ALASKA LEGISLATURE COMMITTEE FILES 1987-1988 8672
4600 HHES SB 32 (FILE 5)

conservative recommendation to avoid all drugs, including cannabis, that are not absolutely neccessary.[19]

Many of the women involved in studies suggesting lower birth weight also smoked tobacco. There are also questions as to what extent diet affected the birth weight in the cases studied. Women who have smoked marijuana during pregnancy, had appropriate diets and did not smoke tobacco, have produced childen of normal birth weights.

There is no evidence that marijuana has ever caused congenital anomalies[20]; there is persuasive evidence that "...neither marijuana nor delta-9-THC causes chromosome breaks."[21]

Findings 11 and 12 are refuted by both the National Academy report and the Harvard Mental Health Letter. The additional findings relate to evaluating data about trends of marijuana use in Alaska. Being unfamiliar with the data, I am reluctant to offer criticism. However, anomalies in data on the supply and consumption of marijuana in the United States suggest that far more people use marijuana than surveys have indicated in the past. It may be that in a non-criminal atmosphere such as Alaska's, people are more open with surveyors concerning personal marijuana use. If so, the supposed increase in mairjuana use is actually a reflection of more accurate polling.

An example of this anomoly can be found in the June report of the National Narcotics Intelligence Consumers Committee report. On page 6 they list marijuana consumption in the United States as being close to 10 million pounds per year. On pages 12 and 13 they list supply as being approximately 30 million pounds a year. The low consumption figure is based on the NIDA household survey of how many people use marijuana and how frequently. Since consumption figures do not account for all the marijuana available on the market, it obviously underreports the extent of marijuana use. Furthermore, government reports about marijuana seizures typically include "tip of the iceberg" comments which suggest that their estimate of supply, if anything, is low.[22]

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[19]L. Grinspoon, ed. (1988), 4.

[20]A.S. Relman (1982), 99.

[21]A.S. Relman (1982), 101.

[22]National Narcotics Intelligence Consumers Committee (NNICC) "The Supply of Illicit Drugs to the United States from Foreign and Domestic Sources in 1985 and 1986" (1987).

In my opinion, concerns about adolescent marijuana use can best be addressed by educational programs - such as discussions by groups of parents and children about the differences between adulthood and adolescence. I suggest that raising the age requirement for the purchase and use of tobacco to 21 would send a far stronger message of disapproval of teenage smoking than the recriminalization of adult possession of marijuana.

Thank you for requesting this information. On behalf of NORML's members in Alaska, we appreciate the opportunity to comment on these proceedings. Please let me know if I can be of any further assistance in this matter.

Sincerely,

Jon B. Gettman
National Director

JBG:jje
enclosures

ALASKA STATE LEGISLATURE
HOUSE OF REPRESENTATIVES
RESEARCH AGENCY

P.O. Box Y, State Capitol
Juneau, Alaska 99811-3100
Mail Stop 3100
(907) 465-3991

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March 10, 1987

MEMORANDUM

TO: Representative Pat Pourchot

ATTN: Jeannie Larson

FROM: Penelope Weyhrauch
Legislative Analyst

RE: The Physiological Effects of Marijuana, Alcohol, Tobacco, Aspirin, and Salt
Research Request 87.155 (Supplemental Information)

I have attached some information I recently received on the effects of salt, sugar, caffeine and tobacco on the body. I hope this information is of use to you.

Attachment

Defective salt excretion proposed as cause of essential hypertension

ST. PETERSBURG, FLA.—Essential hypertension evolves from a defect in the body's salt excretion mechanism, two investigators told the American Heart Association's science writers' forum here.

Both researchers focus on natriuretic chemicals in their hypotheses, and they predict eventual development of assays to detect the chemicals and identify people whose salt intake should be restricted. But they differ in their opinions on the ultimate cause of salt sensitivity and on the type of assays needed.

One line of research, presented by biochemist Tadashi Inagami, implies that salt sensitivity predisposing to hypertension results from a genetic deficiency of certain cardiac peptides. He says an abundance of these peptides can protect people from the ravages of high-salt diets.

On the other hand, Dr. Mordecai P. Blaustein points to an inherent kidney defect as the underlying cause of essential hypertension. "It may be that the disease we call essential hypertension is really several different diseases," says Dr. Blaustein, chairman of physiology at the University of Maryland School of Medicine.

Peptides probed. Dr. Inagami and his colleagues at Vanderbilt University School of Medicine in Nashville, Tenn. have purified—and are attempting to synthesize—atrial peptides that produce diuresis and increase sodium excretion by the kidneys.

"The atrium senses blood volume expansion due to excess salt and releases atrial natriuretic factor [ANF] directly to the kidneys," says Dr. Inagami, director of Vanderbilt's hypertension center. "We do not yet know the normal concentrations of ANF, but we are driving at this hypothesis: Clinical significance and dietary recommendations can be drawn from ANF levels, and the peptide can also be given to patients in acute renal failure."

The Tennessee researchers expect to complete peptide and antibody synthesis within a year, and Dr. Inagami says that ANF radioimmunoassay should be feasible within five years.

Dr. Blaustein

Dr. Inagami

An as-yet-unidentified natriuretic agent is crucial to Dr. Blaustein's approach to the relationship between sodium and hypertension. Natriuretic hormone (NH), thought to originate in the hypothalamus, has eluded discovery for 20 years, but its existence is accepted on the basis of its biologic activity.

NH is released in response to increased extracellular fluid, which signals the kidneys' inability to excrete sufficient amounts of sodium. The hormone inhibits renal sodium-potassium exchange, thereby reducing sodium resorption and promoting its excretion.

Inhibition of the kidneys' sodium pumps isn't a problem in itself. But NH also inhibits sodium pumps in surface membranes of cells all over the body, explains Dr. Blaustein, including blood cells, arterial-wall muscle cells, and nerve cells. The resulting increase in intracellular sodium causes increased intracellular calcium, which in turn increases arterial contraction and elevates blood pressure.

"We think a functionally defective kidney is the culprit to begin with," says Dr. Blaustein. "If too much salt is ingested, the defective kidney can't handle it, the brain hormone is released, and the sodium-calcium mechanisms come into play. The final common pathway of all types of hypertension may be increased vascular reactivity due to increased calcium in the vascular smooth muscle."

Screening potential. Once NH is purified, persons with family histories of hypertension could be screened for high levels of the hormone, which would indicate a need to restrict their dietary salt. Hypertensive patients also could be tested, first to confirm the hypothesis linking natriuretic hormone, sodium-calcium exchange, and hypertension, says Dr. Blaustein, and then to monitor efficacy of antihypertensive regimens.

Dr. Inagami notes that atrial natriuretic factor—unlike natriuretic hormone—doesn't appear to affect the salt-retention mechanism of cells outside the kidney. And Dr. Blaustein concedes ANF could play a pivotal role in the development of one class or subgroup of hypertension.

But he maintains an intrinsically defective kidney is the problem for many hypertensives. In support of his position, he cites a report of six kidney transplant patients who remained normotensive without medication for six months to six years posttransplant, despite having had essential hypertension, which culminated in the earlier nephrosclerosis. ■

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Surveillance and Control of Infectious Diseases: Progress Toward the 1990 Objectives

WALTER R. DOWDLE, PhD

Dr. Dowdle is Director, Center for Infectious Diseases, Centers for Disease Control, Atlanta, Ga. 30333. Contributors to this report were Dr. John Bennett, Dr. Claire Broome, Dr. Donald Francis, and Ms. Ladene Newton, Center for Infectious Diseases; Dr. Kenneth Powell, Center for Prevention Services; Dr. Philip Brachman, Global Epidemiology Program; Dr. Carl Tyler, Epidemiology Program Office; Dr. Joyce Essien, Laboratory Program Office, all of the Centers for Disease Control; Dr. Dennis McIntyre, Indian Health Service; and Dr. George Galasso, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Tearsheet requests to Dr. Dowdle.

SYNOPSIS

Great progress has been made in the United States in reducing infectious disease mortality. However, infectious diseases remain the greatest cause of morbidity in this country. Newer infectious diseases or agents have been recognized, but newer tools for surveillance and control have also been made available. Specific objectives for the reduction of infectious diseases by 1990 have been set by the Public Health Service. The opportunities appear to be good for achieving by 1990 objectives for nosocomial infections, Legionnaires' disease, tuberculosis, and surveillance and control of infectious diseases. Achievement of the 1990 objectives for hepatitis B, pneumococcal pneumonia, and bacterial meningitis, however, will require both scientific advances and additional resources.

GREAT PROGRESS HAS BEEN MADE in the United States in this century in reducing mortality attributable to infectious diseases. Infectious diseases were the fourth leading cause of death in the United States in 1976 (fig. 1) after heart disease, malignant neoplasms, and cerebrovascular diseases, according to data extracted from information published by the National Center for Health Statistics (*1*). Data are not available for all infectious diseases, but in 1980, influenza and pneumonia ranked seventh in years of potential life lost by the total U.S. population ages 1 to 64 years (*2*), as the following tabulation shows.

Cause	*Total years lost*
1. Accidents and adverse effects	2,684,850
2. Malignant neoplasms	1,804,120
3. Diseases of the heart	1,636,510
4. Suicides, homicides	1,401,880
5. Chronic liver disease	301,070
6. Cerebrovascular diseases	280,430
7. Pneumonia and influenza	124,830
8. Diabetes mellitus	117,340
9. Chronic obstructive pulmonary diseases and allied conditions	110,530
All causes	10,006,060

By comparison, in 1900 tuberculosis, influenza and pneumonia, and diphtheria were the three leading

• to monitor changes in sodium consumption and sodium content of foods, trends in sodium labeling of retail foods, and shifts in consumer perceptions and marketplace practices—all in order to assess progress toward achieving objectives; and
• to consider the need for legislation in the event this voluntary program does not succeed.

This program was discussed with food industry representatives on June 30, 1981, and was presented in detail in the Federal Register proposal of June 18, 1982 (47 FR 26580). Both the Department of Health and Human Services and the FDA have stressed that the goals of the sodium program are to provide more information to the public about the sodium content of foods they buy and to encourage industry to reduce the amount of sodium in processed foods, where this is safe and feasible.

Results have been encouraging. For example, several major food manufacturers have stated that they will supply sodium labeling for all of their products containing more than 35 mg of sodium per serving. In addition, many manufacturers have indicated that they have programs in progress to study the feasibility of reducing sodium in their products. FDA representatives have met with some 30 major groups from the food industry, including both large individual firms and trade associations representing them. Each of these groups has made a commitment either to moderate the sodium content of the foods they process or to provide much more sodium labeling. Collectively, these efforts already affect processed foods amounting to many billions of dollars in retail sales value. We estimate that the amount of sodium labeling in the marketplace will double or triple over the next year, applying to 40 percent or more of the processed food supply in terms of retail sales value. By mid-1982, 19 percent (by dollar volume) of the foods regulated by FDA carried quantitative sodium labeling, up from 14 percent in the preceding year.

We believe that another positive aspect of the program has been the perspective and balance that have been built into it. We are not advocating measures that have the potential for risk to the population. We simply seek to lower sodium consumption to a moderate level—one that still will provide more than two times the physiological need for sodium for virtually all environmental conditions. We recognize that hypertension is likely to have a multifactorial etiology and that other hypotheses, not associated with sodium intake, have been put forth that may be proven to be valid for some individuals. No aspect of our program is designed to conflict in any way with the investigation of such hypotheses, and we encourage continued research where such hypotheses are judged to have merit.

'We are not advocating measures that have the potential for risk to the population. We simply seek to lower sodium consumption to a moderate level—one that still will provide more than two times the physiological need for sodium for virtually all environmental conditions.'

But the most significant part of this program, from a scientific perspective, is its capacity to measure any positive or negative benefits that accrue as the program is implemented. The FDA is currently involved in several monitoring programs designed to do just that. These programs include measurement of sodium consumption and the prevalence of hypertension in the population, estimation of the prevalence of quantitative sodium declarations on the labels of processed foods, and annual assessment of the effectiveness of public education campaigns and the impact of the sodium-labeling initiative on buying habits. A thorough discussion of this aspect of the overall program was presented in the September-October 1982 issue of Hypertension (*10a*).

These efforts, together with fundamental and applied research by the National Institutes of Health, will contribute measurably to our understanding of the basic mechanisms underlying development of hypertension and to our knowledge about the benefits of moderation of sodium intake as a preventive measure.

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1/3 RK From BH

passion. We are seeing the breakdown of values through Hollywood jive; the brutal funniness of this play draws blood. Working on their scripts, their shows, these guys are professional junk artists and they know it (with different degrees of rationalization). Junk looms over this play like a Moloch of the technopop age; Rabe sees the human spirit itself in danger of turning into spiritual junk. The one who feels this the most is Eddie. He stays up most of the night watching TV and talking back to it. He sees all their lives with the eye of the minor casting director that he is: "We're all just background in one another's lives, cardboard cutouts bumping around in this vague hurlyburly, this spinoff that was once prime-time life."

One of the strongest things in the play is Rabe's vision of wasted intelligence. Eddie and Mickey are smart guys, but their intelligence floats uselessly in a moral void. Rabe has a marvelous ear for their speech; masters of b.s., they take pride in snakelike sentences that are arabesques of evasiveness, showbiz sophistry turned into a dialectic of nihilism. The women, too, are affected by this hollowness: Darlene says, "Everything is always distracting me from everything else." Intentionally or not, this is an echo of T. S. Eliot's "Four Quartets": "Distracted from distraction by distraction." Rabe shares Eliot's vision of a world of intelligent nervous wrecks who've lost their moral center and, not knowing where to turn, turn everywhere. The climax, with its casual, nutty, almost comedic violence, has a frightening inevitability.

Vitality: Rabe's vision of the wasteland may not be impeccably structured, but it has a savage sincerity and a crackling theatrical vitality. Mike Nichols's staging has never had more electricity, and the interplay of the extraordinary cast has the energy and emotional fearlessness of American acting at its best. This is the kind of play and the kind of cast that will produce some fascinatingly different performances on any given night. The actors are all superb: Keitel's complex, scary primitivism; Walken's slick, flip, self-protective cynicism; Weaver's razor-edged beauty and haute-couture vulnerability, and Jerry Stiller's pathos and malarkey. Cynthia Nixon brings a Felliniesque redemptive innocence to what may be the best bimbo part ever written. Tony winner Judith Ivey is sensational as the smart stripper. In the two performances I saw, William Hurt was tremendously implosive once and tremendously explosive once. He is a clear, powerful center for one of the best ensemble performances on any American stage.

This deeply felt play deserves as wide an audience as possible. David Rabe's wishes for it are reasonable enough. "I'd like to think a play like this could go to Broadway and have a year's worth of vital life. Having come from off-Broadway, that would be good for both." Off or on Broadway, "Hurlyburly" is going to be seen all over America for a long time.

JACK KROLL

MEDICINE

Salt: Should I or Shouldn't I?

Americans by the millions have been hiding their salt shakers in the hope of protecting themselves against high blood pressure. But some experts r question whether a high level of sodi chloride in the diet is really all that bad d last week, in a controversial report r ntradicts the diet advice Americans have been getting for many years, researchers sprinkled more doubt on the issue by suggesting that too little calcium and other nutrients rather than too much sodium may be major culprits in hypertension.

In the study, described in the journal Science, a team headed by Dr. David McCarron of the Oregon Health Sciences University analyzed the diets of more than

BILLY GRIMES—BLACK STAR

Hypertension: New questions about diet

10,000 U.S. adults. They found, somewhat to their surprise, that the prevalence of high blood pressure was lowest among those consuming the most salt and highest among people with low salt intake. At the same time, the analysis showed that people whose diets were low in calcium and potassium had an increased risk of hypertension, as were those with reduced intakes of vitamins A and C.

Milk, cheese and other dairy products are prime sources of calcium and potassium, and it was in a deficiency in this food group that McCarron and his colleagues found the strongest link to high blood pressure. Some dairy foods are also a rich source of sodium and would be among the foods to avoid by anyone going on a low-salt diet. The report notes that sodium chemically interacts with both calcium and potassium in the physiology of the body, which may be why a deficiency in all three might be related to elevated blood pressure. The findings are important, says McCarron, because they suggest that the part played by nutrition in high blood pressure is more complex than had been thought. "We have dietary patterns that are deficits, not excesses," he says. "One of the real risks of a low-sodium diet is that you inadvertently restrict other nutrients."

The new report drew quick fire from both consumer groups and hypertension experts. A spokesman for the Center for Science in the Public Interest, which takes a strong anti-salt stand, suggested that McCarron's emphasis on dairy products stems from the fact that "much" of his research support comes from the dairy industry. McCarron replies that, of the $500,000 his Oregon Hypertension Program received last year, only $28,000 came from the industry. Moreover, this particular study was supported by two private foundations unrelated to dairy interests.

Recall: Others criticized the way the study was carried out. They noted, for example, that the diet data were based on what the study subjects recalled eating in the previous 24 hours and should have covered at least one week. Also, it did not include the amount of salt added from the shaker, but only the natural content of sodium in the foods consumed. And they warned that people should not base any changes in diet on this single study. "If it gets misread and misinterpreted, people could act inappropriately," said Dr. William Friedewald of the National Heart, Lung and Blood Institute. Friedewald argued that the findings about sodium fly in the face of most previous studies and that none ever suggested that hypertension was linked to too little sodium in the diet.

McCarron himself emphasizes that the study doesn't prove a cause-and-effect relationship between low sodium or a deficiency of other nutrients and hypertension. And in his view the results shouldn't be taken as a license to eat salt. There is no doubt, he says, that salt intake is involved in some cases of hypertension and these patients can benefit from low-sodium diets. The important issue, he feels, is whether a blanket recommendation for everyone to reduce salt intake is really justified. The findings, McCarron says, "should be a note of caution, particularly to public-health people and government agencies, that perhaps we should rethink what we've been telling our society."

MATT CLARK with MARY HAGER in Washington and DEBORAH WITHERSPOON in New York

13 LUNG CANCER

Paul Van Houtte, M.D., Radiation Oncology
Omar M. Salazar, M.D., Radiation Oncology
Clay E. Phillips, M.D., Surgical Oncology
Robert F. Asbury, M.D., Medical Oncology

Why do people smoke?
The heart has its reasons which reason knows not.
Blaise Pascal (78).

Perspective

Lung cancer accounts for 22% of all cancer in men, compared with 9% in women. It is responsible for 35% of cancer-related deaths in men and 17% in women. Furthermore, the overall 5-year survival rate is still below 10% (75). Only one third of the patients are eligible for surgical resection with curative intent, and among them, less than one third will be alive 5 years later. Little progress has been made in the past decade to improve long-term survival significantly. Nevertheless, all disciplines involved in lung cancer management have advanced notably. Today, lung cancer is not considered to be a single disease entity, but 1 composed of several diseases conditioned by histopathologic types that determine patterns of spread, treatment, and prognosis. Furthermore, the modern management of lung cancer requires, more than ever, cooperation between all specialties involved in diagnosis and therapy.

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

1. In 1983, there will be about 94,000 new cases of lung cancer in men and about 41,000 in women (75).

2. Most striking is the rising incidence among women during the last decade. The percentage of change in the rate of lung cancer incidence over the period from 1947 to 1969 was 133% for men and 108% for women (20,75).

3. The average age at onset is about 60 years (less than 1% of cases occurred under the age of 30).

Etiology

A variety of agents have been proven to be carcinogens in humans:

1. *Tobacco smoke* is the dominant agent and represents a complex mixture of physical and chemical carcinogens. There is a direct relationship between the amount of tobacco exposure and risk for developing lung cancer (Fig. 13.1). In addition to the increased lung cancer risk, smoking is also associated with an increased risk of upper respiratory and digestive tract cancer. The type of cigarettes seems to also influence the risk, i.e., a filter apparently decreases the risk. Stopping smoking is associated with a gradual decrease in the risk, but a long period of time (more than 6 years) is necessary before an appreciable diminution of the risk occurs (Fig. 13.2) (86).

2. *Asbestos* exposure is associated with the development of mesothelioma and also bronchogenic carcinoma. The risk from asbestos is particularly more pronounced when combined with cigarette smoking (73).

3. *Atmospheric pollution* has been implicated as a causative agent in view of the higher incidence of lung cancer in urban as opposed to rural areas.

4. A more direct relationship has been also shown in cases of *pitchblende miners* who are involved with radioactive ores.

5. *Metals*, mostly nickel and silver, but also chromium, cadmium, beryllium, cobalt, selenium, and steel have proven to be carcinogenic in animals and are occupational hazards, particularly when combined with other factors.

6. *Chemical products* such as chloromethyl ethers have been associated with the development of lung cancer, especially small cell cancers (10).

DETECTION AND DIAGNOSIS (23)

Clinical Detection

1. *Clinical manifestations* are varied and mimic other pulmonary conditions.

a. A change in pulmonary habits is the most significant sign of lung cancer.

b. Cough, chest pain, rust-streaked or purulent sputum production, hemoptysis, and dyspnea are common symptoms of this disease.

2. *Local complications* depend upon the location of the tumor and include:

a. Superior vena caval obstruction.

Caffeine Scoreboard

Caffeine seems to pop up in all sorts of places.

This central nervous system stimulant is found in many foods, beverages, and drugs in addition to coffee. In fact, caffeine removed from coffee through decaffeination is sold to beverage and drug makers who then add it to their products.

The main health problem connected with caffeine is caffeineism whose well-known symptoms include insomnia, nervousness, and anxiety. But there also appears to be an association between caffeine intake and birth defects, benign breast lumps, irregular heartbeats, and other serious medical problems. In 1980, the Food and Drug Administration advised pregnant women to avoid or minimize consumption of products containing caffeine.

While sensitivity varies greatly from person to person, CSPI considers it prudent to minimize consumption of products containing caffeine.

Unfortunately, there may still be slight risks for those who have switched to decaffeinated coffee. The high temperatures of the roasting process may create cancer-causing substances in the beans themselves. Test results are mixed, but there are some indications that both regular and decaffeinated coffee may contribute to bladder and pancreatic cancers.

Concerns have also been raised in recent years about methylene chloride, the main chemical solvent used in the decaffeination process.

Research released in 1981 sponsored by the National Toxicology Program, showed that methylene chloride caused liver cancer in laboratory mice. The tests have since been questioned because of improper laboratory practices, and more reliable experiments are needed. But methylene chloride—a popular industrial solvent—is a chlorinated hydrocarbon that is chemically related to other, demonstrated cancer-promoting agents.

At the extremely low concentrations present in decaffeinated coffee, methylene chloride is only a very small health hazard. Nevertheless, for those who would prefer to avoid the chemical, we list below by brand name a sampling of coffees decaffeinated with methylene chloride and coffees that use other processes.

Caffeine Content of Beverages And Foods

Item	Milligrams of Caffeine Ave.	Range
Coffee *(5-oz. cup)*		
Brewed, drip method	115	60-180
Brewed, percolator	80	40-170
Instant	65	30-120
Decaffeinated, brewed	3	2-5
Decaffeinated, instant	2	1-5
Tea *(5-oz. cup)*		
Brewed, major U.S. brands	40	20-90
Brewed, imported brands	60	25-110
Instant	30	25-50
Iced (12-oz. glass)	70	67-76
Cocoa beverage (5-oz. cup)	4	2-20
Chocolate milk beverage (8 oz.)	5	2-7
Milk chocolate (1 oz.)	6	1-15
Dark chocolate, semi-sweet (1 oz.)	20	5-35
Baker's chocolate (1 oz.)	26	26
Chocolate-flavored syrup (1 oz.)	4	4

Source: FDA, Food Additive Chemistry Evaluation Branch, based on evaluations of existing literature on caffeine levels.

Which Decaffeinated Coffee Brands Use Methylene Chloride?

*Brands using methylene chloride, includes both ground roast and instant by manufacturer**

Chase & Sanborn
Chase & Sanborn

Chock Full O'Nuts
Chock Full O'Nuts

Coca-Cola
Butter-Nut
Maryland Club

General Foods
Sanka
Brim
Maxwell House
Yuban

Schonbrunn
Savarin

Tetley
Martinson

Brands using decaffeination processes without methylene chloride, includes instant only by manufacturer

Nestle
Taster's Choice
Nescafe

Nestle says it uses a "component occuring naturally in the coffee bean itself" and does not add any "foreign substance solvent" to decaffeinate its products. The company says categorically that the component is not methylene chloride, but otherwise refuses to identify it.

Procter & Gamble
High Point

Procter & Gamble uses ethyl acetate to decaffeinate High Point. Ethyl acetate occurs naturally in many foods, and is safe.

Other
Specialty coffee stores, groceries, co-ops, and health food shops offer a variety of instant, ground roast, and whole bean brands. Ask to learn what decaffeinating agents they use.

Hills Brothers uses either methylene chloride or ethyl acetate "depending on the decaffeination facility," according to a company spokesperson. The representative was unable to say how often Hills Brothers uses one solvent compared to the other.

Caffeine in Soft Drinks

(12-oz. serving)	Caffeine (mg)
Sugar-Free Mr. PIBB	58.8
Mountain Dew	54.0
Mello Yello	52.8
TAB	46.8
Coca-Cola	45.6
Diet Coke	45.6
Shasta Cola	44.4
Shasta Cherry Cola	44.4
Shasta Diet Cola	44.4
Mr. PIBB	40.8
Dr. Pepper	39.6
Sugar-Free Dr. Pepper	39.6
Big Red	38.4
Pepsi-Cola	38.4
Aspen	36.0
Diet Pepsi	36.0
Pepsi Light	36.0
RC Cola	36.0
Diet Rite	36.0
Kick	31.2

Source: Institute of Food Technologists (IFT), April 1983, based on data from National Soft Drink Association.

CAFFEINE

Caffeine is a powerful central nervous system (CNS) stimulant. Caffeine can cause an increase in blood pressure (2-3 cups of coffee can increase the blood pressure by about 14%), muscle tension, and stomach acid, metabolic rate and wakefulness. It is also implicated in fibrocystic breast disease and birth defects. Large doses can be fatal - 10 grams, or 80 to 100 cups of coffee.

Caffeinism may affect about 4-15% of Americans. This is a condition similar to anxiety neurosis. Ever experience any of these?

Extreme nervousness
Irritability
Shakiness
Chronic muscle tension
Sleeping problems
Rapid and extra heartbeats
Frequent urination and loose stools
Gastrointestinal upsets

Caffeine is addictive. When deprived of caffeine, addicts can experience depression, throbbing headache, disorientation, constipation, nausea, and/or irritability. Yet, two billion pounds of coffee are drunk each year in the U.S.A. Caffeine is also found in teas, chocolate, many over-the-counter drugs, and colas. Its effects depend on dose and body weight. A child who drinks a cola may experience an effect similar to an adult drinking four cups of coffee.

People tend to underestimate their caffeine intake. What is your caffeine intake?

Table One
Caffeine content of coffee, tea, and cocoa (*milligrams per serving—average values*)

Coffee, instant	66
Coffee, percolated	110
Coffee, drip-olated	146
Teabag—3 minute brew	46
Teabag—1 minute brew	26
Loose tea—3 minute brew	40
Cocoa	13

Table Two
Caffeine content of cola beverages (*milligrams per 12-ounce can*)

Coca Cola	65
Dr. Pepper	61
Mountain Dew	55
Diet Dr. Pepper	54
TAB	49
Pepsi-Cola	43
Diet RC	33
Diet Rite	32

Table 3
Caffeine Content of Over-the-Counter Drugs (*per tablet*)

Anacin	32mg
Aqua-ban	100mg
Bivarin	200mg
Caffedrine	200mg
Dristan	16mg
Empirin	32mg
Excedrin	64mg
Midol	32mg
No Doz	100mg
Pre-mens Forte	100mg
Vanquish	33mg

Source: M.L. Bunker and M. McWilliams, "Caffeine Content of Common Beverages," Journal of the American Dietetic Association, Vol. 74, pp. 28-32, January 1979

Carefully consider the health risk factors involved in consuming caffeine.

Food And Drug Interactions

If you're taking a drug, the food you eat could make it work faster or slower or even prevent it from working at all. Eating certain foods while taking certain drugs can be dangerous. And some drugs can affect the way your body uses food.

by Phyllis Lehmann

Would it occur to you not to swallow a tetracycline capsule with a glass of milk? Or to avoid aged cheese and Chianti wine if you are taking a certain medicine to combat hypertension? Or to eat more green leafy vegetables if you are on The Pill? Probably not. Yet the effects foods and drugs have on each other can determine whether medications do their job and whether your body gets the nutrients it needs.

The extent of interaction between foods and drugs depends on the drug dosage and on the individual's age, size, and specific medical condition. In general, though, the presence of food in the stomach and intestines can influence a drug's effectiveness by slowing down or speeding up the time it takes the medicine to go through the gastrointestinal tract to the site in the body where it is needed.

Food also contains natural and added chemicals that can react with certain drugs in ways that make the drugs virtually useless. Some reactions can be downright dangerous, triggering a medical crisis or, in rare instances, even death.

It is because of these interactions that your doctor tells you to take certain medications on an empty stomach, some just before meals, and some with meals.

A major way food affects drugs is by enhancing or impeding absorption of the drug into the bloodstream. There are a few cases in which foods speed up absorption. For example, blood levels of griseofulvin, a substance that combats fungus infections such as ringworm, rise markedly if the patient eats fatty foods before taking the drug.

More commonly, though, food and beverages interfere with absorption. A classic interaction is the one between tetracycline compounds and dairy products. The calcium in milk, cheese, and yogurt impairs absorption of tetracycline. On the other hand, taking some iron supplements with citrus fruits or juices which contain ascorbic acid enhances absorption of the iron.

In general, it is unwise to take drugs with soda pop or acid fruit or vegetable juices unless you check with your doctor first. These beverages can result in excess acidity that may cause some drugs to dissolve quickly in the stomach instead of in the intestines where they can be more readily absorbed into the bloodstream.

Some foods contain active substances which can enhance a drug effect or which can interact with a drug to produce an unexpected or counter effect. For example, licorice extracted from natural sources contains a substance which, when consumed regularly in excess amounts, may cause an elevation in blood pressure. Licorice is a favorite ingredient in candy and a flavoring for some pharmaceuticals. Most American manufacturers now use a synthetic flavoring but many imported products still contain licorice from natural sources. Continued regular use of products containing natural licorice extract could aggravate high blood pressure or counteract the effect of medication for high blood pressure.

Excessive consumption of foods high in vitamin K, such as liver and leafy green vegetables, may hinder the effectiveness of anticoagulants. Vitamin K, which promotes clotting of the blood, works in direct opposition to these drugs, which are intended to prevent clotting.

Perhaps the most hazardous food-drug interaction is the one between monoamine oxidase (MAO) inhibitors, drugs at times prescribed for depression and high blood pressure, and such foods as aged cheese, Chianti wine, and chicken livers. MAO inhibitors can react with a substance called tyramine in these foods and force the blood pressure to dangerous levels, sometimes causing severe headaches, brain hemorrhage, and, in extreme cases, death.

To prevent a possible reaction, anyone taking MAO inhibitor drugs should avoid aged and fermented foods, including pickled herring; fermented sausages, such as salami and pepperoni; sharp or aged cheeses; yogurt and sour cream; beef and chicken livers; broad beans, such as fava beans; canned figs; bananas; avocados; soy sauce; active yeast preparations; beer; Chianti wine, sherry, and other wines in large quantities. MAO inhibitors also are suspected of reacting adversely with cola beverages, coffee, chocolate, and raisins.

Alcohol, which is actually a drug itself, although not regulated as a drug under the Food, Drug, and Cosmetic Act, does not mix well with a wide variety of medications, such as antibiotics; anticoagulants; antidiabetic drugs, including insulin; antihistamines; high blood pressure drugs; MAO inhibitors; and sedatives. Alcohol combined with antihistamines, tranquilizers, or antidepressants causes excessive drowsiness that can be especially hazardous to someone driving a car, operating machinery, or performing some other task that requires mental

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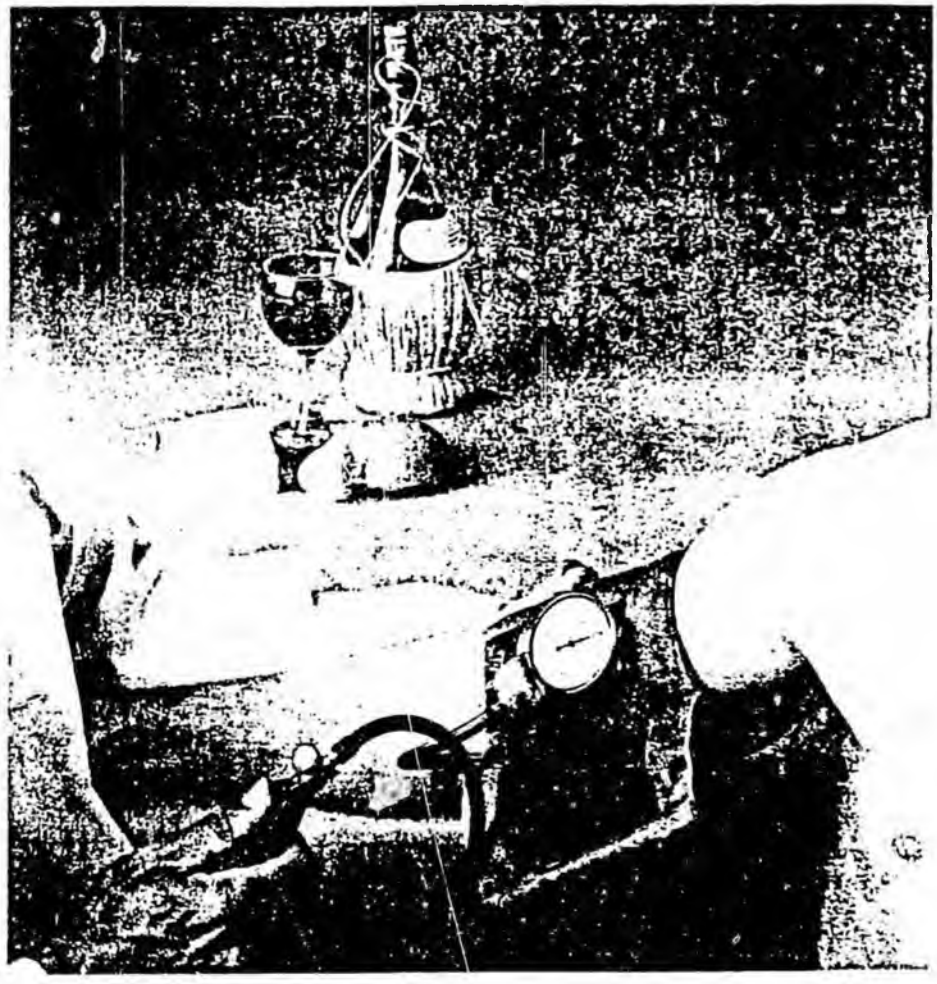

alertness. A good rule of thumb is to avoid alcoholic beverages when taking any type of prescription or over-the-counter medication.

Just as some foods can affect the way drugs behave in the body, so some drugs can affect the way the body uses food. Drugs may act in various ways to impair proper nutrition: by hastening excretion of certain nutrients, by hindering absorption of nutrients, or by interfering with the body's ability to convert nutrients into usable forms. Nutrient depletion of the body occurs gradually, but for those taking drugs over long periods of time these interactions can lead to deficiencies of certain vitamins and minerals, especially in children, the elderly, those with poor diets, and the chronically ill.

Some drugs inhibit nutrient absorption by their effect on the bowel wall. Among these are colchicine, a drug prescribed for gout, and mineral oil, an ingredient used in some over-the-counter laxatives.

A number of drugs affect specific vitamins and minerals. The antihypertension drug hydralazine and the antituberculosis drug INH can deplete the body's supply of vitamin B_6 by inhibiting production of the enzyme necessary to convert the vitamin into a form the body can use or by combining with the vitamin to form a compound that is excreted.

Similarly, anticonvulsant drugs that are used to control epilepsy can lead to deficiencies of vitamin D and folic acid because they increase the turnover rate of these vitamins in the body.

Quite a few drugs—for example, colchicine, oral antidiabetic agents, and the antibiotic neomycin—can

impair absorption of vitamin B_{12}. But because most Americans have good stores of B_{12} in their livers, it takes prolonged ingestion of these drugs to cause a deficiency.

Long term use of diuretics, or "water pills," to treat such conditions as congestive heart failure, can lead to serious potassium depletion. If the potassium loss is not corrected in heart patients taking digitalis, the heart may become more sensitive to the effects of the drug. People taking diuretics regularly should eat foods which are good sources of potassium. These include tomatoes and tomato juice, oranges and orange juice, dried apricots, cantaloupes, figs, raisins, bananas, prunes, potatoes, sweet potatoes, and winter squash.

Modifying the diet to include more foods rich in the vitamins and minerals that may be depleted by certain drugs generally is preferable to taking vitamin or mineral supplements. In fact, supplements of some vitamins can counter the effectiveness of certain drugs.

Fortunately, the diets of most Americans are sufficiently well-balanced so that the threat of drug-related nutritional deficiencies can be easily overcome.

Because oral contraceptives are used so widely, their effect on nutrition has been getting increasing attention. The Pill is known to deplete the blood's content of certain vitamins, notably folic acid and vitamin B_6, but usually the vitamin depletion is not serious enough to cause overt symptoms. In most healthy women with good diets, these vitamin levels do not go down to a point that is alarming, says Dr. Daphne Roe, a Cornell University nutritionist. "But in a poverty group of young women who are trying to make do with very little and who have limited nutritional knowledge, you may find a different situation," Dr. Roe says. "It is this group we are most concerned about."

Because her requirements for several vitamins may be increased, it is especially important for any woman on The Pill to eat a nutritionally balanced diet. In particular, if a woman on The Pill is living on snack foods, she is more likely to develop folate deficiency than her neighbor who every day eats green leafy vegetables, which are a good source of folic acid, according to Dr. Roe.

Drugs readily available without prescription also can lead to nutritional problems. The worst offenders are antacids, Dr. Roe says, because they are so widely abused by the public. Chronic use of these remedies without a doctor's supervision can cause phosphate depletion, a condition that in its milder form produces muscle weakness and in more severe form leads to a vitamin D deficiency. "Unfortunately," says Dr. Roe, "some people get into the habit of taking enormous amounts of these drugs to treat gastric upset that in itself is due to their abuse of some other substance, such as alcohol, coffee, or food."

Mineral oil, an old-fashioned laxative still widely used by elderly people and in nursing homes, can hinder absorption of vitamin D. One study reported that as little as 20 milliliters (4 teaspoons) of mineral oil twice daily can interfere with absorption of vitamin D, vitamin K, and carotene, a substance the body converts to vitamin A.

What can consumers do to prevent undesirable food-drug interactions? Here are a few suggestions:

- Read the labels on over-the-counter remedies and the package inserts that come with prescription drugs.
- Follow your doctor's orders about when to take drugs and what foods or beverages to avoid while taking medications.
- Don't be afraid to ask how drugs might interact with your favorite edibles, especially if you consume large amounts of certain foods and beverages. While taking drugs, be sure to tell your doctor about any unusual symptoms that follow eating particular foods.
- Eat a nutritionally well-balanced diet from a wide variety of foods. Use of a needed drug, even on a long term basis, is less likely to cause depletion of vitamins and minerals if your overall nutritional status is good.

Drug labeling and informed health professionals can be helpful to you, but your doctor and pharmacist cannot follow you to the dinner table or the snack bar. Remember that warnings about food-drug interactions are only as good as the patient's willingness to heed them.

Phyllis Lehmann is a freelance writer.

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FDA CONSUMER

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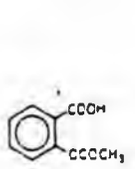
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
5600 Fishers Lane
Rockville, Md. 20857

Aspirin

Acetylsalicylic Acid
ASA



Chemistry and Stability

CHEMISTRY

Aspirin, the prototype of the salicylates, is a nonsteroidal anti-inflammatory agent (NSAIA). Aspirin is the salicylate ester of acetic acid. In vivo, the drug rapidly hydrolyzes to salicylate and acetate. Aspirin occurs as white crystals, which are usually tabular or needle-like, or as a white, crystalline powder. The drug may have a faint odor, is slightly soluble in water and freely soluble in alcohol, and has a pK_a of 3.5. Each gram of aspirin contains approximately 760 mg of salicylate.

STABILITY

Aspirin is stable in dry air. However, in moist air or in aqueous or hydroalcoholic solutions, the drug gradually hydrolyzes to salicylate and acetate and emits a strong vinegar-like odor; the rate of hydrolysis is increased by heat and is pH-dependent.

In aqueous solutions, aspirin is most stable at a pH of 2–3, less stable at a pH of 4–8, and least stable at a pH less than 2 or greater than 8. In a saturated aqueous solution at a pH of 5–7, aspirin is almost completely hydrolyzed within 1 week at 25°C. If a liquid dosage form of aspirin is desired for short-term treatment of pain, an oral solution may be prepared from commercially available buffered effervescent tablets (Alka-Seltzer®). Following dissolution of one Alka-Seltzer® tablet in approximately 90 mL of water, the solution has a pH of 6–7. In the resultant solution, aspirin is about 99% ionized and is at least 90% unhydrolyzed for approximately 10 hours at room temperature and about 90 hours at 5°C.

Chewable aspirin tablets containing 81 mg of the drug should be stored in child-resistant containers holding not more than 36 tablets each in order to limit the potential toxicity associated with accidental ingestion in children. Aspirin suppositories should be stored at 2–15°C.

Pharmacology

Aspirin exhibits analgesic, anti-inflammatory, and antipyretic activity. Although aspirin hydrolyzes to salicylate and acetate, the drug does not require hydrolysis to produce its effects and appears to have some pharmacologic effects that are distinct from those of salicylate. The ability of aspirin to acetylate proteins (e.g., platelet proteins, hormones, DNA, hemoglobin) results in some effects, such as inhibition of platelet aggregation, which other currently available salicylates do not exhibit.

ANALGESIC, ANTI-INFLAMMATORY, AND ANTIPYRETIC EFFECTS

While unhydrolyzed aspirin has been shown to be more potent than sodium salicylate in relieving pain in animals, it remains to be clearly established that aspirin has greater analgesic effect than salicylate in humans. A direct correlation between onset, intensity, or duration of analgesia and the time course of serum aspirin (or salicylate) concentrations or peak serum aspirin (or salicylate) concentrations also remains to be established. There are relatively few controlled comparative studies of aspirin and other salicylates (e.g., salicylate salts), but the analgesic, anti-inflammatory, and antipyretic effects of aspirin and other salicylates are generally considered to be comparable. However, in terms of antipyretic activity, aspirin is approximately 1.6 times as potent as sodium salicylate on an equimolar basis.

For further information on analgesic, anti-inflammatory, antipyretic, and other effects of aspirin, see Pharmacology in the general statement on Salicylates 28:08.04.

HEMATOLOGIC EFFECTS

At usual dosages (e.g., 1.3–6 g daily), aspirin may rarely prolong the prothrombin time (usually only by 2–3 seconds) by inhibiting hepatic synthesis of blood coagulation factors VII, IX, and X.

Aspirin (but not other salicylates) inhibits platelet aggregation induced by epinephrine or low concentrations of collagen but not that induced by thrombin or high concentrations of collagen. Aspirin inhibits the second phase of platelet aggregation by preventing release of adenosine diphosphate (ADP) from platelets. The drug also prevents release of platelet factor 4 from platelets. Mean bleeding time may be prolonged by several minutes (approximately doubled) in healthy individuals and longer in children or in patients with bleeding disorders (e.g., hemophilia). In healthy individuals receiving a single 325-mg oral dose of aspirin, bleeding time may increase to a maximum within 12 hours and generally return to normal within 24 hours; any increase is usually of little clinical significance. Some clinicians have reported that mean bleeding time is progressively prolonged with increasing single doses of up to 1 g, but may be only slightly prolonged or unaffected by higher single doses; however, this has not been consistently found. The effect on bleeding time depends on the measurement method (e.g., Duke, Ivy, Mielke) used and technical variables (e.g., venostasis), and this may partially account for conflicting reports.

Like the analgesic and anti-inflammatory effects, the effects of aspirin on platelets appear to be mainly associated with inhibition of prostaglandin synthesis. Aspirin irreversibly acetylates and inactivates cyclooxygenase in circulating platelets and possibly in megakaryocytes. A single 325-mg oral dose of the drug results in about 90% inhibition of the enzyme in circulating platelets. This inactivation prevents platelet synthesis of prostaglandin endoperoxides and thromboxane A_2, compounds which induce platelet aggregation and constrict arterial smooth muscle. Since cyclooxygenase in platelets is not resynthesized, this effect of aspirin on platelet function persists for the life span of platelets (4–7 days). When approximately 20% of circulating platelets have not been exposed to aspirin (about 36 hours after the last dose), the hemostatic function of the platelet pool generally returns to normal; however, altered hemostasis has been reported to persist longer in some patients receiving long-term therapy.

ANTITHROMBOTIC EFFECT

Because of its ability to inhibit platelet aggregation via platelet cyclooxygenase inhibition, aspirin has been extensively investigated for potential therapeutic effects in the prevention of thrombosis (particularly arterial thrombosis). Uses: Thrombosis.] Aspirin has also been found to inactivate cyclooxygenase in venous endothelium and thereby inhibit venous synthesis of prostacyclin (epoprostenol, PGI_2). Since prostacyclin inhibits platelet aggregation and causes vasodilation, it appears to oppose the effects of thromboxane A_2 and prostaglandin endoperoxides on hemostasis. Therefore, it has been suggested that the relative extent to which the formation of these compounds is inhibited by aspirin might result in an increased or decreased likelihood of thrombosis. Although prostacyclin is synthesized by arterial endothelium and in vitro studies suggest that arterial cyclooxygenase is less sensitive to inhibition by aspirin than venous cyclooxygenase, the actual effects of aspirin on arterial synthesis of prostacyclin in healthy or diseased human arteries remain to be established.

In most clinical studies to date which evaluated the effect of aspirin in preventing thrombosis, the dosages of aspirin (900 mg to 1.5 g daily in divided doses) probably inhibited the synthesis of prostacyclin as well as that of thromboxane A_2. Although concomitant inhibition of prostacyclin synthesis by aspirin may potentially decrease the antithrombotic efficacy of the drug, it is unlikely that this effect increases the risk of thrombosis since an increased risk has not been observed in these studies or in patients with rheumatoid arthritis receiving higher dosages of the drug. Cyclooxygenase in both platelets and venous endothelium has been found to be inhibited by single oral aspirin dosages of 80–300 mg. However, at these doses, the duration of inhibition of thromboxane A_2 synthesis in platelets (about 48–96 hours) is longer than inhibition of prostacyclin synthesis in venous endothelium (about 24–48 hours), apparently because cyclooxygenase is resynthesized in venous endothelium but not in platelets. Since cyclooxygenase in platelets appears to be more sensitive to inactivation than cyclooxygenase in venous endothelium, it has been suggested that low dosages of aspirin might prevent thrombosis by selectively inhibiting prostaglandin endoperoxide and thromboxane A_2 synthesis; however, an optimum dose and schedule of administration of aspirin have not been clearly determined, and the actual clinical importance of such a selective inhibitory effect remains to be clearly established. In addition, salicylate appears to competitively inhibit the effect of aspirin on platelets; the relevance of this effect to the prevention of thrombosis is not known.

Since results of numerous clinical studies indicate that the antithrombotic effect may be limited to males, it has been suggested that this effect of aspirin is sex related and may be related to differences in hormonal factors, sensitivity of cyclooxygenase inhibition in platelets and blood vessel walls, and/or other platelet factors in the pathogenesis of thrombosis. However, this has not been clearly established and further evaluation is needed.

Aspirin and dipyridamole appear to have at least additive inhibitory effects on platelet function (e.g., aggregation) in vivo. Aspirin has been shown to potentiate the effect of dipyridamole in normalizing reduced platelet sur-

in patients with prosthetic heart valves. Aspirin and dipyridamole also appear to have a synergistic antithrombotic effect, at least in small blood vessels. The exact mechanisms have not been fully elucidated, but the platelet-inhibiting effects of the combination appear to depend on aspirin dosage. Since prostacyclin appears to be necessary for the action of dipyridamole on platelet function, it has been suggested that the inhibition of platelet aggregation and antithrombotic effect of dipyridamole may be potentiated by selective inhibition of platelet cyclooxygenase and thromboxane A_2 synthesis with low dosages of aspirin. In one study, the combination of 120 mg of aspirin once daily and 75 mg of dipyridamole 3 times daily was shown to maximally inhibit platelet functions (e.g., aggregation) in vivo without prolonging bleeding time; it was suggested that prostacyclin synthesis was not substantially inhibited by this regimen. Further studies evaluating the effects of varying dosages of the drugs in combination are needed.

Pharmacokinetics

Since both unhydrolyzed aspirin and its metabolite, salicylate, are pharmacologically active, the pharmacokinetics of both compounds must be considered.

For additional information on the distribution and elimination of *salicylate*, see Pharmacokinetics in the general statement on Salicylates 28:08.04.

ABSORPTION

Approximately 80–100% of an oral dose of aspirin is absorbed from the GI tract. However, the actual bioavailability of the drug as unhydrolyzed aspirin is lower since aspirin is partially hydrolyzed to salicylate in the GI mucosa during absorption and on first pass through the liver. There are relatively few studies of the bioavailability of unhydrolyzed aspirin. In one study in which aspirin was administered IV and as an oral aqueous solution, it was shown that the solution was completely absorbed but only about 70% reached the systemic circulation as unhydrolyzed aspirin. There is some evidence that the bioavailability of unhydrolyzed aspirin from slowly absorbed dosage forms (e.g., enteric-coated tablets) may be substantially decreased. Food does not appear to decrease the bioavailability of unhydrolyzed aspirin or salicylate; however, absorption is delayed and peak serum aspirin or salicylate concentration may be decreased.

Most studies reported to date determined the bioavailability of aspirin preparations in terms of salicylate. Effervescent or noneffervescent oral aqueous solutions of aspirin appear to be completely absorbed. Oral buffered aspirin tablets, uncoated plain aspirin tablets, and methylcellulose film-coated (nonenteric) plain aspirin tablets are approximately 80–100% absorbed. Erratic and incomplete absorption of some enteric-coated aspirin tablets (particularly those with shellac coatings) has been reported, but recent studies indicate that the extent of absorption of currently available enteric-coated aspirin tablets is similar to that of buffered, uncoated plain, and film-coated plain aspirin tablets. Although well-designed studies are lacking, the extent of absorption of extended-release aspirin tablets appears to be similar to that of uncoated plain aspirin tablets. There are apparently no published studies on the bioavailability of aspirin capsules. Following rectal administration as a suppository, aspirin is slowly and variably absorbed; the extent of absorption increases with increasing rectal retention time. In general, 20–60% of the dose is absorbed if the suppository is retained for 2–4 hours and 70–100% is absorbed if the suppository is retained for at least 10 hours.

The rate of absorption of aspirin depends on the same factors that determine the rate of absorption of other salicylates and the relative rates of absorption from various oral aspirin dosage forms are generally the same as for oral dosage forms of other salicylates (e.g., aqueous solutions are the most rapidly absorbed). As with other salicylates, dissolution is usually the rate-limiting process in the absorption of tablets containing aspirin; however, the in vitro dissolution rate of a specific preparation does not necessarily reflect the in vivo absorption rate. According to the manufacturer, the in vitro dissolution of film-coated aspirin tablets does not differ from that of uncoated plain tablets; however, the film-coated tablet does not undergo dissolution in the mouth during administration.

Effects of Buffers

There has been controversy over the relative rates of absorption of buffered aspirin tablets and uncoated plain aspirin tablets and their relative potential for producing gastric irritation and analgesia.

The buffers contained in buffered aspirin tablets may increase the pH in the microenvironment of aspirin particles and thereby increase solubility of the drug in surrounding GI fluids; as a result, the dissolution rate of the tablets may be increased. However, it cannot be stated that *all* buffered aspirin tablets are dissolved and absorbed more rapidly than *all* uncoated plain aspirin tablets. The types and amounts of buffers affect dissolution rate, and claims for a specific preparation should be substantiated by appropriate data. Conflicting reports of the relative rates of absorption of buffered or uncoated plain aspirin tablets are most likely due to differences in the specific preparations studied. Some studies have shown that, like aqueous aspirin solutions, some buffered aspirin tablet preparations may be absorbed slightly more rapidly than some uncoated plain aspirin tablet preparations and may produce slightly higher peak serum salicylate concentrations; however, clinically important differences in the onset or intensity of analgesia produced by these dosage forms or specific preparations have not been established. Crossover studies directly comparing peak serum concentrations of unhydrolyzed aspirin attained with these dosage forms are lacking.

It has been suggested that buffered aspirin tablets cause less gastric irritation than uncoated plain aspirin tablets since the potentially more rapid dissolution of the former may reduce contact time between aspirin particles and gastric mucosa. However, several recent, well-designed studies indicate that buffered aspirin tablets do not cause less gastric irritation than uncoated plain aspirin tablets.

Rapidly Absorbed Dosage Forms

Following oral administration of single doses of rapidly absorbed aspirin dosage forms, salicylate is detected in serum within 5–30 minutes, and peak serum salicylate concentrations are attained within 0.25–2 hours, depending on dosage form and specific formulation. Clinically important differences in the onset or intensity of analgesia produced by rapidly absorbed dosage forms or specific preparations have not been established.

Following oral administration of a single 650-mg dose of aspirin as an effervescent or noneffervescent aqueous solution in healthy adults, average peak plasma aspirin concentrations of about 13 µg/mL are attained within 15–40 minutes and average peak plasma salicylate concentrations of about 40–55 µg/mL are attained within 30–60 minutes. After a single 650-mg oral dose of aspirin (as two 325-mg uncoated plain tablets) in fasting healthy adults, average peak plasma aspirin concentrations of about 7–9 µg/mL occur within 25–40 minutes and average peak plasma salicylate concentrations of about 35–50 µg/mL occur within 1.5–2 hours. Following oral administration of a single 650-mg dose of buffered aspirin (as 2 tablets, each containing 325 mg of aspirin), average peak plasma salicylate concentrations of about 40–60 µg/mL are attained within 45–60 minutes.

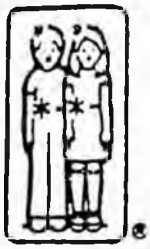
In one study in healthy fasting adults given a single 975-mg oral dose of aspirin (as three 325-mg uncoated plain tablets), peak serum salicylate concentrations averaged 60–75 µg/mL and occurred within 2 hours. In another study in fasting rheumatoid arthritis patients given a single 1.95-g oral dose of aspirin (as six 325-mg uncoated plain tablets), peak plasma aspirin concentrations of about 12–16 µg/mL occurred within 1 hour and peak plasma salicylate concentrations of about 110–160 µg/mL occurred within 4 hours. When these patients were given the same dose of buffered aspirin (as 6 tablets, each containing 325 mg of aspirin), peak plasma aspirin concentrations of about 14–18 µg/mL occurred within 1–2 hours and peak plasma salicylate concentrations of about 140–160 µg/mL occurred within 1–2 hours.

Enteric-Coated Tablets

There are few published studies reporting plasma aspirin or salicylate concentrations after single oral doses of enteric-coated aspirin tablets. In one crossover study, following single 975-mg oral doses (three 325-mg tablets) of 2 commercially available enteric-coated aspirin preparations in healthy adults, average peak serum salicylate concentrations of 48 µg/mL occurred at 8 hours with one preparation, and average peak serum salicylate concentrations of 25 µg/mL occurred at 14 hours with the other preparation. In one study in fasting rheumatoid arthritis patients given a single 1.92-g oral dose (as six 320-mg enteric-coated tablets), peak plasma aspirin concentrations of about 4–7 µg/mL occurred within about 4 hours and average peak plasma salicylate concentrations of about 70 µg/mL occurred within about 8 hours.

Extended-Release Tablets

There are few published studies reporting plasma aspirin or salicylate concentrations after single oral doses of extended-release aspirin tablets. Combining data from several small studies, some clinicians report that following a single 1.3-g oral dose of aspirin as two 650-mg extended-release tablets, an average peak serum aspirin concentration of about 3 µg/mL was attained within 1 hour and peak serum salicylate concentrations of about 70–80 µg/mL were attained within 4 hours; the serum aspirin concentration declined to less than 1 µg/mL by 3 hours and the serum salicylate concentration was about 60 µg/mL



BE WISE ABOUT REYE'S

• AWARENESS BULLETIN •

The flu or various symptoms identified as influenza occur more frequently during the winter months. Influenza is a viral infection, and as such, warrants our special attention because a fatal children's disease is associated with it. The disease, *Reye's Syndrome*, affects children from infancy through adolescence and can develop 3 to 5 days after the onset of the chicken pox, an upper respiratory illness, or other viral infections. It affects the liver and brain, is non-contagious and is often misdiagnosed as encephalitis, meningitis, diabetes, poisoning, drug overdose, or sudden infant death.

After a viral infection has seemingly run its course and the child is feeling better the following symptoms should be treated as serious and as possibly the first indication of *Reye's Syndrome*. Anti-nausea medication may mask the symptoms of the disease and because of the possible association of aspirin with *Reye's Syndrome*, parents should consult their physician before using these drugs. Watch for these symptoms, usually occurring in this order:

- PERSISTENT OR CONTINUOUS VOMITING
- LISTLESSNESS (LOSS OF PEP AND ENERGY, DROWSINESS)
- PERSONALITY CHANGE (SUCH AS IRRITABILITY, COMBATIVENESS OR SLURRED SPEECH)
- DISORIENTATION (UNABLE TO IDENTIFY WHEREABOUTS, OR FAMILY MEMBERS)
- DELIRIUM, CONVULSIONS

A child's life can depend on <u>early</u> diagnosis. *Reye's Syndrome* should be suspected in any child with chicken pox who vomits repeatedly. Phone your physician immediately if these symptoms develop and tell him you suspect *Reye's Syndrome*. If your doctor is not available take your child to an emergency room promptly. Two liver function tests (SGOT/SGPT) can be done to determine the possibility of *Reye's Syndrome*. There is a 90% chance of recovery when the syndrome is treated in its earliest stages by physicians and nurses experienced in the treatment of Reye's.

Epidemiologic research has shown an association between the development of *Reye's Syndrome* and the use of aspirin for treating the symptoms of influenza-like illnesses, chicken pox, and colds. The U.S. Surgeon General, the Food and Drug Administration, and the Centers for Disease Control recommend that aspirin and combination products containing aspirin not be given to children 18 years of age and under during episodes of these illnesses.

The NRSF is a non-profit, tax-exempt organization with chapters in forty states. The NRSF has pioneered the movement to disseminate knowledge about the disease in an effort to aid in early diagnosis, and also provides funds for research into the cause, cure, care, treatment, and prevention of *Reye's Syndrome*.

For more information contact the NATIONAL REYE'S SYNDROME FOUNDATION, P.O. BOX 829AB, BRYAN, OHIO 43506, OR CALL 419/636-2679, 800/233-7393, OHIO RESIDENTS CALL 800/231-7393.

The human body has no physiological need for refined sugar, yet the average American consumes 128 pounds of it every year.[1] That's a per capita consumption of one teaspoon every hour, 24 hours a day,[2] more than any other nation on earth. It's difficult *not* to eat sugar. To sweeten or not to sweeten is no longer a matter of individual discretion. In 1910, 75 percent of the sugar Americans consumed was added to foods in the kitchen; the other 25 percent came from processed foods.[3] Today, the situation is almost reversed. The sugar added by food and beverage manufacturers to what we eat and drink accounts for 65 percent of American sugar consumption[4]; these days only 35 percent is added in the kitchen. Sugar has become a staple ingredient in a staggering number of processed foods (see sidebar)—even cigarettes are laced with sugar.

Average Americans obtain about one-quarter of their calories from sugar.[5] Only a small proportion of that amount comes from the natural sugars in carbohydrates, fruits, vegetables and dairy products. Most of it is refined white sugar, sucrose. Children consume even more sugar than adults. Some children obtain as much as 48 percent of their calories from sugar—almost *half* their caloric intake.[6] Growing evidence strongly suggests that this level of sugar consumption is a major factor in increased rates of degenerative diseases, including dental caries (cavities), obesity, diabetes, coronary heart disease, vitamin deficiencies and psychological disturbances.

Eating sugar can be worse than eating nothing. Refined sugar provides only empty calories. It contributes none of the protein, fat, vitamins or minerals needed for its own metabolism in the body, so these nutrients must be obtained elsewhere. Sugar tends to replace nourishing food in the diet. It is a thief that robs us of nutrients. A dietary emphasis on sugar can deplete the body of nutrients. If adequate nutrients are not supplied by the diet—and they tend not to be in a sugar-rich diet—they must be leached from other body tissues before sugar can be metabolized. For this reason, a U.S. Senate committee labeled sugar as an "antinutrient."[7]

Sucrose and the Blood Sugar Roller Coaster

Of the more than 100 chemicals called "sugar," one of them, glucose, is essential to human metabolism. Refined white sugar, however, can interfere with the body's delicate metabolism. The human body manufactures life-sustaining glucose from carbohydrates. Carbohydrates come in two forms: simple sugars in fruits, vegetables and dairy products and starches, complex chains of simple sugars in grains, beans and vegetables. Unrefined foods contain enough sugars and/or starches to provide all the glucose necessary for a healthy metabolism *without adding any sucrose to the diet.* Carbohydrates also provide a variety of other nutrients lacking in refined sucrose, for example, vitamins, minerals, protein, fiber and fats.

The body processes simple sugars and carbohydrates in the same way, but at different speeds. Sucrose is digested quickly into two simple sugars, glucose and fructose (fruit sugar). These sugars enter the blood stream through the small intestine, and are carried to the liver where they are either used immediately or converted into glycogen for storage until needed. When glycogen storage space in the liver is filled to capacity, excess glycogen is returned to the blood in the form of fatty acids, which are stockpiled first in the inactive parts of the body—buttocks, breasts, abdomen and thighs—then in active organs, for example, the heart and kidneys. The minerals sodium, potassium, magnesium, calcium and chromium, and the B-complex vitamins, are all used to create glucose.

The sugar units bound together into starch chains are metabolized the same way as simple sugars, but their complex structures take longer to break down. During carbohydrate digestion, these complex glucose chains are converted first into dextrine, then into maltose, and finally into individual glucose molecules.

The amount of glucose circulating in the blood determines our appetite. When blood sugar levels fall below a certain trigger point, we experience hunger. The feelings of weakness, irritability and anxiety that often accompany hunger result from a low level of glucose in the blood, a condition called "hypoglycemia." The feeling of hunger is a signal that our cells are not

Jacquetta Nisbet

THE SWEET THIEF

By Janice Fillip

getting enough glucose to function properly. Eating a meal readjusts the amount of sugar in the blood. The simple sugars in unprocessed foods provide an immediate burst of glucose-energy to our bodies. Then, the more complex sugar chains in the starches in the meal provide a slower but sustained supply of glucose-energy.

Glucose circulating in the blood cannot enter cells to nourish them without the help of insulin, a hormone produced by the Islets of Langerhans, a group of cells in the pancreas. Fructose enters the blood stream somewhat more slowly than glucose, and is metabolized by the enzyme fructokinase rather than insulin. This difference between glucose and fructose metabolism allows some diabetics, whose bodies do not produce enough insulin to metabolize glucose, to have fructose-sweetened foods in their diets.

Since simple sugars work faster than the sugars in starches to counteract the effects of hypoglycemia, many people prefer to satisfy their hunger pangs with a sugary snack instead of a balanced meal. But substituting a brief burst of energy for a gradual, sustained supply of glucose has significant adverse consequences for the body.

Although blood sugar levels are suddenly boosted by a sucrose "rush," they drop just as quickly after that sugar has been metabolized, often leaving a person feeling droopy, tired and irascible. To recapture the same sugar-induced feeling of energy and alertness, a person may eat more sugar. As sucrose-induced glucose rushes replace the sustained glucose release from carbohydrates, the peaks and valleys of blood sugar concentration tend to become more pronounced. This cycle of sugar highs and lows is similar to the kind of physiological dependence produced by some drugs. Although sucrose is not addictive in the same way that, for example, narcotics are, it may be considered to have some addictive properties, and many people refer to themselves as "sugar addicts."

The minor feelings of weakness, irritability and anxiety that accompany normal hunger are magnified by the large variations in blood sugar levels that result from replacing carbohydrates in the diet with so much sucrose. These fluctuations have been shown to trigger changes in behavior, including reduced ability to concentrate, fatigue, depression, confusion, forgetfulness and headaches. As a result, a growing number of physicians and nutritionists now consider hypoglycemia not only a state of low blood sugar, but also a factor in health and behavioral problems as well. They reason that meals high in refined sucrose quickly boost blood sugar levels and stimulate the pancreas to secrete large quantities of insulin. This insulin spurt allows too much sugar to pass from the blood into the cells, thus lowering the blood sugar level *below normal*. This low blood glucose level may interfere with the proper functioning of nerve cells by depriving them of glucose fuel and resulting in the symptoms of hypoglycemia. A survey of 134,000 people conducted by the Department of Health, Education and Welfare showed that 49.2 percent said they suffered symptoms typically associated with hypoglycemia.[8] And one psychiatric study of people with emotional problems showed that 70 percent of those diagnosed as schizophrenic showed some form of hypoglycemia.[9]

Hypoglycemia's role in emotional problems remains a point of controversy. Much of the medical establishment maintains that the emotional problems experienced by alleged sufferers of hypoglycemia reflect not dietary imbalances but rather psychological problems best treated with drugs. (Editor's note: For more on the traditional medical view of the role of nutrition in health, see "Doctors and Nutrition: A Conversation with Marion Nestle," in this issue.)

The precipitous drop in blood sugar level that follows a sugar binge decreases the functional capacity of brain cells. The brain then signals the adrenal glands to secrete the hormone adrenalin (epinephrine), which stimulates the liver to release stored glycogen into the blood, and the pituitary gland to secrete hormones to aid the conversion of glycogen into glucose. Adrenalin also activates many metabolic processes necessary to respond to emergencies. It accelerates heart rate, makes breathing more rapid and stimulates feelings of anxiety and apprehension, reactions that tend to influence emotions and behavior.

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Average Americans obtain about one-quarter of their calories from sugar

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The adrenal glands supervise the glucose-oxygen balance in the blood. Excessive sucrose intake alters this balance and stimulates the adrenals to release hormones which stimulate the production of gastric juices in the stomach. This heightened gastric activity tends to duplicate conditions found in people with gastric or duodenal ulcers,[10] and may explain why some people develop upset stomachs after eating sugary snacks or sugar-rich processed foods.

The Sweet Thief Steals Teeth—and Health

Although sugar was judged "safe" in 1976 by the Senate Select Committee on Substances Generally Regarded as Safe (GRAS), mounting evidence strongly suggests that sucrose consumed in quantities typical in the American diet is associated with diabetes, obesity, tooth decay, heart disease, vitamin deficiencies and possibly premature aging. The chief of the U.S. Department of Agriculture's Human Nutrition Institute estimated that as many as 20 million Americans may be "sugar sensitive," meaning that they experience adverse health effects from sugar.[11] Other scientists are more outspoken. John Yudkin, M.D., Ph.D., professor emeritus of nutrition at London University, has written: "... if only a small fraction of what is known about the effects of sugar were revealed in relation to any other food additive, that material would promptly be banned."[12]

Even the sugar industry is hard-pressed to deny that sugar is a leading cause of dental caries. Sugar makes foods sticky, so they adhere to teeth more tenaciously. Bacteria in the mouth feed on food residues glued in place by sugar and produce acid that eats away at teeth. The National Institute for Dental Research has determined that sucrose is the favorite growth medium for the acid-producing bacteria that cause tooth decay.

Sugar that has not been denatured in the refining process appears less instrumental in promoting tooth decay. One study[13] exposed cavity-free teeth from the same source to either saliva mixed with sugar cane juice or saliva mixed with sucrose. After a few weeks, the teeth in the sugar cane juice had not decalcified as much as about one-half of those in the refined sugar had.

Dental caries are the most prevalent degenerative disease in the world. Virtually all Americans have some tooth decay and one-half the U.S. population has *no teeth left* by age 55.[14] We pay dearly for our national sweet tooth—every year Americans spend $10 billion for dental care.[15]

In a nation where about one-third of the population is overweight,[16] obesity is a major health problem. Animal studies show that a high-sugar diet increases the body's fat content while reducing the amount of protein.[17] Eating sugar makes people fat in several ways. First, when sugar is a staple in the diet, the overall nutritional value of the foods consumed is reduced, and a person must eat more to obtain adequate nutrition. Second, the sugar hidden in processed foods adds to the number of calories we unwittingly consume. But sugar has a more sinister link to obesity. It appears that children who consume large amounts of sugar during childhood may become physiologically predisposed to obesity later in life. Scientists have observed that babies bottle-fed with formulas that contain sucrose show a higher rate of obesity than breast-fed babies.[18] Feeding babies sugar-empty calories not only packs more fat into existing fat cells, it may also cause the body to produce *more* fat cells, cells that tend to stay with the child throughout life. Later dieting may reduce the size of fat cells, but not their total number.[19]

Diabetes is another sugar-related illness. Insulin regulates the metabolism of sugar and the passage of glucose into the cells. When the body cannot produce enough insulin to metabolize all the sucrose present, excess sugar remains in the blood. Cells cannot function without glucose, and if a body lacks sufficient in-

Sweet Deals: The International Sugar Trade

The hunger for sweet treats has profoundly influenced world history. The African slave trade originated to provide labor for sugar plantations in Spain and the Caribbean. British historian Noel Deerr writes, "The 'death' toll of the slave trade was 20 million Africans of which two-thirds should be charged against sugar."[1]

After slavery was abolished, the United States obtained most of its sugar from Cuba. Cuba's most fertile land was diverted from food crops for Cubans to sugar cane plantations to produce sugar for export. Until the Castro government came to power in 1960, Cuba remained an economic colony of the United States, governed to a considerable extent by the boards of directors of a few sugar companies.

This system is not unique to Cuba. In most sugar-producing countries, the richest lands are appropriated for sugar cane, an export crop, precluding self-sufficiency in food production and forcing these nations to import food. In 1980, more than half the raw sugar imported into the U.S. came from the Dominican Republic, Brazil, the Philippines, Guatemala, and South Africa.[2] Every one of these countries is ruled by an authoritarian regime accused of major human rights violations by Amnesty International. The political strife in these nations today can, to some extent, be traced to the inequities that result when a small group of landowners controls most of the arable land and plants it with sugar cane or other export crops, for example, bananas and coffee, while the majority of the population lacks land to grow food.

Sugar production and pricing are determined by the International Sugar Organization (ISO), a cartel similar to OPEC, composed of representatives of the major sugar exporting and importing nations. The United States, which buys 20 percent of the sugar traded on world markets, wields great influence in the ISO. The importing nations have always refused to buy finished refined sugar from the exporting nations. This trade restriction was developed to protect the profits of sugar refining industries in the importing nations, many of which could not compete with sugar refined in producer nations and sold on a free-trade basis. In effect, the ISO has prevented producer nations from industrializing their sugar industries.

U.S. sugar policy, outlined in the Sugar Act of 1934, was designed to protect U.S. sugar refiners from foreign competition and at the same time to protect American consumers from speculative price increases. This program cost U.S. taxpayers more than $300 million in 1972 alone.[3] But despite abundant world sugar supplies, sugar prices have steadily increased over the past few years. The Federal Trade Commission has pronounced U.S. sugar policy "spectacularly unsuccessful in protecting consumers from rising world sugar prices."[4] The world price for sugar, at eight cents a pound in 1979, jumped to 24 cents a pound by February 1980. Consumers grumbled at paying 300 percent more for sugar, but that's only part of the story. According to the U.S. Department of Agriculture, every one-cent-per-pound increase in the price of sugar adds $215 million to America's annual food costs[5]—a bitter pill, even if it has a sugar coating.

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sulin, cells may die. Diabetics lack sufficient insulin, and 4.5 million Americans suffer from this serious illness. Diabetes is usually controlled by dietary restrictions or by injection of commercially-produced animal insulin. These treatments allow diabetics to live reasonably normal lives, but they do not cure the illness.

Dr. Frederic Banting, whose discovery of insulin won him the Nobel Prize, recommended that the best way to deal with diabetes was to prevent it, and that the best prevention was to reduce sugar consumption.[30] Persuasive evidence supports his opinion. During the two World Wars, incidence of diabetes dropped sharply among civilians whose sugar supply was severely rationed, but rose steadily among soldiers who continued to receive ample sugar allotments.[31] Although the cause of diabetes is not entirely clear, some physicians and nutritionists maintain that a diet high in sugar overtaxes the body's ability to produce insulin and promotes diabetes, particularly adult-onset diabetes. Animal studies have shown that high-sugar diets cause abnormalities in the pancreatic cells that produce insulin, and studies of humans have shown that as sugar consumption increases, so does the blood insulin level.[32] Harvard Nutrition Professor Jean Mayer has noted that adult-onset diabetics "usually produce near-normal amounts of insulin, but apparently not enough to cope with the demand."[33]

Diabetics usually develop mild myopia or far-sightedness, and sometimes severe retinal disease if their blood sugar level is not properly controlled. Both animal and human studies show that a high-sugar diet can change the refraction of the eye and cause these problems.[34]

Although the evidence linking sugar consumption to coronary heart disease is controversial and far from conclusive, it suggests that sucrose consumption may play a significant role in the development of the nation's leading killer. Sucrose deprivation in Europe during World War II was associated with a significant drop in coronary heart disease,[35] an association strengthened by recent European research. Finnish researchers monitoring the incidence of heart attacks among patients at two mental hospitals there, found the hospital with the lower number of heart attacks also had 40 percent less sugar in its institutional diet. In England and Israel, separate studies show that a high-sugar diet raises cholesterol levels, particularly in young men and post-menopausal women. High cholesterol level is a significant risk factor for heart disease. Another study[36] showed that sugar and salt, the second most popular food additive, tend to work synergistically to increase susceptibility to high blood pressure, another risk factor for heart disease. Other studies[37] have suggested that the relationship between sugar and heart disease is stronger

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As many as 20 million Americans may . . . experience adverse health effects from sugar

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than the one between fat consumption and heart disease.

The connection between sugar and vitamin deficiency is clearer. In fact, researchers use sucrose-based diets to induce riboflavin (B_2) deficiency in test animals.[28] Because refined sucrose does not supply the B vitamins or minerals necessary for its own digestion, these nutrients must be supplied by other foods or leached from stored deposits in the body, but these vitamins are needed elsewhere. B vitamins, for example, are essential to the formation of glutamic acid, required for the proper functioning of the brain. Not only does sucrose "steal" vitamins for its metabolism, it also harms the intestinal bacteria that produce the B vitamins.[29] The trace mineral chromium is particularly important in sucrose metabolism. Chromium deficiency may contribute to diabetes and to the eye problems associated with it.

Few Americans believe that the serious illnesses that result from nutritional deficiencies could occur in the richest nation on earth. But American teenagers who consumed large quantities of high-sugar junk foods were recently shown to have hazardously low levels of thiamin (B_1), and some early symptoms of beriberi, the thiamin-deficiency disease.[30] While the sometimes severe behavior problems symptomatic of this disease improved through treatment with thiamin supplements, the researchers who monitored the cases concluded: "Our experience suggests that such (vitamin deficiency) states may well be seen in an affluent modern society, and possibly be dangerous since (the resulting) personality changes were frequently aggressive in nature."

Another behavior problem apparently linked to sugar consumption is "hyperactivity." Although it is poorly defined and highly controversial, hyperactivity is a label applied to a broad range of behavior problems that make children moody, indigent, unable to concentrate and subject to temper tantrums. Up to 20 percent of school-aged children in the United States may be hyperactive.[31] Children diagnosed as hyperactive at the New York Institute of Child Development registered abnormal results on glucose tolerance tests, suggesting that they have a problem metabolizing sugar.[32] Dr. Keith Conners, who has investigated the sugar-hyperactivity link at Children's Hospital in Washington, D.C., speculated, "Sugar may act like a stimulant drug insofar as it alters body metabolism."

Related research at the Massachusetts Institute of Technology is focusing on the possibility that sugar may alter the brain chemicals serotonin, acetylcholine and norepinephrine, neurotransmitters known to affect aggressive, sexual and eating behavior, sleep and sensitivity to pain. Neurobiologist Richard Wurtman explained: "We know that all carbohydrates affect brain serotonin because they cause insulin to be released. Since sugar causes insulin to be released more rapidly, it may have a greater effect on serotonin levels."[33]

Finally, sugar may even accelerate human physical maturation and the aging process. Studies show that sugar promotes the release of hormones involved in sexual maturation, and extrapolations from longevity studies with rats suggest that high-sugar diets may reduce human life expectancy as much as several years.[34]

Kicking the Habit

Faced with the growing evidence linking sugar consumption to various health problems, many people are trying to kick their sugar habits. Many health authorities caution people to eat less sugar: the American Heart Association, the Department of Health and Human Services, the Surgeon General, the U.S. Department of Agriculture and the American Medical Association. But a sweet tooth can be hard to control. Some people who try to renounce sugar are surprised to find that it feels like an addiction, not quite a clinical addiction, but certainly a habit that's hard to break.

Eliminating sugar from the diet is easier said than done. Most of the sugar in our food is put there by processed food and beverage manufacturers. The amount of sugar in these foods and drinks is often surprising (see sidebar), but it is very difficult to know exactly how much sugar is in any food because food labels do not list the amount of each ingredient. Many consumer organizations have pennoned the

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Other Sugars

Honey is a combination of fructose, glucose, maltose and sucrose formed through enzyme action on nectar gathered by bees. It also contains some vitamins and minerals—but not much. Honey is sometimes promoted as a "healthier" substitute for sugar. It isn't. It has basically the same effects on the body as white sugar. In fact, some commercial honey has sugar added to it.

Brown Sugar (turbinado) is simply white sugar mixed with either molasses, or artificial colors and flavors that mimic molasses. The physiological effects of white sugar and brown sugar are identical.

Corn syrup and *dextrose* are processed sugars made from corn starch. They are popular with the food industry. They are no better for you than white sugar.

EATING

High sugar diets may reduce human life expectancy as much as several years

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Food and Drug Administration to require percentage labeling, so consumers can make more informed decisions about the amount of sugar—and other additives—in their diets, but to date the agency has taken no action.

Although food labels do not specify the proportions of ingredients, the more sugar in a product, the closer to the beginning of the ingredient list it is placed. Read food labels carefully, and select products without sugar, or those that place it toward the end of the ingredient list.

One way to assess your sugar consumption is to write down how much sugar you eat in one week. You may be surprised at how much you consume.

Then, try to cut back on the sugar added to foods and beverages. It's not that much of a hardship. Sugar tends to blunt the sensitivity of the palate. When sugar is restricted, the natural flavors of foods tend to become more noticeable. Try to treat sugar as a condiment, not as a staple to be eaten in bulk.

When you do eat sugar, try to eat it at the end of a meal, not between meals. Sugary snacks on an empty stomach can put you on the road to the sugar rush/sugar crash cycle. Sugar's effects on the body are reduced when eaten at the end of a meal because the foods eaten before it slow its entry into the blood stream.

Reducing your sugar consumption may produce some symptoms of withdrawal, for example, irritability, depression or nervousness. These generally pass in about a week. It's a good idea to continue to keep a sugar diary as you reduce your sugar consumption. It allows you to see where you're making progress and where more effort needs to be applied.

In Chicago, a group called Sugar Beaters Anonymous has formed to help people kick their sugar habits. Sugar Beaters began as a wager between two brothers, Lawrence and James McManus. They both decided to give up sugar, and to "sweeten" the deal, they laid $100 on the line. Whoever ate sugar first would lose his money. Two years later, the bet remains to be collected. The brothers said they felt so much healthier after giving up sugar, they decided to help others do the same.

Sugar Beaters is organized along the lines of Alcoholics Anonymous (see "Alcoholics Anonymous: 45 Years of Self-Help One Day at a Time," in MSC #11). At meetings three times a week, members discuss their feelings of powerlessness over sugar, and the ways they deal with the problems sugar causes them. Lawrence McManus, a nutritionist, said there are many similarities between the obsessions for sugar and alcohol. "To us, sugar is an addiction. Whether it's sugar or alcohol, people are hooked on a chemical high (they're) unable to control, and suffer malnutrition because neither alcohol nor sugar has nutritional value."

Sugar Beaters appears to work for some people. One alumnus said, "For the first time in about three years, I'm not spaced out, my vision isn't blurred, I'm not tired and best of all, I feel satisfied with a normal amount of food. I feel like my old self again." ☐

Janice Fillip has written extensively on nutrition, food politics and ecology for Whole Foods, Women's Sports, Not Man Apart *and other publications.*

Resources

Sugar Beaters Anonymous,
Sugar Detox Center
4800 N. Milwaukee
Chicago, IL 60630
(312) 736-8888

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Sugar Content of Selected Foods:

Sugar Smacks	61%
Cap'n Crunch	43%
Count Chocula	44%
100% Bran	19%
Lucky Charms	51%
Heartland	23%
Carnation Instant Breakfast (chocolate)	23%
Pepperidge Farm Pirouettes	
Cookies	40%

Figure 10-3. Satisfaction from Consuming Sugar.

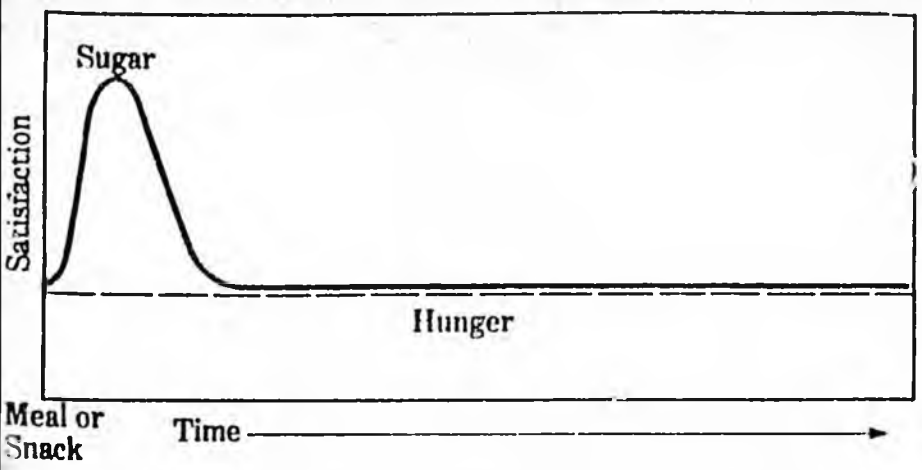


Figure 10-4. Satisfaction from Consuming Sugar and Starch.

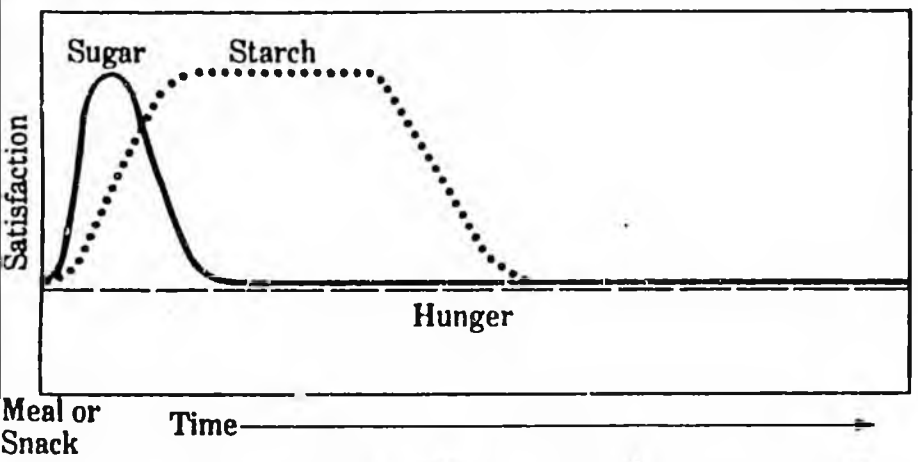


Figure 10-5. Satisfaction from Consuming Sugar, Starch and Protein.

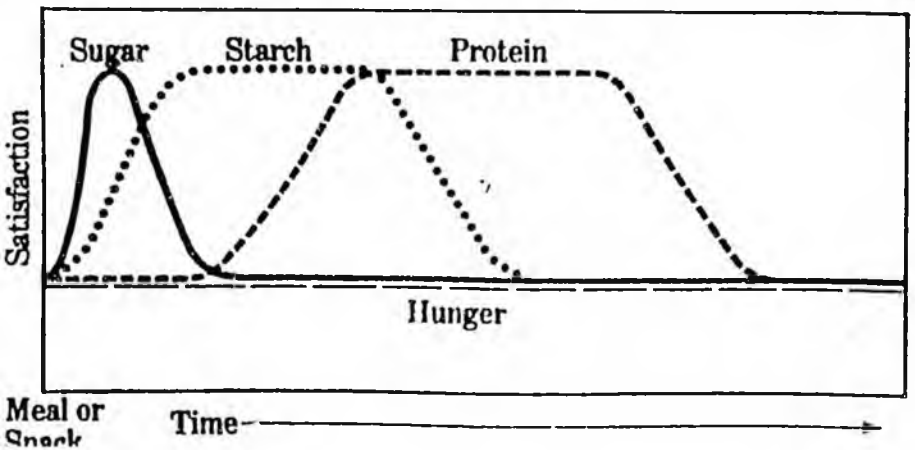


Figure 10-6. Satisfaction from Consuming Sugar, Starch, Protein and Fat.

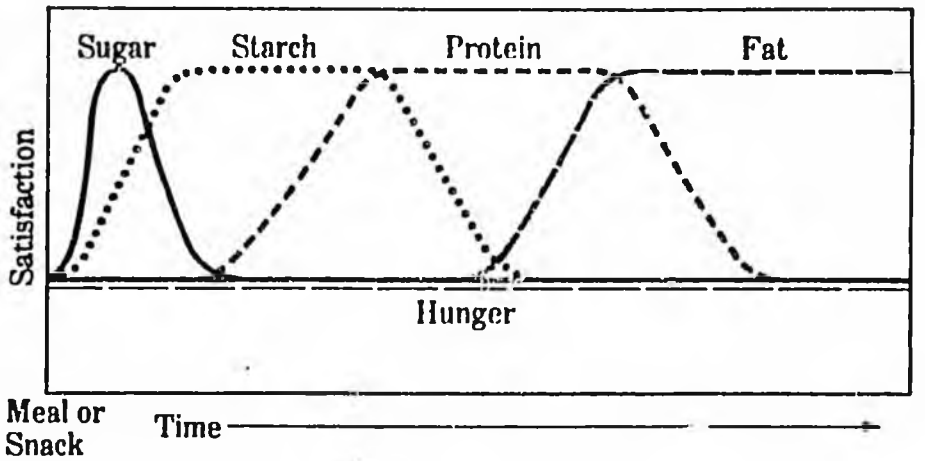
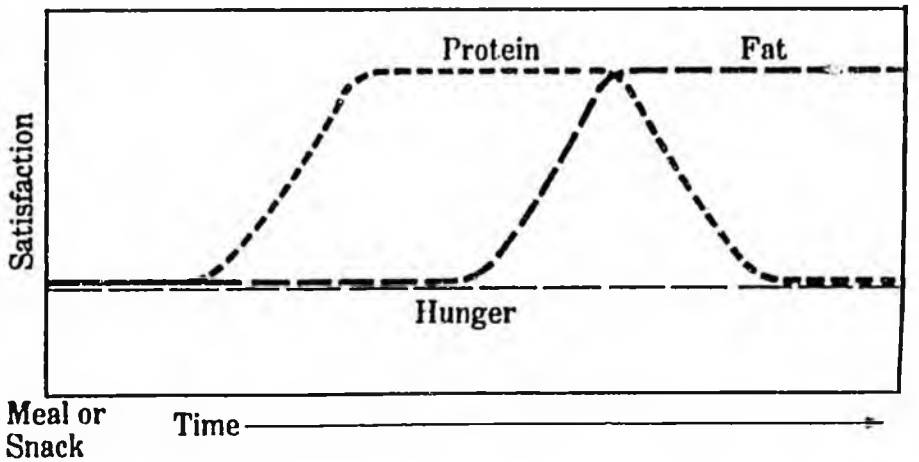


Figure 10-7. Satisfaction from Consuming Protein and Fat.



SUGAR IN BREAKFAST CEREALS

Percent Total Sugar (Dry Weight)

0.1%	Puffed Rice
0.5	Puffed Wheat
0.6	Shredded Wheat-spoon size
3.0	Cheerios
3.6	Corn Chex
3.7	Wheat Chex
4.4	Rice Chex
4.6	Kix
5.1	Special K
5.4	Post Toasties
5.4	Corn Flakes
7.1	Rice Krispies
7.1	Grape Nuts
8.1	Total
8.2	Wheaties
9.6	Concentrate
9.8	Product 19
12.0	Buckwheats
12.8	Grape Nut Flakes
13.0	Bran Flakes, 40%
13.6	Team
16.5	Life
18.3	Fortified Oat Flakes
19.4	All Bran
20.5	100% Bran
21.2	Life Cinnamon
21.7	Country Crisp
25.6	Frosted Mini Wheats
27.8	C. W. Post (Plain)
29.1	Raisin Bran
29.3	C. W. Post (Raisin)
29.6	Golden Grahams
30.0	Raisin Bran
30.1	Cracklin' Bran
31.7	Cap'n Crunch Peanut Butter
34.5	Cocoa Puffs
35.7	Trix
36.5	Frosted Rice
37.4	Honey Combs
37.7	Alpha Bits
39.4	Count Chocula
39.9	Cap'n Crunch
40.2	Quisp
40.2	Cookie Crisp, Oatmeal
40.2	Crazy Cow, Strawberry
40.6	Sugar Frosted Flakes
40.8	Corny Snaps
41.3	Lucky Charms
41.5	Cookie Crisp, Chocolate Chip
41.6	Fruity Pebbles
42.1	Cocoa Pebbles
42.7	Cookie Crisp, Vanilla
42.8	Frosted Rice Krinkles
43.3	Cocoa Crispies
43.7	Cap'n Crunch, Crunchberries
44.5	Frankenberry
45.3	Crazy Cow, Chocolate
45.4	Super Sugar Crisp
46.0	Sugar Corn Pops
48.4	Fruit Loops
54.0	Apple Jacks
55.5	Sugar Smacks

Source: Li, B.W., and Schuhmann, P.J., "Gas-Liquid Chromatographic Analysis of Sugars in Ready-to-Eat Breakfast Cereals". J. Food Sci. (in press).

Hidden Sugar

The approximate sugar content of popular foods expressed in teaspoons

100 grams sugar = 20 teaspoons = 1/2 cup = 3 1/2 oz. = 400 calories

			tsp. sugar
Candy*	Chocolate bar	1 average size	7
	Chocolate cream	1 average size	2
	Chocolate fudge	1 1/2" sq. (15 to 1 lb.)	4
	Chocolate mints	1 medium (20 to 1 lb.)	3
	Marshmallow	1 average (60 to 1 lb.)	1 1/2
	Chewing gum	1 stick	1/2
Cakes and cookies	Chocolate cake	1/12 cake (2 layer icing)	15
	Angel food cake	1/12 of large cake	6
	Sponge cake	1/10 of average cake	6
	Cream puff (iced)	1 average custard filled	5
	Doughnut, plain	3" diameter	4
	Macaroons	1 large or 2 small	3
	Gingersnaps	1 medium	1
	Molasses cookies	3 1/2" diameter	2
	Brownies	2" x 2" x 3/4"	3
Ice cream	Ice cream	1/8 quart (1/2 cup)	5-6
	Sherbet	1/8 quart (1/2 cup)	6-8
Pie	Apple	1/6 med. pie	12
	Cherry	1/6 med. pie	14
	Raisin	1/6 med. pie	13
	Pumpkin	1/6 med. pie	10
Soft drinks	Sweet carbonated beverage	1 bottle, 6 oz.	4 1/3
	Ginger ale	6 oz. glass	3 1/3
Milk drinks	Chocolate	1 cup, 5 oz. milk	6
	Cocoa	1 cup, 5 oz. milk	4
	Eggnog	1 glass, 8 oz. milk	4 1/2
Spreads and sauces	Jam	1 tbs. level	3
	Jelly	1 tbs. level	2 1/2
	Marmalade	1 tbs. level	3
	Syrup, maple	1 tbs. level	2 1/2
	Honey	1 tbs. level	3
	Chocolate sauce	1 tbs. thick	4 1/2
Cooked fruits	Peaches, canned in syrup	2 halves, 1 tbs. syrup	3 1/2
	Rhubarb, stewed, sweetened	1/2 cup	8
	Apple sauce (unsweetened)	1/2 cup scant	2
	Prunes, stewed, sweetened	4 to 5 med., 2 tbs. juice	8

* Candy is from 75 to 85% sugar. Popular candy bars are likely to weigh from 1 to 5 oz. and may contain 5 to 20 teaspoons of sugar. Adapted from current publications on food values. Courtesy of Dr. Herman Becks, University of California.

Dried fruits	Apricots, dried	4 to 6 halves	4
	Prunes, dried	3 to 4 medium	4
	Dates, dried	3 to 4 stoned	4 1/2
	Figs, dried	1 1/2 to 2 small	4
	Raisins	1/4 cup	4
Fruits and fruit juices	Fruit cocktail	1/2 cup, scant	5
	Orange juice	1/2 cup, scant	2
	Pineapple juice, unsweetened	1/2 cup, scant	2 3/5
	Grapefruit juice, unsweetened	1/2 cup, scant	2 1/5
	Grapefruit, commercial	1/2 cup, scant	3 2/3

Information from the American Dental Association, 211 E. Chicago Avenue, Chicago Illinois 60611

A Basic Sugarless SHOPPING GUIDE

On the following pages is a shopping list free of refined sugar, starch, and flour. But it's only a beginning list, because processors are realizing the need for natural products and are introducing more of them regularly. More sugarfree foods are coming to the grocery shelves.

Read labels very carefully. A brand in one area of the country may be sugarless while the same brand in another part of the country may have sugar added.

I believe shopping can be fun. Here are a few suggestions to help make it so:

1. Set aside a time of day or night when you can do your shopping in a leisurely manner.

2. Avoid the peak hours of shopping.

3. Make sure you have just eaten so as not to run the risk of becoming tired and irritable (and of overspending your budget).

4. Choose a pleasant store, one that gives you wide aisles, soothing music, appealing produce, fresh poultry, seafood, and meat, with much variety.

5. Snack while you shop. Take along some nuts, seeds, or cheese.

Grocery Items without Refined Sugar, Starch, or Refined Flour
Sample Brands Shown
Other brands are usually available—please read the label.

Crackers, etc. (if allowed)
Natural RyKrisp
Hol-Grain Brown Rice Wafer-ets
Hol-Grain Whole Wheat Wafer-ets

Fruit, canned (fresh preferred)
Pineapple in own juice—Dole, Townhouse
Grapefruit in own juice—Dole, Townhouse
Peaches—S & W Nutradiet Blue Label
Pears—S & W Nutradiet Blue Label
Fruit Cocktail—S & W Nutradiet Blue Label
Apple sauce—S & W Nutradiet Blue Label

Fruit, frozen
Strawberries—Bel Air Whole Unsweetened
Boysenberries, Bel Air
Blueberries, Bel Air
Most loose-bag packs

Fruit Juice, canned or bottled
Most items labeled simply "juice" are without sugar. For example:
Apple—Tree Top, Townhouse
Pear-apple—Townhouse
Grapefruit—Texsun Pink, Libby's, S & W
Pineapple—Dole, S & W
Prune—Townhouse
Grape—Welches, Empress
Cranberry—Ocean Spray
Orange and grapefruit—Townhouse
Orange—Libby's, Texsun
Avoid fruit drink, nectar, cocktail, and punch.

Fruit Juice, frozen concentrate
Orange—Minute Maid, Bel Air
Grapefruit—Bel Air
Apple—Tree Top
Pineapple—Minute Maid
Avoid frozen grape—sugar added.

Dairy Items
Cream, butter, milk
Cottage cheese
Cream cheese
Natural cheddar cheese (not processed)
Plain yogurt

Gelatin
Knox unflavored

Grains and Cereals (if allowed)
Brown rice, wild rice
Oatmeal, unflavored
Wheat germ
Whole grain mixes, 4-grain or 7-grain cereals

Meat, Poultry, Seafood, canned
Normally without sugar:
Tuna, salmon, sardines (except with tomato sauce), shrimp, clams, crab, and oysters.
Chicken—Swanson boned
Turkey—Swanson boned
Following brands are sugarless but unfortunately contain nitrite:
Luncheon meat—Majesty
Corned beef—Hereford
Ham—Armour Golden Star

Meat, etc., frozen
Unbreaded fish or meat patties

Nuts (preferably raw)
Most bag packages

Oils
To avoid hydrogenation and preservatives, pure cold-pressed vegetable oils are preferred—available at health food stores.

Olives
All

Pasta (if allowed)
Whole grain spaghetti, macaroni, and noodles are available in health food stores.

Peanut Butter
The "old fashioned" type is not hydrogenated and is therefore preferred.

Pickles
Dill

Salad Dressings
French--Girard's Original
Trader Vic's Javanese
Others at health food stores.

Salt
Morton's 5-lb. bag pack
Shilling Garlic Salt
Vegetable salt—health food stores
Sugars are often added to salt—please read label.

Sauces and Condiments
Prepared mustard--French's, Kraft
Tomato sauce—Del Monte, Progresso, Contadina
Maggi Seasoning
Tobasco Pepper Sauce
Ketchup—health food store
Soy sauce—Kikoman's, Tamari

Sausage, etc.
Although Ball Park wieners and Jones sausage are sugarless, they contain nitrite. Check locally made brands and health food stores for products without sugar or nitrates/nitrites. Some physicians feel pork should be avoided.

Vegetables, canned (fresh vegetables are much preferred)
Normally sugarless:
Green beans
Carrots
Asparagus
Spinach
Beets (except pickled)
Tomatoes—Townhouse, Hunts, Gardenside
Mixed veg—Freshlike, Veg-All
Sweet potatoes—Taylor's
Hearts of artichoke—S & W
Garbanzo beans—Janet Lee
Lima beans—Del Monte
Avoid canned peas, corn, and kidney beans, which are typically canned with sugar. Packaged dry beans are without sugar.

Vegetables, frozen
Normally any plain frozen vegetable (that is, without sauce) is sugarless. Read the label.

Basic Dietary Guidelines for Hypoglycemics

If you are hypoglycemic, your doctor will give you special instructions on nutrition. As a reminder, some basic instructions are listed below. If your doctor's instructions differ, please disregard these and follow his advice.

1. **Avoid refined sugar, starch, and flour** and everything containing them. Get in the habit of *reading labels*. Look not only for sugar, starch, and flour, but also for:

Dextrin	Sucrose	Honey
Dextrose	Sorbitol	Raisin syrup
Lactose	Hexitol	Malt syrup
Fructose	Arrow root	Corn starch
Maltose	Brown sugar	Corn syrup
Glucose	Molasses	Corn sweeteners
		Natural sweeteners

Foods containing refined sugars, starches, and flours (not allowed):

Candy	Cocoa	Most steak sauces
Cookies	Chocolate milk	Cheese spreads
Cakes	Chocolate drinks	Processed cheeses
Pies	Soft drinks	Certain canned meats
Pasteries	Alcohol	Most luncheon meats
Ice cream	Fruit drinks (not juices)	Sausage
Doughnuts	Dessert toppings	Most hot dogs
Most breads	Chewing gum	Most commercial soups
Various jellos	Sweet pickles	Most canned fruits
Pretzels	Ketchup	Some frozen fruits
Potato chips	Mayonnaise	Some canned vegetables
White rice	Relishes	Some frozen vegetables
Chocolate	Most condiments	Pancakes
		Pastas (spag., macaroni)

2. **Avoid natural sweeteners** such as honey, molasses, and date sugar until your doctor allows them. Thereafter, use only in small amounts (for example, one-fourth teaspoonful).

3. **Follow your doctor's advice on quantity of fruit.** Physicians vary in amount of fruit allowed. Some feel that fruit intake should be restricted; others allow unlimited amounts.

> Dates, prunes, raisins, and other dried fruits are very high in fruit sugar. Grape juice and prune juice are also high.

4. **Limit other high carbohydrate foods.** Restrict, for example, wheat, rice, corn, beans (other than green), and potatoes. If you are permitted to have whole grains, take only *half* a slice of bread. Take only *half* a potato.

5. **Eat at least 4 vegetables a day.** Expand your taste to include at least 15 to 20 different vegetables in your regular diet. Such variety will give you important vitamins and minerals.

6. **Use mostly fresh foods** and cook them as little as possible. Raw vegetables are very desireable. Fresh is better than frozen, and frozen is better than canned, bottled, or otherwise processed.

7. **Include a moderate amount of protein** in whatever number of portions per day your doctor directs. Protein is essential, but we frequently eat more than we can digest. Use moderate portions of eggs, seafood, poultry, cheese, and meat. Examples of portions: 2 eggs, 4-5 ounces of seafood, 2 pieces of chicken, a slice or two of cheese, a medium sized hamburger patty. Milk is considered by many to be difficult to digest and is often not permitted in a hypoglycemic diet. Cream, however, is a wonderful substitute. It can be used as is or diluted with water to the consistency of milk.

8. **Eliminate caffeine.** This means no coffee, tea, cola drinks, or Tab. Substitutes include weak herb teas and Sanacaf.

9. **Avoid chemical additives as much as possible.** The dangers of some widely used additives (e.g., sodium nitrite and BHT) are known. Others are probably equally as harmful.

10. **Limit alcohol.** Ideally it should be eliminated altogether because it breaks down into sugar very quickly.

11. **Include vegetable oils in your diet.** Most contain polyunsaturated fatty acids (if not hydrogenated in processing), which are needed for weight control.

12. **Snack at night if necessary.** If you tend to waken during the night, have snacks available at your bedside.

13. **Eat many small meals a day.** This rule is important. Eating often is essential to maintaining an even blood sugar level. For many people this means preparing adequate mini-meal snacks for mid-morning and afternoon breaks, eating smaller meals, and snacking before bedtime. Some individuals may need to snack as often as every hour in the beginning.

SUGAR

How Sweet It Is — And Isn't

Sugar is getting a lot of attention because it's in so many processed foods. Many people want to know how much they're getting in their food, and many nutrition and health experts are dubious of its contribution to the American diet and health. We find that more than one kind of sugar is getting into food, and so we're eating more of the stuff all the time.

by Chris W. Lecos

Sugar, "that honey from reeds," as one author described it more than 2,000 years ago, has been a part of mankind's diet for as long as anyone cares to remember.

Cave drawings tell us of prehistoric man's taste for honey, figs, and dates. The beekeeping practices of Egyptians are depicted in the artwork in tombs dating around 2600 B.C.

The Bible tells us that the "promised land" flowed with milk and honey. It turned into a flood once sugarcane was discovered.

In the writings of an obscure officer in Alexander's army during its invasion of India, one finds the first written mention of sugarcane. That was around 325 B.C.

Yet, despite this long history, the use of sugar in the diet has become a controversial issue in recent years that has involved doctors, scientists, nutritionists, private citizens, the Government, and the industry itself.

Why all the fuss?

- Because there is a growing body of expert opinion that believes Americans would be healthier if they ate less sugar, not because it's bad for you, but because its only real contribution is taste and Calories.
- Because sugar has become the leading ingredient added to foods in the United States today. That is, most of the sugar consumed is added before it gets to the consumer.
- Because most people don't know how much sugar they eat, and many want to know. This is a principal reason the Food and Drug Administration wants the total amount of all sugars identified on more foods. The total would include both naturally occurring and added sugar.
- Because sugar, though blamed wrongly for many ills, is one of a number of contributors to dental caries. Americans are spending $10 billion a year for dental care.

To most people, sugar is what you find on the kitchen table, put into coffee, or mix in a cake. This, of course, is the sugar refined from cane and beets.

Actually, there are more than a hundred substances that are sweet and which chemists can correctly describe as sugars. Sucrose, or table sugar, is just the most common and abundant of them all.

Industry literature describes sugar as a cheap source of food energy, a major contributor to food processing and general nutrition, and a substance that makes many foods with other nutrients taste better.

"Good nutrition," says a brochure from the Sugar Association, "begins with eating."

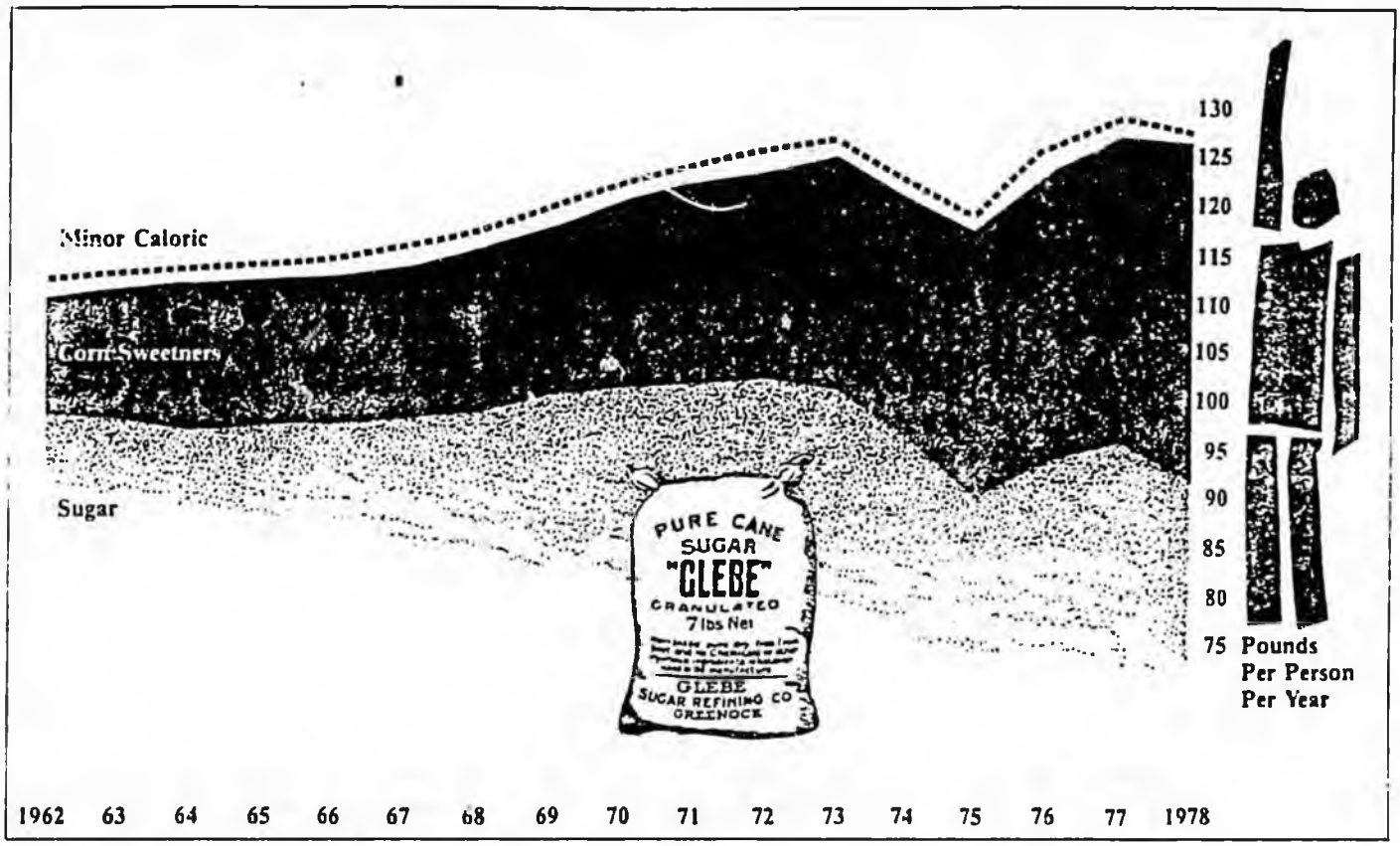
Its point, of course, is that if food is sweetened, people will eat the foods with the nutrients they need. However, many nutritionists and others concerned with American eating habits dispute sugar's value.

In a 1976 evaluation of the health aspects of sucrose as a food ingredient, the Federation of American Societies for Experimental Biology (FASEB) stated in a report to FDA: "Unlike most other foods, sucrose furnishes virtually only energy."

Many nutritionists concur and describe sugar as an "empty Calorie." If sugar is to be part of the diet, they say, it is preferable to get it from fruits, vegetables, and other items where it's a natural part of the product.

As it does with most other carbohydrates, the body converts sugar into glucose, the primary fuel of the body. During digestion it is broken down into equal parts of two simple sugars: glucose (dextrose) and fructose (levulose).

These components enter the bloodstream through the walls of the small intestine, and the blood carries the sugars to the tissues and the liver. There it is used or converted into glycogen and stored until the body needs it. The hormone insulin makes it possible for glucose, or



blood sugar, to enter nearly all the cells of the body, where it is used as an energy source.

When more energy is needed, the liver converts glycogen into glucose, which is then delivered by the bloodstream to other organs or muscle tissue. Glucose not needed by the cells is metabolized in the liver into fatty substances called triglycerides. The body can call upon this stored energy during dieting and fasting.

Because of these energy reserves, nutritionists discount the argument that sugar is useful for quick energy needs before physical activity.

Americans get about 24 percent of their Calories from sugar—of which 3 percent comes in natural form from fruits and vegetables, 3 percent from dairy products, and the balance from sugar added to foods.

If sugar provides about 20 percent of a person's Calories, he must get the other 80 percent by selecting foods that supply the other nutrients his body needs—which is not easy to do, say some nutritionists, if one is trying to lose weight.

For many Americans, weight is a problem. A study released in 1978 by the National Center for Health Statistics indicated that one-third of the population was overweight.

In a study of 13,600 people whose weights between 1971 and 1974 were compared with adults of equivalent height a decade earlier, the Center found that men and women under 45 were, on the average, 3.8 and 4.7 pounds heavier, respectively. Those over 45 had gained an average of 4.8 pounds.

There is no accurate measurement of how much sugar the average American eats. The best available barometer of sugar use is the per capita consumption figures of the U.S. Department of Agriculture (USDA).

Although the per capita figures do not tell how much a person actually eats, they do show the amount of sugar that "disappears" into the marketplace—that is, the amount shipped by sugar producers for industrial, home, and other uses.

Citing USDA figures, sugar industry spokesmen maintain that sugar consumption in the United States has been relatively stable for more than 50 years now, at around 100 pounds a year per person.

However, that figure refers only to the consumption of refined cane and beet sugar. It does not reflect the growing impact of a variety of corn sweeteners now in use. The term "corn sweeteners" includes various corn sirups (high fructose corn sirup, glucose) plus other Caloric sweeteners, such as dextrose, that are derived from corn.

Refined sugar, corn sirup, and corn sugar account for the bulk of the sweeteners consumed in this country. Among the remainder are honey, maple, and other edible sirups.

All of these are Caloric, and when all are taken into account, USDA figures show a rise in per capita consumption from 122 pounds in 1970 to 128 pounds in 1978.

Per capita consumption of just refined sugar hovered around the 100 pounds per year level between 1960 and 1974. Since then, the trend generally has been downward, falling below 93 pounds in 1978, according to USDA. Fred Gray, an agriculture economist for USDA, predicted a further drop of several pounds for 1979.

The decline in refined sugar consumption has been more than offset by the steady rise in corn sweetener usage—from a per capita rate of 19 pounds in 1970 to almost 34 pounds in 1978.

Norris Bollenback, scientific director for the Sugar As-

sociation, said the primary impetus for the increase has come from the growing industrial use of high fructose corn sirups, especially by soft drink producers.

The use of high fructose corn sirups was neglible—less than a pound per capita, on the average—in the early 1970's. The industry was in its infancy then, and food and beverage manufacturers relied almost entirely on cane and beet sugar for their products because those sugars were cheap and plentiful, selling for about 11 or 12 cents a pound wholesale.

The rapid escalation of sugar prices in 1974—up to around 33 cents a pound wholesale—compelled the food and beverage industries to turn to other sweeteners, and the most attractive of them all was the high fructose corn sirups.

By the end of 1975, USDA figures show that per capita consumption of those corn sirups had risen to 5 pounds and 3 years later up to 11 pounds. Gray predicted that high fructose corn sirup usage would reach 15 pounds in 1979 and 18 pounds by the end of 1980.

Bollenback cited figures that showed that high fructose corn sirup producers have maintained their product's price consistently below that of refined sugar—roughly from 3 to 10 cents a pound less at the wholesale level. Last year, the wholesale price of high fructose corn sirup was around 13 cents a pounds compared to 20 cents for refined sugar.

"If (refined) sugar proponents think things will be back the way they were, they are being unrealistic," Bollenback noted.

Things also aren't the way they used to be in how sugar gets to our stomachs. Fifty years ago, two-thirds of the sugar produced went directly into the home, which meant control was directly in the hands of the housewife or individual who bought it. The balance was used mostly by industry.

Now, the reverse is true. Sixty-five percent of the refined sugar produced today is being consumed by the food and beverage industries and only 24 percent is going for home use.

The beverage industry—comprised of soft drink bottlers and beer and wine producers—is the leading industrial user of refined sugar and of high fructose corn sirups. It used 26 percent of the 9.8 million tons of refined sugar shipped in 1978 and about 40 percent of the high fructose corn sirups.

Although there has been a considerable amount of public controversy over the amount of sugar in cereals, the bakery and cereal industries combined used only 13.4 percent of all the sugar produced for food purposes in 1978. USDA figures did not separate the two.

Producers of confectionery products had the next highest usage at 9.2 percent, followed by 7 percent for the processed food and canning industries, and 5.6 percent for dairy products.

The consumer today is confronted by a wide variety of sugars and other nutritive sweeteners, and there is no significant difference in the amount of Calories each provides.

Below is a brief explanation of the more common sugars and sweeteners:

Sucrose, obtained in crystalline form, from cane and beets, is a double sugar or disaccharide and is composed of two simple sugars, glucose and fructose. It is about 99.9 percent pure and is sold in either granulated or powdered form.

Raw sugar, tan to brown in appearance, is a coarse, granulated solid obtained from evaporation of sugarcane juice. FDA regulations prohibit the sale of raw sugar unless impurities—dirt, insect fragments, etc.—are removed.

Turbinado sugar is sometimes viewed erroneously as a raw sugar. Actually, it has to go through a refining process to remove impurities and most of the molasses. It is produced by separating raw sugar crystals and washing them with steam. It is edible if produced under proper conditions. However, some samples in the past have been found to contain contaminants, the Sugar Association warns.

Brown sugar consists of sugar crystals contained in a molasses sirup with natural flavor and color. However, some refiners make brown sugar by simply adding sirup to refined white sugar in a mixer. It has 91 to 96 percent sucrose.

Total invert sugar, a mixture of glucose and fructose, is formed by splitting sucrose in a process called inversion, which is accomplished by the application of acids or enzymes. It is sold only in liquid form and is sweeter than sucrose. It helps prolong the freshness of baked foods and confections and is useful in preventing food shrinkage.

Honey is an invert sugar formed by an enzyme from nectar gathered by bees. Its composition and flavor depend on the source of the nectar. Fructose, glucose, maltose, and sucrose are among its components.

Corn sirups, produced by the action of enzymes and or acids on cornstarch, are the result of hydrolysis of starch. High fructose corn sirup is a derivative of corn. The amounts of fructose vary with the manufacturer. One major producer's sirups contain 42 percent, 55 percent, and 90 percent fructose. Dextrose comprises most of the balance.

Levulose, or fructose, is a commercial sugar, considerably sweeter than sucrose, although its sweetness actually depends on its physical form and how it is used in cooking. Fructose, known as a fruit sugar, occurs naturally in many fruits.

Dextrose, or glucose, is also called corn sugar. It is made commercially from starch by the action of heat and acids, or enzymes. It is often sold blended with regular sugar.

Lactose, or milk sugar, is made from whey and skim milk for commercial purposes. It occurs in the milk of mammals. The pharmaceutical industry is a primary user of prepared lactose.

Sorbitol, *mannitol*, *maltitol*, and *xylitol* are sugar alcohols or polyols. They occur naturally in fruits but are commerically produced from such sources as dextrose. Xylitol is a sugar alcohol made from a part of birch trees. Sorbitol, mannitol, and maltitol are about half as sweet as sucrose; xylitol has a sweetness about equal to sucrose.

Although fructose and the other sugar alcohols are promoted as suitable substitute sweeteners, especially for diabetics, many health scientists question their supposed advantages pending more research and long-term studies. This will be the subject of the next article in this series in FDA CONSUMER.

Chris Lecos is a member of FDA's public affairs staff.

at 8 hours, 45 µg/mL at 12 hours, and 25 µg/mL at 16 hours. Following a single 1.6-g oral dose (as two 800-mg tablets) of one commercially available extended-release aspirin preparation in healthy adults in one crossover study, an average peak plasma aspirin concentration of about 1 µg/mL was attained within 2 hours and average peak plasma salicylate concentrations of about 22 µg/mL were attained within 8–12 hours; the plasma salicylate concentration declined to about 15 µg/mL by 24 hours.

Suppositories

In one study in children given a rectal dose of 150–300 mg of aspirin as a suppository, peak serum salicylate concentrations of 20–140 µg/mL generally occurred within 3–4 hours.

DISTRIBUTION

Aspirin is rapidly and widely distributed, apparently into most body tissues and fluids. The volume of distribution of aspirin is approximately the same as that of salicylate and is generally 0.15–0.2 L/kg.

In one study in patients with rheumatic disease who received a single 650-mg oral dose of buffered aspirin, aspirin was detected in synovial fluid within 10–30 minutes and salicylate was detected in synovial fluid within 15–35 minutes. In this study, peak aspirin concentrations in synovial fluid occurred after an average of 1.3 hours and were about 75% of peak blood concentrations; peak salicylate concentrations in synovial fluid occurred after an average of 2.2 hours and were about 60% of peak blood concentrations.

Aspirin is poorly bound to plasma proteins; the unhydrolyzed drug is 33% bound at a serum salicylate concentration of 120 µg/mL. However, aspirin acetylates serum albumin at the ε-amino group of lysine; the acetylation may alter binding of other drugs (e.g., phenylbutazone) to the protein. Acetylation of serum albumin by aspirin is inhibited by salicylate.

ELIMINATION

The elimination half-life of aspirin in plasma is approximately 15–20 minutes. Unlike salicylate, unhydrolyzed aspirin does not undergo capacity-limited metabolism and does not accumulate in plasma following multiple doses.

Following oral administration, aspirin is partially hydrolyzed to salicylate during absorption by esterases in the GI mucosa. Following absorption, unhydrolyzed aspirin is rapidly and almost completely hydrolyzed by esterases principally in the liver but also in plasma, erythrocytes, and synovial fluid; hydrolysis occurs more slowly in synovial fluid apparently because the amounts of esterases in synovial fluid are lower. It has been reported that aspirin may be hydrolyzed more slowly in women because women apparently have lower amounts of plasma aspirin esterases.

Only about 1% of an oral dose of aspirin is excreted unhydrolyzed in the urine. The remainder is excreted in the urine as salicylate and its metabolites.

Uses

Aspirin is used extensively in the treatment of mild to moderate pain, fever, and inflammatory diseases. Aspirin is also used in the prevention of arterial and possibly venous thrombosis. Aspirin, however, should be used with extreme caution, if at all, in patients in whom urticaria, angioedema, bronchospasm, severe rhinitis, or shock is precipitated by other salicylates or other NSAIAs. (See Cautions: Sensitivity Reactions, in the general statement on Salicylates 28:08.04.)

PAIN

Aspirin is used to relieve headache, neuralgia, myalgia, arthralgia, and other low-intensity pain of nonvisceral origin, particularly pain associated with inflammation. Aspirin may also relieve mild to moderate postoperative pain, postpartum pain, oral surgery or other dental pain, dysmenorrhea, or other visceral pain such as that associated with trauma or cancer. Many studies have shown that the analgesic effects of aspirin are greater than those of placebo in the treatment of these types of pain. The drug, however, does not usually relieve severe acute pain of visceral origin. In addition, use of chewing gum tablets or gargles containing aspirin has not been shown to be effective in relieving sore throat pain.

The analgesic effect of aspirin appears to increase with increasing single oral doses up to at least 1.2 g; however, single oral doses of aspirin greater than 650 mg apparently do not result in a greater incidence or degree of pain relief in most patients. Multiple oral doses of aspirin greater than 650 mg each have not been shown to be more effective in relieving pain than multiple oral doses of 650 mg.

When used to relieve postoperative pain, 600-mg oral doses of aspirin appear to be as effective as 60-mg oral doses of codeine or 50-mg oral doses of pentazocine. When used to relieve oral surgery pain, 650-mg oral doses of aspirin appear to be more effective than 30-mg oral doses of codeine, as effective as 650-mg oral doses of acetaminophen, about as effective as 50-mg oral doses of zomepirac, and less effective than 250-mg, 500-mg, or 1-g oral doses of diflunisal or 100-mg oral doses of zomepirac.

In the treatment of postpartum uterine pain, the analgesic effect of 650-mg oral doses of aspirin is about equal to that of 300- or 600-mg oral doses of naproxen or 275-mg oral doses of naproxen sodium and greater than that of 60-mg oral doses of codeine or codeine sulfate. When used to relieve episiotomy pain, several studies have shown that 600-mg to 1.2-g oral doses of aspirin are more effective than placebo; in one study, the analgesic effect of 900-mg oral doses of aspirin was about equal to that of 300- or 900-mg oral doses of ibuprofen. In another study, the analgesic effect of 600-mg oral doses of aspirin was less than that of 500-mg oral doses of diflunisal.

In the treatment of nonspecific pain associated with cancer, 650-mg oral doses of aspirin appear to be at least as effective as 650-mg oral doses of acetaminophen, 65-mg oral doses of codeine, 250-mg oral doses of mefenamic acid, or 50-mg oral doses of pentazocine, and more effective than 75-mg oral doses of ethoheptazine citrate or 65-mg oral doses of propoxyphene hydrochloride. When used to relieve nonspecific pain associated with cancer, 650-mg oral doses of aspirin in combination with oral doses of codeine (65 mg), oxycodone (976 µg), or pentazocine hydrochloride (25 mg) appear to be more effective than 650-mg oral doses of aspirin alone or in combination with oral doses of caffeine (65 mg), ethoheptazine citrate (75 mg), pentobarbital sodium (25 mg), promazine hydrochloride (25 mg), or propoxyphene napsylate (100 mg).

Results of studies comparing aspirin (500–650 mg 4 times daily) with placebo to relieve primary dysmenorrhea have been inconsistent. Although the effects of higher dosages of aspirin remain to be evaluated, most clinicians consider aspirin to be one of the *least* effective NSAIAs currently available for the treatment of primary dysmenorrhea.

In several double-blind placebo-controlled studies with small numbers of patients with migraine, prophylactic therapy with aspirin (650 mg twice daily) alone or aspirin (300 mg twice daily) with dipyridamole (25 mg 3 times daily) has reportedly been effective in reducing the frequency of headache; however, further evaluation is needed.

Aspirin has been used in the treatment of pain in various combinations with acetaminophen, caffeine, opiates, salicylamide, and/or other agents. However, combinations of aspirin with agents such as acetaminophen, caffeine, or salicylamide have not been clearly shown to have greater analgesic effect than an optimal dose of aspirin alone. In addition, there is little evidence that such combinations cause fewer adverse effects than higher doses of the individual agents alone. In one study, the simultaneous administration of 325- or 650-mg oral doses of acetaminophen with 650-mg oral doses of aspirin resulted in increased blood concentrations of unhydrolyzed aspirin compared to 650-mg oral doses of aspirin alone; however, the clinical importance of such an effect remains to be established. Aspirin (650-mg oral doses) in combination with oral doses of an opiate (e.g., codeine, oxycodone) produces greater analgesic effect than that produced by either aspirin or higher doses of the opiate alone. There is also some evidence that aspirin/opiate combinations may cause fewer adverse effects than equianalgesic doses of the individual drugs alone.

FEVER

Aspirin is used frequently to lower body temperature in febrile patients in whom fever may be deleterious or in whom considerable relief is obtained when fever is lowered. However, antipyretic therapy is generally nonspecific, does not influence the course of the underlying disease, and may obscure the course of the patient's illness. For information on salicylates and Reye's syndrome, see Cautions: Pediatric Precautions, in the general statement on Salicylates 28:08.04.

Aspirin and acetaminophen are equally effective as antipyretics. In one study in febrile children, the combination of oral doses of aspirin and acetaminophen was at least as effective in reducing fever as either drug alone, and the duration of fever reduction was longer with the combination than with the individual drugs. However, because of the study design, it could not be concluded that the combination had additive effects. Many clinicians use regimens of alternating doses of aspirin and acetaminophen; however, combined overdosage with both drugs has occurred with such a regimen and the efficacy and safety of these regimens remain to be established.

Several clinical studies have shown that the antipyretic effect of usual dosages of aspirin is about equal to that of usual dosages of mefenamic acid and naproxen, and less than that of usual dosages of indomethacin. However, efficacy of these other NSAIAs as antipyretics remains to be clearly established

and they should not be used for routine treatment of fever because of their potential adverse effects.

INFLAMMATORY DISEASES

Many clinicians consider aspirin to be a drug and the salicylate of first choice for anti-inflammatory and analgesic effects in the initial and/or long-term symptomatic treatment of rheumatoid arthritis, juvenile arthritis, and osteoarthritis. Aspirin may also be useful in the treatment of other polyarthritic conditions (e.g., psoriatic arthritis, Reiter's syndrome, ankylosing spondylitis), systemic lupus erythematosus, and nonarticular inflammation; however, other NSAIAs may be preferred in the treatment of some of these conditions (e.g., ankylosing spondylitis).

Most clinical studies have shown that the anti-inflammatory and analgesic effects of usual dosages of aspirin in the treatment of rheumatoid arthritis or osteoarthritis are greater than those of placebo and about equal to those of usual dosages of fenoprofen calcium, ibuprofen, indomethacin, meclofenamate sodium, naproxen, piroxicam, sulindac, and tolmetin sodium, and somewhat less than those of usual dosages of phenylbutazone. In the treatment of osteoarthritis, aspirin is used principally for its analgesic effect rather than anti-inflammatory effect, although inflammation may be part of the symptomatology. In the treatment of juvenile arthritis, the anti-inflammatory and analgesic effects of usual dosages of aspirin are about equal to those of usual dosages of fenoprofen, naproxen, or tolmetin sodium. Patient response to NSAIAs is variable, however, and patients who do not respond to one agent may be successfully treated with a different agent.

Aspirin has been used in conjunction with other NSAIAs in the treatment of some patients with rheumatoid arthritis, but such combination therapy is generally not recommended because there is inadequate proof that such combination therapy is more efficacious than the individual agents alone. In addition, the potential for adverse reactions may be increased, and there is evidence that aspirin alters plasma concentrations of some other NSAIAs.

Aspirin may be effective in the treatment of some patients with psoriatic arthritis or Reiter's syndrome but usually only when the disease is mild. Aspirin is seldom effective in the treatment of ankylosing spondylitis unless the disease is mild. In one study in patients with ankylosing spondylitis, the anti-inflammatory and analgesic effects of aspirin were less than those of indomethacin or phenylbutazone.

Some clinicians consider aspirin to be a drug of first choice for the treatment of fever, arthritis, pleurisy, and pericarditis in patients with systemic lupus erythematosus (SLE). In one study in patients with SLE, the anti-inflammatory and analgesic effects of aspirin were greater than those of ibuprofen. Aspirin has also been used in the treatment of symptomatic pericarditis following myocardial infarction; in one study, the effects of 2.6 g of oral aspirin daily were comparable to those of 100–200 mg of oral indomethacin daily, with either drug relieving symptoms within 48 hours. The anti-inflammatory and analgesic effects of aspirin may also be useful in the symptomatic treatment of nonarticular inflammation such as bursitis and/or tendinitis (e.g., acute painful shoulder) and fibrositis.

Most clinicians consider aspirin to be the salicylate of choice when salicylate therapy is indicated in the treatment of rheumatic fever. For information on salicylate therapy in the treatment of rheumatic fever, see Uses: Rheumatic Fever, in the general statement on Salicylates 28:08.04.

THROMBOSIS

Since there is considerable clinical and experimental evidence that thrombosis (particularly arterial thrombosis) may result from platelet-mediated processes which can be inhibited by aspirin, the drug has been extensively evaluated in the prevention of arterial and venous thrombosis. However, results are largely conflicting and/or inconclusive. This may be due in part to the complexity of thromboembolic disorders, problems in study design, and the possibilities that the antithrombotic effect of aspirin is dosage dependent and/or sex related. (See Pharmacology: Antithrombotic Effect.) Presently, the most widely accepted indication for prophylactic aspirin therapy is for reducing the risk of recurring transient ischemic attacks (TIAs) and stroke or death in men who have had single or multiple TIAs. Further controlled studies are necessary to determine the safety and efficacy of prophylactic aspirin therapy in many thrombosis-related conditions.

Cerebrovascular Disease

Aspirin has been shown to reduce the risk of recurring transient ischemic attacks (TIAs) and stroke or death in men who have had single or multiple TIAs; however, it has not been established that aspirin prevents stroke. In addition, it is not clear whether aspirin is similarly effective in women. Aspirin is not beneficial in the treatment of completed stroke.

In one study in patients with TIAs, oral doses of aspirin (650 mg twice daily) were more effective than placebo after 6 months of therapy, but only when the occurrence of TIAs, nonfatal cerebral or retinal infarction, and death were considered together as end points. After 2 years of treatment, aspirin was more effective than placebo only in those patients who had multiple TIAs before starting treatment and in those having stenotic lesions of the carotid artery on the side appropriate to their symptoms. In another placebo-controlled trial, aspirin alone (325 mg 4 times daily) was more effective than placebo or sulfinpyrazone alone (200 mg 4 times daily) in reducing the risk of recurring TIAs, stroke, or death in men but not in women; although no interaction between aspirin and sulfinpyrazone was definitely found, a trend favoring the efficacy of the combination was observed in men. No differences in therapeutic response were evident for the vascular site of TIAs (carotid or vertebrobasilar) or for single or multiple TIAs before treatment. When the recurrence of TIAs was considered in combination with stroke and death as end points in both this study and the previous study, there was no sex difference in treatment response; however, it is not clear that reducing the risk of TIAs necessarily reduces the risk of stroke. Results of several other studies have also supported the efficacy of aspirin therapy and suggested that therapeutic benefit may be limited to males.

Combination therapy with aspirin (500 mg twice daily) and dipyridamole (75 mg twice daily) after 2 months of therapy with an oral anticoagulant (e.g., warfarin) has also been reported to reduce the risk of cerebral infarction in patients with TIAs. However, no controlled trials comparing aspirin with an oral anticoagulant have been reported to date.

In men (and possibly in women) who have had TIAs for 2–12 months and are not treated surgically, many clinicians recommend aspirin therapy unless a recent increase in frequency, duration, or severity of TIAs has occurred, in which case an oral anticoagulant is given for 3–6 months followed by aspirin therapy. Patients who have had TIAs for less than 2 months and who are not treated surgically, generally receive an oral anticoagulant (unless contraindicated) for 3–6 months before treatment with aspirin is started. Aspirin therapy is generally continued until the patient has been free of TIAs for 1 year. No specific therapy is recommended for patients who are not treated surgically and have not had a TIA for longer than 1 year. Additional controlled trials evaluating the effect of aspirin alone or in combination with dipyridamole in patients with TIAs are ongoing.

Coronary Artery Disease

The value of prophylactic aspirin therapy in patients surviving a myocardial infarction remains to be clearly determined. In several randomized, placebo-controlled studies, oral doses of aspirin (300 mg once daily or 900 mg to 1.5 g daily in divided doses) were generally shown not to reduce the risk of death, sudden cardiac death, or nonfatal recurrent myocardial infarction. However, a trend favoring the efficacy of aspirin has been observed. In 2 of these studies, aspirin reduced the risk of nonfatal recurrent myocardial infarction. Further studies are needed to determine the efficacy of aspirin alone or in combination with other platelet-aggregation inhibitors in reducing the risk of death and/or recurrent myocardial infarction in patients surviving a myocardial infarction. Although the efficacy of aspirin or oral anticoagulant therapy (compared to placebo) in reducing the mortality of patients surviving a myocardial infarction has not been clearly established, the results of one comparative study indicate that the effect on mortality and recurrent myocardial infarction of aspirin (1.5 g daily) are about the same as those of oral anticoagulants.

Since no therapeutic effects have been unequivocally shown to date and aspirin has potential adverse effects, many clinicians recommend that prophylactic aspirin therapy should not be used routinely in patients surviving a myocardial infarction. Pending further accumulation of clinical data on aspirin, prophylactic therapy with other agents (e.g., β-adrenergic blockers) should be considered.

In one study in men with unstable angina, low doses of aspirin (324 mg once daily) reportedly reduced the risk of nonfatal myocardial infarction, although not conclusively demonstrated, a reduction in mortality was suggested. Further studies are needed to evaluate the efficacy of aspirin in patients with unstable angina.

Thrombosis in Other Arteries and Arteriovenous Communications

Although aspirin has generally been ineffective in preventing thrombosis after arterial catheterization, a single 600-mg oral dose the evening before surgery has been reported to reduce the incidence of thrombosis following

radial-artery catheterization for surgery. Oral doses of aspirin (325 mg to 1.3 g daily) have been given prophylactically alone or in combination with oral doses of dipyridamole (50–75 mg 3 times daily) to prevent thrombosis in patients undergoing percutaneous transluminal angioplasty of the coronary, iliac, femoral, popliteal, or tibial artery; aspirin and/or dipyridamole are usually given for 2–3 days before and for 3–9 months after the procedure.

Oral doses of aspirin (160 mg once daily) have been shown to be safe and effective in reducing the incidence of thrombosis in silastic arteriovenous shunts in patients undergoing hemodialysis.

Microcirculatory Thrombosis

Aspirin has been used as a component of various regimens for the treatment of thrombotic thrombocytopenic purpura, but its therapeutic value in this condition has been difficult to determine. In one study, combination therapy with aspirin and dipyridamole was considered ineffective and patients receiving the combination had an increased risk of severe bleeding complications; therefore, some clinicians have recommended that aspirin no longer be used in the treatment of thrombotic thrombocytopenic purpura. However, other clinicians believe that platelet-aggregation inhibitors (e.g., aspirin) are useful in the treatment of this condition. The combination of aspirin and dipyridamole has been shown to reduce blood concentrations of circulating platelet aggregates and β-thromboglobulin in patients with scleroderma; however, the long-term effect of such therapy on the disease is not known.

Aspirin has been effective in the treatment of some patients with thrombocytosis associated with a syndrome of spontaneous platelet aggregation and symptoms of digital ischemia.

Prosthetic Heart Valves

Because oral anticoagulant therapy alone does not completely prevent thrombosis in patients with prosthetic heart valves, aspirin or dipyridamole has been used in conjunction with an oral anticoagulant to reduce the incidence of thrombosis in these patients. The combinations appear to be more effective than an oral anticoagulant alone. In 2 studies comparing treatment regimens of an oral anticoagulant alone or in combination with 500-mg or 1-g daily doses of aspirin, patients receiving 1 g of aspirin daily had an increased risk of GI bleeding while those receiving 500 mg daily did not. In another study comparing treatment regimens of an oral anticoagulant alone or in combination with aspirin (500 mg daily) or dipyridamole (400 mg daily), the combination regimen with aspirin was associated with an increased risk of bleeding complications compared to the other regimens. Although some clinicians consider the risk-to-benefit ratio of combination therapy with aspirin acceptable, many others do not. Pending further evaluation of the safety and efficacy of therapy with aspirin and an oral anticoagulant, most clinicians recommend therapy with dipyridamole and an anticoagulant. The value of platelet-aggregation inhibitors alone has not been established; however, some clinicians suggest that combination therapy with aspirin and dipyridamole may be useful in patients unable to tolerate an oral anticoagulant.

Venous Thrombosis

The value of aspirin alone or in combination with dipyridamole in preventing venous thrombosis remains controversial.

Although results of many studies suggest that oral doses of aspirin (1.2–1.5 g daily in divided doses) may reduce the incidence of postoperative venous thrombosis (particularly following hip operations), this has not always been found. For the prevention of postoperative venous thrombosis in patients undergoing major abdominal or thoracic surgery, most clinicians recommend low-dose heparin therapy. However, low-dose heparin prophylaxis is usually ineffective in reducing the incidence of thrombosis after orthopedic surgery, including total hip replacement. Some clinicians recommend aspirin prophylaxis in men undergoing total hip replacement. In one well-controlled study, oral doses of aspirin (600 mg twice daily) were more effective than placebo in reducing the incidence of thrombosis in men (but not in women) following total hip replacement. In another study, aspirin prophylaxis appeared to be effective in patients undergoing total knee replacement. However, further studies are needed to establish the efficacy of aspirin for the prevention of postoperative venous thrombosis following these and other types of surgery. Aspirin has also been used in combination with dihydroergotamine for prevention of postoperative deep-vein thrombosis following major abdominal surgery. Although limited data show that the combination may be more effective than aspirin alone, further study is required to determine the safety, efficacy, and dosage of combination therapy with these drugs.

In one placebo-controlled study, oral doses of aspirin (300 mg 4 times daily) given in combination with oral doses of dipyridamole (25 mg 4 times daily) were reportedly effective in reducing the incidence of thrombosis in patients with recurring venous thrombosis who had decreased platelet survival and were refractory to treatment with oral anticoagulants.

Aspirin has been used alone or in combination with dipyridamole to prevent thrombosis in vein grafts in patients who undergo aortocoronary-artery bypass, but results have been conflicting and inconclusive. However, in one study in which treatment with dipyridamole was started before surgery (and continued) and aspirin was added soon after surgery, the combination therapy appeared to effectively reduce the incidence of vein-graft occlusion during the first 6 months after surgery; the long-term effects remain to be established.

OTHER USES

In some patients, aspirin appears to prevent or reduce adverse GI effects (e.g., vomiting, abdominal pain, diarrhea) associated with food intolerance or radiation therapy. Aspirin also appears to reduce intestinal fluid loss in some patients with gastroenteritis; however, further evaluation of aspirin therapy is necessary and fluid and electrolyte replacement remain the principal therapeutic modalities in the management of this condition. Aspirin has also been reported to effectively prevent flushing episodes in one patient with metastatic renal carcinoma. Although the exact mechanism(s) by which aspirin reduces these adverse GI effects or flushing is not clearly established, the drug may inhibit the synthesis and/or release of prostaglandins which mediate or cause these effects.

Aspirin may occasionally be useful for the treatment of hypercalcemia that occurs with certain types of solid tumors associated with prostaglandin-mediated osteolytic activity; however, other therapies (e.g., IV hydration and diuresis) are usually preferred. In one study in hypercalcemic patients with such tumors (lung carcinoma), aspirin therapy (1.8–4.8 g daily for 5–7 days) reduced serum calcium concentrations and urinary excretion of a metabolite of prostaglandin E; both variables returned to elevated levels 3–4 days after aspirin was discontinued.

Because of its ability to inhibit the synthesis of prostaglandins, aspirin has been used in the treatment of patent ductus arteriosus in premature infants and in the treatment of Bartter's syndrome; however, in both of these conditions, other agents (e.g., indomethacin) appear to be more effective.

Some clinicians have observed a decreased prevalence of cataracts in patients with rheumatoid arthritis, with or without diabetes mellitus, who were treated with aspirin (2.3–2.7 g daily for 8–10 years). Therefore, it has been suggested that aspirin may prevent the development of cataracts; however, this has not been clearly established and further studies are needed. There is no evidence to date that aspirin can reverse cataracts that have already formed.

Aspirin, alone or in combination with dipyridamole, is also being evaluated for potential efficacy in preventing progression of diabetic retinopathy in patients with diabetes mellitus.

Dosage and Administration

Aspirin is usually administered orally, preferably with food or a large quantity (240 mL) of water or milk to minimize gastric irritation. In patients unable to take or retain oral medication, aspirin suppositories may be administered rectally; however, rectal absorption may be slow and incomplete. (See Pharmacokinetics: Absorption.) *Aspirin tablets should not be administered rectally since they are likely to cause irritation and erosion of the rectal mucosa.* Aspirin preparations should not be used if a strong vinegar-like odor is present. (See Chemistry and Stability: Stability.)

If an unpleasant taste or aftertaste, burning in the throat, or difficulty in swallowing occurs with uncoated aspirin-containing tablets, these effects may be reduced with film-coated tablets. Although specific data are not available, these effects are also likely to be reduced with enteric-coated tablets. If gastric irritation and/or symptomatic GI disturbances occur with uncoated aspirin-containing tablets, these effects may be reduced with enteric-coated tablets or extended-release tablets. If a liquid dosage form of aspirin is desired for short-term treatment of pain, an oral solution may be prepared from commercially available effervescent tablets (Alka-Seltzer®). Dosage must be carefully adjusted according to individual requirements and response, using the lowest possible effective dosage.

PAIN AND FEVER

Aspirin should not be used for *self-medication* of pain for longer than 10 days in adults or 5 days in children, unless directed by a physician, since pain of such intensity and duration may indicate a pathologic condition requiring medical evaluation and supervised treatment. Aspirin chewing gum/tablets should not be used for *self-medication* of sore throat pain for longer than 2 days

in adults or children, unless directed by a physician, since prolonged use could cause mucosal erosions in the mouth. Aspirin or buffered aspirin preparations should not be chewed before swallowing for at least 7 days following tonsillectomy or oral surgery because of possible injury to oral tissues from prolonged contact with aspirin particles. In addition, aspirin or buffered aspirin tablets should not be placed directly on a tooth or gum surface because of possible injury to tissues.

Aspirin should not be used in adults or children for *self-medication* of marked fever (greater than 39.5°C), fever persisting longer than 3 days, or recurrent fever, unless directed by a physician, since such fevers may indicate serious illness requiring prompt medical evaluation.

To minimize the risk of overdosage, no more than 5 doses of aspirin should be administered to children for analgesia or antipyresis in any 24-hour period, unless directed by a physician.

For analgesia or antipyresis in adults or children older than 11 years of age, the usual oral or rectal dosage of aspirin is 325–650 mg every 4 hours as necessary, but should not exceed 4 g daily; higher single doses (e.g., 975 mg or 1 g) may be useful for analgesia in some patients. If a rapid response is required, the more slowly absorbed dosage forms (i.e., enteric-coated, extended-release tablets) should not be used. In children 2–11 years of age, the usual oral or rectal dosage for analgesia or antipyresis is 1.5 g/m^2 daily or 65 mg/kg daily, administered in 4–6 divided doses; total daily rectal dose should not exceed 2.5 g/m^2. Alternatively, children may receive the following *approximate* oral or rectal doses every 4 hours as necessary: children 11 years of age, 480 mg; children 9–10 years of age, 400 mg; children 6–8 years of age, 325 mg; children 4–5 years of age, 240 mg; and children 2–3 years of age, 160 mg. Dosage in children younger than 2 years of age must be individualized. Chewable aspirin tablets may be chewed, crushed, and/or dissolved in a liquid, or swallowed whole, followed by approximately 120 mL of water, milk, or fruit juice immediately after administration of the drug.

The usual dosage of aspirin (as chewing gum tablets) for analgesia in adults and children older than 11 years of age is 454 mg, repeated as necessary; total daily dose should not exceed 3.63 g. The chewing gum tablets should be thoroughly chewed for about 15 minutes to ensure adequate dosing and then the gum should be expelled from the mouth and discarded. Children 6–11 years of age may be given 227–454 mg, repeated as necessary, not to exceed 1.82 g daily unless directed by a physician. Children 3–5 years of age may be given 227 mg, repeated as necessary, not to exceed 681 mg daily. Aspirin chewing gum tablets should not be used in children younger than 3 years of age unless directed by a physician; dosage must be individualized.

The usual oral dosage of aspirin as a highly buffered effervescent solution (Alka-Seltzer®) for analgesia in adults and children older than 11 years of age is 648 mg every 4–6 hours as necessary; total dose in any 24-hour period should not exceed 2.59 g. Because of the high sodium content of this preparation (approximately 24 mEq of sodium per 324 mg of aspirin), it should be used with extreme caution, if at all, in patients in whom excessive amounts of sodium may be harmful. The solution is prepared by adding each tablet for oral solution containing 324 mg of aspirin to approximately 90 mL of water; the entire solution must be ingested to ensure adequate dosing. If the solution is not ingested immediately, it should be refrigerated. (See Chemistry and Stability: Stability.) The usual oral dosage for patients 60 years of age or older and children 6–11 years of age is 324 mg every 4–6 hours as necessary, not to exceed 1.3 g in any 24-hour period. Children 3–5 years of age may receive 162 mg every 4–6 hours as necessary, not to exceed 648 mg in any 24-hour period. The preparation should not be used in children younger than 3 years of age unless directed by a physician; dosage must be individualized. In addition, higher than usually recommended dosages of this preparation should not be used unless directed by a physician.

The usual oral dosage of aspirin (as 650-mg extended-release tablets) for analgesia in adults is 650 mg to 1.3 g every 8 hours as necessary, not to exceed 3.9 g daily. For patients who have difficulty swallowing the 650-mg tablets whole, the tablets may be gently broken or crumbled before administration (or in the mouth), but they must *not* be ground up if they are to retain the property of extended release. An 800-mg extended-release aspirin tablet is also commercially available but is indicated for use only in the symptomatic treatment of inflammatory disease; the 800-mg tablet *cannot* be broken or crumbled and must be swallowed whole. Most clinicians believe that extended-release aspirin tablets offer no therapeutic advantage over other types of aspirin tablets; this is particularly true at high dosages since the elimination half-life of salicylate is dose dependent and prolonged at high dosages. However, symptomatic GI disturbances and/or occult GI bleeding may be reduced with extended-release tablets.

INFLAMMATORY DISEASES

For the symptomatic treatment of rheumatoid arthritis, osteoarthritis, or other polyarthritic or inflammatory conditions, the usual initial adult dosage of aspirin is 2.4–3.6 g daily, administered in divided doses. When necessary, dosage is generally increased by 325 mg to 1.2 g daily no more frequently than at weekly intervals. The usual adult maintenance dosage is 3.6–5.4 g daily; however, higher dosages may be necessary. Dosage should be adjusted according to the patient's response, tolerance, and serum salicylate concentration.

For the symptomatic treatment of juvenile arthritis, the usual initial dosage is 60–90 mg/kg daily in children weighing 25 kg or less, or 2.4–3.6 g daily in children weighing more than 25 kg, administered in divided doses. Alternatively, some clinicians recommend an initial dosage of 1.5 g/m^2 daily, administered in divided doses. When necessary, dosage is generally increased by 10 mg/kg daily no more frequently than at weekly intervals. The usual maintenance dosage is 80–100 mg/kg daily; up to 130 mg/kg daily may be required in some children. Although some clinicians have reported a high incidence of chronic intoxication in children receiving 90–100 mg/kg daily, this has not been found by many others. However, it appears that dosages of 100 mg/kg daily or greater should not be used in children weighing more than 25 kg. Based on body surface area, dosage should generally not exceed 3 g/m^2 daily. Dosage should be adjusted according to the patient's response, tolerance, and serum salicylate concentration. In addition to potentially reducing adverse GI effects, some clinicians suggest that enteric-coated tablets may be swallowed more easily by children and may therefore result in increased compliance.

Because of the prolonged elimination half-life of salicylate at high dosages, at least 5–7 days are generally required to achieve steady-state serum salicylate concentrations in the treatment of inflammatory diseases. Therefore, some clinicians have suggested that loading-dose regimens of aspirin may be useful to more rapidly attain serum concentrations associated with an anti-inflammatory effect. In one small study, healthy individuals were given oral doses of 650 mg of aspirin every 4 hours for 4 days (conventional-dose regimen) or two 1.3-g doses 4 hours apart followed 2 hours later by initiation of a maintenance dosage of 650-mg oral doses every 4 hours through 4 days (loading-dose regimen). In this study, the time required to reach a serum salicylate concentration of 150 µg/mL was approximately 15 hours with the loading-dose regimen and approximately 48 hours with the conventional-dose regimen; serum salicylate concentrations were higher during the first 36 hours with the loading-dose regimen. However, the actual clinical importance of any difference between these regimens in patients with inflammatory diseases is not known; further evaluation of loading-dose regimens in such patients is needed.

RHEUMATIC FEVER

For the symptomatic treatment of rheumatic fever, dosage and duration of aspirin therapy are generally determined by the severity and duration of acute manifestations. For maximal suppression of acute inflammation, the usual initial dosage of aspirin is 4.9–7.8 g daily in adults and 90–130 mg/kg daily in children, administered in divided doses every 4–6 hours. Patients with only polyarthritis and fever usually respond to lower dosages. Subsequent dosage should be adjusted according to the patient's response, tolerance, and serum salicylate concentration. The initial dosage is generally administered for up to 1–2 weeks, then decreased to approximately 60–70 mg/kg daily for 1–6 weeks or as long as necessary, and then gradually withdrawn over 1–2 weeks. Various aspirin regimens have been suggested depending on the severity of acute manifestations, and the clinician should consult published protocols for more information on specific dosages and schedules of administration.

In patients with carditis and cardiomegaly or congestive heart failure who are treated with corticosteroids, aspirin therapy is usually initiated as steroid therapy is gradually withdrawn. In these patients, some clinicians recommend an aspirin dosage of 60 mg/kg daily, administered in divided doses. High dosages should be used with caution in patients with carditis since congestive heart failure or pulmonary edema may be precipitated. Aspirin is usually administered for approximately 2–4 weeks after steroids are discontinued. Only extremely severe clinical rebounds of rheumatic activity require reinstitution of therapy, in which case aspirin is administered in the usual dosage for 3–4 additional weeks.

THROMBOSIS

For reducing the risk of recurring transient ischemic attacks (TIAs) and stroke or death in men (and possibly in women) who have had single or multiple TIAs, the usual oral dosage of aspirin is 1.3 g daily, administered in 2 or 4 divided

doses. Only uncoated or film-coated, plain aspirin or buffered aspirin tablets or capsules should be used since differences in the bioavailability of unhydrolyzed aspirin might theoretically affect antithrombotic efficacy; however, no data are available comparing different preparations in this regard. Lower dosages may also be effective (e.g., 40–150 mg every 24–48 hours), but further evaluation is needed.

Aspirin has also been used in varying dosages alone or in combination with other platelet-aggregation inhibitors (e.g., dipyridamole) or oral anticoagulants for prophylaxis of other thrombosis-related conditions. (See Uses: Thrombosis.)

For further information on chemistry and stability, pharmacology, pharmacokinetics, uses, cautions, chronic toxicity, acute toxicity, drug interactions, laboratory test interferences, and dosage and administration of aspirin, see the Salicylates General Statement 28:08.04.

Preparations

ASPIRIN

Oral

Capsules

325 mg

A.S.A.® Pulvules®, Lilly

Capsules (containing enteric-coated aspirin particles)

325 mg

Ecotrin® Duentric®, Menley & James; *Encaprin®*, Norwich Eaton

500 mg

Ecotrin® Maximum Strength Duentric®, Menley & James; *Encaprin® Maximum Strength*, Norwich Eaton

Tablets

324 mg*

325 mg*

A.S.A.®, Lilly; *Empirin®*, Burroughs Wellcome; *Norwich® Aspirin*, Procter

487.5 mg

Hipirin®, Blaine

500 mg*

Norwich® Aspirin Extra Strength, Procter

650 mg*

Tablets, chewable

65 mg

Aspirin Children's, Lannett

81 mg

Bayer® Children's Chewable Aspirin, Glenbrook; *St. Joseph® Aspirin for Children*, Plough

Tablets, chewing gum

227 mg

Asperguin®, Plough

Tablets, enteric-coated

324 mg*

325 mg*

A.S.A. Enseals®, Lilly; *Cosprin® 325*, Glenbrook; *Ecotrin® Duentric®*, Menley & James

500 mg*

APF® Arthritis Pain Formula®, Whitehall; *Ecotrin® Maximum Strength Duentric®*, Menley & James

650 mg*

A.S.A. Enseals®, Lilly; *Cosprin® 650*, Glenbrook

975 mg

Easprin®, Parke-Davis

Tablets, extended-release

650 mg

Arthritis Bayer® Timed-Release Aspirin (scored), Glenbrook; *Measurin®*, Winthrop-Breon; *Vetin®*, Verex

800 mg

Zorprin®, Boots

Tablets, film-coated

325 mg

Bayer® Aspirin, Glenbrook

500 mg

Bayer® Aspirin Maximum Strength, Glenbrook

Rectal

Suppositories

60 mg*

65 mg*

120 mg*

125 mg*

130 mg*

195 mg*

200 mg*

300 mg*

325 mg*

A.S.A.®, Lilly

600 mg*

650 mg*

A.S.A.®, Lilly

1.2 g*

*available in unspecified dosage

ASPIRIN WITH BUFFERS

Oral

Capsules

324 mg with buffers

Bufferin®, Bristol-Myers

500 mg with buffers*

Bufferin® Extra-Strength, Bristol-Myers

Tablets

324 mg with buffers*

Asperbuf®, Bowman; *Bufferin®*, Bristol-Myers

325 mg with buffers*

Ascriptin®, Rorer; *Ascriptin® A/D*, Rorer; *Bufferin®*, Mallard; *Speedrin®*, Columbia

486 mg with buffers*

Arthritis Pain Formula®, Whitehall; *Bufferin® Arthritis Strength*, Bristol-Myers

500 mg with buffers*

Bufferin® Extra-Strength, Bristol-Myers

650 mg with buffers

Salagen® (scored), Lannett

Tablets, film-coated

500 mg with buffers

Cama® Inlay-Tab®, Dorsey

Tablets, for oral solution

324 mg

Alka-Seltzer® Effervescent Pain Reliever and Antacid (with citric acid and sodium bicarbonate 1.9 g), Miles

*available in unspecified dosage

ASPIRIN COMBINATIONS

Oral

Capsules

250 mg with Acetaminophen 250 mg and Caffeine 65 mg

Excedrin®, Bristol-Myers

325 mg with Butalbital 50 mg and Caffeine 40 mg

Fiorinal® (C-III), Sandoz

325 mg with Butalbital 50 mg, Caffeine 40 mg, and Codeine Phosphate 30 mg

Fiorinal® with Codeine No. 1 (C-III), Sandoz

325 mg with Butalbital 50 mg, Caffeine 40 mg, and Codeine Phosphate 15 mg

Fiorinal® with Codeine No. 2 (C-III), Sandoz

325 mg with Butalbital 50 mg, Caffeine 40 mg, and Codeine Phosphate 30 mg

Fiorinal® with Codeine No. 3 (C-III), Sandoz

325 mg with Propoxyphene Hydrochloride 65 mg

Darvon® with A.S.A.® Pulvules® (C-IV), Lilly

356.4 mg with Caffeine 30 mg and Dihydrocodeine Bitartrate 16 mg

Synalgos®-DC (C-III), Ives

356.4 mg with Caffeine 30 mg

Synalgos®, Ives

380 mg with Caffeine 30 mg and Codeine Phosphate 30 mg

A.S.A.® and Codeine Compound No. 3 Pulvules® (C-III), Lilly

ALASKA STATE LEGISLATURE
HOUSE OF REPRESENTATIVES
RESEARCH AGENCY

P.O. Box Y, State Capitol
Juneau, Alaska 99811-3100
Mail Stop 3100
(907) 465-3991

P

March 3, 1987

TO: Representative Pat Pourchot

FROM: Penelope Weyhrauch
Legislative Analyst

RE: The Physiological Effects of Marijuana, Alcohol, Tobacco, Aspirin, and Salt
Research Request 87.155

Please check the appropriate box and return to Mail Stop 3100 or the above mailing address.

( ) I approve the release of this information.

( ) I approve the release of this information, but remove my name.

( ) Keep Confidential.

_____ _____
Date Signature

To assist us in improving the quality of our research services, we would appreciate your response to the following questions. Please be assured that we will take your comments seriously in performing future research for you.

Was the information objective?

Was it clearly written?

Did it provide answers to (or, at least, useful information on) all the questions you posed?

Was the research completed and delivered to you in a timely manner?

TABLE 2
A Comparison of the Ingredients and Effects of Marijuana and Alcohol

	Marijuana	Alcohol
Active constituent	delta-9-tetrahydrocannabinol (THC)	ethyl alcohol (ethanol)
Excretory product	dihydroxy-THC and others	$C0_2$ and H_20
Pharmacologic class	sedative-hallucinogen	sedative-anesthetic
Half life	24-52 hours	½-2 hours
LD_{50}	human	500 ml, human
Solubility	lipophilic	hydrophilic
Tolerance	proven	proven
Psychological dependence	proven at high doses	proven
Physical dependence	slight	proven
Heart rate	increased	unchanged
Respiration	unchanged	unchanged
Blood pressure	slight decrease	unchanged with acute use, chronic use elevates
Temperature	slight decrease	slight decrease at high doses
Brain	intoxication at high doses	intoxication at high doses
Blood vessels	variable dilation	dilation
Lungs	irritant, contains carcinogens	no effect
Heart	no known effect	toxic, chronically
Gastrointestinal tract	no effect	inflammatory changes
Liver and pancreas	no effect	inflammatory changes
Endocrine glands	variable	variable
Gonads	changes reported	changes reported
Conjunctiva (white of eyes)	reddening	slight reddening
Nerves	unchanged	injury with chronic use
Adrenals	release of corticotropins	release of corticotropins
Pupil size	slight constriction	no effect
Teratogenic effect	not known	fetal alcohol syndrome
Intraocular pressure	reduced	no effect
Memory	impaired immediate recall	impaired transfer to long term memory on high dose
Time perception	overestimation	no effect
Food intake	may increase	increase or decrease
Food value	no effect	7 calories/gram
Speech	blocking	slurred
Sleep pattern	blocks REM sleep	blocks REM sleep
Driving skills	impaired	impaired

Source: Sidney Cohen, "Marijuana and Alcohol," American Council for Drug Education, 1982, pp. 11-12.

ALASKA STATE LEGISLATURE
HOUSE OF REPRESENTATIVES
RESEARCH AGENCY

P.O. Box Y, State Capitol
Juneau, Alaska 99811-3100
Mail Stop 3100
(907) 465-3991

March 3, 1987

MEMORANDUM

TO: Representative Pat Pourchot

ATTN: Jeannie Larson

FROM: Penelope Weyhrauch
Legislative Analyst

RE: **The Physiological Effects of Marijuana, Alcohol, Tobacco, Aspirin, and Salt**
Research Request 87.155

You asked for a comparison of the physiological effects of marijuana, alcohol, tobacco, aspirin, and salt. I was unable to find a clinical comparison of these substances; this memorandum discusses each of the substances on which you requested information and compares the effects and/or ingredients of marijuana to tobacco and alcohol.

Marijuana

Acute Short-Term Effects. Marijuana affects the intellectual and psychomotor processes of humans. Intellectual impairment has been documented in tests of: reading comprehension; concept formation; speech; choice reaction time (a reaction-time task in which the response depends on rapidly discriminating between choices); and the ability to repeat in forward and backward order a succession of digits, and to mentally make a succession of repeated subtractions. There is evidence that suggests that marijuana use impairs driving ability and related skills.[1] Marijuana also produces some acute short-term effect on the cardiovascular and respiratory systems.

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[1] "Marijuana Research Findings: 1980", Research Monograph Series 31, National Institute on Drug Abuse, pp. 15, 16.

CORRECTION

THIS DOCUMENT
HAS BEEN REPHOTOGRAPHED
TO ASSURE LEGIBILITY

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Chronic Effects. There is no substantial evidence which exposes the possible long-term effects of marijuana. The National Research Council stated: "We agree with the conclusion that long-term heavy marijuana use will be shown to result in measurable damage to health, just as long-term chronic tobacco and alcohol use have proven to cause such damage. At this time, however, our judgment as to behavioral and health-related hazards is that the research has not established a danger both large and grave enough to override all other factors affecting a policy decision."[2]

Pulmonary Effects. There is no direct evidence that links the smoking of marijuana with lung cancer. Recent studies, however, showed that when cannabis residuals are applied to the skin of animals, the cannabis "tar" produced tumors. Marijuana has also been found to contain larger amounts of cancer-producing hydrocarbons than tobacco smoke. Benzopyrene, a known cancer-producing chemical found in tobacco smoke, has been reported to be 70 percent more abundant in marijuana smoke. Several clinical studies of marijuana users have reported symptoms similar to those of laryngitis, cough, hoarseness and bronchitis. These symptoms resembled those experienced by heavy tobacco smokers.[3]

Reproductive and Chromosomal Effects. According to the National Institute on Drug Abuse (NIDA), "...the evidence is consistent--cannabis causes decreases in the weight of organs such as testes and ovaries, as well as altering various hormone levels that are involved in reproduction and lactation." The NIDA also stated that "...although there were early reports of increases in chromosomal breaks and abnormalities in human cell cultures, more recent results have been inconclusive."[4]

Other Effects. Studies have found that a significant increase in heart rate occurs after smoking. Changes found in the functioning of the heart, however, appeared to be temporary and were free of adverse consequences. Additional evidence showed that "...in patients with already impaired heart functions, use of marijuana may precipitate chest pain more rapidly and following less effort than tobacco cigarettes." Virtually all the studies completed up to 1979 showed no evidence of chronically impaired neuropsychologic test performance.[5]

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[2]"An Analysis of Marijuana Policy," National Research Council, Committee on Substance Abuse and Habitual Behavior, Commission on Behavioral and Social Sciences and Education, 1982, pp. 5, 6.

[3]"Marijuana Research Findings: 1980," pp. 18, 19.

[4]"Marijuana Research Findings: 1980," p. 23.

[5]"Marijuana Research Findings: 1980," pp. 22, 25.

Tobacco

There is conclusive evidence that cigarette smoking is the most prominent cause of lung cancer, and is also a major factor in deaths from heart disease, chronic bronchitis, emphysema, and other diseases. There is also evidence of increased illness and a notable shortening of life expectancy among smokers.[6] According to the National Organization for the Reform of Marijuana Laws, tobacco was responsible for more deaths (in 1979) than alcohol, aspirin, caffeine and marijuana put together (Attachment A).

Both marijuana smoking and tobacco smoking draw smoke into the lungs, where it can harm the cells that line the airways (trachea, nasopharynx, bronchi, and alvoloi) and impair such cells as lung macrophages, which are part of the immune system. While continued exposure to tobacco smoke has been proven to cause a high risk of chronic bronchitis and/or carcinoma of the lungs, there is no substantial evidence that the smoking of marijuana presents similar risks.[7] Contemporary information that exists in regard to marijuana's effects on the lungs is confounded by the fact that most marijuana smokers are also tobacco smokers.[8]

The materials in tobacco cigarette and marijuana cigarette smoke are compared in Table 1. Toxic substances, such as carbon monoxide, hydrogen cyanide, and nitrosamines occur in similar concentrations in tobacco and marijuana smoke; so do the amount of the particulate material known as "tars." According to the study which accompanies Table 1, "...It is not easy to compare the toxicity of a given number of marijuana cigarettes to a given number of tobacco cigarettes. There are general similarities in the composition of the smoke, but the variations in composition of both tobacco and marijuana cigarettes and differences in smoking techniques make simple extrapolations of risks of tobacco versus marijuana smoking not valid."[9]

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[6]Edward M. Brecher and the Editors of Consumer Reports, "Licit and Illicit Drugs," the Consumers Union Report on Narcotics, Stimulants, Depressants, Inhalants, Hallucinogens and Marijuana--including Caffeine, Nicotine and Alcohol, 1972.

[7]"An Analysis of Marijuana Policy," 1982, p. 5.

[8]"Marijuana and Health," Report of a Study by a Committee of the Institute of Medicine, Division of Health Sciences Policy, 1982, p. 57.

[9]"Marijuana and Health," p. 27.

TABLE 1

TABLE 3 Marijuana and Tobacco Reference Cigarette Analysis of Mainstream Smoke

	Marijuana Cigarette (85 mm)	Tobacco Cigarette (85 mm)
A. Cigarettes		
Average weight, mg	1115	1110
Moisture, percent	10.3	11.1
Pressure drop, cm	14.7	7.2
Static burning rate, mg/s	0.88	0.80
Puff number	10.7	11.1
B. Mainstream smoke		
I. Gas phase		
Carbon monoxide, vol. percent	3.99	4.58
mg	17.6	20.2
Carbon dioxide, vol. percent	8.27	9.38
mg	57.3	65.0
Ammonia, ug	228	199
HCN, ug	532	498
Cyanogen $(CN)_2$, ug	19	20
Isoprene, ug	83	310
Acetaldehyde, ug	1200	980
Acetone, ug	443	578
Acrolein, ug	92	85
Acetonitrile, ug	132	123
Benzene, ug	76	67
Toluene, ug	112	108
Vinyl chloride, ng[a]	5.4	12.4
Dimethylnitrosamine, ng[a]	75	84
Methylethylnitrosamine, ng[a]	27	30
pH, third puff	6.56	6.14
fifth puff	6.57	6.15
seventh puff	6.58	6.14
ninth puff	6.56	6.10
tenth puff	6.58	6.02
II. Particulate phase		
Total particulate matter, dry, mg	22.7	39.0
Phenol, ug	76.8	138.5
o-Cresol, ug	17.9	24
m- and p-Cresol, ug	54.4	65
Dimethylphenol, ug	6.8	14.4
Catechol, ug	188	328
Cannabidiol, ug	190	-
Δ^9-Tetrahydrocannabinol, ug	820	-
Cannabinol, ug	400	-
Nicotine, ug	-	2850
N-Nitrosonornicotine, ng[a]	-	390
Naphthalene, ug	3.0	1.2
1-Methylnaphthalene, ug	6.1	3.65
2-Methylnaphthalene	3.6	1.4
Benz(a)anthracene, ng[a]	75	43
Benzo(a)pyrene, ng[a]	31	21.1

[a]Indicates known carcinogens.
SOURCES: Hoffmann et al., 1975, 1976; Brunnemann et al., 1976, 1977.

Source: "Marijuana and Health," Report of a Study by a Committee of the Institute of Medicine Division of Health Sciences Policy, 1982, page 17

Alcohol

Alcohol is a central nervous system depressant. Although its occasional use appears to be relatively harmless, excessive or long-term use can be harmful and even deadly. Alcohol accounts for roughly 75,000 deaths annually in the United States. About two-thirds of these are caused by trauma (accidents, suicide, and homicide) and one-third are caused by acute and chronic alcohol-related illness.[10]

Alcohol users have an increased risk for liver cirrhosis, acute pancreatitis, and cancers of the liver, esophagus, larynx, and mouth. Damage from alcohol abuse can occur in the brain and in the peripheral nerves. Alcohol also has an effect on the endocrine system and has properties which can cause genetic and birth defects.[11]

A comparison of some of the effects of alcohol and marijuana is provided in Table 2.[12] Matt Felix, Coordinator of the State Office of Alcoholism and Drug Abuse, said that the detrimental effects of marijuana are innocuous as compared with the effects of alcohol. He said that alcohol is more acceptable in the United States because it has been around longer.

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[10]"Medicine for the Layman," United States Department of Health and Human Services, Public Health Service, National Institute of Health, p. 20.

[11]"Medicine for the Layman," pp. 21-24.

[12]Sidney Cohen, M.D. and Phyllis J. Lessin, "Marijuana and Alcohol," Neuropsychiatric Institute, Center for the Health Sciences, University of California at Los Angeles, American Council for Drug Education, 1982.

Aspirin

Aspirin can cause heartburn, dyspepsia, stomach discomfort, nausea and vomiting. It can also cause stomach ulcers, erosion of and bleeding from the lining of the stomach, kidney dysfunction, and gastrointestinal hemorrhage. When aspirin is taken over a long period of time, there is sometimes enough loss of blood in the lining of the stomach to cause iron-deficiency anemia. Studies have also shown that aspirin may pose special risks for certain groups--including pregnant women, people with bleeding disorders, those with ulcers and children with viral illnesses.[13] Aspirin leads over-the-counter drugs as a cause of adverse reactions leading to hospitalization and is a major cause of child poisoning.[14]

Excessive amounts of ingested aspirin is considered a possible cause of malformations in fetuses and is believed to create the danger of infant mortality. A study of Australian women showed that the infants of aspirin users had significantly lower birth weights and were more likely to die around the time of birth. Studies also associate the use of aspirin with significant increases in post maturing (the birth of an overdeveloped infant), length of time spent in labor, the likelihood of a complicated delivery, and increased hemorrhaging in both mothers and newborn infants.[15]

Caffeine

Caffeine stimulates the central nervous system, makes the heart beat faster, speeds up metabolism, promotes secretion of stomach acid, and steps up the production of urine. It also widens some blood vessels, narrows others, and increases the capacity of muscular work. Studies show that coffee (decaffeinated as well as regular) can stimulate stomach-acid secretion, thus, physicians commonly advise ulcer patients to avoid its consumption.[16] Caffeine is also addictive, producing withdrawal effects at some dosages. These effects include headaches, irritability, inability to work effectively, nervousness, restlessness and lethargy.[17]

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[13]Children with viral illnesses such as chicken pox and the flu are susceptible to Reyes Syndrome if they take aspirin. Reyes Syndrome causes the brain to swell, causes a fatty infiltration of the liver and can cause death.

[14]Flora Taylor, "All About Aspirin," Consumers Research Magazine, August 1984, p. 21.

[15]"All About Aspirin," p. 22.

[16]"Is Coffee Safe to Drink?," Consumer Reports Magazine, May 1985, pp. 267-268.

[17]"Licit and Illicit Drugs," p. 22.

According to Consumer Reports Magazine, although studies suggest that coffee can contribute to higher blood cholesterol levels, there is as yet no evidence that reducing coffee consumption will help lower cholesterol levels or prevent them from rising. Researchers in a study conducted in 1985 noted that "...the preponderance of current evidence 'fails to support' a relationship between coffee and coronary disease." Consumer Reports also stated that no well-controlled studies of human birth defects have linked any common malformations to caffeine intake, and that studies linking coffee consumption with cancer have produced inconsistent and conflicting findings.[18]

Salt

Research has linked excessive consumption of salt to hypertension (high blood pressure) and its potentially fatal consequences, heart and kidney disease and strokes. The main precipitant of hypertension is the mineral sodium, which is 40 percent of the substance of salt. Hypertension afflicts an estimated 34 million Americans, usually producing no symptoms until the signs of permanent organ damage suddenly appear as a chronic illness or death.[19]

I hope this information is helpful to you. If you have any questions or would like additional information, please contact our agency.

Attachment

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[18]"Is Coffee Safe to Drink?," pp. 267-268.

[19]Jane Brody, "Jane Brody's Nutrition Book--A Lifetime Guide to Good Eating for Better Health and Weight Control by the Personal Health Columnist of the New York Times," 1981, p. 199.

ATTACHMENT A

"HOW DANGEROUS IS MARIJUANA . . . IN *COMPARISON* TO OTHER SUBSTANCES?"

According to World Almanacs, Life Insurance Actuarial (death) Rates, and the last 12 years of the U.S. Surgeon General's Reports, Americans DIE, directly or primarily, from the following *(selected)* causes per year Nationwide. *(Figures are for 1979 from the Federal Government's Bureau of Mortality Statistics, and NIDA, the last complete year at the time of this writing.)*

TOBACCO . . . . . 200,000 to 300,000

ALCOHOL *(not including 50% of all highway deaths and 65% of all murders)* . . . . . 18,951 to 130,000

ASPIRIN *(including deliberate overdose)* . . . . . 180 to 1,000 plus

CAFFEINE *(from stress, ulcers, and triggering irregular heartbeats, etc.)* . . . . . 1,000 to 10,000

OVERDOSE *(deliberate or accidental) from prescribed legal or patent medicines and/or mixing with alcohol e.g., Valium/alcohol* . . . . . 7,101 to 21,000

OVERDOSE *(deliberate or accidental) from all illegal drugs* . . . . . 981 to 3,600

MARIJUANA *(including overdose)* . . . . . — 0 —

Marijuana users also have the same or lower incidence of murders and highway deaths and accidents than the general non-marijuana using population as a whole. *Crancer Study, UCLA;* U.S. Funded *($6 million),* Jamaican Study(s) 1st and 2nd, 1968 to 1974; Costa Rican Studies, 1980 to 1982; et al.

LOWEST TOXICITY

100% of the studies done at dozens of American universities and research facilities show pot toxicity does not exist. Medical history does not record anyone dying from an overdose of marijuana *(UCLA, Harvard, Temple, etc.)*

Official Actions

American Psychiatric Association

1400 K Street, N.W.
Washington, D.C. 20005
Telephone: (202) 682-6000

Position Statement on Psychoactive Substance Use and Dependence: Update on Marijuana and Cocaine

This statement is an adjunct to the position statement on substance abuse published in the June 1981 issue of the American Journal of Psychiatry, *which emphasizes diagnosis and treatment. It replaces the position statement on marijuana laws published in the May 1979 issue of the* American Journal of Psychiatry. *The statement was prepared by the Committee on Drug Abuse[a] of the Council on Psychiatric Services and was approved by the Assembly in November 1986 and by the Board of Trustees in December 1986.*

The misuse of psychoactive substances is the nation's foremost public health challenge. The use and abuse of alcohol, cigarettes, illicit drugs (heroin, cocaine, marijuana, etc.), and licit drugs (sedatives and tranquilizers) are by far the largest cause of preventable and premature illness, disability, and death in our society. The annual economic cost of alcohol and drug abuse has been estimated to be $136 billion, over four times that of cancer and nearly a third greater than that of cardiovascular disease (1). Illicit drug use has increased so rapidly over the past 25 years that it may be difficult for someone over age 50 to comprehend the extent to which drugs have permeated our society. Experience with illicit psychoactive drugs was restricted to 2% or less of the population in most areas of the country in the early 1960s (2). In contrast, the 1982 household survey (3) found that almost a third of the household population in the United States age 12 and older had had some experience with illicit drugs. Almost 60 million household residents had tried marijuana, and an estimated 20 million were current users. In 1982, it was estimated (4) that over 20 million had tried cocaine and over 4 million were current users. The prevalence of cocaine use and abuse has increased dramatically in the ensuing 4 years (4).

Illicit drug use is most prevalent in young adults. Typically, children begin experimenting with drugs of abuse by trying alcohol and cigarettes in early adolescence. By the time they complete secondary school, they have established attitudes toward drugs and patterns of use that will carry them through much of their lives. Most adults addicted to nicotine through smoking cigarettes established regular smoking in their teens. Adult users of cocaine and opiates generally began drug use in adolescence and may have been heavy marijuana users (5). In addition to exposing themselves to the risks of drug use (automobile accidents, overdose, or impaired physical, emotional, and psychological development), adolescents are establishing attitudes toward and actual patterns of use that have profound long-term consequences on health. By the time they graduate, more than half (54%) of high school seniors have tried marijuana and a fourth (26%) are current users. Cocaine use tends to begin a few years later than marijuana use, and heavy marijuana use is an important risk factor for cocaine use. Nevertheless, cocaine use now is increasing among our high school population. In the 1985 national survey of high school seniors (6), it was found that 17% had tried cocaine and almost 7% were current users.

In addition to statistics on the prevalence of use, there are now data from National Institute of Mental Health (NIMH) catchment area studies (7) on the lifetime prevalence of substance abuse disorders, which was found to vary from 15.0% to 18.1% among the three sites reported. These rates were significantly higher than the lifetime prevalence of any other group of disorders (except for phobic disorders at one site).

SOCIAL CONSEQUENCES OF USE OF MARIJUANA AND OTHER DRUGS

Young people may use drugs in an attempt to alleviate problematic family relationships. Over the short term, drugs may allow the young person temporarily to ignore intrafamilial strife, including developmental adjustments between child and parents and among siblings. Regular or heavy drug use undermines the adolescent's ability to work through these problems with other family members, thereby exacerbating family problems over the long term. The heavy drug user may withdraw socially from other family members, refuse to consider their needs and concerns, and put his or her own needs above those of the family. Theft from other family members (to obtain drugs) and lying (to hide drug use) undermine the trust necessary for coexistence within the family. Angry outbursts, property destruction, and intrafamily violence can ensue. Alienation of the drug user from the family, once present, is difficult to repair (8). Adult substance abusers also exert powerful effects on their families. Families react variably but often go through stages of denial, overprotection, personal mental illness, and family disruption. The effects on children in such families have been so profound that a national movement, the Adult Children of Alcoholics, has recently emerged to provide support and understanding (9–11).

Heavy drug use can precipitate financial problems in two ways. First, drugs themselves cost money; drug expenses are proportional to the cost of the drug, frequency of use, and dose consumed. Such costs mount as tolerance develops, habitual use becomes established, and larger amounts of drug are consumed more often. A second source of financial problems is unemployment or job loss. Early drug use may seem to facilitate work by alleviating fatigue or boredom or helping the user tolerate work-related stresses. Eventually, continued drug use undermines the person's energy, ambition, concentration, problem-solving abilities, performance, productivity, and social skills in dealing with co-workers and supervisors. Drug-induced paranoia, if present, further exaggerates interpersonal dissensions. In addition to individual financial loss, theft and unpaid loans from other family members can cause financial difficulties for the entire family.

The heavy drug user may resort to criminality to financially support the drug habit. Theft and illicit drug selling are the most

[a]The Committee on Drug Abuse includes Edward Kaufman, M.D. (chairperson), Edward Khantzian, M.D., Joseph Westermeyer, M.D., Dorynne Czechowicz, M.D. (consultant), Steven Mirin, M.D. (consultant), and Roger Meyer, M.D. (former member).

common illegal activities, but prostitution, robbery, and drug smuggling also occur. Easy money from criminal behavior impedes later rehabilitation, since the youthful person has been learning criminality rather than a licit occupation during this critical development period. Learning a job skill or profession requires hard work, willingness to make a commitment and risk failure, and learning responsibility, tasks not easily accomplished. Frustration, anxiety, and fear result to a greater or lesser extent, feelings that marijuana, cocaine, and other drugs can alleviate temporarily. Continued drug use undermines the persistence and industriousness needed to succeed at this developmental task. Drug intoxication and, later, withdrawal, impair the ability to concentrate, synthesize, and organize material, learn new material, apply general principles to specific problems, exert judgment in complex tasks and situations, and make timely decisions (12).

In developing friendships and, later, intimacy with persons of the opposite sex, most youthful persons experience anxiety, embarrassment, and fear of rejection. They may believe that drugs can relieve these aversive feelings as well as alleviate premature ejaculation (in males) and vaginismus (in females). However, prolonged heavy use can reverse these temporary gains in sexual performance, leading to anhedonia, amenorrhea, impotence, and rejection by a sexual partner (13). The lack of judgment seen in young drug and alcohol users often results in teenage pregnancy.

Adolescence is the time to acquire hobbies, sports, and other avocations that may last decades, even a lifetime (14). By and large, drug use does not enhance these activities. Drug use may in fact lead to abandonment of these pursuits and may intensify social isolation. Instead, the drug user pursues activities that focus on the drug use experience and that tend to be banal and boring if done without drug use. Thus, without drugs, the chronic user may be bored and at a loss for stimulating and rewarding activities. Recreational pastimes usually require a period of learning and acquiring skills, another lengthy process that is abandoned with drug use. Drug use during activities involving rapid psychomotor coordination, speed, and judgment (e.g., driving a car or motor boat, water or snow skiing) places the intoxicated person at risk of harming self or others.

In the process of becoming an adult, an adolescent learns to accept responsibility and cope with adversity. Maturation demands a focus outside oneself, task orientation, and the ability to delay gratification for a time. This personality development is impaired by the use of drugs, which furthers an egocentric and present-oriented attitude. If regular drug use began early in adolescence and was continued over several years, the recovering abuser often has the personality characteristics and maturation level of a much younger person (15). It is important to note that alcohol and cigarettes are "gateways," predecessors of marijuana use, which is in turn a predecessor of other drug use and abuse (16).

CONSEQUENCES OF MARIJUANA USE

General Medical Consequences

Two distinguished independent scientific groups separately have reported on marijuana in the past 6 years. The Institute of Medicine, National Academy of Sciences, prepared a report on marijuana and health that was published in 1982 (17). The Addiction Research Center, World Health Organization, prepared a report on the Conference of Adverse Health and Behavioral Consequences of Cannabis, which was published in 1981 (18). Both reports concluded that cannabis has both known and suspected health hazards that should be of serious national concern.

The health consequences of chronic marijuana use depend to some extent on the frequency, duration, and intensity of use, the age at which use begins, and biopsychosocial characteristics of the user, which may contribute to risk in still unspecified ways. For example, not all individuals who smoke tobacco cigarettes will go on to develop carcinoma of the lung, but the risk of this disorder is much greater among smokers, and the relative risk increases with the intensity, frequency, and chronicity of use.

Since the two aforementioned studies were published, further evidence of the harmful effects of marijuana has been established. In particular, the clearest evidence for harmful changes in physical health involves the pulmonary system (19–22 and a December 1979 report of the AMA Council on Scientific Affairs). Bronchitis and related inflammatory changes have been shown repeatedly. More recently, it has been shown that marijuana smoking causes a significant reduction in the gas-diffusing capacity of the lung. Moreover, there is considerable evidence to suggest that long-term use, like tobacco smoking, may lead to pulmonary cancer. Indeed, marijuana has up to 50% more aryl hydrocarbons in its smoke than tobacco, and high levels of these are associated with susceptibility to bronchogenic carcinoma. Many marijuana smokers also smoke tobacco, and it is postulated that the combined effects of smoking both substances may substantially increase the risk of cancer. Most important are the profound acute and chronic psychosocial, cognitive, and behavioral effects associated with marijuana use by youth. Acute toxicity is accompanied by negative effects on learning and memory, as well as psychomotor impairment. The typical effects of cannabis resemble a transient acute brain syndrome; they include deficits in attention span, concentration ability, short-term memory, information processing, and the performance of complex perceptual motor tasks. Thus, accidental injury to persons driving motor vehicles, piloting airplanes, or operating heavy machinery while intoxicated with marijuana is of special concern.

Even when marijuana use is discontinued, the memory loss continues for 3 to 6 months. This particularly affects adolescents who have been having difficulties in school. This consequent negative reinforcement leads them to return to marijuana use.

Specific Psychiatric Concerns

Psychiatrists have described three general complications associated with cannabis: acute adverse reactions, flashbacks, and prolonged reactions. Acute reactions are characterized by errors in judgment and confusion, which may be followed by an amnesic period. These are dose related and fall within the general category of deliria (23, 24). Anxiety may progress to acute pain reaction with overwhelming anxiety and a fear of losing control in response to drug-induced symptoms. Factors related to setting and/or personality may lead to severe anxiety.

Flashbacks refer to brief, spontaneous recurrences of mental states experienced during marijuana intoxication that occur sometime after the last drug use. At this writing, the exact mechanism for flashbacks is uncertain.

Prolonged reactions secondary to marijuana use include psychotic and nonpsychotic reactions. Marijuana smoking may trigger a schizophrenic reaction in vulnerable individuals. Descriptions of long-lasting cannabis-induced psychoses appear mainly in medical journals in Asia and North Africa, where individuals may use cannabis at substantially higher doses than in the United States. Descriptions of cannabis psychoses vary by culture, and most reports suggest a persistent delirium, which includes bizarre behavior and the potential for violence and panic feelings in the absence of a "typical" schizophrenia-like psychotic state. There is fairly general agreement that persons suffering from marijuana psychosis do not develop psychotic thoughts or symptoms characteristic of schizophrenia. Most reports describe cannabis psychosis as lasting 1–6 weeks among very heavy users of high doses of cannabis. However, some reports describe longer-lasting marijuana psychoses in which the psychotic episodes do not clear in the usual time but persist in residual form. Repeated intoxications may result in recurrent psychotic episodes. There has been a problem in relating marijuana psychosis to the experience in Western countries because of differences in smoking patterns in the East and the West, the difficulty of translating the psychiatric symptom picture from one body of literature and culture into another, and the impossibility of generalizing from cases that come to psychiatric attention to the overall marijuana-using population.

Nonpsychotic prolonged adverse reactions have also been described. Chronic anxiety states, depressive symptoms, and changes in life style (including an "amotivational syndrome") have been linked to chronic marijuana use by a number of observers. The amotivational syndrome includes apathy, loss of effectiveness, and diminished capacity or willingness to carry out complex long-term

plans, endure frustration, concentrate for long periods, follow routines, or successfully master new materials. Verbal facility often is impaired both in speaking and in writing. Such individuals experience greater introversion, become totally involved with the present at the expense of future goals, and demonstrate a strong tendency toward regressive, childlike, magical thinking. It remains unclear whether those who are attracted to heavy marijuana use already were inclined toward an amotivational syndrome, of which the marijuana use was symptomatic, or whether the amotivational syndrome developed as a consequence of the chronic marijuana use. What is clear is that chronic marijuana smokers who develop amotivational patterns of behavior need to stop marijuana use if they are to be rehabilitated.

Finally, the question of marijuana's dependence-producing capability is raised frequently. Laboratory animals do not self-administer Δ^9-tetrahydrocannabinol as they do opioids, sedative hypnotic drugs, alcohol, and stimulants. Nevertheless, compulsive patterns of cannabis consumption do develop in human beings, and heavy use of marijuana in humans is associated with the development of a dependence syndrome. Moreover, heavy users of marijuana appear to be at substantially greater risk for other forms of drug abuse than persons who do not use marijuana. Finally, the long persistence of cannabinoids in the body after ingestion (up to 9 days after a single dose) raises the additional prospect of toxicity due to accumulation of the drug and its metabolites in the brain and other lipid-containing organs.

CONSEQUENCES OF COCAINE USE

The growing popularity of cocaine, as a drug of both use and abuse, is testimony of the willingness of human beings to consume psychoactive substances without regard to their effects on the brain or other body organs.

The adverse effects of cocaine on health may be divided into the general medical, specifically psychiatric, and social sequelae of acute and chronic use. The probability that adverse effects will occur is, in turn, related to factors such as dose, route of administration, and frequency and duration of use. Changing routes of cocaine administration (such as "free basing" or using "crack") increases the severity of health consequences. Frequent administration, even over short periods of time, leads to the accumulation of cocaine in plasma and presumably in brain tissue and increases the risk of adverse medical and psychiatric sequelae. Cocaine rapidly depletes endogenous neurotransmitters, leaving the user in a depressed state. Individual tolerance and vulnerability to the physical and psychological effects of the drug also play a role.

General Medical Consequences

Some sequalae of cocaine use stem from the drug's local anesthetic properties, its direct effects on small capillaries, and its ability to stimulate sympathetic nervous system activity. Other medical complications are the indirect result of the drug-using life style.

Until the upsurge of smoking crack cocaine, 80% of all cocaine use was by nasal inhalation (snorting). The direct effects of the drug on mucous membranes are responsible for a number of medical complications. These include rhinitis, erosion of the mucous membranes, and in severe cases, perforation of the nasal septum (25). Intravenous cocaine use, favored by some for the rapidity of onset and intensity of drug effects, is associated with all of the complications that one might expect with any type of unregulated intravenous drug use. These include skin abscess, thrombophlebitis, septicemia, hepatitis B, acquired immune deficiency syndrome (AIDS), and tetanus (26). Smoking the basified extract of cocaine (free basing or crack smoking) delivers the drug into the pulmonary capillary bed, where it is rapidly absorbed and results in a dramatically intense effect and a more rapid onset of addiction. Free basing and crack smoking have been associated with the development of chronic bronchitis and impairment in pulmonary diffusing capacity (27).

Cocaine's ability to stimulate the sympathetic nervous system may result in elevated heart rate and increased susceptibility to premature ventricular beats and, in some vulnerable individuals, ventricular fibrillation, respiratory arrest, and death (28). Acute elevations of blood pressure, with headache and the potential for cerebral hemorrhage, also have been described (29). Increased body temperature due to failure of the brain mechanisms controlling heat regulation, coupled with vasoconstriction and hyperactivity, has led to some deaths from hyperthermia (30).

Another untoward effect of cocaine is the development of status epilepticus. This may occur either as an acute response to high-dose use or as a result of a sensitivity to cocaine developed during chronic administration. The latter may be due to a so-called "kindling" phenomenon, in which brain neurons become increasingly sensitized to the effects of cocaine and fire in response to even relatively low doses of the drug (30).

All of the adverse medical complications of cocaine use are far more likely after acute administration of large doses. In many instances overdose is unintentional, since the user has little knowledge of the purity or even the amount of the drug consumed. Overdose deaths have occurred after the first use in apparently healthy individuals with no preexisting illness. In addition, repetitive use is associated with increasing sensitivity in some of the excitatory effects of cocaine. Finally, a small number of individuals suffer from a congenital lack of the enzyme pseudocholinesterase and thus are unable to metabolize the drug. In these individuals, even small doses can produce dramatic effects. The medical complications of cocaine use are more likely to occur in persons with preexisting heart or respiratory disease, hypertension, seizure disorders, or compromised immune function and in those who are taking other drugs whose effects are potentiated by cocaine.

Specific Psychiatric Complications

The acute subjective response to cocaine is characterized by euphoria, insomnia, increased energy, enhanced mental acuity and alertness, and an increase in sensory awareness. However, some individuals become hyperexcitable, while others, particularly those with underlying depressive disorders, experience dysphoria. Anxiety, concentration difficulties, decreased attention span, and memory problems also have been reported after use of cocaine. In individuals with underlying panic disorder, the drug can precipitate panic attacks. Some cocaine users may misperceive reality and/or experience auditory, visual, and tactile hallucinations. Flight of ideas, distractibility, pressured speech, restlessness, impulsivity, and poor judgment are common. Paranoia and delusions of persecution, coupled with profound irritability and grandiosity, may lead to assaultive and/or homicidal behavior by some cocaine abusers. These alterations in thinking, mood, and behavior may last a short time or, in certain vulnerable individuals, may persist long after the drug has been metabolized (31, 32).

Chronic cocaine use also is associated with untoward effects on psychological health. Several studies have demonstrated a direct relationship between cocaine dose, chronicity of use, and the development of cocaine-related psychopathology. Chronic cocaine users frequently complain of fatigue, headaches, impairment of recent memory, concentration difficulties, and sexual indifference. They also are more likely to develop a cocaine psychosis (described previously).

In some individuals the powerfully reinforcing effects of cocaine lead to increased frequency of use, escalation of dose, and the eventual development of psychological and physical dependence. The onset of dependence is particularly rapid with the use of crack. The primary reinforcing effects of the drug are probably mediated through the limbic system mechanisms responsible for the perception of pleasure—specifically, those neural circuits that use norepinephrine and dopamine as neurotransmitters. Other factors that contribute to the development of dependence include psychological variables, peer pressure, drug availability, and (perhaps) some sort of underlying biological vulnerability.

The tendency toward repetitive use is further enhanced by the occurrence of a cocaine withdrawal syndrome characterized by depression, lethargy, fatigue, feelings of guilt, anxiety, and feelings of helplessness, hopelessness, and worthlessness. In some individuals, particularly those with preexisting underlying depression, transient suicidal thoughts may emerge.

The cocaine withdrawal syndrome is particularly marked after chronic high-dose use. The signs and symptoms usually last 12–36 hours. In some individuals, however, the depression may last up to several weeks. To avoid withdrawal, some chronic users will self-administer the drug every 20–30 minutes. This pattern of use is more likely to be associated with the development of cocaine psychosis. The serious psychosocial consequences of cocaine use include loss of job and problems with one's family, friends, and finances.

In summary, both acute and chronic cocaine use are associated with adverse effects on health. In addition to medical and psychiatric sequelae, chronic cocaine use also is associated with the hazards of a drug-using life style. These include anorexia and associated weight loss, malnutrition and vitamin deficiencies, accidents, and a greater likelihood that one will be the perpetrator or victim of violence.

ROLE AND RESPONSIBILITY OF PSYCHIATRISTS

Psychiatrists should exercise a leadership role in drawing attention to the major public and mental health consequences of substance abuse in our society. Psychiatrists have a responsibility to educate the public about how ubiquitous drug abuse is and how it is both the cause and consequence of emotional problems. We must be aware that drug and alcohol abuse are often the primary problem among patients who present themselves to psychiatrists. Psychiatrists should take leadership responsibility in assuring that adequate training in substance abuse occurs at all levels of medical education and in influencing physician attitudes and behaviors as part of this training process. Psychiatrists also should interface with nonmedical care givers, such as educators, the clergy, counselors, and self-help groups, in imparting an understanding of the psychiatric implications of substance abuse. The psychiatrist's role in working with the family is essential.

Evidence has accumulated over the past decade that there is a significant association between psychopathology and substance abuse. In some instances, substance abuse has resulted from psychopathology and in other cases has been the cause of it. In either case, for most individuals regular reliance on drugs is incompatible with a life of meaningful relationships, productivity, and satisfaction. Substances of abuse are dangerous because they exert powerful deleterious effects on human emotions and behavior. Mind-altering drugs, including alcohol, create illusions that emotional distress can be avoided, that desired states or behaviors can be augmented, and that performance can be enhanced or improved. During adolescence, when particularly intense emotions, behaviors, and performance concerns loom large, this is a seductive and dangerous effect of drug use. However, these dangers also apply to other phases of life, when other developmental challenges are encountered and need to be mastered.

Psychiatrists should address the emotional and mental health needs of substance abusers. Psychiatrists should educate themselves and the public about how substance abuse affects the psychological and social functioning of individuals and their families and should take active roles in developing and establishing guidelines and protocols for the assessment and management of substance abuse problems. Psychiatrists should provide the public with information on the hazards of substance abuse through the media, public education campaigns, and contacts with other care providers and professional associations. Psychiatrists should take the initiative in developing guidelines and procedures for quality assurance and assessment of treatment outcome for substance abuse treatment programs. Finally, psychiatrists, through the American Psychiatric Association, should exercise an ongoing leadership role to assure nondiscriminatory reimbursement practices for substance abuse treatment services.

Each psychiatrist has a responsibility to understand and learn about substances of abuse; their psychoactive, toxic, and withdrawal effects; and how they interact with human emotions and behavior. Practicing psychiatrists must routinely obtain drug and alcohol histories, focusing not only on duration, amounts, and patterns of use but also on the effects that patients seek and obtain from the drugs they choose. Similarly, family histories of drug use and misuse patterns also should be obtained routinely. Psychiatrists should routinely consider whether their patients with psychiatric conditions suffer from concomitant substance abuse disorders and whether patients presenting with substance abuse disorders also might be suffering from coexistent treatable psychiatric problems. Psychiatrists should be cognizant of the life-threatening aspects of substance abuse as background for emphasizing the importance and necessity of obtaining control and abstinence at the onset of treatment. Accordingly, psychiatrists must learn how to use appropriate hospital and other residential treatment, support groups (e.g., Alcoholics Anonymous and Narcotics Anonymous), pharmacological treatment, and psychotherapeutic modalities (33).

Psychiatrists involved in the treatment of children and youth presenting with behavioral and emotional problems should be alert to the possibility that drug use may be a contributing factor. Close cooperation between psychiatrists, primary care providers, parents, and educators is needed to overcome the serious problems of alcohol and other drug abuse among our youth.

Finally, psychiatric practitioners are well suited to work with primary care providers in assessing and managing substance abuse patients in both outpatient and inpatient settings. They also are able to work with and interface with nonmedical caregivers, especially in consulting with self-help programs and drug counselors and helping them appreciate the mental health needs and psychiatric disabilities of their clients. The psychiatrist has a substantial contribution to offer in the management of the substance abuser. The psychiatrist can provide a dynamic understanding of the patient and can plan individualized multidisciplinary treatment and its implementation. It is the responsibility of the psychiatrist to emphasize the danger of drug use. To adopt a more neutral stance toward drug use by youth and refrain from warning of the dangers to mental health is to fail to fulfill an important public health responsibility of our profession.

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ALASKA STATE LEGISLATURE
HOUSE OF REPRESENTATIVES
RESEARCH AGENCY

Pouch Y, State Capitol
Juneau, Alaska 99811
(907) 465-3991

April 15, 1983

MEMORANDUM

TO: Representative Ramona Barnes

FROM: Betty Barton BB
Research Staff

RE: Driving Under the Influence of Drugs
Research Request No. 83-120

You requested information regarding procedures and methods that can be used "in the field" to test individuals driving under the influence of drugs other than alcohol. You also asked that we research the legal implications of such tests.

To respond to your questions, we contacted Mr. Joseph Gormley, of the International Association of the Chiefs of Police, Dr. Kurt Dubowski, a national authority on toxicology at the University of Oklahoma, and Mr. Robert Reeder, an expert on DWI law at Northwestern University's Traffic Institute. Within Alaska, we spoke with Gayle Horetski, in the Criminal Division of the Department of Law, Mr. Charles Smith, who administers the Alaska Highway Safety Program, and Major Mike Korhonen, with the Alaska State Troopers.

Based from our conversations with these individuals, we have found that although there is substantial research in progress pertaining to drugs and driving, no methods have been established for on-site, roadside chemical testing of drug intoxications. Further, forensic scientists project that technology of this nature will not be developed for a number of years. Qualitative and quantitative testing of intoxicating substances other than alcohol is a complex issue that is the subject of continuing research. Consequently, even laboratory-based chemical analysis pertaining to the effects of intoxicating substances other than alcohol is in its developing stages.

Unlike alcoholic beverages which all share a common ingredient, ethyl alcohol, other drugs have varied chemical properties that make them difficult to identify and isolate. As a result, standardized measures of these types of controlled substances are difficult to develop as is the development of any drug equivalencies for "blood alcohol concentrations."[1]

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[1] Blood alcohol concentration, often referred to as BAC, is the standard measurement of impairment. It is generally accepted that a BAC of .10 percent is the level where most individuals become impaired by the intoxicating effects of a substance. A few states, however, have set BAC levels of .08 percent.

Besides the absence of adequate qualitative and quantitative data, forensic scientists lack sufficient experiential research regarding drivers who are under the influence of drugs. Oklahoma, for example, is one of four states that is authorized to conduct experiments on the effects of drugs on human subjects. However, all of the testing occurs in laboratory settings, which can alter the outcome of experiments. The measured effects that drugs would have on a person's decision-making abilities while in a secure, laboratory setting would be much different than they would be, say, for a drugged driver who is being pursued by police. Consequently, while this type of laboratory research is significant, it is of limited value.

Chemical analysis of drugs also can be very costly. Unlike alcohol, where chemical tests can be conducted with relatively inexpensive and portable breathalyzer equipment, the presence of drugs in an individual's blood stream can only be detected by chemical analysis of blood plasma or, in some cases, urine.[2] Equipment for this type of analysis costs between $100,000 and $200,000. Additional expenditures, of course, are incurred from laboratory fees; because of the expertise involved in this type of testing, analysis is often done in special laboratories.

In light of these factors, according to Dr. Kurt Dubowski, forensic methods are rarely used in court as the basis for DWI charges pertaining to drugs. Instead, prosecuting attorneys typically rely on several key issues in developing their cases:

- the officer's probable cause for arrest;
- the demonstrated indication of the driver's impairment;
- the chemical test results that indicate the absence of sufficient alcohol concentration in an individual's system to have caused impairment; and
- the presence or evidence of drugs within the defendant's motor vehicle at the time of the arrest.

In Alaska, DWI cases pertaining to drug intoxication currently represent a very small percentage of the court's caseload. Gayle Horetski commented that this is partially due to the fact that the State has placed greater emphasis on improving its capabilities in alcohol-related cases. However, Ms. Horetski added that the drug-impaired driver is harder for officers to

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[2] Dr. Dubowski noted that urine anlysis is limited because it is not possible to determine whether there was a sufficient concentration of the drug at the time of formal charges.

detect unless there are visible signs of impairment. Ms. Horetski believes that the State's abilities to apprehend and convict drivers who are under the influence of drugs would improve if the technology existed for roadside analysis.

The Alaska Department of Public Safety currently has two gas chromatographs, which can be used for qualitative and quantitative analysis of certain drugs. However, according to Charles Smith, the equipment was purchased and is used primarily to test the alcohol levels of individuals who have died in motor vehicle accidents. According to Major Korhonen, drug testing is not currently emphasized within the Department because generally chemical tests in Alaska cases indicate the presence of alcohol. The costs that would result from additional laboratory testing to determine whether other drugs were also present is viewed to be an unessential added expense.[3]

In light of the limited technology in drug testing, state governments have considered other methods as a means of improving capabilities for enforcement of highway safety laws. In several states, including Maryland and New York, roadblock or checkpoint programs have been established as a means of checking for drunk or drugged drivers as well as other offenders. Officers briefly question drivers and look for symptoms such as slurred speech or indications of blurred vision.

In Westchester County, New York, local police recently set up a roadblock on a parkway for eight hours on a Friday night and early Saturday morning. Three-thousand-two-hundred motor vehicles passed through the checkpoint; 95 drivers were detained on suspicion of DWI. Of these, twelve were arrested, one of whom was charged with driving while impaired by drugs.

Not only can this approach potentially increase the police's abilities to approach impaired drivers, but also can help to give highway safety officers a more visible presence. Westchester County's Deputy Commissioner of Public Safety commented that checkpoints assist in conveying "a message that we're going to be out in full force from time to time; so if you're going to drink, don't drive."[4] According to some professional opinions,

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[3] Charles Smith added that excessive alcoholic consumption among Alaska's driving population appears to be a larger problem than drug intoxication. According to Mr. Smith, between April 1977 and March 1978, the Municipality of Anchorage Police Department administered involuntary blood tests on individuals who had refused breathalyzer examinations. During this period, 254 persons were administered tests. Of these, the average blood alcohol content was .26 percent and 35 cases had alcohol levels of .300 or higher. While some these individuals may have been under the combined influence of drugs and alcohol, in only two cases were impaired conditions solely attributed to drug intoxication.

the impact that this type of message may have on the drinking driver is significant. In recent testimony presented before the Alaska Senate State Affairs Committee, Dr. Laurence Ross, a national authority on the deterrent effect of DWI penalties, stated that highway safety laws, regardless of the level of penalty imposed, tend to lose their effectiveness as a preventive measure because most people recognize that the likelihood of their being caught is low. However, if enforcement capabilities measurably increase, individuals may weigh the risks of apprehension more seriously.

While the checkpoint method does appear to offer some promise in terms of enforcement and prevention, public support for this type of program is often limited. The courts have ruled that roadblocks do not violate constitutional protections against search and seizure as long as all vehicles are checked and certain measures are followed by the police.[5] Nonetheless, this type of program is perceived by some as placing an undue hardship on lawabiding drivers.

We hope this information has assisted you. If you would like us to provide you with additional information regarding the checkpoint system or other enforcement methods, please let us know.

BB/bb

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4 Lena Williams, "Three Thousand Two Hundred Cars Halted in a Check on Drunken Drivers," New York Times, March 27, 1983, P. 1.

5 Delaware v. Prouse Supreme Court, 47 US Law Week 4323 1979. Guidelines for police are established in State v. Hillesheim 291 NW 2nd 314, Iowa Supreme Court, 1980.

Andrew P. Mason,[1] *B.S. and Arthur J. McBay,*[2] *Ph.D., DABFT*

Cannabis: Pharmacology and Interpretation of Effects

REFERENCE: Mason, A. P. and McBay, A. J., "*Cannabis:* Pharmacology and Interpretation of Effects," *Journal of Forensic Sciences*, JFSCA, Vol. 30, No. 3, July 1985, pp. 615-631.

ABSTRACT: A selective introductory review of the *Cannabis* literature is presented. Subjects reviewed include the relative psychoactivities of *Cannabis* constituents, the disposition and distribution of THC and its metabolites, the relative psychoactivities of THC metabolites, and the use of cannabinoid concentrations in physiological fluids in interpretations of the significance of *Cannabis*-induced effects. The pharmacology of cannabinoids in humans is emphasized.

KEYWORDS: toxicology, marijuana

Marijuana and other *Cannabis* products are used by a significant proportion of people in our society. When smoked or ingested, these substances produce perceptual, cognitive, affective, and behavioral changes in the user. The *Cannabis* constituent that is responsible for the production of the majority of this psychoactive response is (−)-trans-delta-9-tetrahydrocannabinol or THC [*1*]. There has been great concern that the psychoactive response experienced by marijuana users has a detrimental effect on the performance of complex coordinated psychomotor skills. Naturally, the impairment of performance would be of greatest concern in those individuals with direct responsibility for the health and safety of others and in individuals whose impaired actions could potentially be dangerous to themselves or to others near them. Motor vehicle operators, pilots, air traffic controllers, law enforcement or emergency aid personnel, military personnel, and industrial workers are all good examples of people whose impaired performance could potentially be dangerous.

During the last decade, remarkable progress has been made in the ability to analyze biological samples for cannabinoid compounds. This ability was developed as a prerequisite for, and was instrumental in the acquisition of data concerning the pharmacology, pharmacokinetics, metabolism, behavioral effects, and toxicology of *Cannabis* constituents. These analytical methods and the knowledge derived from their use in basic research on cannabinoids are now being used in attempts to interpret the significances of cannabinoid concentrations found in forensic science specimens. The frequency with which these analytical methods are used and the frequency with which forensic scientists are required to provide estimates of the probable significances of *Cannabis*-induced effects or the degree of impairment experienced by a *Cannabis* user based on cannabinoid concentrations in biological specimens are both expected to increase. Use of these methods and in-

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[1]Graduate student, Division of Medicinal Chemistry and Natural Products, School of Pharmacy, and Office of the Chief Medical Examiner, University of North Carolina, Chapel Hill, NC.

[2]Chief toxicologist, Office of the Chief Medical Examiner, and professor, Division of Pharmaceutics, School of Pharmacy, and Department of Pathology, School of Medicine, University of North Carolina, Chapel Hill, NC.

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Andrew P. Mason,[1] *B.S. and Arthur J. McBay,*[2] *Ph.D.; D.A.B.F.T.*

Ethanol, Marijuana, and Other Drug Use in 600 Drivers Killed in Single-Vehicle Crashes in North Carolina, 1978–1981

REFERENCE: Mason, A. P. and McBay, A. J., "Ethanol, Marijuana, and Other Drug Use in 600 Drivers Killed in Single-Vehicle Crashes in North Carolina, 1978–1981," *Journal of Forensic Sciences*, JFSCA, Vol. 29, No. 4, Oct. 1984, pp. 987–1026.

ABSTRACT: Although the use of ethanol, marijuana, and other drugs may be detrimental to driving safety, this has been established by direct epidemiological evidence only for ethanol. In this study, the incidences of detection of ethanol (and other volatile substances), delta-9-tetrahydrocannabinol (THC), barbiturates, cocaine and benzoylecgonine, opiates, and phencyclidine were determined in an inclusive population of 600 verified single-vehicle operator fatalities that occurred in North Carolina in 1978 to 1981. The incidence of detection of amphetamines and methaqualone were determined for drivers accepted for study during the first two years ($n = 340$) and the last year ($n = 260$), respectively. Blood concentrations of 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (9-carboxy-THC) were determined in THC positive drivers. EMIT cannabinoid assays were performed on blood specimens from all drivers accepted for study during the third year, and the feasibility of using the EMIT cannabinoid assay as a screening method for cannabinoids in forensic blood specimens was investigated. The incidence of detection of ethanol (79.3%) was far greater than the incidences determined for THC (7.8%), methaqualone (6.2%), and barbiturates (3.0%). Other drugs were detected rarely, or were not detected. Blood ethanol concentrations (BECs) were usually high; 85.5% of the drivers whose bloods contained ethanol and 67.8% of all drivers had BECs greater than or equal to 1.0 g/L. Drug concentrations were usually within or were below accepted therapeutic or active ranges. Only a small number of drivers could have been impaired by drugs, and most of them had high BECs. Multiple drug use (discounting ethanol) was comparatively rare. Ethanol was the only drug tested for that appears to have a significantly adverse effect on driving safety.

KEYWORDS: toxicology, motor vehicle accidents, alcohol, marijuana

It is accepted that ethanol use has a detrimental effect on the performance of drivers because it impairs sensory input and perception, judgement and cognition, motor control, and their integration and coordination. It is also known that the use of ethanol is strongly associated with traffic fatalities. Nationally, between 40 and 55% of all drivers involved in fatal crashes have blood ethanol concentrations (BECs) greater than or equal to 1.0 g/L [1],[3] the

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[1]Graduate student, Division of Medicinal Chemistry and Natural Products, School of Pharmacy; and Office of Chief Medical Examiner, University of North Carolina, Chapel Hill, NC.

[2]Chief toxicologist, Office of the Chief Medical Examiner and professor, Division of Pharmaceutics, School of Pharmacy, and Department of Pathology, School of Medicine, University of North Carolina, Chapel Hill, NC.

[3]1.0 g/L = 100 mg/dL = 100 mg% = 0.10%.

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This Week

Research Notes

Articles

Cover: A young marijuana plant glistens with crystals rich in psychoactive delta-9-tetrahydrocannabinol. Although marijuana has been used for millennia as a medicinal, the U.S. government says it has no accepted medical value. Proponents of pot-by-prescription are taking their case to court. (Photo: Ed Rosenthal)

Departments

Letters

Hail and Farewell

As a poet delighted not only by the discoveries of physics but also by its serendipitous and colorful nomenclature, I have been surprised by the reticence of those probing for new fundamental forces to name them.

As I was reading "Evidence for New Force — May Be No. 6" (SN: 12/19&26/87, p.388), Hail and Farewell struck me as apt designations: the former for the attractive Force 6, apparently dominant from a few feet to hundreds of yards over the repulsive Force 5, its influence more circumscribed to a range approximating distances habitual for conversation. The gladiatorial allusion, too, has much to recommend it, given their contention for supremacy, however transitory.

Less abstract than the equally anthropocentric Beauty and Charm, Hail and Farewell have the further advantages of the balance and tangential anthropomorphism of Sunrise and Sunset.

Daniel Zimmerman
Metuchen, N.J.

The chicken, or the egg?

Re your report on new research supporting the old Air Force myth that fighter pilots are more likely to sire daughters than sons ("What do you suppose B-forces make?" SN: 12/12/87, p.377): Is it possible that cause and effect are reversed here? Could it be that that type of occupation attracts a certain type of man, and that that type may in some way be more likely to sire daughters?

[illegible] Hellman
Leonia, N.J.

Some years ago, while employed at NASA at a randomly selected division, I surveyed all the bosses to determine the sex of their children. The result of my small survey showed that of 19 bosses contacted, 9 had all girls while only 3 had all boys, and the ratio of all the girls of the bosses to all the boys was over 2:1. This, of course, did not mean that being a boss made one have girls.

Since I assumed the rest of the employees had the then-prevailing average ratio of girls to boys (100:94), my conclusion was that girls gave their fathers a lot of self-esteem, which is a characteristic required not only to seek a boss's job but also to seek a fighter pilot's job. Thus there is a strong possibility that men become fighter pilots because of having more girls rather than the other way around.

[illegible]d characteristic I noticed is that [illegible] married males tend to sire children [illegible]one sex. Since fighter pilots must be [illegible]iant to cope with all the tin-soldier rules and regulations and safety precautions, any second or third children born during training or while on active duty would tend to be also girls.

A. P. Sabol
Lewisburg, N.C.

TAKE TWO PUFFS AND CALL ME IN THE MORNING

Proponents of marijuana's medical benefits take their case to court

By RICK WEISS

Once a month, Robert Randall strolls into his neighborhood pharmacy in Washington, D.C. He chats with the pharmacist while his prescription is filled, and a few minutes later walks out the door with a 30-day supply of the medicine he needs — 300 prerolled marijuana cigarettes.

Such has been Randall's routine for the past 10 years, ever since he won a court order that recognized his medical need to smoke marijuana. Marijuana lowers the pressure that builds up in his eyes as a result of his having glaucoma. He is the only glaucoma patient in the United States to have won such an order. But if he and others have their way — that is, if Federal Administrative Law Judge Francis Young Jr. rules in their favor later this year — thousands of patients may get easier access to the drug for a variety of ailments ranging from chemotherapy-induced nausea to spasticity.

Such a decision would be the climax of a tedious, decade-long battle by a coalition of groups convinced that pot's therapeutic potential has been unjustly ignored. "It's been like a play by Ionesco with footnotes by Kafka," Randall says of the unusual legal struggle. "It's been absurd, venal and bizarre."

Such surrealism is not a part of his everyday experience, Randall assures. Although he smokes eight to 10 "joints" per day, he says he developed a tolerance to marijuana's psychoactive effects many years ago. Meanwhile, he says, a "fixation" on marijuana as a drug of abuse has kept the Drug Enforcement Administration (DEA) from appreciating the drug's medical merits.

Marijuana (*Cannabis spp.*) is classified by the DEA as a "Schedule 1" drug — one that has "no currently accepted medical use as a treatment in the United States" and is considered unsafe even under medical supervision. A prescription version of delta-9-tetrahydrocannabinol (THC), the primary active ingredient in marijuana, is less tightly restricted and was approved by the Food and Drug Administration in 1985 as an antinausea agent for cancer patients. But its effectiveness is hotly disputed; many patients and physicians claim that purified THC is not nearly as effective as a puff of pot.

As part of a campaign to reverse what they believe is a political bias against marijuana, the Alliance for Cannabis Therapeutics and the National Organization for the Reform of Marijuana Laws, both based in Washington, D.C., have challenged the drug's Schedule 1 status. The groups contend that, at minimum, marijuana should be classified as a Schedule 2 drug — a status that would keep it illegal but would ease the restrictions on research into its medical applications. Although researchers can apply for permission to perform human trials with Schedule 1 drugs, few applications are ever granted. Proponents of reform say a schedule change would speed the recognition, acceptance and availability of marijuana as medicine.

In one of the final stages of the rescheduling challenge, completed earlier this month, court-ordered hearings were held in New Orleans, San Francisco and Washington, D.C. Closing briefs are now being prepared by attorneys on both sides and should be completed by May. After reviewing the briefs and scores of volumes of testimony, Judge Young is expected to make a recommendation to the chief administrator of the DEA before the end of the year.

But even then the battle may not be over. The DEA is not bound by the judge's recommendation, and in either case the DEA's decision can be appealed.

The case may get even more complicated because the DEA is expected within the next few weeks to announce its decision in a similar case involving MDMA — an illegal drug that some believe has potential as an adjunct to psychotherapy. Last year, after lengthy hearings, Judge Young recommended that the DEA drop MDMA from Schedule 1 to Schedule 3. Schedule 3 drugs are illegal to possess except with a DEA license, but are acknowledged as having medical potential.

Illustration of Cannabis *from the works of Dioscorides, a first-century physician.*

The DEA ignored that recommendation, kept MDMA in Schedule 1 and was subsequently sued by one of the drug's proponents, Harvard psychiatry professor Lester Grinspoon. Grinspoon claimed that Schedule 1 was an overly restrictive status for a drug that had, he said, "been taken in a therapeutic setting by thousands of people, apparently with few complications." Grinspoon won his case in the U.S. Court of Appeals and the DEA is now reconsidering its stand. Among other things, the case is forcing the DEA to redefine some of its schedule definitions, which may have an impact on the marijuana decision.

A central issue in both cases is the DEA's definition of the "no accepted medical use" clause that relegates a drug to Schedule 1 status.

"The original definition was that in order for a drug to have an accepted medical use it had to be lawfully marketed in the United States under the Food, Drug and Cosmetic Act," says Charlotte Mapes, a DEA attorney. "What the court said [in the MDMA case] is that the administrator cannot rely exclusively on lack of marketing approval as a condition

for no accepted medical use."

Indeed, proponents of rescheduling say a simple lack of FDA approval hardly counterbalances marijuana's long record as a therapeutic agent. Chinese herbal catalogues have listed the plant as an aid to digestion for thousands of years, and as many as 30 marijuana preparations were listed in the *U.S. Pharmacopoeia* as recently as 1937. "It appears that every society that encounters marijuana acknowledges its therapeutic properties," says Alice O'Leary, a cofounder of the Alliance for Cannabis Therapeutics.

In the United States, researchers have been most interested in marijuana's usefulness as an anti-emetic for cancer patients suffering from chemotherapy-induced nausea. Several FDA-approved Investigational New Drug studies have demonstrated its value as such, and in some cases its advantages over THC pills.

"Never mind the absurdity of giving an oral medicine to someone who is throwing up all the time," Randall says of the FDA-approved pills. The tablets have negative side effects of their own, he says, adding that in one study "50 percent of the patients said they'd rather throw up."

According to testimony by John Morgan, a professor of medicine at City College of New York, "Marijuana's use in reducing nausea appears to be quite widespread and generally, albeit discretely, accepted within the oncologic community and among patients. Physicians confront profoundly difficult ethical, legal and moral questions because of marijuana's inappropriate classification."

Marijuana may also be useful for reducing some of the neurological complications inherent to multiple sclerosis, Parkinson's disease and paraplegia. Preliminary studies show that it seems to work quickly and effectively against severe episodes of muscle spasticity, according to testimony by Denis Petro, director of clinical research at Fidia Pharmaceuticals, a major Italian drug company that specializes in neurological therapeutics. Other studies have suggested that marijuana may be useful in the treatment of asthma, anxiety and eating disorders and for improving the quality of life in terminally ill patients.

The DEA says that most such studies have been poorly designed, are fraught with subjective errors and represent little more than collections of anecdotal evidence. Proponents of rescheduling concede that few case-controlled, double-blind studies have been performed on marijuana in its natural form. However, they add, that shortage exists in large part because it is so difficult to get research approval for Schedule 1 drugs.

In addition to the controversy over marijuana's "accepted medical use," there is considerable debate over the issue of its safety and how to apply the "lack of accepted safety" clause in the Schedule 1 definition.

"Marijuana has not killed anyone in 5,000 years," Randall says flatly. But the DEA is not convinced.

"Our perception of safety is different from theirs," DEA attorney Mapes told SCIENCE NEWS. "They're saying it's safe because nobody's died. We're saying that it has to be shown to be safe."

Fitz Hugh Ludlow Memorial Library

Broadsides such as this one characterized the campaign against marijuana in the 1930s and 1940s.

Research has suggested that marijuana can suppress the body's immune system (SN: 7/18/87, p.46), and deficits in short-term memory among users have been reported. According to the most thorough U.S. examination of the health-related effects of marijuana, a 15-month study by the Institute of Medicine of the National Academy of Sciences published in 1982, "marijuana impairs motor coordination and affects tracking ability and sensory and perceptual functions important for safe driving and the operation of other machines." However, the report adds, "we have no convincing evidence thus far of any effects persisting in human beings after cessation of drug use. . . ."

Perhaps most significantly, marijuana has a variety of psychological effects. Depending on the individual, the dose and the setting, it has been known to produce everything from sensory enhancement and euphoria to intense anxiety and paranoia.

"Most doctors do not want to give a psychoactive drug to someone when they can give a nonpsychoactive one that is more effective," says Madeleine Shirley, a DEA attorney working with Mapes in the current case. With so many new drugs being created, she says, "Frankly, there's not a lot of interest in marijuana any more."

The debate goes on. The government says marijuana is notoriously variable in potency, containing dozens of active ingredients in unpredictable concentrations. Randall counters that the marijuana he buys at his local pharmacy – grown on a government pot plantation in Oxford, Miss. – is routinely blended to a uniform potency, tested and certified by the National Institute of Drug Abuse.

In addition, the DEA claims that smoking is a poor way to get a measured dose of a drug, since depth of inhalation and the length of time before exhaling can affect the amount of drug that gets into the bloodstream. But other experts note that inhalation has many benefits as a means of drug delivery, providing rapid absorption and avoiding gastric complications (see related story, p.120).

Given the lack of scientific consensus on such issues, the discussion ultimately turns to politics. Statements from the Alliance for Cannabis Therapeutics clearly suggest that the government's hard line on marijuana is motivated by political considerations.

But if Alliance members believe there is a federal cabal aimed at nipping marijuana research in the bud, federal officials are equally suspicious of the reformers' motivations.

"I think this whole thing has got more to it than meets the eye," says Paul Leber, director of the FDA's division of neurological and pharmacological drug products. "I'm not interested in suppressing a drug just because somebody says it's bad. But I do have to ask myself, 'Is it likely to benefit the patient? Or is this being used by someone in an unscrupulous attempt to foster some nonsense?' "

Proponents of reform note that pot would still be illegal and tightly controlled under Schedule 2 or 3. Rescheduling would simply encourage much-needed research, they say, and might open the door to "compassionate use." Under its compassionate use rule, the FDA allows unapproved drugs to be prescribed when effective alternatives are not available. In addition, if the number of studies begins to increase, hundreds of patients might gain long-sought access to the drug as subjects in licensed studies.

In any case, neither of the parties to the marijuana dispute foresees immediate or widespread availability of the drug. Even if the current rescheduling effort is successful, the government may still be slow to approve new research and to appropriately scale up its marijuana accounting and distribution mechanisms. Because of marijuana's potential for abuse, says the DEA, it would be important to keep careful inventories of the drug.

Happily, sighs Shirley, drug approval and distribution are not the DEA's responsibilities. "We just decide what schedule it's in. Getting the drug to the people is the FDA's problem."

ENCLOSED ARTICLES ON THC

Dear Mr. Nordlund,

I have enclosed selected articles on the toxic effects of Marijuana. There are at probably 2-3000 articles on the toxic effects of this drug since the Alaska Supreme Court decision.These I selected are from refereed journals and have been authenicated prior to publication. I want to emphasize the effects on the immune system and birth defects. Also the records of cardiac deaths from Marijuana smoking are significantly relevant. The birth defects and immune system are problems that affect the whole of society and surpass the rights of the individual to get stoned at home and get stoned, while damaging his or her brain and risking lung cancer. The society cannot tolerate an agent that is producing birth defects. Driving under the influence of THC is plain foolish.

Articles:

1. Marijuana effects on Immunity 1986
2. The new Immunomodulator 1987 Nicotine and Marijuana
3. Developmental effects of cannabis 1986
4. Marijuana Use by pregnant women 1981
5. Cannabinoid Exposure: Effects on Development 1986
6. Induction of sister-chromatic exchanges in marijuana-cannabis 1981
7. Effect of Marijuana use in pregnancy on fetal growth,1986
8. Maternal Marijuana Use and neonatal Outcome 1985
9. Perinatal Cannabinoid Exposure 1985
10. The effects of Alcohol , Marijuana and the combination on driving about
11. The effects of Marijuana and alcohol on actual driving performance.
12. Epidemiology of road accidents involving Marijuana
13. The clinical syndrome of marijuana dependence 1986
14. Effects of Long term Marijuana use
15. The addictive potential of cannabis, 1980
16. Marijuana 1987
17. Health aspects of cannabis 1982
18. Marijuana: an overview 1987
19. Marijuana's effects on Human Cognitive functions etc 1986
20. The chronic cerebral effects of cannabis 1986
21. Pulmonary hazard of smoking marijuana 1988
22. Fatal coronary artery thrombosis associated with cannabis smoking 1984
23. Myocardial infarction during marijuana smoking in a young female, 1985

You can see from these dates that I am more current with my information than some of the opponents of the bill who testified. It is clear that the witness selection was biased. Please try to correct that error by making copies of this literature available to the committee members.

Sincerely yours,

Jeanne F. Stein, M.D.

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MARIJUANA EFFECTS ON IMMUNITY: SUPPRESSION OF HUMAN NATURAL KILLER CELL ACTIVITY BY DELTA-9-TETRAHYDROCANNABINOL

STEVEN C. SPECTER, THOMAS W. KLEIN, CATHERINE NEWTON, MARLENE MONDRAGON, RAYMOND WIDEN and HERMAN FRIEDMAN

Department of Medical Microbiology and Immunology, University of South Florida College of Medicine, Tampa, FL 33612, U.S.A.

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Abstract—Delta-9-tetrahydrocannabinol (THC), the major psychoactive component of marijuana, was tested for its ability to modulate human natural killer (NK) cell function. THC was toxic for peripheral blood lymphocytes at 20 μg/ml but not at 10 μg/ml or less. This component of marijuana also was inhibitory for NK activity against K562, a human tumor cell line at concentrations down to 5 μg/ml when pre-incubated with the effector cells. Suppression of NK function was dependent upon the concentration of THC and the length of time of pre-incubation but was independent of the ratio of effector to target cells. Prostaglandins were not involved in suppression of NK activity.

The psychoactive effects of marijuana, as well as some of the physiological and biochemical effects of this drug, are well documented. There is considerably less information, however, concerning the ability of marijuana and its components, such as delta-9-tetrahydrocannabinol (THC), to influence various aspects of the immune system. Acute or chronic exposure of human or mouse peripheral blood leukocytes (PBL) to marijuana have yielded equivocal results when these cells were exposed to specific (antigens) or nonspecific (plant mitogens) stimuli (Matsuyama & Jarvik, 1977; Munson & Fehr, 1983; White, Brin & Janicki, 1975). A number of reports have appeared indicating that marijuana has detrimental effects on immunity, suppressing antibody responses (Levy, Farrar, Harris, Dewey & Munson, 1975; Levy & Heppner, 1981; Rosenkrantz, Miller & Esber, 1975), cell-mediated immune responses and macrophage function (Huber, Pochay, Pereira, Shea, Hinds, First & Sornberger, 1980; Levy & Heppner, 1979; Nahas, Suciu-Foca, Armand & Morishima, 1974), but there are a number of other reports indicating no effects of THC on these responses (Lau, Tubergen, Barr, Domino, Benowitz & Jones, 1976; Peterson, Graham & Lemberger, 1976; Rachelefsky, Opelz, Mickey, Lessin, Kiuchi, Silverstein & Stiehm, 1976).

Natural killer (NK) cells, which are recognized as being important in host defenses against tumor cells and microbial infections, have not been examined for their susceptibility to modulation by THC. These cells are considered a first line of defense against infections and often inhibit tumors before they can become well established. NK cell function has been demonstrated to be influenced by a variety of substances which inhibit or enhance imunologic responsiveness (Brunda, Herberman & Holden, 1980; Droller, Schneider & Perlman, 1978; Henney, Kuribayashi, Kern & Gillis, 1981; Oehler, Lindsay, Nunn, Holden & Herberman, 1978). Prostaglandins and corticosteroids clearly inhibit NK function, while interferons and interleukins enhance activity. Considering the importance of NK cells in host resistance, it was of interest to examine the effects, if any, of THC on NK activity. The results of the present study indicate that THC suppresses human NK cell activity *in vitro*.

EXPERIMENTAL PROCEDURES

Blood donors

Healthy donors who denied a history of marijuana use served as a source of PBL for these studies. Thirty ml blood were collected by venepuncture and

Table 1. Cytotoxicity of THC over a 3 h time period for human peripheral blood leukocytes

Addition to cultures*	Mean percent cytotoxicity after treatment for† 30 min	60 min	120 min	180 min
Medium	4.0‡	6.7	10.5	13.9
DMSO (0.1%§)	4.2	8.4	9.7	16.5
THC (μg/ml)				
20	21.9	36.6	40.5	51.4
10	4.3	7.0	8.5	14.6
5	3.7	5.8	7.1	11.3
2	4.0	6.5	6.6	15.3
1	3.9	6.0	7.6	—

*Cells incubated in THC at indicated concentration, washed twice in medium to remove excess THC and tested for cytotoxicity at the times indicated.

†Mean percent cytotoxicity = $\frac{\text{counts/min experimental}}{\text{counts/min maximum release}} \times 100$

measured by ^{51}Cr release from three separate cultures using 2×10^4 cells/well. Variation between replicates was always less than 5% of the counts/min. Representative experiment from one patient.

§Concentration of DMSO equivalent to that used to dilute THC to 20 μg/ml.

Table 2. Suppression of natural killer cell activity by THC as function of time of exposure

Addition to cultures	Percent specific cytotoxicity after incubation with THC for* :8 h	4 h	3 h	2 h	1 h	0 h
Control (medium)	31.0	43.0	32.5	57.3	48.5	54.0
DMSO (0.1%)†	36.0	40.6	33.0	47.5	46.4	39.7
	(116.3)‡	(94.4)	(101.5)	(82.9)	(95.7)	(73.5)
THC (20 μg)	—	0.6	0.5	4.0	4.3	55.3
		(1.4)	(1.5)	(7.0)	(8.9)	(102.4)
(10 μg)	0.6	15.6	8.6	26.4	28.17	47.4
	(1.8)	(36.3)	(26.5)	(46.1)	(59.2)	(87.8)
(1 μg)	—	41.7	35.5	52.3	45.2	50.3
		(97.0)	(109.2)	(91.3)	(93.2)	(93.1)

*Cells incubated in THC at times indicated, washed twice in medium to remove excess THC and tested in 4 h NK assay against K562 target cells.

†Concentration of DMSO equivalent to that used to dilute THC to 20 μg/ml.

‡Percent of control.

PBLs separated by Ficoll–Hypaque centrifugation for use in the NK assay. Cells were adjusted to 1.1×10^6/ml RPMI 1640 medium supplemented with 10% fetal bovine serum and antibiotics and distributed into 12 × 75 mm plastic tubes (0.9 ml per tube).

THC treatment

Tetrahydrocannabinol (THC) was obtained from the National Institute on Drug Abuse, Research Technology Branch, Rockville, MD and reconstituted at 20 mg per ml in dimethyl sulfoxide (DMSO). This stock was diluted in RPMI 1640 medium immediately prior to addition to cultures. DMSO was also diluted in a similar RPMI 1640 and included as controls. THC was added to tubes in 0.1 ml amounts to yield final concentrations of 20, 10, 5, 2 and 1 μg/ml. Control cultures were incubated in either medium only or DMSO diluted in medium to a final concentration of 0.1%. Cells were incubated with THC for various times, ranging from 1 to 18 h at 37°C, in a humified atmosphere of 5% CO_2, 95%

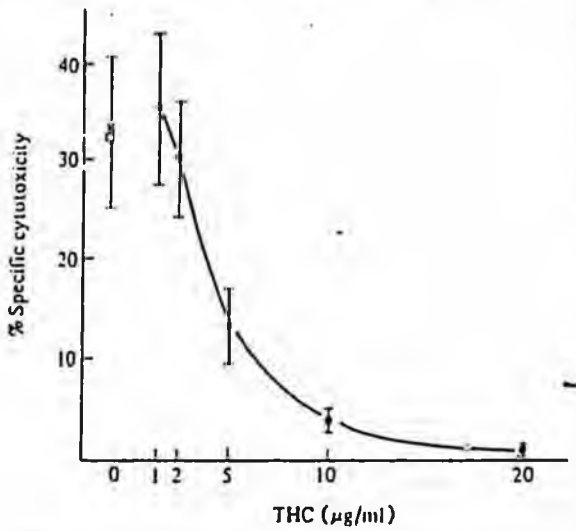

Fig. 1. Effect of THC on human natural killer cell activity. Effector cells were incubated in increasing concentration of THC (●), DMSO (○) or RPMI 1640 medium (X) for 3 h, then washed and incubated with 5 × 10^3 target cells at a ratio 50:1. Each point represents the mean of seven experiments ± S.E.M.

air. After incubation, cells were suspended in 5 ml RPMI 1640 to dilute the THC; then centrifuged at 500 *g* for 10 min at 4°C. The supernatant fluid was removed, the pellet was resuspended in 5 ml RPMI 1640 and centrifuged again to remove unbound THC. Supernatant fluid was again removed and cells were resuspended in RPMI 1640 and adjusted to 2.5 × 10^6 viable cells/ml, as assessed by trypan blue dye exclusion.

Natural killer cell assay

Target cells were the NK sensitive K562 erythroleukemia cell line which is commonly used to assess human NK activity. Cells were labelled with chromium-51 (Na_2 $^{51}CrO_4$) as described previously (Moody, Specter, Bendinelli & Friedman, 1984). Cells were washed free of execess chromium and adjusted to 5 × 10^4/ml RPMI 1640. 0.1 ml was added to wells of a 96 well round bottom microtiter plate for the assay. Effector cells were added to wells in 0.1 ml medium so that 2.5 × 10^6 cells/ml yielded an effector: target ratio of 50:1. The microtiter plate received also target cells only or target cells plus 0.1 ml medium. The former were used to measure maximum release and the latter spontaneous release. The plates were centrifuged at 250 g for 2 min and then incubated for 4 h at 37°C. Maximum release was attained by lysing target cells with 0.1 ml 10% sodium dodecyl sulfate, mixing well and removing 0.1 ml of the mixture. The remaining cells in the plates were then centrifuged at 500 g for 10 min and 0.1 ml supernatant fluid removed and placed in 7 × 35 mm glass tubes for counting in a gamma counter (United Technologies, Downers Grove, IL). Specific cytotoxicity was calculated using the formula

$$\% \text{ specific cytotoxicity} = \frac{\text{experimental release} - \text{spontaneous release}}{\text{maximum release} - \text{spontaneous release}}$$

Toxicity of the THC for lymphocytes was measured using lymphocytes labelled with ^{51}Cr. As can be seen in Table 1, when cultured for up to 3 h in THC lymphocytes were killed by the 20 μg/ml dose but not lower doses ranging from 10 to 1 μg/ml. The DMSO control was not substantially different from leukocytes incubated in culture medium alone. Visual counting for viability using trypan blue dye exclusion confirmed these results. On the basis of these findings cells were always readjusted after incubation in THC so that cell counts reflected the number of viable cells at the time of initiation of the NK assay.

RESULTS

Pretreatment of leukocytes with THC in doses ranging from 1 to 20 μg/ml for up to 18 h revealed that there was a direct relationship between the time of exposure and the resulting suppression of NK activity (Table 2). Virtually all NK activity was lost upon exposure to 20 μg/ml THC for 3 h and 10 μg/ml for 18 h. Incubation for 1 or 2 h resulted in proportionately less suppression, whereas addition of THC directly into the 4 h NK assay (time 0) had no appreciable effect even at 20 μg/ml.

Additional experiments were performed using a pre-incubation of 3 h in THC, then removal of the drug for the NK assay. As can be seen in Fig. 1, as little at 5 μg/ml THC had a marked suppressive effect on NK function. However, 2 or 1 μg/ml had no noticeable effect. Suppression was highly dose dependent with a stronger effect noted as the dose increased to 20 μg/ml. The NK depressive effects of THC were observed over a broad range of effector to target cell ratios. However, examination of percent reduction of cytotoxicity vs positive controls revealed that a consistent suppressive effect of THC at 10 and 20 μg/ml is achieved at all E:T ratios (Table 3).

Table 3. Effect of THC on natural killer cell activity at difference effector to target cell ratios

Additions to cultures	Percent specific cytoxicity 50:1*	25:1	12:1	6:1	3:1
Control (medium)	49.1†	38.8	22.2	12.1	7.0
DMSO (0.1%)	65.8	47.1	31.2	17.3	10.3
	(134.0)‡	(121.4)	(140.5)	(144.2)	(147.1)
THC (20 μg)	0.9	0.0	0.8	0.2	0.0
	(1.8)	(0)	(3.6)	(0.2)	(0)
(10 μg)	9.8	5.0	3.4	2.8	1.3
	(20.0)	(12.9)	(15.3)	(12.2)	(18.6)
(1 μg)	53.0	38.4	23.9	12.8	7.9
	(107.9)	(99.0)	(107.7)	(106.7)	(112.9)

*Effector:target.
†Mean of two individuals.
‡Percent of control.

DISCUSSION

The data presented demonstrate that delta 9-THC, when added to human peripheral blood leukocytes, decreases their ability to function in the 4 h NK cell cytotoxicity assay. This activity was dependent upon the length of time the effector cells were exposed to THC and the dose of THC. Killing was independent of the effector to target cell ratio over a wide range. Although THC was cytotoxic for PBL at a dose of 20 μg/ml, this cannot be the explanation for the suppressive effects of the drug since cells were readjusted at initiation of the NK assays. Lower doses, i.e. 10 μg/ml and 5 μg/ml, were also highly suppressive for NK cell function but did not have any effect on effector cell viability.

The mechanism by which THC is capable of suppressing NK activity is as yet unclear. Preliminary experiments to delineate this mechanism have shown that indomethacin has no effect in reversing this suppression (unpublished data). Thus suppression cannot be attributed to induction of prostaglandins, since indomethacin is known to inhibit prostaglandin synthesis (Brunda *et al.*, 1980). This is an important observation since prostaglandins have been shown to suppress NK function in other systems (Brunda *et al.*, 1980; Droller *et al.*, 1978; Kendall & Targan, 1980). It is also possible that the lipophilic nature of THC results in an interference with ion channels in the NK cell membrane. Recently, a preliminary report has appeared (Schlichter & Sidell, 1985) demonstrating a suppression of NK killing by potassium and calcium channel blockers. This reduced NK activity in THC exposed PBL may be a highly significant observation since THC has been implicated, in experimental infection models, in enhancement of susceptibility to infection (Bradley, 1984; Juel-Jenson, 1972; Morahan, Klykken, Smith, Harris & Munson, 1979). Such enhanced susceptibility could be due to suppressed NK activity.

Interestingly, other psychoactive agents have recently been reported to alter NK cell function. Two separate reports indicate that either endorphins (Kay, Allen & Morley, 1984) or enkephalin (Faith, Liang, Mungo & Plotnikoff, 1984) can enhance NK activity. Conversely, morphine and "opioid stress" resulted in depression of NK cytotoxicity (Shavit, Lewis, Terman, Grale & Liebeskind, 1984). While these data do not allow any generalization about psychoactive agents and NK activity, they do lead to speculation about possible mechanisms for the immunomodulatory activities. Suppression of NK function could be generated indirectly by THC by stimulating the release of immunosuppressive hormones like adrenocoritcosteroids, which are known to inhibit NK activity (Cox, Holbrook, Grasso, Specter & Friedman, 1982; Hochman & Cudkowitz, 1979); or by inhibition of interferon synthesis. Morphine, for example is known to depress interferon levels (Hung, Lefkowitz & Geber, 1973). While the mechanism of THC induced suppression remains to be determined, the results generated by other psychoactive agents have yielded clues as to how this may be pursued.

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MINIREVIEW

IMMUNOMODULATION BY MORPHINE AND MARIJUANA

M. Danial Yahya[1,2] and Ronald R. Watson[2,3]

[1]Department of Microbiology, Universiti Kebangsaan Malaysia
43600 UKM Bangi, Malaysia
[2]Department of Family and Community Medicine
University of Arizona, Health Sciences Center
Tucson, AZ 85724

Summary

The immunomodulatory effects of morphine and the active components of marijuana, particularly tetrahydrocannabinol, on various aspects of the host immune parameters include alterations in humoral, cell-mediated and innate immunity. Most studies have shown immunosuppressive effects due to use of these abused substances, although there are reports that they may not produce any deletrious effect and may even enhance some aspects of host immunity. They reduce resistance to cancer growth and microbial pathogens in animals.

Morphine and marijuana have profound effects on the immune parameters of their users. The adverse effects of morphine can lead to various immune dysfunctions including increased susceptibility to infections and neoplasms. Similarly, the widespread use of marijuana for recreational purposes have raised concerns about its' cardiac complications, psychomotor impairment, genetic hazards, psychopathological conditions and immune suppression (1). Ironically, delta-9-tetrahydrocannabinol (THC), the major psychoactive ingredient in marijuana has been shown to be an antiemetic drug in cancer patients. The combination of these factors has made THC an actively investigated drug. Human and animal studies have revealed a myriad of effects attributed to THC (2). This review summarizes studies that have been performed in man and animals to understand morphine and marijuana modulation of immune responses.

Morphine-Induced Immune Alterations in Man.

Several studies have drawn a parallelism between morphine abuse and immune inhibition. In vitro studies showed that polymorphonuclear cells (PMN) and monocytes from patients subjected to morphine treatment were severely depressed in their phagocytic and killing properties, as well as their ability to generate superoxide (3). Opiate addiction also caused alterations in the frequencies of T and null lymphocytes in human peripheral blood. A study by McDonough et al showed that as a result of opiate addiction there was a significant decrease in the number of T lymphocytes that form rosettes with sheep red blood cells (SRBC). This decrease was accompanied by a concurrent increase in the number of null cells. However, there was no significant change in the number of B lymphocytes. These alterations in T and null cell

[3]To whom the reprint request should be addressed

0024-3205/87 $3.00 + .00

Table 1.. Summary of the effects of morphine or marijuana on various aspects of the immune system.

Immune Response	MORPHINE			MARIJUANA OR THC		
	Suppressed	Enhanced	Not Altered	Suppressed	Enhanced	Not Altered
Resistance to:						
C.albicans	10*			61		
L.monocytogenes						
K.pneumoniae	10					
Tumor	14					
Viral infections				60,61,62		
Phagocytosis	3,10,20			33,51,54		42
Phagocyte killing	3,20					
Superoxide generation	3,10,20					
Antibody levels				31,49,50		46
Primary antibody response	11			49,53,54		
Secondary antibody response				49		
Interferon levels	15,16			55,57,59		
Blastogenic response to:						
PHA	4			26,27		37,38,39
Con A	21,22			51		
LPS				51		
PWM				52		40
Lymphocyte frequencies:						
T cells	4	6		28,29,30		
Null cells	4	6				
NK cell activity	13,17	12		32,52,58		
Cellular immunity	18,19			39,49,50		36,41

*Numbers indicate reference(s) in which the observations were reported.

frequencies were reversed by treatment of the lymphocytes in naloxone, a morphine antagonist. This reversal was paralleled by an increase in the ability of these lymphocytes to be stimulated by phytohemagglutinin (PHA) (4). Subsequently, it was shown that the decrease in SRBC-rosetting was due to a morphine-induced depression of SRBC receptor levels on T cells (5). In contrast to the results of these studies, Bocchini et al showed that incubation of normal human lymphocytes in either morphine or naloxone caused an increase in the frequencies of these cells as well as their response to PHA stimulation (6).

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There is also convincing evidence of the presence of opioid receptors on various types of human immune cells. Wybran et al were the first to provide evidence of receptors specific for morphine on normal human T lymphocytes (7). This observation has been confirmed by other workers (4,8). Subsequently, the presence of opioid receptors have been demonstrated on human PMN and monocytes (9), and platelets (8). The presence of opioid receptors on immune cells may allow for modulation of specific immune functions in the presence of exogenous opiates.

Morphine-Induced Immune Alterations in Animals

Studies have been performed in animals to elucidate the mechanisms by which morphine affects the immune system. Morphine administration in mice caused a profound increase in susceptibility to bacterial and fungal infections. Various administration schedules were shown to potentiate infections due to Klebsiella pneumoniae and Candida albicans (10). The increased susceptibility was partly due to a decreased reticuloendothelial system activity as well as a reduction in the number of phagocytes and not due to a direct cytotoxic effect of the drug. A reduced capacity to produce superoxide was also observed. These observations are in agreement with altered disease resistance in man (3).

Chronic administration of morphine also inhibited the primary antibody response of mice to SRBC, and the spleen:body weight ratio. These effects were antagonized by naloxone indicating that morphine inhibits the immune system in a specific manner via its interaction with opioid receptors (11).

Other studies in animals have shown that morphine can affect natural killer (NK) cell activity (12,13,17) perhaps yielding reduced resistance to tumors (14). Interferon (15,16) and a variety of other cell-mediated reactions are also altered (18-23). The effect of morphine on NK cell activity in animals is not well defined. The drug has been shown to enhance the activity of these cells in mice (12) but a suppression was observed when similar experiments were performed in rats (13,17). The ability of animals to mount a response to tumor challenge was also affected by morphine treatment. Rats given injections of morphine either before or after challenge with a mammary ascites tumor showed a significant decrease in survival time and percent survival. It was postulated that morphine enhances the susceptibility to tumor via its inhibition of NK cell activity (14). Reduced phagocytic or cytotoxic actions of monocytes could also affect cancer resistance. In vitro studies using cells from morphine-treated mice have demonstrated that PMN and mononuclear cells from these animals were reduced in their ability to phagocytize and kill C. albicans and also in their generation of superoxide (20).

In vivo studies in rats revealed that animals chronically- treated with morphine exhibited an inability to produce a tuberculin reaction (18), a measure of cell-mediated immunity (CMI), as well as a depressed ability to produce an inflammatory reaction in response to carrageenan (19). This effect was dose-dependent and inhibited by naloxone. Reduced mitogenesis may also be important in disease resistance functions associated with inflamation. Lymphocytes from morphine-treated mice (21) and guinea pigs (22) were decreased in their mitogenic response to stimulation with Concanavalin A (Con A).

Such changes, which can also include morphine suppression of spleen and body weight, and plaque-forming cells of mice (23), show evidence of significant changes in immune functions. A reduction in number and size of splenic germinal centers, total spleen cellularity and thymic size was

observed. Histological examination revealed that there was a loss of peripheral definition of splenic follicles (23). There is limited information on morphine and production of immunological proteins. Another adverse effect of morphine is the depression of serum interferon titers. Mice that were treated with morphine had depressed levels of serum interferon following injection with polyinosinic: polycytidylic acid (poly I:C) (15,16).

These studies have shown that there is a strong parallelism between host susceptibility to diseases as a result of exposure to morphine and alterations in the physiology and functions of immune cells.

Effects of THC on Human Immune Systems

Several approaches have been used to study the effects of marijuana or its active component, tetrahydrocannabinol (THC), on human immune systems. These include using cells isolated from chronic marijuana smokers, cells from normal volunteers exposed to marijuana smoke or using cells from normal donors and exposing these cells to THC in vitro. Results obtained from human studies have been equivocal. Several studies have found THC to be immunosuppressive while others have been equivocal.

A survey of 51 chronic marijuana smokers showed that the response of their cells to stimulation with allogeneic cells or PHA was depressed. These observations were supported by in vitro studies which showed that normal human lymphocytes incubated in THC were depressed in their blastogenic response to similar stimuli (26,27). Peripheral blood lymphocytes from chronic marijuana smokers contained reduced number of T lymphocytes that form rosettes with SRBC (28-30). A similar reduction could also be achieved by in vitro incubation of normal lymphocytes in THC (28). Although marijuana use was able to interfere with T lymphocyte function as measured by rosetting and PHA-stimulation, this effect was transient and varied between individuals (30).

However, several other studies have shown that marijuana smoking or THC is not immunosuppressive. The skin responses of 22 chronic marijuana smokers against 2,4-dinitrochlorobenzene (DNCB) showed no significant difference from those of normal controls (36). The blastogenic response of cells from chronic marijuana smokers to PHA (37-39) and pokeweed mitogen (PWM) (40) were also similar to those of cells from normal controls. An evaluation of the immune status of 12 healthy chronic marijuana smokers revealed that while there was an initial depression of various immune parameters in several subjects, these values returned to normal over time (41). The values in the other subjects were not significantly different from normal. The authors concluded that marijuana smoking did not produce any significant impairment of either humoral or cell-mediated immunity (41). Functional comparisons of macrophages from marijuana smokers and non-smokers showed that these cells have similar capacities to phagocytose C. albicans (42) although marijuana smoking has been shown to be more injurious to the lungs than cigarette smoking (43).

Other immune alterations that have been associated with marijuana or THC include significantly reduced serum IgG levels in chronic smokers (31), inhibition of NK cell activity (32), inhibition of phagocytic activity (33), elevation of serum IgD levels (31), decreased T:B cell ratio as a result of reduced T cell numbers (29,33) and inhibition of leukocyte migration (34). THC also inhibited DNA, RNA and protein syntheses in PHA-stimulated normal human lymphocytes (35).

Results from human studies have thus shown many inconsistencies. The findings probably reflect how various parameters may affect the outcome of any study. Factors such as sex, age, hormonal balance, nutritional status, length

of exposure to the drug as well as its quality, and other drugs may have had a significant influence on the outcome of these investigations. Some studies may be suspect if carried out in the past six years in areas where rates of infection with human immunodeficiency virus (HIV) were significant in intravenous drug users, as the virus is immunosuppressive.

Effects of THC on the Humoral Immune System of Animals

Studies performed in animals have produced more consistent findings than those in humans. In most cases THC is associated with immunosuppression of various immune parameters. The greater consistency observed in animal studies probably reflects the influence of genetic factors, consistent dosage levels, controlled diets, and use of other drugs.

Several studies have shown an immunosuppressive effect of THC on the humoral immune response of animals. Administration of THC prior to or post immunization of mice with SRBC significantly reduced the number of plaque forming cells in their spleens (44-48) as well as hemagglutinin titers (49,50). A concurrent loss of germinal centers and follicular definition, together with a reduction of splenic lymphocytes, and reduced spleen and body weights were observed in mice treated with THC either before or after immunization with SRBC (44,45). Although THC caused an inhibition of the primary anti-SRBC response, it did not suppress the secondary response if THC was given together with the secondary antigenic challenge. However, if THC was given during primary immunization, the response to secondary challenge was suppressed indicating an inhibition of the memory aspect of humoral immunity (49). A study by Levy and Heppner (46) found that THC only changed the kinetics of plaque forming cell production. Mice treated with THC were shown to produce peak plaque forming cell numbers 24 - 48 hours later than control mice while the numbers did not vary significantly. In contrast to the finding of other investigators, they did not observe any significant reduction in hemagglutinin titers in THC-treated mice.

In vitro observations that support other findings of THC-induced suppression of humoral immunity include demonstration of a reduced blastogenic response of splenic lymphocytes to Escherichia coli lipopolysaccharide (51) or PWM (52), which are both B cell mitogens, and a depressed in vitro primary-like immune response of mouse splenocytes against SRBC (53,54). THC was suppressive if it was present during the entire 6 day culture period or for the first 24 hours following antigenic stimulation. This indicates that the presence of THC during the period following antigenic stimulation was critical for an immunosuppressive effect (53).

Effects of THC on Cell-Mediated Immunity of Animals

The immunomodulatory effect of THC on the CMI of animals has also been demonstrated. In vitro and in vivo measures of CMI that have been studies in relation to THC-induced immune modulation include delayed type hypersensitivity (DTH) to SRBC (39,47), rosette-forming T cell numbers (45), blastogenic responses of lymphocytes to PHA (51) and Con A (54), skin graft survival (50), mixed lymphocyte reaction and migration inhibition factor activity (55). Most of these studies revealed an immunosuppressive effect of THC. For example, the DTH response to SRBC was significantly lowered in mice treated subcutaneously with THC at a dose of 100 mg/kg for 4 days (49), or in mice fed THC perorally at a dose of 30 mg/kg (39). Skin graft survival was increased in mice as a result of treatment with THC (50). This indicates a suppression of the cellular mechanism involved in graft rejection. Finally, the blastogenic response of lymphocytes to PHA and Con A, which are both T

cell mitogens, was depressed in mice treated with THC (51), and in monkeys administered marijuana smoke (52).

Other studies have demonstrated an immunosuppressive effect of THC on other mechanisms involved in immunity. These include inhibition of phagocytic function (54,56), interferon production (55,57) and NK cell activity (52,58). THC, at levels that are attainable by smoking marijuana, inhibited macrophage spreading and phagocytic function (51). In vitro and in vivo interferon production were also depressed by THC. Mice treated with THC produced lower titers of interferon in response to stimulation with poly I:C or Herpes simplex Type 2 virus (57). Splenocytes from normal mice also produced less interferon in in vitro cultures in the presence of THC (59).

These studies have thus been able to provide strong evidence of the immunosuppressive effects of THC particularly in animals. Such effects were clearly demonstrated by studies that showed that animals exposed to THC were more susceptible to infections. THC is capable of exacerbating viral infection, as has been shown in mice (60,61) and guinea pigs (62), as well as reducing resistance to bacterial pathogens (61,63). The resistance of mice to Listeria monocytogenes, which is used as a measure of CMI, was inhibited by THC in a dose dependent manner (61). Thus, these findings reflect an inhibition of CMI by THC, supporting in vitro observations.

There are thus obvious differences in the susceptibility of man and animals to the immunomodulatory effects of marijuana and THC. Clearly animals studies show that THC is immunosuppressive and reduces disease resistance. Whether such changes occur regularly in man is less clear due to fewer studies and problems of determining dose. Due to these differences it is very difficult to make definitive conclusions on the suppressive effects of this drug on the human immune system. They may have significant relevance due to the current AIDS epidemic, where immunomodulation of T cells would be expected to alter the growth of the virus, and possibly its infectivity.

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Developmental Effects of Cannabis

GABRIEL NAHAS AND HENRY CLAY FRICK

College of Physicians and Surgeons of Columbia University, New York, New York 10032

Cannabis preparations (Marihuana, Hashish) have become the most frequently used illicit drug in the United States and the Western World. Besides the chemical euphoriant Delta-9-Tetrahydrocannabinol which Cannabis contains, 60 other cannabinoids have been identified as well as 360 other compounds such as Sterols, Terpenes, Flavinoids, Furan derivatives and alkaloids. Marihuana smoke of a marihuana cigarette contains in its gas phase: Carbon Monoxide, Acetaldehyde, Acrolein, Toluene, Nitrosamine, Vinyl Chloride and in its particulate phase: Phenol, Cresol, Methyl. It also contains twice as much Napthalene and Carcinogens (Benzanthracene and Benzopyrene) than in a tobacco cigarette of the same weight.

Available evidence indicate that Cannabis exerts significant effects in all phases of reproduction and development in members of both sexes in all species which have been studied: these include fish, birds, rodents (mice, rats, hamsters) rabbits, dogs, horses, monkeys and homo sapiens. Several reviews have been written on the subject (Nahas 1984, Rosenkrantz 1985).

Experimental studies have reported that negative developmental effects can be caused by Cannabis in three ways:

1. Preconception exposure with resulting damage to the gametes, sperm or ovum (gametotoxicity).
2. Prenatal exposure with resulting damage to the embryo and to the fetus during organogenesis.
3. Postnatal exposure through maternal milk, with resulting damage to the growing offspring, and behavioral toxicity.

PRECONCEPTION EXPOSURE

Cannabis may be gametotoxic in male and female.

Evidence in the male.

Administration of delta-9-THC or crude marihuana extract (CME) decreases testicular size in pigeons (Vyas and Singh, 1976), rodents (Dixit et al., 1974), and dogs (Dixit et al., 1977). This organ is sensitive to Cannabis preparations in many different routes (Bloch et al., 1978). Immature and mature animals are equally affected. Fujimoto et al. (1978) reported that adult rats treated with CME (15 and 75 mg/kg orally) for 77 days presented a significant reduction in prostate, seminal vesicle, and epididymal weight. Oligospermia in the epididymis was also present.

Please send requests for reprints to Dr. Gabriel Nahas.

Thirty days after cessation of treatment, testicular function and organ weight appeared to return to control levels. Abnormal forms of sperm were reported in mice treated for 5 days with delta-9-THC (5-10 mg/kg, i.p.) or CBD (10-25 mg/kg) (Zimmerman et al., 1979), and in rats exposed to marihuana smoke for 75 days (Huang et al., 1979). CBD decreased testicular size and spermatogenesis (at all stages) in rhesus monkeys (30-300 mg orally) (Rosenkrantz et al., 1981).

Hembree et al. (1976) observed 16 patients in a hospital ward before, during, and after a 4-week period of marihuana smoking (5-20 cigarettes a day, equivalent to 100-400 mg delta-9-THC). Marihuana administration was associated with decreased sperm count, sperm motility, and an increased incidence of abnormally non-ovoid shaped sperm cells (Fig.1). These changes were most marked 4 weeks following onset of smoking and 1 week after the smoking period had terminated, indicating that effect of the cannabinoid is exerted on spermiogenesis since hormonal suppression of spermatogenesis takes longer than a month and is usually not associated with an increase in abnormal form and decrease in motility. Hembree et al. (1979) concluded that the inhibitory effect of Cannabis smoke on spermatogenesis was also exerted directly on the testicular germinal epithelium (besides the possible indirect effect of THC on spermatogenesis through gonadotropin suppression). Many experiments reviewed elsewhere (Rosenkrantz, 1985) and beyond the scope of this paper have been carried out to clarify the mechanism causing morphological changes in sperm: THC exerts its effects on the hypothalamo-pituitary axis and also with other non-psychoactive cannabinoids directly on testicular cells. All of these alterations of gonadal function in the male have not been associated in man with an increased incidence of developmental defects in his offspring.

However male preconception exposure to Cannabis has been associated in mice with developmental defects of his offspring. Dalterio et al. (1982) treated male mice orally with large doses of CME (25 mg/kg for 5 days, or a single dose of 50 mg/kg), and with CBN or THC (single 100 mg/kg dose). Such treatment was associated with a reduction in fertility, increased pre- and post natal losses, and reduced litter size persisting several weeks after discontinuation of treatment. Cytogenetic studies of sperm cells indicated increased frequency of chromosomal abnormalities including ring translocations and nondisjunction. These same effects were observed in 30% of the F1 offspring of the treated mice. Major teratology was recorded in three of these F1 offspring. Dalterio et al. (1982) conclude that cannabinoids can be gametotoxic.

Evidence in the female.

Henrich et al. (1983) have reported that 30-day old female mice were given 0.1 mg THC i.p. for 21 days. Ovulation was indu-

FIG. 1. Top: Normal ovoid shape human spermatozoa sampled from tobacco smoker and moderate alcohol drinker. Bottom: Non-ovoid and immature form present among ovoid shape human spermatozoa sampled from daily marihuana smoker. (From Hembree et al., 1978, with permission.)

ced by FSH and chorionic gonadotropin, injected to the treated females and controls, which were then mated and sacrificed 24 to 48 hrs later. THC treated animals presented a higher incidence of abnormal fertilized ova in their early stage of development than untreated mice. Such studies suggest that chronic THC administration may have a significant effect on ovarian oocyte or on early embryonic development of the mice.

In the nonhuman female primate, THC acutely inhibits FSH, LH and prolactin, and disrupts ovarian cycles and ovulation (Smith 1979). Tolerance to these effects develops (Smith et al. 1983). In women smoking marihuana, a disruption of the mensrual cycle has been reported. Tolerance to these effects also develops (Mendelson et al., 1985). Possible gametotoxic effects of THC in the human female needs to be ascertained.

PRENATAL EXPOSURE

Radioactive delta-9-THC crosses the placenta to accumulate in the fetus of pregnant mice (Freudenthal et al., 1972; Harbison and Mantilla-Plata, 1972; Kennedy and Waddell, 1972; Pace et al., 1973) hamsters, (Idänpän-Heikkila et al., 1969) and dogs (Martin et al., 1976). The drug deposits in yolk sac, fetal tissues, and amniotic fluid. Martin et al. (1977) reported that radioactive delta-9-THC was concentrated in the brain of the dog fetus 20 min after injection into the mother. There is a THC concentration gradient of mother → placenta → fetus (Bloch, 1983). Loss of delta-9-THC from fetus and placenta was lower than that found in the mother, which may prolong fetal exposure to the drug (Mantilla-Plata and Harbison, 1976 a,b).

As is the case with other xenobiotics that cross the placenta embryotoxicity, teratogenicity and fetotoxicity have all been reported in different pregnant animals of different species treated with cannabinoids. Incidence of either of these three developmental defects is dependent upon time and length of administration, dose administered, or nature of substance administered, and route of administration and species studied (Rosenkrantz, 1979; Bloch, 1983). The higher the dose, the more likely one of these defects will occur.

Embryotoxicity. Oral doses of delta-9-THC of 5 to 50 mg/kg in mice and of 12 to 50 mg/kg in rats during day 6 to 15 of pregnancy increases incidence of resorption (Rosenkrantz, 1979). Optimal susceptibility to embryotoxicity occurred between days 7 and 9 of gestation. When doses administered were increased from 450 to 600 mg/kg, 21 to 100% fetal resorption was observed. Mice exposed to inhalation of marihuana (0.8-3.8 mg/kg) during the same period of gestation also displayed an increased incidence of fetal resorption. These findings are in agreement with those of Joneja (1976, 1977) and of Mantilla-Plata and Harbison, observed in mice, and of Fried (1976) who reported increased resorption of rat fetus expo-

sed to marihuana smoke from day 1 to 14 of gestation.

The mechanism of embryotoxicity of the cannabinoids has not been identified but Rosenkrantz (1979) noted that there was a correlation between midgestation vaginal bleeding and excessive fetal resorption. This observation suggested a possible direct effect on the endometrium and associated development of feto-placental circulation. A similar result could also have been caused by the effect of these substances on maternal control of neuropeptides and hormones required for maintenance of normal pregnancy.

Fetotoxicity. The growth of the fetus was also impaired by prenatal administration of crude marihuana extract or THC in mice, rats, rabbits, and hamsters. The same dose given orally that increased resorptions (5-30 mg/kg) resulted in retardation of growth, smaller weight, and reduced survival of the fetus (Banerjee et al., 1975; Harbison et al., 1977; Joneja, 1977; Mantilla-Plata and Harbison, 1976 a.b; Soffia, 1979; Wright, 1976). Nahas et al. (1982) reported that oral administration of CME (not exceeding 25 mg/kg of cannabinoid) from day 6 to 19 of gestation was associated with decreased fetal and placental weights (Table 1). Szeto and Cook (1983) administered 5 mg THC, i.v., to a pregnant ewe, with measurable THC. Decrease in heart rate and disruption of sleep cycle were observed in fetus and ewe with measurable THC.

Table 1.

Effects of Cannabis Extracts on Fetal Development in the New Zealand Rabbit (mean litter data)

Group	Number of animals	Number of viable fetuses ♂	♀	total	Number of resorptions early	late	total	Imp. placta	Corpora lutea	% Loss pre-implantation	% Fetal loss	Litter weight (g)	Fetus weight (g)	Total placental weight (g)	Placenta weight (g)
4[a]	14	3.8	4.6	8.4	0.5	0.5	1.0	9.4	11.2	16.5	10.9	363.4	45.26	47.7	5.94
5[b]	14	4.2	5.2	9.4	0.9	1.0	1.9	11.3	11.9	5.1	19.3	330.7	37.02***[d]	43.2	4.91***[d]
6[c]	14	3.8	5.2	9.0	0.5	0.3	0.8	9.8	11.2	12.7	8.0	351.6	39.90*[d]	43.4	4.98*

[a]Control treated by subcutaneous injection of 1 ml/kg of isotonic solution containing 1% Tween 80.
[b]Treated by subcutaneous injection of 1 ml/kg of cannabis extract dissolved in the preceding solution and containing 5 mg of THC, 0.65 mg of CBD + CBC, and 0.45 mg of CBN.
[c]Treated by intragastric administration of 1 ml/kg of cannabis extract in sesame oil and containing 5 mg THC, 0.65 mg of CBD and CBC, and 0.45 mg of CBN.
[d]* $p < 0.05$ (Kruskal-Wallis test).
** $p < 0.01$ (Kruskal-Wallis test).
*** $p < 0.001$ (Kruskal-Wallis test).

from Nahas et al. (1982)

Blood concentration in both for 8 hours. The fetotoxicity and embryotoxicity related to Cannabis exposure and reported in rodents has also been observed in primates (Sassenrath et al., 1979). A group of female rhesus monkeys given an oral daily dose of 2.4 mg/kg to 4.8 mg/kg delta-9-THC for 1 to 4 years had no decrease in number of conceptions but presented a 42% loss of the products of conception at all stages of development, from first trimester to early infant death. There was no specific, consistent congenital

anomaly. The reproductive loss in the control group was 8 to 11%. Surviving male infants had a reduced birth weight and showed altered autonomic and behavioral responsiveness to visual, auditory, and social environmental stimuli. There was no evidence of a deficit related to drug exposure of the sperm of delta-9-THC fathers. Also, evidence for a contribution of direct damage to the ova was lacking. These studies did not suggest any cumulative effect over sequential pregnancies in individuals drugged females. Sassenrath states that "the absence of frank specific teratology and the nonspecific nature of pregnancy interruption and morphological changes suggest that the drug might have impaired the maternal support of the fetus", e.g., placental circulation and function, a conclusion similar to that reached by Rosenkrantz (1979).

Teratogenicity. "High doses of crude marihuana extract or of delta-9-THC are teratogenic in animals" (Marihuana and Health, IOM Report 1982). One might add in certain species. Gerber and Schramm (1969) reported that subcutaneous injection of crude marihuana extracts greater than 200 mg/kg in hamsters and 250 mg/kg in rabbits were teratogenic (runting, encephalocele). Bloch (1978, 1983) has evaluated the conflicting reports concerning the teratogenic potential of Cannabis, and found evidence of a clear teratogenic response in mice (Mantilla-Plata et al., 1973, 1975; Mantilla-Plata and Harbison, 1976 a,b; Harbison et al., 1977; Joneja, 1976; Kostellow et al., 1978). The most frequently described lesion was cleft palate and exencephaly. As reported by Joneja (1976) in mice treated orally with 400 mg/kg of THC, 12% of live fetuses were deformed. Other investigators have found congenital defects in dental developments in rats (delta-9-THC, 3-20 mg/kg/day) including impaired incisor eruption (Fried, 1976) and maxillary asymmetry (Siegel et al., 1977).

Furthermore, substances such as phenobarbital which interact with delta-9-THC metabolism will enhance the teratogenic potential of this drug in mice (production of cleft palate, Harbison et al., 1977). Zebrafish (Thomas, 1975) placed in a medium containing 10 ppm of delta-9-THC produced offspring with curved spine and bulbous tails.

Other species of rodents, such as hamsters and rats, are less sensitive than the mice to the teratogenic effects of large doses of delta-9-THC or Cannabis extract, and several investigators (Harley et al., 1973; Wright et al., 1976) have failed to duplicate the early observations of Persaud and Ellington (1968) who reported malformations in rats treated intraperitoneally with Cannabis resin.

Other studies failed to demonstrate teratogenicity of 1 to 250 mg/kg of THC administered per oz or subcutaneously to rats from gestation day 5 to 15 (Borgen et al., 1971, 1974; Pace et al., 1971; Uyeno, 1975; Banerjee et al., 1975; Vardaris et al., 1976; Wright et al., 1976). The large amounts of cannabinoids

sed to marihuana smoke from day 1 to 14 of gestation.

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required to produce their effects in animals make it doubtful that these xenobiotics could be grossly teratogenic in man. They might however, facilitate the teratogenicity of other teratogens by lowering the threshold at which these exert their effects (Harbison, 1977). Despite the lack of uniformity of aberrations of Cannabis-evoked teratogenic effects, a common observation has been that of a dose-related increased incidence of embryotoxicity and fetotoxicity (Rosenkrantz, 1979) in all species studied, mice, rats, hamsters, rabbits and primates. These toxic effects on embryo and fetus development occur with delta-9-THC doses which are comparable to those of chronic marihuana use in man.

PERINATAL EFFECTS

Dalterio et al. (1981) have reported that maternal exposure in mice to delta-9-THC or CBN the day before parturition, and for 6 days postpartum, produced long-term alterations in body weight regulation, pituitary-gonadal function, endocrine responsivity to females and adult copulatory behavior. Effects of perinatal exposure did not become apparent until just before puberty.

Milk production in pregnant and lactating rodents treated with marihuana extracts or THC was markedly inhibited (Borgen et al., 1971; Szepsenwol et al., 1979).

The passage of delta-9-THC into mother's milk where it is concentrated because of its elevated fat content was first documented by Jacubovic et al. (1973) in the rat given a single intravenous injection of 0.2 to 1 mg/kg dose, and confirmed by Chao et al. (1976) in the squirrel monkey. Radioactivity was also present in urine and feces of suckling infants. Similar findings were reported in two women smoking marihuana (Perez-Reyes et al., 1982) who were feeding their infants. Their milk contained elevated concentrations of the cannabinoids which were eliminated in feces and urine of the infants.

POSTNATAL DEVELOPMENT

Borgen et al. (1971) using a cross-fostering technique, reported that offspring of rats given delta-9-THC on days 10 to 12 of gestation were retarded in the development of visual-placing reflexes and cliff avoidance. Other similar studies of learning defects in offspring of rats injected with cannabinoids (Gianustos and Abbatiello, 1972; Vardaris et al., 1976) have been reviewed earlier.

Marihuana and its purified components administered prenatally impair development process in experimental animals. Learning deficits were demonstrated in 21 to 65 day old pups from rats treated with Cannabis extracts or delta-9-THC during gestation (Gianustos and Abbatiello, 1972; Vardaris et al., 1976). Luthra

(1979) reported that THC 10 to 15 mg/kg administered to gestating and lactating rats by the oral route produced significant decrements in RNA, DNA and protein concentration in the developping brain of the offspring. These findings may be important in the light of the role of protein and nucleic acids in learning and memory (Barondes, 1970; Glassman, 1969). Dalterio et al. (1982) reported that maternal exposure of mice to cannabinoids either 2 or 4 days before parturition reduced brain amine concentration (dopamine, norepinephrine in the adult male offspring).

Sassenrath et al. (1979 a) have also reported behavioral anomalies in offspring of the THC treated rhesus monkeys which display: 1. enhanced responsivity - both autonomic and behavioral - to visual and auditory stimuli, 2. less fear and avoidance behavior in a novel environment, and 3. overstimulation and assertiveness in response to peer serialization.

CLINICAL REPORTS OF DEVELOPMENTAL EFFECTS OF CANNABIS

The use of Cannabis has been mentioned in six clinical reports describing congenital anomalies in offspring of mothers who had consumed the drug during pregnancy (Bogdanoff et al., 1972; Carakushanky et al., 1969; Geleherter, 1979; Hecht et al., 1968; Jacobson and Berlin, 1972; Qazi et al., 1985). In the first five reports, the use of Cannabis was associated with that of other psychoactive drugs (LSD, amphetamines, barbiturates) and major malformations were reported. In the report of Qazi et al., the mothers admitted smoking marihuana daily during pregnancy, while categorically denying use of alcohol and other psychoactive substances. The five resulting infants displayed symptoms of intrauterine growth retardation - lower birth weight, shorter height, smaller head circumference, abnormal neurological manifestations and facial anomalies. These anomalies are similar to those described in the fetal alcohol syndrome, which was first scientifically documented in 1968 (Lemoine et al.), confirming observations made since recorded history.

Two other reports appeared in 1982. In the first, Greenland et al. (1982) report a prospective study on the effects of marijuana use, with the exclusion of other drugs, in 35 pregnancies. Infants born to users exhibited significantly more meconium staining (a condition that doubles the risk of neonatal death). Users had a higher proportion of protracted or arrested labor and of precipitate labor, as well as a higher proporiton of abnormal fetal rests. In the second study, on a cohort of 1,690 mother/child pairs (Hingson et al., 1982), marihuana use during pregnancy (n=181) was associated with infants who were 300g. lighter than infants of non-users ($p < .001$), and controlling for confounding variables lighter by 103g ($p < 0.01$). Compared with non-users, women who had used marihuana during pregnancy delivered smaller infants, as

well as infants who were nearly five times more likely to have features compatible with the fetal alcohol syndrome.

Qazi et al. (1985) reported in five cases abnormalities in offspring associted with prenatal marihuana exposure in Tables 2 & 3. "The weight of evidence indicates that Cannabis is damaging to the fetus and the newborn" concluded Finnegan and Fehr in their 1983 report to the World Health Organization - Addiction Research Foundation on the Health Hazards of Cannabis.

Table 2.

Parental information of 5 cases

	Case No.				
	1	2	3	4	5
Mother					
Age, years	21	20	20	19	20
Previous pregnancies	0	1	1	1	4
Pregnancy complications	0	0	0	0	0
Alcohol	0	0	0	0	1 pint rum/week
Cigarettes, packs/day	–	¼	¼–½	–	1
Other drugs	0	0	0	0	cocaine once in 2 weeks
Marihuana, joints/day	2	2–3	2	14	5–6
Weight gain during pregnancy	?	≈ 10 lbs	–	9 lbs	–
Father					
Age, years	27	29	18	29	20
Marihuana	+	+	?	+	?
Alcohol	+	+	?	–	?
Other drugs	?	–	?	–	?

from Qazi et al. (1985) with permission

Table 3.

Summary of abnormal findings of 5 infants prenatally exposed to marihuana

	Case No.				
	1[a]	2	3	4	5[b]
Gestation, weeks	35	40	38	36	40
Birth weight, g	1,560	2,310	2,116	1,630	2,340
Birth length, cm	29.5	45.5	48	?	?
Small head	+	+	+	+	–
Tremors	+	+	+	?	+
Epicanthus	+	+	+	+	+
Posteriorly rotated ears	+	+	+	–	+
Long philtrum	+	+	+	+	–
High-arched palate	+	–	–	+	+
Abnormal palm creases	+	–	+	–	+
Age at postnatal examination, months	3	2	1	13	11
Percentiles					
Length	<5	5	5	5	<5
Weight	<5	5	5	5	<5
Head circumference	<5	5	<5	<5	5

[a] Died.
[b] Mother also used cocaine and alcohol.

from Qazi et al. (1985) with permission