not during pregnancy is positively related to family income whereas education is negatively related to caffeine use during but not before pregnancy. Caffeine use rarely increases into pregnancy so the likelihood is that women with higher family incomes use more caffeine prepregnancy and then reduce their habits into pregnancy. In addition the better educated women drink less coffee during pregnancy as compared to prepregnancy. Thus a picture emerges of the more well-educated upper middle-class possibly better informed women reducing exposure to a drug during pregnancy.

Although education was not statistically related to birth weight its relationship to caffeine use during

pregnancy prompted further investigation. The birth weight difference between the heavier caffeine users' infants and the remaining sample is explained partially by the mothers' education which varies significantly between the two groups. It seems probable that the more poorly educated women tend not to reduce their caffeine habits and that the caffeine is more responsible for the birth weight difference. However, it is also possible that some associated aspect of having lower education may be responsible for the effect.

No significant relationships were noted between any of the dependent variables under investigation and alcohol use. Maternal alcohol use during pregnancy has been investigated by many researchers. Whereas heavier social drinking has been found to be negatively related to birth weight (Hingson, Dooling & Oppenheimer, 1982), moderate levels of social drinking, as characteristic of the present sample, have not been associated with birth weight (Kuzma & Sokol, 1982; Staisey & Fried, 1983; Tennes & Blackard, 1980). When caffeine use was dichotomized, the groups did not vary significantly in their average alcohol consumption. This result may be explained by Gilbert's (1976) description of a curvilinear relationship between alcohol and caffeine use. A positive correlation exists between caffeine and alcohol consumption up to 40 ml of alcohol daily. Daily alcohol consumption of more than 40 ml is associated with reduced

caffeine intake. Thus in the present work, the more heavily exposed caffeine group is likely to contain the moderate and not the heavy drinkers in the sample. Thus alcohol use was not regarded as an explanatory variable in the birth weight discrepancy.

Nicotine use is the most apparent confounding variable in the assessment of caffeine's effects. Despite the close association among dichotomized caffeine use (0-300mg;>300mg), smoking and birth weight, caffeine remained negatively related to birth weight after controlling for nicotine use. The nature of the distribution of nicotine use allowed for statistical control by means of an analysis of covariance procedure when caffeine use was dichotomized. However, the reverse was not possible: only caffeine use above 300 mg daily was associated with adverse effects and the small sample size of heavy users prevented the study of residual effects of nicotine after accounting for caffeine's action. The lack of heavy users also handicapped the examination of potentiating or additive effects of nicotine and caffeine.

Another potentially confounding variable when investigating reproductive effects of caffeine use is the mother's weight. Caffeine is distributed to all tissues of the body in the same concentration as in the plasma, (Axelrod

& Reichenthal, 1953). Thus with heavier women, less caffeine is available to the fetus. The strongly positive relationship between the mother's prepregnancy weight and caffeine consumption during pregnancy may reduce the effect of this confounding variable. However, caffeine exposure levels were also computed by dividing caffeine intake by the mother's weight to control for this confound. The birth weight discrepancy, but not the head circumference difference, between the more heavily exposed caffeine group and the remaining sample persisted after accounting for the mother's weight.

Both gravida and parity are very positively related to caffeine use during pregnancy and yet not before pregnancy. Most women reduce their caffeine consumption into pregnancy and thus it seems likely that women with fewer children and/or pregnancies tend to cut back on caffeine consumption more than the women with more children and/or pregnancies. However, although parity did differ between the heavier caffeine group and the rest of the sample, the birth weight discrepancy persisted after its control.

In retrospective studies of this nature, the problems associated with remembering past habits must be recognized. Little, Mandell and Schultz (1977) describe the cost of retrospective measurement of alcohol consumption as less when a more approximate rather than precise method of

measurement is employed. Considering caffeine consumption in terms of milligrams of caffeine consumed daily does allow for fine distinctions but if error in recall is involved, these small differences may be spurious. Thus estimates of caffeine intake were used not only as continuous variables but were categorized and considered in a less precise but more stable manner.

The mothers in the study are all volunteers and have been accustomed to questions regarding drug intake. An effort has been made to establish an accepting and relaxed relationship between interviewers and mothers. Goldstein and Kaiser (1969) contend that the validity of self-report depends on the intelligence, understanding and cooperation of the subject group. With objective data, they were able to confirm self-reports with such a group (Goldstein et al., 1969).

A selection bias did not exist because all women regardless of caffeine habits but with children over one year of age were sent the questionnaire.

However recall bias may be present. If all the women either under or over-reported their caffeine intake, effects of caffeine use could emerge without bias but inferences regarding risk levels would be hazardous. However if women who had adverse pregnancy outcomes were biased in their

report, interpretation of results becomes difficult. False negative results might occur if this group under-reported; false positive results might occur with over-reporting. Linn et al. (1982) note that in retrospective epidemiologic studies, recall bias takes the usual form of over-reporting of adverse exposures by women with poor pregnancy outcomes. In the present study the latter recall bias was unlikely for two reasons. The major focus of the larger study has been on other drug use such as alcohol, tobacco and marihuana. Caffeine questions in the questionnaire were contained in a life styles section which included other drug-related questions. Information regarding potential effects of caffeine use was requested in other sections. Secondly, caffeine has not had the same publicity exposure as a dangerous habit to be avoided during pregnancy that alcohol and tobacco have had. Thus if women were inclined retrospectively to inflate exposure to a drug, the inclination would not likely exist with caffeine.

Thus the presentation and organization of the questionnaire as well as the personal friendly contact maintained through the efforts of the interviewers, combined to encourage the respondents to answer honestly and without concern about cause-effect relationships, whether justified or not.

Estimates of caffeine intake. An effort has been made

with this study to devise a more valid algorithm for measuring caffeine intake. Incorporation of various dietary sources and portion sizes increases measurement accuracy. An assessed strength variable has also proved to be both valid and reliable for coffee and tea beverages. Although the proportion of variance in caffeine concentration predicted by the strength variable is important to acknowledge, some caution must be exercised. The validity and reliability of the strength variable may be dependent on time: The women tested for the algorithm were assessing strength of coffee and tea as consumed currently whereas their retrospective judgment of strength may be less accurate and stable. Another concern is that of compounded error. If, among those women who inaccurately record a beverage's strength, there exists a higher proportion of heavy users, then the resulting estimated caffeine intake will be increasingly distorted by the multipliers of cup size and number of cups and thus spurious relationships would occur when daily caffeine intake is related to such outcome variables as birth weight and gestation.

Despite the previous reservations, correlational and means analyses yielded similar results with both general and strength-adjusted estimates of caffeine use although the level of significance often varied with the two estimates.

With dichotomized caffeine intake, the strength-adjusted versus general estimates resulted in more women in the heavier category. The self-reported strength assessment may be a good method for reducing error in categorization.

Caffeine use. The high proportion of women (99%) found to consume caffeine in this study is consistent with the findings of Gilbert (1976). During pregnancy between 90 and 95 percent of women consumed caffeine, a greater proportion than reported in some studies (Graham, 1978; Kuzma & Sokol, 1982) but consistent with the study by Hill et al. (1977) which also included medications as a source of caffeine.

In contrast to the findings of Gilbert (1976), rather than 25 percent who drank more than four cups of tea or coffee or both, 18 percent reported drinking this quantity in the prepregnancy years. In the present study, approximately two percent of pregnant women consumed more than 400 mg of caffeine, the rough equivalent of six cups of coffee daily, and 12 percent consumed more than 200 mg or three cups of coffee daily. These proportions are lower than those reported by others (Martin, 1982; van dan Berg, 1977) but consistent with the study by Rosenberg et al. (1982). The study by Linn et al. (1982) reported use of four or more cups of coffee by five percent of the sample which is similar to the six percent found in the present study. The

consistency of the findings of the present study with these latter two recent studies suggests the modification of caffeine consumption over the previous six to seven years. Gilbert's (1976) findings were based on data from Ontario but the results of the present study indicated a general decline in caffeine intake from 1978 to 1981.

More women in the sample used coffee than any other dietary source of caffeine both pre and post pregnancy. Consistent with Gilbert (1981), coffee and tea accounted for approximately 60 percent and 30 percent respectively of all caffeine consumed. However, during pregnancy, perhaps because of declared distaste for coffee or an effort to reduce caffeine, tea users outnumber coffee users. Coffee's contribution to total caffeine intake declines to about 55 percent while tea increases to about 38 percent. Decaffeinated coffee was consumed by 17 percent of the sample compared with 15 percent found by Gilbert (1981). Both beverages over all time frames are the most popular sources of caffeine. Following in popularity are chocolate bars before, during and after pregnancy. Before pregnancy, caffeinated soft drinks, drugs containing caffeine and chocolate drinks are used in order of declining popularity. During pregnancy, chocolate drinks are used by more women than caffeinated soft drinks followed by only a few women

who report use of caffeinated drugs. Approximately the same proportion of women report use of caffeinated soft drinks and chocolate drinks after pregnancy followed by the number of women using caffeinated drugs.

The decline in caffeine use during pregnancy and the subsequent increase during the year postpregnancy that did not reach prepregnancy levels are consistent with the findings of Rosenberg et al. (1982). Although some decrease in tea use was apparent, the main habit change involved coffee, a result also reported by Hook (1976). Approximately a dozen women noted on the questionnaire an intolerance to coffee during pregnancy. Unfortunately the data available for studying the reason for such a habit change were not sufficient. However, in an attempt to reveal the impact of the recent years' adverse caffeine publicity, the sample was split into two periods on the basis of the infant's birth date after 1979 resulting in approximately equal sized sample (see Table 11). It is interesting that in five of the seven time frames studied, the self-reported caffeine intake was less in the period since 1979. The question remains, however, as to whether the women actually consume less caffeine or remember or record falsely.

Further breakdown into the five years of 1978 to 1982 inclusive substantiated the general decline in mean caffeine

use. The proportion of women using various sources did not vary systematically over the years other than showing an increase in the use of tea and chocolate drinks. When, however, the caffeine means for users of various sources were compared over time, both coffee and caffeinated soft drinks manifested an overall decline in mean intake among users for the prepregnancy years from 1978 to 1981. Thus although the number of women using various sources of caffeine appears to be fairly consistent across the years in study, a general decrease in caffeine intake in the prepregnancy years over 1978 to 1981 is apparent. Perhaps in reaction to high coffee prices or adverse caffeine publicity, women may have reduced their caffeine intake from coffee and/or replaced some coffee intake with tea.

In the year following pregnancy, women do not resume their prepregnancy caffeine habits. Unfortunately the format of the postnatal questionnaire pressured the women into condensing caffeine habits of various sources into one typical consumption pattern for the postpregnancy year. Whereas this approach may be reasonable for women in the non-pregnant, non-breast-feeding state, changing patterns within the year after pregnancy raised conflicts. Repeatedly women would write two distinct patterns on the questionnaire in reference to the year following pregnancy.

It seems reasonable to assume that the means associated with this time frame are aggregates of two habit patterns, one of reduced caffeine intake during breast-feeding or post-pregnancy similar to pregnancy intake and the other of greater caffeine intake later in the year more similar to prepregnancy intake levels.

As part of the Ottawa Prospective Prenatal Study, the 24 hour dietary recall including caffeine use was collected at least once for most of the women during their pregnancies. The correlation of the prospective 24 hour recall and the retrospective responses in the study questionnaire ($r=.52$) provided an acceptable index of reliability of self-reported caffeine use. The error may be explained by the difference in methodology and/or the cost of retrospective assessment. However, the women were given the opportunity to respond with "can't remember" codes on the postnatal questionnaire and few elected to do so, (see Appendix 8F). Inference is that most of the women thought that they could remember. The question remains as to the accuracy of their recall. However compared with the errors involved in generalizing from one day's dietary recall, the individual's assessment over time is likely to yield a more typical pattern of caffeine use. Hingson et al. (1982) describe inconsistencies in prenatal and postnatal comparison of both alcohol and marihuana self-reports.

The same women in their study were questioned both prenatally and postnatally about alcohol and marihuana use during pregnancy. Lower levels of alcohol and marihuana use were reported postnatally compared with prenatally. Despite the discrepancy in the self-reports, both self-reports of alcohol use were associated with an adverse effect on fetal growth and both marihuana self-reports were associated with fetal risk variables.

In the study of habit reduction of alcohol, smoking and caffeine into the pregnancy period, alcohol is the habit reduced by the majority of the women followed by smoking and coffee-drinking and a small proportion of tea users. One cannot assume that alcohol was the easiest habit of the three to reduce but speculation as to the reason may involve consideration of changing life-styles in pregnancy and lack of a daily established habit. Reasons for persistent tea habits into pregnancy may involve a lack of knowledge about caffeine content and an absence of distaste for tea as described for coffee.

Miscarriages and prematurity. Although Linn et al. (1982) found elevated risks of induced abortions as well as spontaneous abortions with heavy coffee drinkers, in the present work the investigation only involved reported miscarriages which were likely to include all known

spontaneous abortions but may not include all therapeutic abortions. The data were further limited because, as Nishimura (1976) notes, losses at early stages in pregnancy that may not be recognized, obscure abortion incidence in humans. Although the number of coffee and tea drinkers was significantly greater in the miscarriage group, average caffeine use during the pregnancy in question was only slightly more than the rest of the sample. Alcohol and nicotine use was not significantly associated with miscarriage incidence. Thus no striking relationship was noted between maternal caffeine use and the incidence of prematurity and miscarriages other than the disparity in caffeinated drug use. It is important to recognize that the increased caffeinated drug use for the year may be a consequence of caffeine-containing medications prescribed by a physician for the threatened miscarriage and/or for after the reproductive loss.

The father's coffee habits were not associated with the incidence of prematurity or miscarriage. However, some limitations on interpretations exist. Data on the father's habits referenced a current time frame, not necessarily when the potential effect occurred. If the father's coffee habits remain stable over time, present intake may be a valid representation of past habits. Another problem exists with the accuracy of the mother's

assessment of the father's coffee habits. Providing an option of responding with a "don't know" code may have promoted accuracy. Also because of the rapport established with the mothers and the fathers in the study, the fathers were probably consulted for a more valid recording of their habits. Finally the lack of complete information on the father's caffeine intake may compromise the results of the investigation. However, coffee is the main source of caffeine. Heavy users would correctly be assessed as having a high caffeine intake; conversely light or non-users could be inaccurately classified as having a low caffeine intake if other caffeine sources were used extensively.

Birth weight and head circumference. The category split in caffeine intake at 300 mg defines a minimum-intake level criterion for the heavy group comparable to other studies defining heavy use as about four or more cups of coffee a day (Linn et al., 1982; Rosenberg et al., 1982). The study by Linn et al. (1982) found no association between drinking four or more cups of coffee daily and low birth weight. However the low birth weight in the 1982 study was defined as less than 2500 grams. In fact Linn et al. (1982) did find a lower average birth weight among the infants of heavy coffee users which was not specified or investigated. In the large study by Kuzma and Sokol (1982) average birth

weight reductions for all categories of smoking were in evidence with increasing caffeine use. Particularly of interest and consistent with the result in this study, is a lower average birth weight for those women consuming more than 300 mg of caffeine daily after adjustment for gestation, mother's weight and weight gain, and frequency of wine use. The lowered birth weights were consistent across all categories of nicotine and beer use.

The positive relationship found when caffeine intake (used as a continuous or ranked variable) of the heavier group only was correlated with the outcome variables of birth weight and head circumference is not clearly understood at this time and may be an artifact associated with the small sample size.

The ponderal index is a ratio of body weight to body length. Research has indicated that if the fetus were malnourished, a low ponderal index would be expected, that is, an infant of decreased weight for body length which usually reflects retardation in third trimester growth (Dalby, 1978). On the other hand, infants born to nicotine users tend to have normal ponderal indices but are inclined to be small-for-dates. Thus nicotine is thought to affect fetal growth in a different manner than malnutrition. In the present study, the average ponderal index of the infants of the heavier caffeine group was lower ($p=.06$) than that of

the remaining sample and thus may represent a malnourished or similar effect. The decreased average weight coupled with the normal average length of the babies born to the heavier caffeine users is also suggestive that these infants tended to be underweight for their length, a result more consonant with malnutrition than a nicotine-effect.

The observed stability of caffeine intake among the three trimesters of pregnancy may have consequences for the fetus at higher caffeine consumption levels. The delayed maternal metabolism and elimination of caffeine as pregnancy progresses and the slow fetal caffeine clearance increase fetal exposure if caffeine intake remains relatively constant. It is during the last trimester of pregnancy that the greatest spurt in fetal growth occurs and the concurrent presence of caffeine may interfere with normal growth.

One possibility for the action of caffeine on growth may be derived from that drug's action on cyclic AMP. As described in the Introduction, the level of this nucleotide is increased by caffeine. An increase in cyclic AMP has been found to inhibit cellular proliferation (Abell & Monahan, 1973; Dunlop & Court, 1981). A second possibility may lie in the differential nutritional habits of the heavier caffeine users. As described in the Results section, although not statistically different, small

reductions in nutrient intake among the heavier caffeine users were noted. It should be emphasized that women in the heavier caffeine group were, on an average, well-nourished as defined by Canadian Dietary Standards (Watkinson, 1979). However the small reductions as observed may contribute to the heavy caffeine-lower birth weight association. Heavier caffeine use may be directly related to lower intake of nutrients or may indirectly interfere with the absorption or metabolism of these nutrients.

Although small differences occurred in significance with various estimates of intake and exposure, higher intake levels of caffeine were associated with smaller head circumference and lowered birth weight after controlling for confounding variables. The observed small reductions may be of minor import to a healthy full-term baby of acceptable weight but may be of major clinical significance for a preterm or small infant.

The more heavily exposed caffeine group tended to have a lower family income, less education, have more children and use more nicotine. The possibility exists that some variable that prompts these life-style traits or the combination of life-style habits is responsible for the effects noted. Nevertheless, the likelihood is greater that a woman will have a lighter baby with a smaller head circumference with consumption of a minimum of approximately

300 mg of caffeine daily.

Implications for future research. The prevalence of caffeine use underlines the need to assess its safety. Complacency has developed because of caffeine's long term use with no overwhelming negative effects. However, if adverse effects occur above a threshold level of caffeine exposure, the association may be more difficult to detect. In this country heavy caffeine consumption is rare and usually accompanied by heavy nicotine use, both factors masking a potential effect of heavy caffeine use.

Both nicotine and caffeine are central nervous system stimulants and have been associated with lowered birth weight and reproductive loss. Because of their highly correlated use, investigation should be directed toward exploring additive and potentiating effects of the two drugs.

Consideration of a threshold effect raises concern about establishing a level of exposure that constitutes a risk. Improvement in the assessment of total caffeine intake is important: not only recognition of various sources of caffeine but also the variation in the caffeine content of beverages. The weaker caffeine concentrations for coffee and tea found with this study are compatible with Gilbert's (1976) suggestion that home preparation is

inclined to be weaker than laboratory prepared samples. When caffeine intake is estimated from the frequency of coffee and tea use, realistic values for caffeine content should be used to avoid misrepresentation of risk levels if adverse effects are noted. In this study, 72 mg of caffeine per eight ounce cup of coffee and 37 mg of caffeine per eight ounce cup of tea were median values representing samples manifesting a great deal of variation of caffeine concentration.

The sample of women who consumed heavier levels of caffeine was too small to make strong conclusions about the associations observed. However the results suggest the need for further research with larger sample sizes of women consuming these higher levels of caffeine. If the more poorly educated pregnant women with lower incomes tend to continue with heavier caffeine use into pregnancy, educational anti-caffeine campaigns need to direct efforts toward this group.

Some women declared a distaste for coffee during pregnancy. Reasons for the observed reduction in coffee use during pregnancy would be of interest.

A study of differential effects of the different sources of caffeine should be undertaken. In addition, because coffee contributed the major part of overall caffeine intake, the contribution of other substances in

coffee to associations found with caffeine must be investigated.

Conclusions

Caffeine from a variety of sources is commonly used by Canadian women. During pregnancy fewer women consume caffeine and the amount consumed is usually reduced. After pregnancy, caffeine habits tend to continue at lower intake levels for several months and then to return to prepregnancy levels. After controlling for nicotine use, lowered birth weight and smaller head circumference of the infant were associated with maternal caffeine intake of more than 300 mg daily during pregnancy. This result is compatible with earlier findings of lowered birth weight with animal and human offspring after heavy maternal caffeine use. Although the clinical significance of the deficits remains to be evaluated, the results of this study lend support to recommendations that caffeine use be limited during pregnancy.

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APPENDIX 1

Consent Form

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Ottawa, Canada K1S 5B6

Informed Consent Agreement

I hereby acknowledge that I have been informed about the nature of the study to be conducted by Drs. Fried and Knights. I understand that the purpose of the study is to examine the effects of the fetus being exposed to a number of different factors in its environment.

The procedures will involve the following:

- (1) Several times during the pregnancy a research assistant will administer a questionnaire which will include questions about eating, drinking, smoking and drug habits.
- (2) During the pregnancy when blood and urine specimens are left with the obstetrician for routine analysis a small amount of these samples will be analyzed for drug content (including alcohol, nicotine and marihuana) or we may ask for urine samples, during the interviews.
- (3) At birth, the weight, length and general health of the infant will be recorded and the umbilical cord blood will be analyzed for antibodies and chromosomes.
- (4) In the hospital nursery the activity of the infant and the infants suckling ability will be measured.
- (5) If breast milk is available a small amount of it may possibly be analyzed for nutritional content.
- (6) Once the baby is at home periodic visits will be made for a few months to record growth rates and behavioral development.

All information - both that obtained from the mothers and babies will be treated in an entirely confidential nature.

I understand the procedures to be followed and am willing to cooperate in this research knowing I am free to withdraw from the study at any time.

Signed _____

Date _____

APPENDIX 2

Ottawa Prospective Prenatal Study:

Prenatal Questionnaire

PREGNANCY QUESTIONNAIRE

Name: _____

Date of 1st Contact: _____

Doctor's Name: _____

Date of 2nd Contact: _____

Due Date: _____

Date of 3rd Contact: _____

Contact # if father is present: _____

* 1. Mother's I.D. no.: _____

* 2. Child's I.D. no.: _____

* 3. Record No: _____

* 4. Study no: _____

* 5. ~~Number~~ of child
involved in this study ? _____

* 6. How many of your pregnancies have been
involved in this study ? _____

* 7. How many times have you been pregnant ? _____

* 8. Will this be a multiple birth ? _____

9. Have you read, understood and signed
the Informed Consent Agreement ? _____

*10. What is your family income ? _____

*11. How old is the father (at conception) ? _____

*12. How much does the father weigh ? (kg.) _____

*13. How tall is the father ? (cm.) _____

*14. What is the father's education ? _____

99-no data

1 - less than H.S.

2 - H.S. grad.

3 - coll., univ. or nurse

4 - post-grad

*15. What is the mother's education ? _____

*16. How old is the mother ? (at conception) _____

*17. How tall is the mother ? (cm.) _____

1

6 0 0 1

9

10

11

13

15

17

18

97-refusal

24

26

9-no data

29

32

34

36

38

* 18. In what cultural environment were you (mother) raised ?

41

--	--

99- no data

1- anglophone

2- francophone

3- mixed (f & e)

4- other

* 19. How much did you weigh prior to pregnancy ? 43
9- no data

--	--	--

20. How much do you weigh at present ? 1st mo. 46

--	--	--

2nd mo. 49

--	--	--

3rd mo. 52

--	--	--

4th mo. 55

--	--	--

5th mo. 58

--	--	--

6th mo. 61

--	--	--

7th mo. 64

--	--	--

8th mo. 67

--	--	--

9th mo. 70

--	--	--

* 21.

73

--	--	--

total wt. gain

* 22. Child's I.D.no:

1

--	--	--	--	--

* 23. Record no.:

6

0	0	2
---	---	---

24. What month of pregnancy are you in at present? 9

--	--

0- not interviewed

10- postpartum

Contact #2

11

--	--

Contact #3

13

--	--

* 25. In which trimester did you begin to receive medical care for this pregnancy ?

15

--	--

0- no prenatal care

1,2,3-trimester

26. In this pregnancy, are you having any of the following difficulties ?

17

--	--

- a. unusual nausea
- b. albumine or protein in urine
- c. bleeding from the vagina
- d. early rupture of membranes
- e. fluid retention requiring medication
- f. toxemia
- g. high blood pressure
- h. convulsions
- i. mechanical injuries
- j. chemical problems
- k. diet problems
- l. other. Specify:

99-no data

N-no

Y=yes

m. medication this pregnancy:

27. Have you had any X-rays or Ultrasound ?
What month of pregnancy were you in ?

19

--	--

28. Have you been exposed to rubella,
chickenpox, mumps or rheumatic fever ?

21

--	--

* 29. At any time in your lives, have you
or your husband ever had any of the
following ?

23

--	--

- a. heart disease
- b. tuberculosis
- c. diabetes or hypoglycemia
- d. nervous or mental disease
- e. migraine headaches
- f. epilepsy or convulsions
- g. cancer
- h. venereal disease
- i. asthma, hay fever, hives, allergies
- j. kidney disease
- k. arthritis or rheumatism Q only
- l. bleeding disorders Q only
- m. thyroid problems
- n. other. Specify:

* 30. Have either of your immediate families
ever had any of the following: (includes
parents, grandparents, siblings, aunts, uncles)

- a. tuberculosis
- b. bleeding disorders
- c. nervous or mental disease
- d. mental retardation
- e. alcoholism
- f. diabetes or hypoglycemia

25

--	--

* 31. Have you ever had any miscarriages, abortions or stillbirths ? How many ?

27

--	--

* 32. Did you have any of the following difficulties in previous pregnancies?

- a. unusual nausea
- b. albumine or protein in the urine
- c. bleeding from the vagina
- d. early rupturing of the membranes
- e. fluid retention requiring medication
- f. toxemia
- g. high blood pressure
- h. convulsions
- i. mechanical injuries
- j. chemical problems
- k. diet problems
- m. other. Specify:

29

--	--

* 33. Were any of the births of your other children in some way unusual ?

* 34. Did any of the other newborns require a longer hospital stay than usual ?

* 35. Have your children ever been seriously ill or had developmental difficulties ?

31

--	--

* 36. What method of contraception were you using for the last two years ?

99-no data 2-IUD 5-diaphragm
0- none 3-condom 6- other
1- pill 4-rhythm

33

--	--	--	--	--	--	--

* 37. Child's I.D. no.:

1

--	--	--	--	--	--

* 38. Record no.:

6

0	0	3
---	---	---

9

--	--

Inconsistency
Alcohol

CONTACT #

I

II

III

11

--	--	--	--	--	--

a a /day
pre-pregnancy

Table I

Intake Combinations		Beer		Wine	Liquor
		light	regular		
CODE					
A ₂	1	1.80	3.60	3.60	4.20
A ₁ B ₂	2	1.30	2.60	2.60	3.03
A ₁ B ₁ C ₀	3	1.43	2.85	2.85	3.33
A ₁ B ₁ C ₁	4	1.10	2.20	2.20	2.57
A ₁ B ₁ C ₂	5	.94	1.88	1.88	2.19
A ₀ B ₂ C ₀	6	1.10	2.10	2.10	2.45
A ₀ B ₁ C ₀	7	1.10	2.10	2.10	2.45
A ₀ B ₁ C ₁	8	.80	1.50	1.50	1.75
A ₀ B ₁ C ₂	9	.70	1.30	1.30	1.56
A ₁	10	1.80	3.60	3.60	4.20
A ₁ B ₀ C ₁	11	1.13	2.25	2.25	2.63
A ₁ B ₀ C ₂	12	.90	1.80	1.80	2.10
A ₀ B ₀ C ₂	13	.45	.90	.90	1.05
A ₀ B ₀ C ₁	13	.45	.90	.90	1.05
A ₂ B ₁ C ₀	15	1.60	3.10	3.10	3.62
A ₂ B ₀ C ₁	16	1.40	2.70	2.70	3.15
A ₂ B ₁ C ₁	17	1.28	2.55	2.55	2.98
A ₁ B ₂ C ₁	18	1.09	2.18	2.18	2.54
A ₀ B ₂ C ₁	19	.90	1.70	1.70	1.98

39. If you drank beer in the year preceding pregnancy, was it light or regular beer ?
40. During the year preceding this pregnancy, how often did you have a bottle of beer ?

- a. 3 times a day .3.00
- b. 2 times a day .2.00
- c. once a day 1.00
- d. 3 or 4 times a week .50
- e. once or twice a week .20
- f. 2 or 3 times a month .10
- g. once a month .05
- h. less than once a month .01
- i. never

Contact #:

I _____
 II _____
 III _____

16

a a/day beer
 product of
 quest. #40 X
 Table I

A

41. How often did you have 5 or 6 beers or more at one time ?

- a. nearly every time
- b. more than $\frac{1}{2}$ the time
- c. less than $\frac{1}{2}$ the time
- d. once in a while
- e. never

B

42. How often did you have 3 or 4 beers at one time?

- a. nearly every time
- b. more than $\frac{1}{2}$ the time
- c. less than $\frac{1}{2}$ the time
- d. once in a while
- e. never

C

43. How often did you have 1 or 2 beers at one time ?

- a. nearly every time
- b. more than $\frac{1}{2}$ the time
- c. less than $\frac{1}{2}$ the time
- d. once in a while
- e. never

Contact #

I _____
 II _____
 III _____

21

Quantity Frequency
 Index-derived from
 quest. #41,42,43,
 & Table I

Contact

I _____
 II _____
 III _____

23 _____
 # of sittings/day
 derived from quest.
 #40

44. During the year preceding this pregnancy,
 how often did you have a 4 oz. glass of
 wine ?

A B C 1st contact
 A B C 2nd "
 A B C 3rd "

Contact

I _____
 II _____
 III _____

27 _____
 a a /day wine
 product of quest #44
 & Table I

Contact

I _____
 II _____
 III _____

32 _____
 a a /sitting
 from quest. 44

Contact

I _____
 II _____
 III _____

34 _____
 # sittings/day
 from quest. #44

45. During the year preceding pregnancy,
 how often did you have a 1 1/2 oz.
 shot of liquor or liqueur ?

A B C 1st contact
 A B C 2nd "
 A B C 3rd contact

Contact

I _____
 II _____
 III _____

38 _____
 aa/day liquor
 product of quest
 #45 & Table I

Contact

I _____
 II _____
 III _____

43 _____
 aa/sitting from
 quest. #45

Contact

I _____
 II _____
 III _____

45 _____
 # of sittings/
 from quest. 45

46. List in order of most favourite, types of liquor consumed in the year preceding pregnancy.

99-no data 4-vodka 8-liqueurs
1-rum 5-gin 9-cinzano
2-scotch 6-sherry 10-dubonnet
3-rye 7-brandly 11-other

Code for type of drink in B.D.

99-no data 2-wine
0-no b.d. 3-liquor
1-beer 4-combination

Code for frequency weights

99-no data 1-once in a while
0-never 1-less than $\frac{1}{2}$ the time
2-more than $\frac{1}{2}$ the time
2-nearly every time

1st TRIMESTER

47. Did you drink light or regular beer in the 1st trimester ?

48. In the 1st trimester, how often did you drink beer ?

A B C 1st contact
A B C 2nd contact
A B C 3rd contact

49

57

B.D.
type

59

B.D.
pattern

Contact #

I
II
III

61

aa/day
1st trimester

Contact #

I
II
III

66

aa/day beer
product of quest
#48 & Table I

Contact #

I
II
III

71

aa/sitting
from quest.48

Contact #

I
II
III

73

sittings/day
from quest.48

* 49. Child's I.D. no.:

1

* 50. Record no.:

6

0 0 4

51. In the 1st trimester how often did you drink wine ?

A B C 1st contact

A B C 2nd contact

A B C 3rd contact

I

II

III

Contact #

I

II

III

Contact #

I

II

III

9 a a/day wine
product of quest
#51 & Table I

14 a a/sitting
from quest.
#51

16 # sittings/day
from quest.51

52. In the 1st trimester how often did you drink liquor ?

A B C 1st contact

A B C 2nd contact

A B C 3rd contact

Contact #

I

II

III

Contact #

I

II

III

20 a a / day
liquor-product
quest#52 &
table I

25 a a /sitting
from quest.52

Contact #

I

II

III

27 # sittings/day
from quest.#52

53. List in order of most favourite, types of liquor consumed in the 1st trimester.

31

--	--	--	--	--	--	--	--

39

B.D.
type

41

B.D.
pattern2nd TRIMESTER

54. Did you drink light or regular beer in the 2nd trimester ?

55. In the 2nd trimester, how often did you drink beer ?

A B C 1st contact
A B C 2nd contact

56. In the 2nd trimester, how often did you drink wine ?

A B C 1st contact
A B C 2nd contact

Contact #

I _____

II _____

III _____

43

a a /day
2nd trimester

Contact #

I _____

II _____

48

aa/day beer
prod. quest#55
& Table I

Contact #

I _____

II _____

53

aa/sitting from
quest #55

Contact #

I _____

II _____

55

sittings/day
from quest#55

Contact #

I _____

II _____

59

aa/day wine
prod. quest#56
& table I

Contact #

I _____

II _____

64

aa/sitting from
quest.#56

66

sittings/day
from quest.#56

57. In the 2nd trimester, how often did you drink liquor?

A B C 1st contact
A B C 2nd contact

Contact #

I _____

II _____

70

aa/day liquor
prod.quest 57
& table I

Contact #

I _____

II _____

75

aa/sitting from
quest. # 57

Contact #

I _____

II _____

77

sittings/day
from quest.57

* Child's I.D. no.:

1

* Record no.:

6

0 0 5

58. List in order of most favourite,
types of liquor consumed in the
2nd trimester.

9

17

B.D. type

19

B.D. pattern

3rd TRIMESTER

21

aa/day
3rd trimester

59. Did you drink light or regular beer
in the 3rd trimester?

60. In the 3rd trimester, how often did
you drink beer?

26

aa/day beer
prod.quest#60
& table I

A B C

31

aa/sitting from
quest.#60

61. In the 3rd trimester, how often did you drink wine ?

A B C

62. In the 3rd trimester, how often did you drink liquor ?

A B C

63. List in order of most favourite, types of liquor consumed in the 3rd trimester.

33

sittings/day
from quest. 60

37

aa/day wine
prod. quest. 61
& table I

42

aa/sitting from
quest. 61

44

sittings/day
from quest. 61

48

aa/day liquor
prod. quest 62
& table I

53

aa/sitting from
quest. 62

55

sittings/day
from quest. 62

59

67

--	--

B.D. type

69

--	--

B.D. pattern

* Child's I.D. no.:

* Record no.:

1 _____
6 _____

9 _____
Inconsistency
nicotine

64. If you smoke cigarettes, do you inhale ?

99 missing data 3 change of habit
0 no or inconsistent
1 always 95 not applicable

11 _____

65. How much smoking does your husband do
in your presence per day ?

Contact #

I _____

II _____

III _____

13 _____

99 missing data 4 > 20/day
0 non-smoker 5 uncertain am't
1 < 5/day 6 pipe
2 5 - 10/day 7 cigars
3 10 - 20/day 8 combo
9 Other

66. Are you regularly exposed to a
smoke-filled environment ?

15 _____

67. In the year preceding pregnancy,
did you smoke cigarettes ?

Contact #

I _____

II _____

III _____

17 _____

am't: brand: .

19 _____
mg/day nicotine

68. Did you smoke cigarettes in the 1st
trimester ?

Contact #

I _____

II _____

III _____

24 _____

am't: brand:

26 _____
mg/day nicotine

69. Did you smoke cigarettes in the 2nd
trimester ?

Contact #

I _____

II _____

III _____

31 _____

am't: brand:

33 _____
mg/day nicotine

70. Did you smoke cigarettes in the 3rd trimester ?

38

am't:

brand:-

40

mg/day nicotine

45

Inconsistency
marihuana

71. How much marihuana did you smoke
in the year preceding pregnancy ?

Contact #

I

II

III

47

99 no data

0 non smoker

1 0, $\frac{1}{2}$, 1 joint/wk or passive inhalation

() actual # joints/wk

72. How many joints/week did you
smoke in the 1st trimester ?

Contact #

I

II

III

50

73. How many joints/week did you
smoke in the 2nd trimester ?

Contact #

I

II

53

74. How many joints/week did you
smoke in the 3rd trimester ?

56

59

Inconsistency
Hard Drugs

(a) 75. Did you do any LSD, heroin or amphetamines
in the year preceding pregnancy ?

61

(b) In the 1st trimester ?

63

(c) In the 2nd trimester ?

65

(d) In the 3rd trimester ?

67

69

Inconsistency
tranquilizers

76. Did you take any valium or librium
in the year preceding pregnancy ?

(a)

71

(b) In the 1st trimester ?

73

(c) In the 2nd trimester ?

75

(d) In the 3rd trimester ?

77

* Child's I.D. no.:

1

* Record no.:

6

77. Do you intend to nurse the baby ?

9

78. Is the baby active these days ?

79. What is the baby's favourite time of day to be active ?

80. In which position is the mother when the baby is most active ?

NUTRITION

List all food and beverage intake in the last 24 hours, excluding water. Please give as much detail as possible.

APPENDIX 3

Explanatory Letter Given to Mothers

Carleton University
Ottawa, Canada K1S 5B6

January, 1983

Dear

Happy New Year! We hope that you had a happy holiday season and thank you for agreeing to complete our follow-up questionnaire when we spoke to you recently.

The reason for this follow-up is to enable us to compare the lifestyles of the mothers in our study before and after the birth of their child(ren). Due to financial restraints it is not possible for us to personally interview each of our mothers, so the questionnaire was designed to collect the information quickly and efficiently.

This first mailing of the questionnaire is being sent to all the mothers in the study whose children are at least one year old this month. Because all the mothers are getting the questionnaire at this time some of the questions may be difficult to answer, especially if your child is 4 1/2 years old and you have to remember back several years. Please do not become discouraged, all we ask is that you give us your closest approximations. Similarly, if your child is just one year old you should not be anxious if your child has not attained some of the developmental milestones asked about, as they may relate to older children. A number of you may have more than one child in the study who are older than one year, in these cases you will find a questionnaire for each child included, with the redundant questions struck out.

If you look now at the questionnaire you will see that it is divided into four parts;

Part I - General Health and Development of your Child

Part II - Infant Feeding

Part III - Lifestyle Habits

Part IV - Home/Family

In order to simplify the completion of the questionnaire we have standardized the method of answering questions;

If you see a _____ please write something on it.

If you see a ☐ please put a ✓ in the circle next to the appropriate response.

If you see a ☐ please write the appropriate code in it.

If you see a → please follow it to avoid answering questions that are not applicable.

.../2

When you have completed the questionnaire please return it to us as soon as possible in the stamped envelope provided. We hope to begin receiving completed questionnaires within the next two weeks so that we can begin tabulating the answers and, as in the past, we will be reporting back to all the mothers who responded, summarizing our results.

In order to guarantee confidentiality within the mail service, each questionnaire has been marked with a number so that your name does not appear on the questionnaire. The number is written in the top right hand corner of your questionnaire and will enable us to identify it when it returns to our office.

We hope that we have asked our questions in a way that makes sense to all our mothers. If you have any difficulty understanding or answering a question, or if you have any suggestions please feel free to call our office at 231-5549 during the day and we will do our best to help. In addition, if you feel that your answer needs to be explained or if you would like to express a thought or idea, please use the space at the end of the questionnaire.

Thank-you for your help.

Yours very truly,

P. A. Fried
Professor

PAF/ed

APPENDIX 4

Ottawa Prospective Prenatal Study:
Follow-up Questionnaire

OTTAWA PRENATAL STUDY

FOLLOW-UP QUESTIONNAIRE

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of this publication shall be
used without the written
permission of P.A. Fried.

Ottawa Prenatal StudyFollow-up Questionnaire

PART I - GENERAL HEALTH AND DEVELOPMENT OF YOUR CHILD

1. How old is your child in months? _____
2. How much does your child weigh at present? _____ lbs.
(or, if you prefer) _____ kg
3. How tall is your child at present? _____ ft./in.
(or, if you prefer) _____ cm
4. Has your child spoken in two word "sentences" that someone other than the mother or father can understand? (e.g., "Me thirsty")

1) No. ☐2) Yes ☐

IF YES, how old was your child in months? _____

Could you give us an example? _____

5. Has your child walked three or four steps without support?

1) No. ☐2) Yes ☐

IF YES, how old was your child in months? _____

6. Has your child had any problems with his/her eyesight?

1) No. ☐2) Yes ☐

IF YES, please specify _____

7. Has your child had any problems with his/her hearing?

1) No. ☐2) Yes ☐

IF YES, please specify _____

- 2 -

8. We are interested in a respiratory condition called "apnea". Children who have apnea show irregular breathing patterns. Some babies may not breathe for a short time and then breathe rather rapidly to "catch-up"; others may require external stimulation to regulate breathing.

Did your child have apneic spells, that is, noticeable periods of longer than 10 seconds when s/he did not breathe?

- 1) No. ☐ → Go to Question 9
- 2) Yes ☐ → IF YES, at what age was the first spell noticed in months? _____

If the spells continued to occur, please elaborate as to how often, over what time period, and what treatment, if any, was used. _____

PART II -- INFANT FEEDING

Decisions made before your child was born

9. Did you decide on a method of feeding your child before s/he was born?

- 1) No. ☐ → Go to Question 13
- 2) Yes ☐ → IF YES, what method did you choose?
- 1) Breastfeeding. ☐
- 2) Bottle feeding ☐
- 3) Combination. ☐

10. When did you decide on this feeding method?

- 1) Before marriage. ☐
- 2) Before pregnancy ☐
- 3) First trimester. ☐
- 4) Second trimester ☐
- 5) Third trimester. ☐

11. What was your reason for deciding on this method of feeding? If appropriate you may check more than one reason.

- 1) Cost. ☐
- 2) Past experience ☐
- 3) Personal conviction ☐
- 4) Cosmetic reasons. ☐
- 5) Husband/partner can help. ☐
- 6) Going back to work. ☐
- 7) Best for baby ☐
- 9) Mother/infant closeness ☐
- 10) Husband's/partner's preference. . ☐
- 11) Natural thing to do ☐
- 12) No reason ☐
- 13) Other ☐

Please specify _____

12. When you originally decided on the feeding method for your child, how long did you intend to feed your child by this method in months? _____

After your child's birth/in hospital

13. Was your child born in a hospital?

- 1) No. ☐ → IF NO, please specify where your child was born. _____

Go to Your child's feeding routine at home on page 5.

- 2) Yes ☐ → IF YES, how many days were you in the hospital? _____

How many days was your child in the hospital? _____

- 4 -

14. During the stay in hospital what was your child ~~usually~~ fed?

- 1) Breast milk ☐
- 2) Formula ☐
- 3) Soya Preparation ☐
- 4) Other ☐

Please specify _____

15. Was your child given any supplement(s) to the above while in hospital?

- 1) No ☐
- 2) Yes ☐ → IF YES, what type of supplement was s/he given?

- 1) Occasional formula supp. ☐
- 2) Regular formula supp. ☐
(e.g., on a daily basis)
- 3) Glucose solution ☐
- 4) Other ☐

Please specify _____

16. Did the type of feeding change during the stay in hospital?

- 1) No ☐
- 2) Yes ☐ → IF YES, how did the type of feeding change?

- 1) Formula to breast milk ☐
- 2) Breast milk to formula ☐
- 3) Other ☐

Please specify _____

What was the major reason for this change? _____

- 5 -

Your child's feeding routine at home

IF YOU BREASTFED YOUR CHILD AT HOME PLEASE COMPLETE THE FOLLOWING QUESTIONS, IF NOT PLEASE GO TO PART III - LIFESTYLES, WHICH BEGINS ON PAGE 7.

17. How old was your child when you first breastfed him/her in days? _____
18. We are interested in your child's feeding pattern from the time s/he arrived home up to the age of 12 months. To get an accurate picture we would like you to use the codes provided below to fill out the chart on Page 6. Write the appropriate letter on the line and please feel free to use the margins to clarify your answers.

CODES to be used to fill out Chart on page 6

1) Type:

What usual type of nourishment did your child receive?

- A) Breast milk
- B) Formula
- C) Regular milk (Please specify - 2%, homogenized, skim, etc.)
- D) Soya preparation
- E) Other (Please specify)

2) Supplement:

Did your child receive any supplement to the above?

- A) No
- B) Yes → IF YES, please specify on the line provided what type of supplement your child received.
 - 1) Formula
 - 2) Milk (Please specify - 2%, homogenized, skim, etc.)
 - 3) Other (Please specify)

3) Reason for any change:

If any of the above changed from one time period to another please specify any reason there may have been for the change on the appropriate line in the chart.

STARTCHARTFINISH

1. For the first few weeks at home, what was the usual routine?

Type? _____

Supplement? _____

How often was the supp. given? _____

Reason for any change? _____

2. At one month of age what was the usual routine?

Type? _____

Supplement? _____

How often was the supp. given? _____

Reason for any change? _____

3. Between 3 to 6 months of age what was the usual routine?

Type? _____

Supplement? _____

How often was the supp. given? _____

Reason for any change? _____

6. Thank-you! (Go to Question 19)

5. At what age did you introduce solids to your child's diet in months? _____

4. Between 6 to 12 months of age what was the usual routine?

Type? _____

Supplement? _____

How often was the supp. given? _____

Reason for any change? _____

19. Are you currently breastfeeding the child we have been discussing?

1) No. ☐

2) Yes ☐

IF NO, how old was this child when s/he was completely weaned in months?

We recognize that it will be difficult to remember at times, but we hope that you will give us your best recollection. Questions 20 to 26 pertain to caffeine.

Typically,

3rd yr. before preg.	2nd yr. before preg.	Year before preg.	Trimesters			Year after birth
			1st	2nd	3rd	

- or

☐ ☐ ☐ ☐☐☐☐

☐ ☐ ☐ ☐ ☐ ☐

--	--	--	--	--	--	--

- ☐ ☐ ☐ ☐ ☐ ☐ ☐

- ☐ ☐ ☐ ☐ ☐ ☐ ☐

Typically,

3rd yr. before preg.	2nd yr. before preg.	Year before preg.	<u>Trimesters</u>			Year after birth
			1st	2nd	3rd	

- or

--	--	--	--	--	--	--

If you entered "?" or "0" you may disregard questions B and C for that particular time period.

- ☐ ☐ ☐ ☐ ☐ ☐ ☐

Typically,

- or

--	--	--	--	--	--	--

If you entered "7" or "0", you may disregard question 8 for that particular time period.

- ☐ ☐ ☐ ☐ ☐ ☐ ☐

- 10 -

24. CHOCOLATE DRINKS

Typically,

- A. How many chocolate drinks (hot or cold) did you have weekly? Please enter the actual number or,

"?" if you drank fewer than one drink a week or cannot remember

or

"0" if you did not have chocolate drinks

If you entered "?" or "0", you may disregard question B for that particular time period.

- B. Of what size? Please enter in number of ounces or,

"?" if you cannot remember

Hint: a small cardboard milk container holds 8 oz.

3rd yr. before preg.	2nd yr. before preg.	Year before preg.	Trimesters			Year after birth
			1st	2nd	3rd	

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
----------------------	----------------------	----------------------	----------------------	----------------------	----------------------	----------------------

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
----------------------	----------------------	----------------------	----------------------	----------------------	----------------------	----------------------

25. MEDICATION?

Typically,

Approximately how many of each of the following did you take? Please enter the number of pills, capsules, or tablets taken weekly.

Anacin

Bromoseltzer

Cafegot

Comeback

Cope

Coricidin

Darvon

Dristan

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

(Continued...)

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25. Continued...

	3rd yr. before preg.	2nd yr. before preg.	Year before preg.	Trimesters			Year after birth
				1st	2nd	3rd	
Empirin	☐	☐	☐	☐	☐	☐	☐
Excedrin	☐	☐	☐	☐	☐	☐	☐
Fiorinal	☐	☐	☐	☐	☐	☐	☐
Midol	☐	☐	☐	☐	☐	☐	☐
Migral	☐	☐	☐	☐	☐	☐	☐
No Doz	☐	☐	☐	☐	☐	☐	☐
Pre-mens	☐	☐	☐	☐	☐	☐	☐
Sinarest	☐	☐	☐	☐	☐	☐	☐
Traminicin	☐	☐	☐	☐	☐	☐	☐
Vanquish	☐	☐	☐	☐	☐	☐	☐
Vivarin	☐	☐	☐	☐	☐	☐	☐
Wampole C-12	☐	☐	☐	☐	☐	☐	☐
222's	☐	☐	☐	☐	☐	☐	☐

If you take any other drugs at least once a week that you know contain caffeine please add the names and amounts below.

26. Did the father of the child drink coffee in the year before pregnancy?

- 1) Do not know ☐
- 2) No ☐
- 3) Yes ☐

IF YES, how many cups a day did he drink typically? _____

Of what type?

- 1) regular ☐
- 2) decaffeinated ☐
- 3) both decaffeinated and regular . . . ☐
- 4) can not remember or do not know . . ☐

BEWARE...THE TIME CATEGORIES TO THE RIGHT ARE DIFFERENT!

27. Since the birth of your child have you drunk any beer?

1) No. ☐ → Go to Question 28

2) Yes ☐ → IF YES,

Typically,

Immed. after birth	One month of age	Six months of age	Twelve months of age	Present
--------------------------	------------------------	-------------------------	----------------------------	---------

A. Which strength of beer did you drink?
Please enter the appropriate code.

1. regular
2. light

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

B. How often did you drink a bottle/can
of beer? Please enter the appropriate
code.

1. four or more times a day
2. three times a day
3. two times a day
4. once a day
5. three or four times a week
6. once or twice a week
7. two or three times a month
8. once a month
9. less than once a month

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

C. How often did you drink 5 or 6 beers
per occasion? Please enter the
appropriate code.

1. every time
2. nearly every time
3. more than half the time
4. less than half the time
5. once in a while
6. never

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

D. Using the same categories as in C above,
how often did you drink 3 or 4 beers
per occasion? Please enter a number
from 1 to 6.

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

E. Using the same categories as in C above,
how often did you drink 1 or 2 beers per
occasion? Please enter a number from
1 to 6.

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

- 13 -

28. Since the birth of your child have you drunk any wine?

- 1) No. ☐ → Go to Question 29
- 2) Yes ☐ → IF YES,

Typically,

Immed. after birth	One month of age	Six months of age	Twelve months of age	Present
--------------------------	------------------------	-------------------------	----------------------------	---------

A. How often did you drink wine? Please enter the appropriate code.

1. four or more times a day
2. three times a day
3. two times a day
4. once a day
5. three or four times a week
6. once or twice a week
7. two or three times a month
8. once a month
9. less than once a month

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

B. How often did you drink 5 or 6 glasses of wine (for our purposes a glass of wine contains 4 oz.) per occasion? Please enter the appropriate code.

1. every time
2. nearly every time
3. more than half the time
4. less than half the time
5. once in a while
6. never

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

C. Using the same categories as in B above, how often did you drink 3 or 4 glasses of wine (4 oz.) per occasion? Please enter a number from 1 to 6.

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

D. Using the same categories as in B above, how often did you drink 1 or 2 glasses of wine (4 oz.) per occasion? Please enter a number from 1 to 6.

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

29. Since the birth of your child, have you ~~drunk~~ any liquor and/or liqueur?

- 1) No. ☐ → Go to Question 30
- 2) Yes ☐ → IF YES,

Typically,

Immed. after birth	One month of age	Six months of age	Twelve months of age	Present
--------------------------	------------------------	-------------------------	----------------------------	---------

A. How often did you drink liquor and/or liqueur? Please enter the appropriate code.

1. four or more times a day
2. three times a day
3. two times a day
4. once a day
5. three or four times a week
6. once or twice a week
7. two or three times a month
8. once a month
9. less than once a month

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

B. How often did you drink 5 or 6 drinks of liquor and/or liqueur (for our purposes one drink contains 1 1/2 oz. of liquor or liqueur) per occasion? Please enter the appropriate code.

1. every time
2. nearly every time
3. more than half the time
4. less than half the time
5. once in a while
6. never

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

C. Using the same categories as in B above, how often did you drink 3 or 4 drinks of liquor and/or liqueur (1 1/2 oz.) per occasion? Please enter a number from 1 to 6.

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

D. Using the same categories as in B above, how often did you drink 1 or 2 drinks of liquor and/or liqueur (1 1/2 oz.) per occasion? Please enter a number from 1 to 6.

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

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30. Since the birth of your child have you been regularly exposed to the tobacco smoke of others?

1) No. ☐

2) Yes ☐

31. Since the birth of your child have you smoked tobacco in any form?

1) No. ☐ → Go to Question 32

2) Yes ☐ → IF YES,

Typically,

Immed. after birth	One month of age	Six months of age	Twelve months of age	Present
--------------------------	------------------------	-------------------------	----------------------------	---------

A. How did you smoke tobacco? Please enter the appropriate code.

1. cigarettes

2. pipes

3. cigars

4. other (Please specify) _____

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

B. How many of the above did you smoke daily? Please enter the appropriate code.

1. more than 20

2. 11 to 20

3. 5 to 10

4. less than 5

5. uncertain amount

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

C. Please enter the name of the brand that you typically smoked during this time period by writing the brand name sideways in the box provided.

<div style="writing-mode: vertical-rl; height: 80px;"></div>	<div style="writing-mode: vertical-rl; height: 80px;"></div>	<div style="writing-mode: vertical-rl; height: 80px;"></div>	<div style="writing-mode: vertical-rl; height: 80px;"></div>	<div style="writing-mode: vertical-rl; height: 80px;"></div>
--	--	--	--	--

D. What size did you smoke? Please enter the appropriate code.

1. regular

2. king size

3. other (Please specify) _____

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

E. When you smoke do you inhale?

1. no

2. yes

"?" cannot remember or do not know

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

F. Do you smoke the entire cigarette/pipe/cigar?

1. no

2. yes

"?" cannot remember or do not know

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

32. Since the birth of your child have you been regularly exposed to the marihuana smoke of others? (Hashish will be discussed in Question 34)

1) No. ☐

2) Yes ☐

33. Since the birth of your child have you used any marihuana?

1) No. ☐ → Go to Question 34

2) Yes ☐ → IF YES,

Typically,

Immed. after birth	One month of age	Six months of age	Twelve months of age	Present
--------------------------	------------------------	-------------------------	----------------------------	---------

A. How often did you use marihuana? Please enter the appropriate code.

1. more than five times a day
2. two to five times a day
3. once a day
4. five or six times a week
5. three or four times a week
6. once or twice a week
7. two or three times a month
8. once a month
9. less than once a month

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

B. How did you use marihuana? Please enter the appropriate code.

1. rolled in a joint
2. baked (e.g., in cookies, brownies, etc.)
3. combination (Please specify) _____
4. other (Please specify) _____

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

C. On each occasion that you used marihuana, how much did you use on average? If you shared (e.g., passed a joint around), we want to know how much you personally used. Please enter number of grams.

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

Hint: one average joint contains approximately 0.6 g of uncut marihuana

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34. Since the birth of your child have you been regularly exposed to the hashish smoke of others?

1) No. ☐

2) Yes ☐

35. Since the birth of your child have you used any hashish?

1) No. ☐ → Go to Question 36

2) Yes ☐ → IF YES,

Typically,

Immed. after birth	One month of age	Six months of age	Twelve months of age	Present
--------------------------	------------------------	-------------------------	----------------------------	---------

A. How often did you use hashish? Please enter the appropriate code.

1. more than five times a day
2. two to five times a day
3. once a day
4. five or six times a week
5. three or four times a week
6. once or twice a week
7. two or three times a month
8. once a month
9. less than once a month

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

B. How did you use hashish? Please enter the appropriate code.

1. rolled in a joint with tobacco
2. in a pipe/chillum
3. with hot knives
4. baked (e.g., in cookies, brownies, etc.)
5. bong
6. combination (Please specify) _____

7. other (Please specify) _____

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

C. On each occasion that you used hashish, how much did you use on average. If you shared (e.g., passed a joint around), we want to know how much you personally used. Please enter number of grams.

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

Hint: if you roll your hashish with tobacco you probably get between 3 - 4 joints from 1 gram of hashish

PART IV - HOME/FAMILY

36. What was your family income before tax between the birth of, and the first birthday of your child?

- 1) less than \$6,000. ☒
- 2) \$6,000 to \$15,999 ☐
- 3) \$16,000 to \$25,999. ☐
- 4) \$26,000 to \$35,999. ☐
- 5) \$36,000 to \$45,999. ☐
- 6) \$46,000 to \$55,999. ☐
- 7) above \$56,000 ☐

37. Could you please indicate below, the year of birth and sex of all those people typically living in your home, excluding the child you have been describing.

<u>Date of Birth</u>	<u>Sex (M/F)</u>
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

38. Since 1980 have you had any miscarriages?

- 1) No. ☐
- 2) Yes ☒

IF YES, in what years did they occur?

39. Since 1980 have you had any stillbirths?

- 1) No. ☐
- 2) Yes ☐

IF YES, in what years did they occur?

40. Since 1980 have you had any children born prematurely?

1) No. ☐

2) Yes ☐

IF YES, in what years were they born?

41. With whom did your child spend most of his/her day during the time periods below. Please enter the appropriate code.

Immed. after birth	One month of age	Six months of age	Twelve months of age	Present
--------------------------	------------------------	-------------------------	----------------------------	---------

1. Mother (yourself)
2. Father
3. Sibling (brother/sister)
4. Grandparent
5. Caregiver (babysitter/nanny/neighbour)
6. Staff of Daycare
7. Other (Please specify) _____

☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

THANK-YOU!

We appreciate you taking the time to fill out this questionnaire. If any of the questions were not clear please call us a 231-5549, and we will be pleased to help.

Finally, if you have any comments and/or additional information that would be relevant please use the space below and the back of this page if necessary!

APPENDIX 5

Questionnaires Related to Coffee and Tea Samples

Please describe your coffee habits:

Typically,

- A.) How many times do you drink coffee daily? _____
- B.) in what size cup? _____
- C.) of what type _____
- 1.) regular
- 2.) decaffeinated
- 3.) regular and decaffeinated _____
- D.) prepared by what method
- 1.) instant
- 2.) percolated
- 3.) dripped
- 4.) other _____
- E.) and do you drink coffee that others
- describe as
- 1.) strong
- 2.) medium
- 3.) weak _____

This sample in a _____ oz cup of _____ type was prepared by _____ method and estimated by others to be of _____ strength.

Please describe your tea habits:

Typically

A.) How many times do you drink tea daily? _____

B.) in what size cup? _____

C.) of what type

1.) black regular

2.) herbal

3.) green

4.) decaffeinated _____

D.) and do you drink tea that others
describe as

1.) strong

2.) medium

3.) weak _____

This sample in a _____ oz cup of _____ type is estimated by
others to be of _____ strength.

APPENDIX_6STUDY_1: Algorithm for Computation of Caffeine Intake

APPENDIX 6A: Analysed Caffeine Concentrations

APPENDIX 6B: Distribution of Caffeine Concentrations

APPENDIX 6C: Determination of Reliability of
Predictors for Caffeine Concentration

APPENDIX 6D: Caffeine values utilized in algorithm

Appendix 6A

Data Required to Compute Caffeine Content of Coffee and Tea

CODES: ID: Identification Number

Beverage: T = Tea

C = Coffee

Type: C = regular caffeinated

DC= decaffeinated

R = black tea

G = green tea

H = herbal tea

Method: D = drip

P = percolated

I = instant

E = espresso

Volume: Est'd = estimated

Meas'd = measured

Strength: as described by "others"

S = strong

M = medium

W = weak

No.: Number of cups consumed daily

Conc'n: Analysed caffeine concentration (ug/ml)

COFFEE

ID	Beverage	Type	Method	Volume(ml) Est'd Meas'd	Strength	No.	Conc'n	
1661	C	C	D	177	200	S	1.5	740.7
3581	C	C	I	237	237	M	2	144.1
3601	C	C	D	237	237	W-M	1.5	188.0
3231	C	C	D	237	210	S	4	351.1
2561	C	C	D	237	210	M	2	249.0
3051	C	C	I	237	210	S	2	373.8
2211	C	C	P	237	270	M	2.5	274.4
5301	C	C	D	177	210	S	1.5	174.5
4741	C	C	D	237	250	M	3	222.6
1491	C	C	D	237	266	M	10	384.4
5101	C	C	D	237	237	S	5	609.4
41	C	C	P	177	210	M	2	297.1
2271	C	C	I	237	237	M	2	262.2
4901	C	C	P	237	237	W	2	156.7
2111	C	C	I	237	237	M	6	479.5
4891	C	DC	I	237	250	S	3	8.6
781	C	C	D	148	148	W	3	303.9
5331	C	C	D	237	300	M	4	270.3
2881	C	C	D	325	300	M-S	4.5	478.8
2801	C	C	I	237	300	M	6	272.2
3211	C	C	P	207	218	M	3.5	587.7
2921	C	C	I	250	250	S	1	468.0
841	C	C	D	296	237	S	1.5	585.8
1691	C	C	E	177	90	S	1.5	709.7
801	C	C	I	237	330	W	2.5	236.8
801	C	C	P	177	160	W	2.5	309.3
2261	C	C	I	251	255	W	4.5	83.5
1211	C	C	I	177	172	M-S	2	469.2
1811	C	DC	I	207	237	M	1	5.3
712	C	DC	P	296	237	W	3	4.3
3761	C	C	P	237	250	S	.5	396.1
3611	C	C	I	177	237	M	3	174.9
2581	C	C	P	177	177	M	2.5	455.6
3511	C	C	P	236	225	S	3	450.4
1241	C	C	D	177	192	M	1.5	230.2
5171	C	C	P	236	211	M	1	276.8
101	C	C	P	296	237	M	1	539.8

TEA

ID	Beverage	Type	Volume (ml)		Strength	No.	Conc'n
			Est'd	Meas'd			
3231	T	R	237	190	M	2	250.1
2561	T	R	237	210	S	4.5	183.9
5301	T	R	177	165	W	3	66.3
4951	T	R	-	355	M	2	147.5
5011	T	R	207	207	S-M	8	192.9
4301-1	T	R	237	237	W	3	137.5
4301-3	T	G	89	89	W	1	316.9
1481	T	R	266	266	M	7	165.9
4901	T	R	207	207	M	1.5	60.3
2111	T	R	207	207	S	1	247.2
4891	T	R	177	148	M	.2	200.5
2921	T	R	237	250	S	3	123.7
2801	T	R	237	200	M	3	137.5
841	T	R	296	237	M	1.5	69.9
1811	T	R	207	237	M	3	134.9
3611	T	H	237	240	M	2	342.1

Appendix 6B

Distribution of Caffeine Concentrations

	<u>coffee</u>				<u>tea</u>		
	drip	perc	inst	overall	black	green	herbal
Caffeine Conc'ns (ug/ml)							
0-99			1	1	3		
100-199	2	1	2	5	8		
200-299	4	3	3	10	3		
300-399	3	2	1	6		1	1
400-499	1	2	3	6			
500-599	1	2		3			
600-699	1			1			
700-799	1			1			

Appendix 6CDetermination of Reliability of Predictors
for Caffeine Concentration

Initially the samples of coffee and tea were split for single cross validation. The medians for method of coffee preparation predicted 13 percent of the variance in caffeine concentration with one-half of the sample and two percent with the other half; the medians did not retain predictability after cross-validation. The low predictive validity and lack of reliability as a predictor led to abandoning the median caffeine concentrations for various methods of preparation as a predictor in the estimate of an individual's daily caffeine consumption.

When the cross-validation procedure was repeated with assessed strength as the only predictor, no shrinkage was observed with either the coffee or the tea subsamples. The lack of shrinkage, however, may not be an indication of reliability but rather an artifact due to the characteristics of the relationship. The strength variable is limited in range and reference points. The regression coefficients as well as the strength ranking are positive leading to identical rank ordering of predicted caffeine concentrations.

Further checks on reliability of the assessed strength

variable were undertaken. Subsamples of both coffee and tea were repeatedly used to construct a distribution of correlations between assessed strength and analysed caffeine concentrations. The coffee sample contained extensive variability with assessed strength and repeated sampling was performed with 60 percent of the sample. However, the tea sample did not display the same complexity and a larger sampling of 80 percent was deemed necessary to ensure adequate representation of variability of the strength factor.

Correlations for coffee displayed high reliability ranging from .5 to .8 inclusive with 10 out of the 15 correlations having a value of .6. The tea correlations were more disperse ranging from .2 to .6 inclusive with six of the 15 correlations having a value of .5.

Another technique for checking reliability (Diaconis & Efron, 1983) involves replicating the pairs of values and randomly sampling the number of original cases. To this end, the coffee and tea paired values of strength and concentration were repeated eight times. Random sampling and subsequent correlations revealed a mode of .6 and a narrow range from .4 to .7 for coffee and a mode of .3 with a broader range from .1 to .7 for tea.

Appendix 6D

Caffeine Values Utilized in Algorithm

Caffeinated soft-drinks

40 mg per 12 oz serving (Consumer Reports, 1981)

Chocolate Bars

20 mg for a small chocolate bar

30 mg for a medium chocolate bar

40 mg for a large chocolate bar

(Consumer Reports, 1971)

Chocolate Drinks

10 mg per 8 oz serving (Consumer Reports, 1976)

Medications

	mg caffeine per tablet	Reference
Anacin	32	(American Pharmaceutical Association, 1977)
Bromoseltzer	32	(American Pharmaceutical Association, 1977)
Cafergot	100	(Consumers Research Magazine, 1982)
Comeback	100	(American Pharmaceutical Association, 1977)
Cope	32	(American Pharmaceutical Association, 1977)
Coricidin	30	(Tull & Brown, 1981)
Darvon	32	(Consumers Reports, 1982)
Dristan	32	(Consumers Reports, 1982)
Empirin	32	(American Pharmaceutical Association, 1977)
Excedrin	68	(American Pharmaceutical Association, 1977)
Fiorinal	40	(Consumer Reports, 1982)
Midol	32	(American Pharmaceutical Association, 1977)
Migral	50	
Nodoz	100	(American Pharmaceutical Association, 1977)
Premens Forte	100	(American Pharmaceutical Association, 1977)
Sinarest	30	(American Pharmaceutical Association, 1977)
Triaminican	30	(American Pharmaceutical Association, 1977)
Vanquish	33	(American Pharmaceutical Association, 1977)
Vivarin	200	(American Pharmaceutical Association, 1977)
Wampole C2	.15	(Label)
222	30	(Label)

APPENDIX 7

STUDY 2: Investigation of Infant Apnea as Related to
Caffeine Withdrawal

APPENDIX 7A: Introductory Letter to Hospital

APPENDIX 7B: Questions for Mother

APPENDIX 7C: Case Studies

Carleton University
Ottawa, Canada K1S 5B6

September 15, 1982

This is an introductory letter informing the Civic Hospital Medical Research Department that Mrs. Barbara Watkinson is a member of my research group at Carleton University.

She is aware of the purpose of my research study and the confidentiality promised to the participants in our research regarding the use of their hospital records.

A handwritten signature in dark ink, appearing to be 'P.A. Fried'.

P.A. Fried, Ph.D.

PAF/mgh

Appendix 7B

Apnea Questions For Mother

Episode #_____

Age occurred:

Time of day:

Feeding: Type:

(bottle, breast, solids)

When and what last fed prior to episode:

Activity frame:

(e.g. sleeping)

Environment:

(e.g. hot, smoky, noisy)

General health of child:

(e.g. allergies - define, colds, headaches)

Medication:

(type, dosage, when administered)

Unusual behaviour of child:

(e.g. irritable)

Unusual occurrence with child:

(e.g. stressed, punished, move, change in babysitter)

Manner displayed:

(e.g. 30 seconds not breathing, then a short breath followed by)

Duration of episode:

(e.g. 10 minutes)

How was mother (or ?) alerted to problem and how did she know that it was over?

Treatment:

Have other siblings had similar problems?

Appendix 7CCase Studies: Descriptions of Infant Apnea as Reported
by Mothers and other potentially Related Factors

Six mothers reported observing apnea in their infants. The following accounts are their personal descriptions of the incidents. The names of both the mothers and their children are fictitious. Information regarding birth variables and maternal drug habits is included.

1.) A 31 year old mother described apneic episodes which occurred with her son, now two years of age. She had known of the condition with young babies and mentioned her concern with her own baby. Joe was to be her only child and she was watchful for problems that might threaten him. The first episode was observed at one or two days of age in the hospital as Joe lay sleeping on her bed between feedings. Mary noted that Joe stopped breathing for about 30 seconds and then seemed to "catch his breath" and started breathing regularly again. Mary noted about five similar episodes occurring sporadically until Joe was five to six months old at which time she feels that the spells "disappeared". At this time Mary began working outside the home and may have thought the spells were not occurring simply because she was not present to observe them. All the episodes observed were in the late afternoon toward the end of Joe's afternoon nap. The longest period of non-breathing occurred when Joe was

four to five months old and lasted for about 60 seconds. Although Joe was fed at first with only breast milk, by five months, he was bottle fed and eating solid foods. Joe was given medication for colic for the first few months after which time it was no longer needed. Joe's general health has been good but some allergies have surfaced: dermatitis and penicillin allergy.

No unusual occurrences or behaviour could be connected with the apnea. However the mother describes Joe as a chronically tense, tight, rigid baby who resisted cuddling and was upset by the fondling of relatives. Her feeling is that a possible reason for the apnea was "over-tired ness". She mentioned that Joe's father is also prone to non-breathing spells.

Both of Joe's parents are allergy-prone. Mary's pregnancy habits included moderate drinking (.4 oz absolute alcohol daily), heavy smoking (23.8 mg nicotine daily) and marihuana use (13 jts. weekly), and moderate caffeine intake (112 mg daily). She took Dimetabb two to three times per week throughout pregnancy and one or two Tylenol tablets once or twice a week in the last trimester.

Joe was a 3657 gram baby born at 38 weeks gestation.

2.) Rebecca is a 34 year old mother who described three episodes of apnea with her daughter, Rachel, now two years

of age.

The first episode occurred when Rachel was one and a half years of age. Her parents were awakened around midnight by crying, gasping and choking sounds, and when they went into Rachel's room, found her manifesting "seizure-like" activity, flailing her arms and turning and twisting in bed. Each gasping episode lasted for approximately four seconds and occurred, at first, every five minutes and gradually tapered off to every 20 minutes by 7:30 in the morning. Rebecca had been taking erythromycin for five days previous to the incident. The parents rushed Rachel to the hospital at the beginning of the attack and doctors as well as parents observed her through-out the night. Doctors retained Rachel in the hospital for five days of observation and testing and concluded that the condition was not life-threatening: An EEG and other tests revealed no abnormality.

Approximately one month later in the early evening, Rachel was being disciplined. The parents felt because of the extra attention that she had received, she had become "spoiled". Rachel was objecting to going to bed and her parents put her to bed against her will. She began crying and then started a similar though less severe manifestation of the problem which persisted throughout the night. No

treatment was initiated.

Again about one month later another episode occurred during the day which was similar in severity to the second but lasted for less than one hour. No treatment was initiated.

Rachel's general health has been poor: at three and five months severe gastroenteritis; multiple ear infections; many colds; allergies (sulpha drugs plus other ill-defined allergies). Rachel has taken medication for various reasons for most of her life and the mother thinks that for the last two episodes, Rachel was probably taking antihistamines.

Rebecca suffers from allergies. During her pregnancy she took Colace as a stool softener, drank moderately (.2 oz a.a. daily), consumed approximately 75 mg of caffeine daily and did not smoke.

Rachel was a 4734 gram baby of 41 weeks gestation. During delivery the cord was wrapped around her neck.

3.) Ruth is a 35 year old woman who related a history of non-breathing with her now four year old daughter, Naomi. Naomi was approximately two weeks of age when periods of non-breathing were first observed and thereafter noted about weekly for the first year followed by periodic episodes which still occur. The non-breathing has always occurred during sleep and varies in length up to eight seconds. Ruth

remembers observing these spells at night but suggests some may have occurred during the day. Naomi would stop breathing for up to eight seconds and then startle and begin a regular breathing pattern again.

Naomi was breastfed as a baby but was intolerant to cow's milk and citrus fruit consumed by Ruth. Allergies persisted in the form of exzema and swollen lymph nodes.

No unusual behaviour or occurrence could be connected with the episodes. The mother does say that Naomi was stressed because of her allergies and a parasitic condition discovered a seven months of age which was cured with medication.

Both parents suffer from allergies. Ruth was a light drinker (1 oz a.a. daily), a non-smoker, and did not consume caffeine during her pregnancy. Occasionally she took anti-histamines while she was pregnant. Bleeding occurred at nine weeks.

Naomi was a 2946 gram baby born at 38 weeks of gestation.

4.) Delia, a 28 year old mother, reported eight apneic incidents with her 15 month old son. The first occurred when Sammy, 11 months old, was playing and excited. As with all the episodes, he was awake and started whimpering, fell

over, became glassy-eyed, limp and white, and stopped breathing. His eyes remained open but seemed lifeless. Delia admitted to difficulty in remembering the duration of the apneic spells but thought that they would range from 30 seconds to one and a half minutes. For the first five episodes, the treatment initiated by the father or relative involved turning Sammy upside down and slapping him between the shoulder blades. For the final two episodes, they have, on a doctor's suggestion, squeezed the rib cage firmly. The treatments have at times been immediately effective and at other times had to be repeated. Always Sammy recovered with a long deep gasp of breath after which he has clung to his mother as if for reassurance and then slept for a long period. The succeeding episodes were described as follows:

Episode 2: The following morning. A doctor was contacted and Sammy spent three days in a hospital. Blood tests were performed, found normal and Sammy was discharged.

Episode 3: Four or five days later during a feeding of solid foods. Again Sammy was hospitalized. An EEG was performed and found normal.

Episode 4: A few weeks later in bed before sleeping.

Episode 5: One month later during a feeding of solid foods. A doctor was contacted and parents were told that Sammy was probably holding his breath voluntarily. The parents were dissatisfied with the explanation, contacted a pediatrician

and Sammy was referred to a neurologist who suggested that the problem was migraine headaches.

Episodes 6,7,8: Over the next few months to the present.

The episodes all occurred during periods of activity and stimulation. The father has a history of migraine headaches.

Delia during her pregnancy was a very light drinker (.02 oz a.a. daily), a light smoker (7 mg nicotine daily) and consumed approximately 102 mg of caffeine daily. Delia reports having mild allergies. She had a difficult time getting pregnant and had been on fertility drugs when she conceived.

Sammy was a 3610 gram baby of 39 weeks gestation. His Apgar was "5" at one minute and "9" at five minutes. Fetal distress occurred because of cord compression. At birth, the cord was wrapped once around Sammy's neck. A laryngoscopy revealed meconium in larynx; meconium was also present in the stomach.

5.) Beth is a single 30 year old mother of Indian descent with a two year old son, David, who has had apneic periods observed on an average of twice a day since 12 to 14 days of age to the present with no diminution in frequency over time. All episodes occur during sleeping periods whether in the afternoon or at night when David sleeps in the same bed

as his mother. When David sleeps, he is a noisy breather often snoring so Beth can recognize when the non-breathing commences. She has counted in 1000's to estimate the duration of the episode and has noted variations from 10 to 20 seconds. At times she has observed facial pallor and has occasionally nudged him in an effort to promote breathing. At the conclusion of the apnea, David takes a long deep noisy breath which seems to "fill his whole lungs" and then returns to normal more shallow breathing.

David has been breast-fed since birth and is now on solid foods and tea. His general health has been good. When the apnea occurs, the environment is usually quiet although at times the radio or television is on. The mother claims that the episodes seem to occur when David is sleeping deeply. If he has a cold and is taking OTC medications, he tends to sleep more restlessly and is less prone to apnea.

The parents report allergies. Throughout her pregnancy, Beth was a moderate drinker (.6 oz a.a. daily), a non-smoker, and consumed approximately 56 mg of caffeine daily.

David was a 3020 gram baby of 37 weeks gestation delivered by C-section because of breech presentation.

6.) Sarah, a 31 year old single mother has had three child-

ren. The oldest boy is eight years of age, a second child, a daughter, died at two months because of a heart defect, and her youngest son, Abe, is two and one half years of age. Sarah was alerted to the problem of apnea with her daughter who had numerous prolonged episodes. Abe's first observed non-breathing spell was at approximately one week of age. About 10 to 15 episodes occurred over the following seven weeks with diminishing frequency. Sarah always noticed the apnea during the day or early evening when she was holding him. She describes a "craning" of the neck initially, followed by three to four seconds of non-breathing occurring when Abe was awake or drowsy. Often the episodes occurred after breast-feeding. Sarah always shook Abe to stimulate breathing again.

Abe's general health has been good although he is thin for his size and the mother reports an infant tendency to cyanotic hands and feet which has persisted.

Sarah took medication throughout her pregnancy for an underactive thyroid as well as allergy injections and vitamin pills. Throughout pregnancy Sarah was a very light drinker (.02 oz a.a daily), a non-smoker and consumed 85 mg daily of caffeine on average.

Abe was a 3000 gram baby born by C-section at 38 weeks of gestation.

APPENDIX 8

STUDY 3: Habit Changes and Effects of Parental Caffeine Use on Offspring. In all diagrams, "." signifies less than one percent and the seven time frames are represented chronologically from left to right.

APPENDIX 8A: Distributions of Frequency of Use of Dietary Sources of Caffeine

APPENDIX 8B: Distribution of Various Methods of Coffee Preparation and Distribution of Tea Types

APPENDIX 8C: Modes and Ranges for Portion Sizes of Dietary Sources of Caffeine

APPENDIX 8D: Distribution of Assessed Strength of Tea and Coffee

APPENDIX 8E: Distributions of Use of Caffeinated-Decaffeinated Products

APPENDIX 8F: Percent of Women Entering "don't remember" Codes

APPENDIX 8G: Mean Caffeine Intakes by Users According to Child's Birthdate

APPENDIX 8H: Correlations of Intake from Various Caffeine Sources and Nicotine and Alcohol Habits Before and During Pregnancy

Appendix BA

Distribution of total maternal daily caffeine use: Percent of mothers using various amounts of caffeine (mg), 1-0, 2-0<X<100, 3-100<X<200, 4-200<X<300, 5-300<X<400, 6-400<X<500, 7-500<X<600, 8->600.

Distribution of daily maternal coffee and tea use: Percent of mothers versus number of cups.

Distribution of maternal caffeinated soft-drink use per day: Percent of mothers versus number of drinks daily.

Distribution of maternal chocolate bar use per week: Percent of mothers versus number of bars weekly.

Distribution of maternal chocolate drink use per week: Percent of mothers versus number of drinks weekly.

Distribution of maternal caffeinated drug use per week: Percent of mothers versus number of pills, tablets, or other taken weekly and percent of mothers versus categories of caffeine intake in mg.

Distribution of paternal coffee use per day: Number of cups versus percent of fathers.

Appendix BB

METHODS OF COFFEE PREPARATION:

TEA TYPES:

Distribution of various methods of coffee preparation: Percent of mothers using different methods, 1-instant, 2-percolated, 3-drip, 4-percolated and drip, 5-drip and instant, 6-drip, percolated and instant, 7-percolated and instant. Distribution of tea types: Percent of mothers using different types, 1-black, 2-herbal, 3-green, 4-decaffeinated, 5-herbal, green and black, 6-black and herbal, 7-black and green.

Appendix 8CModes and Ranges in Portion Sizes of Dietary Sources
of Caffeine

	coffee (oz)	tea (oz)	caffeinated soft- drinks (oz)	chocolate drinks (oz)	chocolate bars (small, medium, large)
3rd Y* pre	6(3-12)	6(3-12)	9(3-12)	8(6-16)	S, M(S-L)
2nd Y pre	6(3-12)	6(3-12)	9(3-12)	8(6-16)	S, M(S-L)
1st Y pre	6(3-12)	6(3-12)	9(4-12)	8(6-16)	S, M(S-L)
1st Tri	6(3-12)	6(3-12)	9(4-11)	8(6-16)	S, M(S-L)
2nd Tri	6(2-12)	6(3-12)	9(4-11)	8(6-16)	S, M(S-L)
3rd Tri	6(2-12)	6(3-12)	9(4-11)	8(6-16)	S, M(S-L)
Year post	6(3-12)	6(3-12)	9(3-12)	8(6-16)	S, M(S-L)

Appendix BD

Distributions of assessed strength of coffee and tea: Percent of mothers assessing coffee and tea as W-weak, M-medium, or S-strong.

Appendix 8E

Distribution of use of caffeinated and decaffeinated products: Percent of mothers using C-caffeinated, C+D-caffeinated and decaffeinated, or D-decaffeinated coffee and percent of mothers using C-caffeinated or D-decaffeinated soft-drinks.

Appendix 8FPercent of Women Entering 'don't remember' Codes

	coffee	tea	caff. soft- drinks	choc. bars*	choc. drinks*	caff. drugs
3rd pre	2	2	9	41	22	11
2nd pre	2	2	9	41	21	11
1st pre	2	2	8	38	21	10
1st Tri	1	2	5	35	19	7
2nd Tri	1	2	6	33	18	8
3rd Tri	1	2	6	34	19	8
Year post	2	2	7	36	19	10

*These proportions include those women who used these sources less often than once a week (see questions 23 and 24, Appendix 4)

Appendix 8G

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Mean daily maternal caffeine intake by users according to infant's birthdate from coffee and tea.

Mean daily maternal caffeine intake by users according to infant's birthdate from caffeinated soft-drinks and chocolate bars.

Appendix 8H

Correlations of intake from various caffeine sources
and nicotine and alcohol habits before and during pregnancy

	Nicotine				Alcohol			
	pre- preg	1st tri	2nd tri	3rd tri	pre- preg	1st tri	2nd tri	3rd tri
Total caffeine	.25**	.40**	.33**	.21**	.13*	.19**	.20**	.11*
Coffee	.24**	.39**	.29**	.17**	.19**	.24**	.29**	.20**
Tea	.04	.08	.09	.05	-.13*	-.03*	-.06	-.04
Caffeinated soft-drinks	.20**	.19	.27**	.36**	.02	.03	-.01	-.05
Chocolate bars	-.05	.09	.11	.09	.02	-.02	.02	-.11
Chocolate drinks	.13*	.12	.06	.09	-.00	-.01	-.06	-.13
Caffeinated	.02	-.03	-.03	-.02	-.01	-.05	-.01	-.02

*p< .05

**p< .01

END

13 1 108 8.4

FIN