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CAFFEINE

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INTRODUCTION

Caffeine is consumed in varying amounts by most people of the world. Several million kg of caffeine are consumed annually in the United States alone, and more than 80% of the adult population consumes caffeine in some form (33). By reason of its ubiquity it is therefore a component of the diet that merits consideration by students of nutrition. The most important nutritional aspects of caffeine are its pharmacokinetics and metabolism and its effects on physiological systems at levels attained by dietary intakes. The present review primarily concerns the latter. Possible therapeutic uses and use in over-the-counter proprietary medicines are of little interest in nutri-

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tion provided they do not interfere with nutriture in other ways. Since such interference does not seem likely and has not been shown to occur in a nutritionally significant manner, the use of caffeine as a drug is not covered here. The effects at high doses of the variety of pharmacologically active components of the diet is not generally considered nutrition.

The chemistry and pharmacology of coffee and caffeine were recently exhaustively reviewed by Eichler et al (20); readers interested primarily in pharmacologic aspects of caffeine are referred to that volume.

SOURCES AND AMOUNTS IN DIET

Dietary caffeine is overwhelmingly derived from beverages. Chocolate and some confectionery, the only other dietary sources of caffeine, contain only a few mg/100 g. The amount in a cup of coffee or tea obviously varies with the strength of the infusion and the size of the cup. A round figure for the caffeine content of a cup of coffee is 80 mg with an extreme range from about one half to twice that amount. Caffeine-containing soft drinks contain about 0.01% caffeine; a 200 ml serving contains about 20 mg of caffeine.

While estimates of caffeine consumption are not well documented in refereed scientific journals, there seems to be little dispute about the general range (23). As one cup of coffee provides about 1 mg of caffeine per kg of body weight for an adult, amounts of up to 3 mg/kg or so can be taken over relatively short periods. The mean consumption of caffeine by people over 18 in the United States was estimated to be about 2.6 mg/kg per day, and the 90th percentile was 5.4 mg/kg per day; that is, 10% of the population consume more than 5.4 mg/kg per day. Both estimates were lower for younger people. These consumption figures come from a Market Research Corporation of America survey (10). Only in recent years have tissue levels of caffeine been measured with any regularity in studies on caffeine, so for most of the work reported on caffeine we know how much was given rather than what tissue levels were produced. Caffeine, however, is a readily absorbed and freely diffusible substance, so dose is a reliable predictor of tissue level under standardized circumstances—e.g. when a dose is taken as a bolus on an empty stomach. When taken in the usual manner in the diet, however—slowly and often with or after food—peak levels following a given intake are much lower and less predictable. There is a dearth of data on the caffeine loads (concentrations and durations of levels of caffeine in body fluids and tissues) that actually occur in the population.

Axelrod & Reichenthal (3) found a plasma level of about 10 mg/l in three subjects one hour after 7 mg/kg caffeine either intravenously or orally. A 250 mg dose of caffeine in 350 ml fluid taken on an empty stomach by 9 young adults produced a mean peak level in plasma of 12 mg/l, falling to

8 mg/l two hours later (59). When Axelrod & Reichenthal (3) had their subjects drink two cups of 80 mg caffeine/cup coffee at 8 A.M., noon, 3 P.M., and 6 P.M., the highest level attained, at 7 P.M., was only about 4 mg/l. The level was close to zero at 8 A.M. next day. From the results just given, it appears that the levels of caffeine attained by high normal consumers might range up to 5–6 mg/l maintained over a few hours per day. Hence, in looking for physiological effects that may be produced regularly by dietary caffeine, one is concerned about effects that occur at plasma caffeine levels of less than 10 mg/l. Such levels will be produced experimentally by single-bolus doses of less than 10 mg/kg.

EFFECTS ON PHYSIOLOGICAL SYSTEMS

Caffeine and other methylxanthines have been studied since the beginning of scientific pharmacology. They are said to "stimulate the central nervous system"; they cause diuresis, relax various smooth muscles; they have positive inotropic effects on the heart muscle and characteristic effects on skeletal muscles. In the following sections we consider how these classical pharmacological effects, obtained usually with large doses and in anesthetized animals or isolated tissues, relate to intakes of caffeine by persons with sane dietary and beverage habits. We then consider studies on the effects of dietary caffeine on health.

It should be emphasized at the outset that the biological effects of reasonable dietary intakes of caffeine are slight and not easy to detect. The most important effects are behavioral, and even these are undramatic and even subtle.

Central Nervous System (CNS)

The injection of doses of 50 mg/kg and greater in animals causes changes in electrical activity of brain. (33). Such doses lead to levels far beyond those achieved in man by dietary intake. When caffeine is described as a CNS "stimulant" it is usually in reference to behavioral effects rather than to directly recorded changes in CNS activity. Behavioral effects are alterations in the interchanges of a subject with the environment. Many authors use the term "behavioral effects" as though it implied direct CNS effects, but such usage is not logically justified. As the techniques and findings in studies of behavioral effects are currently quite different from those of neuropharmacological studies it is convenient to discuss them separately recognizing that, when enough is known, neurological and behavioral phenomena will no doubt be seen to be intimately related.

Directly recorded CNS effects of levels of caffeine achieved by dietary intakes are not well established; they are certainly not conspicuous. Indeed,

neuropharmacological effects do not seem to have been detected in experimental animals following oral ingestion of caffeine. In a recent study in humans, Elkins et al (21) found only equivocal changes in an evoked optical potential in 19 children following a dose of 3 or of 10 mg/kg caffeine in 6 oz of soft-drink. The 10 mg/kg dose taken in this manner produced salivary levels of 10.4 mg/l of caffeine one hour after ingestion. The standard deviation was only 1.2 mg/l, indicating little variability among the subjects.

Effects on the Cardiovascular System

There is a vast literature on pharmacologic effects of caffeine on cardiovascular functions, in which are described relaxation of smooth muscle of blood vessels and positive inotropic effects on heart. Most such studies have involved large doses injected into anesthetized animals or added to tissues in vitro. This work is not reviewed here (see 33). Cardiovascular effects such as increases in blood pressure may be produced by the CNS effects of caffeine. Such CNS-mediated effects, rather than direct effects, are traditionally attributed to the levels of caffeine achieved by dietary intake. However, the mechanisms of such effects, if they occur, are not established and the problem has not been studied with modern neurophysiologic techniques.

In humans, a bolus intake of 250 mg caffeine in 9 normal young adults who did not normally consume coffee (and who were abstaining from tea and chocolate if they normally consumed them) produced unmistakable cardiovascular effects (59). The mean systolic blood pressure rose from about 106 mm Hg to a peak of some 120 mm Hg, the diastolic blood pressure from 75 to 85 mm Hg, at 0.5 to 1.5 hr after ingestion. The heart rate first decreased and then increased. Plasma renin activity and norepinephrine concentration rose significantly. The mean plasma level of caffeine at 1 hr after ingestion approximated 12 mg/l. When subjects were given 250 mg caffeine three times per day for seven days, however, the effects just described ceased to occur (60). Similar bolus doses of 250 mg produced no detectable cardiovascular changes in regular coffee drinkers. Interestingly, when the 750 mg/day caffeine was discontinued no withdrawal symptoms were detected.

Effects on Other Systems

Many studies exist of the pharmacologic effects of caffeine on respiratory, renal, and other systems, but few effects have been demonstrated to occur at levels attained from dietary intakes. In the study by Robertson et al (59) described above, both respiratory and renal effects of the 250 mg bolus dose were found. The mean respiratory rate increased from 13.4/min one hour after placebo to 16.1/min one hour after caffeine. This increase was correlated with the plasma caffeine level, being insignificant when the level was less than 5 mg/l. In the same study, 3-hr collections of urine averaged 366

ml after placebo and 469 ml after caffeine. Bolus intubation of 250 mg caffeine into the stomach increased gastric secretion of acid (61), and 150 or 300 mg into the jejunum or by mouth changed the the fluid exchange in a segment of jejunum or ileum from net absorption to net secretion (74).

BEHAVIORAL EFFECTS

Acute Behavioral Effects in Experimental Animals

Behavioral effects of caffeine have been measured in mice, rats, and monkeys after parenteral doses as low as 1–3 mg/kg. In mice, for example, effects on "discrimination learning" in an underwater Y-maze were described by Castellano (11) at doses of 1 and 2 mg/kg. While the effects reported are unlikely to have been changes in "learning" as suggested by author, they were nonetheless effects on behavior. Reports of consequences at lower doses do not carry convinction. There is one claim of a detectable behavioral alteration in mice with a dose of 0.2 mg/kg (68), but scrutiny of the results does not reveal the alleged effect and the same laboratory reported subsequently in comparable tests that 50 mg/kg caffeine were required to induce changes. (69). Castellano (11) found no effects at 0.5 mg/kg. Kallman & Isaac (43) found altered activity in rats to result from 2 mg/kg caffeine, the alterations being consistent in old and young animals studied in the light or dark. No dose lower than 2 mg/kg was studied. Higher doses (up to 32 mg/kg) caused progressively greater effects. Responding under schedule control by either FI or a postponement schedule was increased by 1, 3, and 10 mg/kg of caffeine in squirrel monkeys (14). The consistency in the doses of caffeine in mg/kg causing behavioral effects in the different species is unusual among drugs. It is interesting to note the similarity of acute toxicity of caffeine in a variety of species (see below).

Effects on Performance in Humans

With levels of caffeine achieved by even high dietary intakes it is hard to detect changes in subjects already performing well. Restorative changes in degraded performance can be measured, however. Goldstein et al (29) write:

> Adequately designed experiments have shown unequivocally that caffeine (and also amphetamine) counteracts the decrement in various kinds of performance that is caused by fatigue or sleep deprivation. The evidence is much less convincing (and often contradictory) as to whether or not these drugs are capable of enhancing performance over control levels. Where physical endurance and capacity are required (as in athletic performance), such enhancement has been shown [for amphetamine]. There is also some indication that caffeine can increase the normal threshold frequency at which flicker fusion occurs [(54, 46)] but carefully designed experiments have also yielded negative results [(19)]. In the case of tasks requiring motor coordination, monitoring (alertness), or intellectual activity, the preponderance of data is negative.

In their own experiments on a group of 20 medical students working under competitive conditions, Goldstein et al (29) found that "Caffeine (150 mg or 300 mg) had no demonstrable effect upon either objectively measured performance [alertness or psychomotor coordination] although at the same time it made the subjects feel more alert and physically active."

After a comprehensive and authoritative review of studies in humans, Weiss & Laties (76) concluded that caffeine did not improve intellectual performance "except, perhaps, when normal performance has been degraded by fatigue or boredom." Weiss & Laties addressed the problem of whether caffeine can enhance optimal performance of any kind. They, too, found no convincing evidence that caffeine appreciably enhanced any performance already optimal for the subject. These investigators also asked whether the restoration of degraded performance by caffeine exacts a psychological "price"—for example by leading to impaired judgment, or to a subsequent "letdown" to still more degraded performance—and concluded that no detectable "price" is paid after either acute or chronic use of caffeine.

While the effects of caffeine in restoring human performance toward optimal levels are undoubtedly real and consistent, it must be emphasized again that the effects are small. They are well within the range of effects produced by a variety of everyday arousing and alerting influences: changes of environment, noises, cool draughts, pungent smells, and the like.

Effects on Sleep

The function most sensitive to modification by caffeine in adult humans is that of going to sleep. Sleep postponement in human adults has been detected following bolus intakes of about 100 mg caffeine 0.5 hr before retiring, but not at lower intakes. The results of three published studies are shown in Figure 1.

There is a general presumption that certain individuals are peculiarly sensitive to caffeine, being rendered sleepless or "nervous" by quite small amounts, and there is abundant anecdotal testimony to support the notion. However, there is noticeably little hard quantitative information; indeed, it seems the more careful and objective the study, the less gross the detected variability. The similarity of effective doses in many species would not lead one to expect large differences within a species.

An informative experiment was performed by Goldstein and his colleagues on 20 medical students (30). On 10 occasions each subject before retiring to bed drank decaffeinated coffee to which had been added lactose on 5 occasions and 300 mg caffeine on 5 occasions in random sequence and without the subject knowing which had been added. On all 10 following mornings the subjects estimated how long it had taken them to fall asleep. In every subject, the mean estimated time to fall asleep on the 5 caffeine

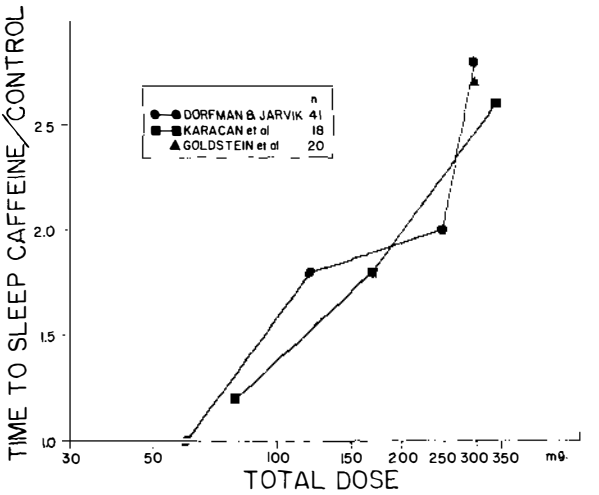

Figure 1 Delay of sleep by caffeine. Caffeine or placebo was taken blindly 0.5 hr before retiring, and the time required to go to sleep was assessed by questionnaire next morning. The delay was expressed as the ratio of mean time to go to sleep after caffeine divided by the mean time on the noncaffeine days. The figure shows the remarkable concordance between the three quite independent studies and also that the effects were slight below 100 mg total dose and undetectable below 80 mg total dose (17, 30, 44).

nights was longer than that on the 5 lactose nights. The mean estimated time that sleep was postponed, however, varied greatly in the 20 subjects from a low of 1.8 min to a high of 53.6 min. But there was also great variability in the estimated time to sleep under the placebo condition, the mean time being 12.2 min with a coefficient of variation of 56%. After caffeine, the mean estimated time was 31.8 min with coefficient of variation of 59%. Thus the caffeine did not appreciably increase the variability in mean estimated time to go to sleep, suggesting a relatively uniform rather than a highly variable response to caffeine.

Yet variability there was. For example, one subject reported a time to sleep of 240 min on one caffeine night, though never reporting more than 45 min on any of the 5 lactose nights; the same subject reported a 15 min time to sleep on another caffeine night. Evidently time to go to sleep was influenced by other factors as much or more than by the presence or absence of caffeine. As has been described, the effect of caffeine on performance is highly dependent on the condition of the subject with respect to fatigue or boredom. While caffeine may consistently establish a tendency, the manifest effect is determined largely by amplification by additional factors. Influences such as slight discomfort, nonoptimal temperature, or noise can postpone sleep and may greatly amplify the effects of caffeine. Even in careful studies, most amplifiers are not identified or controlled, and their

effects are attributed to "innate differences" largely by default. The putatively large individual differences in response to caffeine are probably due mostly to environmental factors. Such innate differences as do exist may be exaggerated by strong expectations of large effects of caffeine and by limitations of intake with consequent less tolerance.

Acute Behavioral Effects in Children

Most of the information on effects of caffeine in children concerns subjects diagnosed as hyperkinetic. Neither the therapeutic effects nor the side effects of caffeine in such children are impressive, even at doses with clearly detectable effects in adult humans and animals (21).

Elkins et al (21) studied the effects of 3 mg/kg and 10 mg/kg caffeine given in a single 6 oz drink to 19 normal prepubertal boys. Salivary levels (which have been shown to correspond well to plasma levels) were measured in some of the children one hour after ingestion of the caffeine. They averaged 3.1 mg/l after the 3 mg/kg dose and 10.4 mg/l after the 10 mg/kg dose. Ratings of mood, side effects, and behavior were made. The children's activity was assessed by means of an inertial device they wore on their belts. Visual evoked potentials (EP) in the EEG to 4 light intensities were assessed. Reaction times were measured. Sustained attention (Vigilance Test) was assessed with a Continuous Performance Test, which permitted recording of errors of both omission and commission and also rapidity of response to stimuli. A simple memory test was conducted. Finally, blood pressure, heart rate, and epinephrine and norepinephrine in urine were measured. The children received mean total doses of 100 mg for the low dose and 369 mg for the high dose. The effects of the 3 mg/kg dose were equivocal. With the high dose reaction time decreased slightly, omissions decreased on the Vigilance Test, and activity increased. There were no effects on EPs. No effects were detected on blood pressure, heart rate, or catecholamine excretion. On some of the tests, scores after 3 mg/kg were between those for placebo and 10 mg/kg, suggesting a trend and that 3 mg/kg might be approaching an active dose. Even the high dose caused no significant change in side effects as a whole. There was a suggestion that a subgroup of 5 children who did not usually consume caffeine showed a slight increase in side effects. Fidgetiness may have increased. To put these findings in context of dietary intakes, the 3 mg/kg dose represented an intake of about a quart of soft drink over the course of a few minutes. The findings of Elkins et al (21) are of particular interest in view of an oft-quoted comment in a standard textbook of pharmacology (Goodman & Gilman's *The Pharmacological Basis of Therapeutics*) that "Children are more susceptible than adults to excitation by xanthines" (58). No authority is cited for this opinion, which was repeated verbatim in the text's first five editions (32, 58). Never-

theless, children appear to be less, and certainly no more, sensitive to measured effects of caffeine than adults, and the clinical reports on hyperkinetic children support such a conclusion (21). Rall (57), writing on methylxanthines in the 6th edition of *The Pharmacological Basis of Therapeutics* makes no claim that children are more susceptible.

Effects of Chronic Intake

Chronic behavioral effects of caffeine have been seen in experimental animals with intakes large enough to cause relatively nonspecific debilitating effects. For example, Estler et al (22) gave mice 150 mg/kg daily caffeine in the drinking water for six weeks. To obtain such high intakes, the concentration in drinking water has to be so high that animals reduce fluid intake, which in turn interferes with food intake. These authors found serious reduction in weight gain of their treated mice as compared to the controls. It is hardly surprising that such debilitated mice performed less well than the controls in swimming performance in cold water. The mice were taking, according to the authors, almost half the acute LD50 of caffeine each day. Even these massive daily doses of caffeine did not have major behavioral effects; the spontaneous motor activity of the treated mice was similar to that of the controls. The lack of information on dose-effect relations in these studies makes extension to lower doses impossible.

In an experiment to see whether dependence on caffeine followed chronic intake, Vitiello & Woods (73) forced rats to drink caffeine solutions at concentrations of 0.17, 0.34, or 0.5 mg/ml for 14 days by making the solutions the only source of drinking water for the experimental groups. Paired controls drank water. The rats were then given for 8 days free choice between the concentration of caffeine they had been drinking, mocha-flavored water (as flavored control for the caffeine), and plain water. If the rats that had been drinking caffeine-solutions were dependent on caffeine it was expected that they would drink more of the caffeine solution to suppress withdrawal symptoms than rats that had not been drinking caffeine-solution. The rats that had been forced to drink caffeine solutions of concentrations of 0.17 or 0.34 mg/ml did not differ, however, in their subsequent choice among the three proffered solutions from rats previously drinking plain water, although the 0.34 mg/ml rats drank more mocha-flavored water. Rats that been drinking 0.5 mg/ml (i.e. intakes of more than 50 mg/kg/day) drank statistically less of the mocha-flavored water than controls. They drank more caffeine solution than their controls, but the difference was not statistically significant. In view of the decrease in intake of mocha-flavored water, the modest increase in intake of caffeine solution could not be attributed to an effect of withdrawal from caffeine. When the control rats for the 0.5 mg/ml group were subsequently forced to drink 0.5

mg/ml caffeine and then given a choice, they too drank significantly less mocha-flavored water. "It is noteworthy" the authors write, "that the rats did not prefer the flavor associated with the caffeine, even on the first day of the free choice period, for there is considerable evidence indicating that the after-effects of drugs are readily associated with flavors." The experiments therefore found no evidence of dependence or withdrawal symptoms from caffeine. It may be noted that the difference between 0.34 mg/ml and 0.5 mg/ml is so small that the increase in consumption of mocha-flavored water in the 0.34 mg/ml group casts serious doubt on the reliability of the decreased consumption by the 0.5 mg/ml group. In any case, the absence of sequelae to intakes of over 50 mg/kg/day is reassuring when the 90th percentile of the distribution of caffeine intakes by humans is about 5.4 mg/kg daily.

HEALTH-RELATED EFFECTS OF CAFFEINE

The previous section concerned measurable effects of dietary caffeine regardless of health consequences. In this section we review studies that have sought to identify any harmful effects of caffeine.

Acute Toxicity

The LD50 of caffeine is fairly consistently approximately 200 mg/kg from species to species (66). It is interesting that it varies little with route of administration; even the intravenous LD50 is only a little lower than the values for oral, subcutaneous, or intraperitoneal administration (66). The consistency is doubtless due to the rapid absorption and distribution of caffeine.

Available evidence suggests that the amount per kg necessary for lethal toxicity in man is not dissimilar from that in experimental animals. Banner & Czajka (4) found case reports in the literature of four adults who had succumbed to caffeine poisoning with post-mortem blood caffeine levels of 1,040, 158, 106, and 79 mg/l. Caffeine has been used in the treatment of apnea in neonates. It was not known at first that neonates metabolize caffeine slowly (1), so the calculated doses of caffeine led to much higher body levels of caffeine than expected. Banner & Czajka (4) report four neonates who received intravenous and intramuscular doses of caffeine of 36–136 mg/kg over a few days. One of the babies developed a plasma caffeine concentration of 80 mg/ml. After a few days there were no detectable sequelae in any of the babies. The authors also report the case of a child who survived a plasma concentration of 190 mg/l caffeine. None of 18 sick infants treated with caffeine for apnea showed detectable sequelae (2). Their plasma levels of caffeine ranged up to 85 mg/l. Only one infant, with a level

of 60 mg/l, showed even transient jitteriness attributable to the caffeine (A. H. Neims, personal communication). Such levels are much beyond those that result from ingestion of caffeine in the diet and are sufficient to cause definite effects in experimental animals. There appears to be no acute danger to life from intakes of caffeine attainable from the diet.

At lower levels bolus intakes of caffeine up to 200–400 mg produce such effects as decreased fatigue or decreased ennui resulting in restored performance. With still higher acute doses, the incidence of side effects increases: "Nervousness, feverishness, irritability, headache, and disturbed sleep" are reported (76). These relatively short-lived symptoms are unpleasant rather than indicative of danger and people would probably not tolerate them if they occurred regularly with ordinary intakes. While our information is limited on the levels of plasma caffeine to which people regularly subject themselves through beverage intake, they must rarely attain levels as high as those resulting from bolus doses of 400 mg.

Significant acute toxicity, such as frankly abnormal irritability, requires doses of about 30 mg/kg in rhesus monkeys (P. B. Dews, personal observation); if humans are similarly susceptible, such effects will not be seen with dietary intakes.

Deleterious cardiovascular effects in mice under certain living conditions have been described by Henry and his colleagues (37). When mice were crowded and competed for food and water, blood pressure and blood urea nitrogen were chronically increased, and more mice died than in control cages. Adding caffeine to the drinking water, either as such or as brewed coffee or tea to yield transitory plasma caffeine levels of the order of 6–9 mg/1, exacerbated the deleterious effects of crowding and competition (38). Humans could attain levels of 6–9 mg/l caffeine by dietary intake. The exacerbation by caffeine intake of the increase in blood pressure and blood urea nitrogen was seen only at 3 months in the experimental situation, however, and had disappeared at 5 months even though crowding and caffeine were maintained. The deleterious effects were attributed to the "psychosocial stress" of crowding and competition, which was aggravated by caffeine. Crowding of animals may influence them in many ways besides imposing psychosocial stress, however—for example, by increasing the transmissibility of infections. Chronic interstitial nephritis occurred in the mice, a condition more commonly associated with infection than as a consequence of hypertension. The deleterious effects of crowding and competition on murine cardiovascular function were described as early as 1967 (36).

There have been epidemiological inquiries into the cardiovascular effects of chronic consumption of caffeine. According to the Boston Collaborative Drug Surveillance Program (BCDSP) patients brought into hospital with

a myocardial infarction reported higher coffee intakes than did matched controls (42). The surveillance program used hospital records as a means of finding leads to possible associations. A case-control study by Klatsky et al (45) found no such association. In the Framingham study, a prospective longitudinal study of 5209 people that began in 1949, caffeine consumptions of 4492 subjects were assessed by questions of examining physicians, starting 6 years after the beginning of the study. No association between caffeine and any cardiovascular disease was found (15). Another case-control study by Hennekens et al (35) concluded that "the risk, if any, of death from coronary heart disease associated with coffee drinking is small." No relation between coffee intake and blood pressure was found in IBM employees by Bertrand et al (6). The consensus seems to be that the BCDSP finding was a false positive. It appears that the routine proscripion by many physicians of caffeine-containing beverages for patients with cardiovascular diseases, notably myocardial infarction, is based on tradition rather than sound evidence.

Reproductive Effects

In many studies maternal caffeine intakes above (usually much above) 50 mg/kg per day in rodents proved to be deleterious to pregnancy and to the health of the offspring (56). Levels that convincingly affect reproduction approach those that cause maternal toxicity. There is little evidence of selectivity in the lesions in the offspring; that is, no particular deformity seems to result from caffeine administration. Particular deformities—e.g. the phocomelia of thalidomide—are generally regarded as the hallmarks of a true teratogen. Nonspecific interference with reproductive capability is a common consequence of maternal toxicity, and dozens, if not hundreds, of substances are known capable of producing teratogenic effects at high dosage in rats and mice. Most have never been implicated as teratogens in humans (71, 64, 77). Consequently, the demonstration of interference with reproduction by a substance in high dosage in rodents usually means little in terms of human effects at ordinary levels of exposure. One effect of caffeine in pregnant rats that seems to be well established is a delay in calcification of fetal bones during the latter part of pregnancy. This effect has been described as occurring at doses lower than those causing nonspecific effects (56, 55). Ectrodactyly has also been reported in rodents (7).

The possibility has been investigated that caffeine ingestion during pregnancy may produce changes in the behavior of the offspring even though no structural or other functional changes are detectable. Two studies have addressed this problem, one in rats and one in mice (65, 16). In neither was there evidence that caffeine, at doses lower than those causing nonspecific reproductive effects, produced significant deleterious behavioral effects on the offspring.

A number of reports contain information about possible effects of caffeine on human reproduction. A study on 202 malformed babies and 175 normal control babies from a population of 17,979 births suggested that heavy coffee consumption was commoner in the mothers of the malformed babies than in the mothers of normal babies (8). The differences were not impressive. The incidence of malformed babies of women less than 35 years of age who consumed more than 8 cups of coffee per day during pregnancy was 1.07 times the incidence in women who did not drink coffee. No dose-response relationship was established. Further, the information about coffee consumption was obtained after the children were born. Epidemiologists are aware that a mother who has borne a malformed baby is more susceptible to selective recollection of events in pregnancy than is the mother of a normal baby. Finally, the total incidence of severe malformations in the population of 17,970 births was only about one third to one half the incidence reported in other studies (72), so the sampling appears to have been biased.

In a study of babies born in the Kaiser-Permanente hospitals, a crude risk-ratio estimate of 1.3 for all severe congenital anomalies was associated with consumption during pregnancy of 7 or more cups as compared to less than one cup of coffee per day (72). The value 1.3 was not statistically significantly different from 1. The study did find a statistically significant deleterious effect of smoking. A study intended primarily to assess effects of alcohol consumption during pregnancy on outcome found no significant effect of caffeine consumption (67). No association was found between neonate malformations and mother's use of caffeine-containing medications during pregnancy (34).

Only one report has claimed a large effect of caffeine on reproduction (75). The study exhibited many serious defects of sampling and reporting. Its claim that 15 of 16 pregnancies in women who consumed more than 600 mg/day caffeine ended in disaster in one way or another is grossly discrepant from all other studies.

Casual consideration might suggest that the question of whether caffeine consumption has any effect on pregnancy outcome could be settled by a definitive epidemiological study. Unfortunately such may not be the case. Present evidence (e.g. 72) is sufficient to indicate that the association, if present, is slight. Caffeine consumption, however, is associated with a whole variety of influences related to life style, any one or combination of which could affect pregnancy outcome. Mau & Netter (50), who found that women with high coffee consumption more often than nonconsumers had children with small birth weight, concluded "It is nevertheless questionable whether a direct causal relationship exists. Based on other findings, the hypothesis is discussed that the habits of alcohol and coffee consumption are an indicator for a certain constitutional and character type." To the

extent that any features of life style with deleterious influences on pregnancy are positively correlated with caffeine consumption, epidemiological studies on caffeine consumption in relation to adverse outcomes of pregnancy would show a positive association, even if caffeine itself in dietary amounts were without effect on pregnancy. Further insight into the effects of caffeine on reproduction is likely to come, not from epidemiological studies, which by nature are not powerful in establishing lack of risk, but from basic research on the physiology of reproduction and embryonic development. When normal mechanisms are known, it is possible to study directly whether additional influences have an effect.

Carcinogenesis

Several studies have been published of long-term administration to rodents of caffeine as such or as coffee in amounts up to the "maximum tolerated level" (79, 78, 56, 70, 5, 49). None of them showed caffeine to be a carcinogen.

In humans, a weak association between coffee consumption and cancer of the lower urinary tract has been reported (13, 9, 62, 51), but further investigations indicate that the association, when it exists, is not due to a causal relation between caffeine and cancer (26, 53, 63) but is due to an association between caffeine consumption and other causal factors.

Of particular interest with respect to caffeine are two recently published case-control studies on pancreatic cancer. One of them identified several factors that were associated with pancreatic cancer, including consumption of decaffeinated coffee but not of untreated coffee (47). The second found an association between pancreatic cancer and coffee drinking but not tea drinking (48). Both studies, therefore, indicate that caffeine itself is not a causative factor.

Fibrocystic Disease of the Breast

Considerable public interest has been generated by a report of effects of methylxanthine consumption on fibrocystic disease of the breast (52). Forty-seven women with clinical fibrocystic disease of the breast were instructed to stop all methylxanthine consumption. Twenty reported that they did stop and 13 of these experienced complete disappearance of all palpable breast nodules and other symptoms within 1–6 months. Only one of the 27 women who said they continued methylxanthine consumption experienced resolution of her disease. Impressive as these figures are as they stand, it must be recognized that they represent no more than clinical impressions. The groups were self-selected, and the assessment was subjective. The results of an uncontrolled clinical study on a disease with a

notoriously variable and fluctuating natural history cannot be accepted as scientific evidence (39). Another completely uncontrolled study (8a) to which the same criticisms apply has been published as confirmation of the Minton study. A controlled study published in abstract by Ernster et al (21a) did suggest, however, that reduction in caffeine intake was positively related to reduced fibrocystic breast disease, although the change was "minor and may be of little clinical significance." Part of the concern over fibrocystic disease has arisen from a fear that it may be precancerous. A review by Ernster et al (21b), which suggests that benign breast disease is not a significant predictor of breast cancer, somewhat allays the fear.

Tolerance and Withdrawal

It is generally accepted that regular consumption of caffeine leads to tolerance to its effects. Goldstein (28) reported that caffeine caused distinctly less wakefulness in subjects who habitually drank a great deal of coffee, although even regular coffee drinkers reported sleeping less soundly after 300 mg caffeine than after placebo (29). A comparison of effects of morning caffeine on 18 housewives who were not coffee drinkers with 38 who drank 5 or more cups daily also showed divers differences in the effects on abstainers and consumers (31). Small but significant differences were demonstrated in both frequency and intensity of effects of 150 mg caffeine on pulse rate and sleep between regular caffeine consumers (more than one cup of caffeine-containing beverage per day) and nonconsumers (no more than one cup per day). Caffeine consumers showed a greater tendency to bradycardia and less tendency to disturbed sleep following caffeine. In all these studies abstainers and consumers were self-selected; if more susceptible subjects chose to abstain and less susceptible subjects chose to consume, the observed differences could result without there being a change in susceptibility to caffeine consequent upon consumption. However, the studies of Robertson et al (60) discussed earlier demonstrate unequivocally the development of tolerance in individual subjects.

It is also generally accepted that regular caffeine consumers develop withdrawal headache during the course of a day on which no caffeine is taken. Many years ago, Dreisbach & Pfeiffer (18) gave subjects increasing doses of caffeine in capsules, up to 780 mg; and then one day, without the subjects' knowledge, gave them a capsule containing no caffeine. In 32 out of 38 trials in the 22 subjects, a headache was reported on the placebo day, and in 21 trials the headache was severe. A withdrawal syndrome starting 12–16 hours after the last intake of caffeine was reported by the regularly consuming subjects in the study of Goldstein et al (31). In addition to

headache, the consuming subjects complained of being less alert, less active, more sleepy, less content or at ease, more irritable, jittery, nervous, and shaky than abstainers. All these symptoms were promptly relieved by caffeine. The list of statistically significant differences between consumers and abstainers is impressively long, though the syndrome itself was mild and inconstant. No signs of withdrawal were detected by Robertson et al (60) following seven days of 250 mg caffeine three times per day.

ARE THERE BENEFITS OF CAFFEINE CONSUMPTION?

Caffeine is a component of the diet that can produce pharmacologic effects. It is not unique in this regard, as a number of regular dietary components can cause pharmacologic effects (25, 24, 12, 27, 40, 41). Most people of the world elect to imbibe caffeine-containing beverages, thus providing prima facie evidence of perceived benefit. The smooth functioning of industrialized society is associated with people working about eight hours, eating and playing about eight hours, and sleeping about eight hours, with everybody more or less in phase, no matter what their internal rhythms might urge. Perhaps most people appreciate a little help in initiating the work phase; hence the widely accepted practice of consuming a caffeine-containing beverage at or before breakfast as part of the ritual of preparing for work. Some also need help through the work session, so that breaks have been institutionalized when caffeine-containing beverages are often consumed which, along with the alerting effects of change in activity itself, may help restore efficiency. It is surely true that people may harm themselves, their performance, and perhaps in other ways, with excessive intakes of caffeine; but gross overconsumption of any article of diet can be harmful. The deleterious effects of excess intake of caffeine, within some limit, seem to be transient and completely reversible.

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