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THE EFFECTS OF CHRONIC ACETAMINOPHEN ADMINISTRATION ON THE DISPOSITION OF THE DRUG AND THE BODY STORES OF SULPHATE

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ABSTRACT

Acetaminophen is a common non-prescription drug used as an analgesic for mild to moderate pain, and as an antipyretic. In therapeutic doses, it is well tolerated but ingestion of excessive amounts of acetaminophen (greater than 5 g) is associated with hepatotoxicity.

The present study examined the effects of long term ingestion of therapeutic dosages of acetaminophen. Little information is known about the effects of acetaminophen on important cosubstrates (sulfate and glutathione, in particular) during chronic administration. Of particular importance are the recent findings that even a single dose of 1.5 g of acetaminophen can cause partial depletion of body stores of sulfate in man (Morris & Levy, 1983).

To study the effects of acetaminophen on sulfate levels in the body, a turbidimetric assay for the determination of inorganic sulfate in biological fluids was used. Acetaminophen and key metabolites in urine were analyzed by a rapid, sensitive and specific high pressure liquid chromatographic procedure. Calibration curves were linear over the concentration range of acetaminophen and metabolites expected. Extraction efficiency for acetaminophen from serum was 82.5 ($\pm$2.3 SD)%.

The study included nine (9) healthy volunteers and ten (10) patients receiving acetaminophen on a chronic basis. Volunteers participated on two occasions; on the first, each received a single 650 mg oral dose of acetaminophen, and the second time, each received a total of 3.25 g of acetaminophen over a 30 hour time period (650 mg every 6 hours).

Patients participating in the study were maintained on their normal treatment and dosage schedules. Concentration of acetaminophen in serum (over 8 h for the volunteer studies; single sample for patients) and acetaminophen and its metabolites in urine (24 hour collection for volunteers; single void for patients) were determined.

The maximum serum concentration of acetaminophen ranged from 3.79 - 8.63 μg/mL for the single dose and 6.81 - 29.63 μg/mL for multiple dosing in volunteers. Mean values for C_{max} were significantly higher in the multiple dose study (13.29 ± 6.35 μg/mL) compared to the single dose (7.12 ± 1.36 μg/mL) ($p < 0.05$). However accumulation was not greater than predicted based on the half-life and dosing interval, indicating that the overall disposition of acetaminophen did not differ significantly after multiple dosing.

The total recovery of the single dose (650 mg) of acetaminophen administered in this study averaged 86.8 (± 7.2 SD)%. Of the total acetaminophen and metabolites recovered in the urine, 47.7 (± 9.3)% consisted of the glucuronide conjugate, 46.9 (± 9.4)% the sulfate conjugate, and 5.4 (±5.7)% unchanged drug. The pattern of acetaminophen elimination was significantly different after multiple dosing and after chronic administration ($p < 0.05$). The sulfate conjugate fraction excreted in urine decreased, the glucuronide increased but the fraction excreted as the parent compound remained the same. This decrease in the sulfate conjugate is consistent with saturation of sulfate pathway, whereupon glucuronidation becomes the preferred route of metabolism (evidenced by the increase in glucuronide fraction).

Inorganic sulfate levels in serum over an 8 hour period were affected by the administration of single as well as multiple doses of acetaminophen. Serum levels of inorganic sulfate in volunteers fluctuated (transient increase seen in single dosing), and dropped to a minimum level approximately 2 hours after acetaminophen administration. In addition, multiple dosing produced a decrease in the mean inorganic sulfate level ($p < 0.05$) and a decrease in the renal clearance of inorganic sulfate, during at least, the first 4 hours after dosing ($p < 0.05$). Assuming that serum sulfate levels reflect the body stores of sulfate, a drop in serum sulfate is expected to be the result of depletion in the sulfate stores in the body, because the body probably would not be able to compensate sufficiently for the increased and continuous need for sulfate in the metabolism of acetaminophen. The decrease seen in the renal clearance of sulfate is thought to be a compensatory mechanism available to help maintain sulfate stores in the body when there is an increased need for sulfate. Unexpectedly, patients on chronic acetaminophen administration showed elevated serum sulfate levels. This is also likely the result of a feedback mechanism (i.e. decreased renal clearance and/or increased sulfate formation).

It is possible that the body is able to compensate sufficiently when there is a prolonged increased need for sulfate and that those taking therapeutic doses of acetaminophen chronically are not at increased risk of liver damage. However further study is needed.

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1. Acetaminophen

1.1 History

Acetaminophen (paracetamol; N-acetyl-p-aminophenol) was first synthesized at John Hopkin's University in 1877. However, it was not until 1893 that it was introduced by Von Mehring into medical therapy (Spooner & Harvey, 1976). At that time very little attention was paid to the new drug. Side effects were frequent and two similar drugs, phenacetin and acetanilid, were already available. Use of acetaminophen did not become extensive until 1949, when Brodie and associates (1949) recognized it to be the principle active metabolite of acetanilid and phenacetin. They proved that acetaminophen was responsible for the analgesic and antipyretic activity of these two more toxic drugs yet, unlike phenacetin, it did not cause methemoglobinemia (Figure 1).

In 1950, acetaminophen was marketed in the United States in an analgesic mixture as a substitute for phenacetin. One year later, however, the manufacturer recalled the drug after several reported incidences of blood dyscrasias. Acetaminophen was available again in 1952, but this time only on prescription. Since 1955, acetaminophen has been marketed without a prescription in the United States and Canada and evidence indicates that its use has been steadily increasing (Manoquerra, 1979).

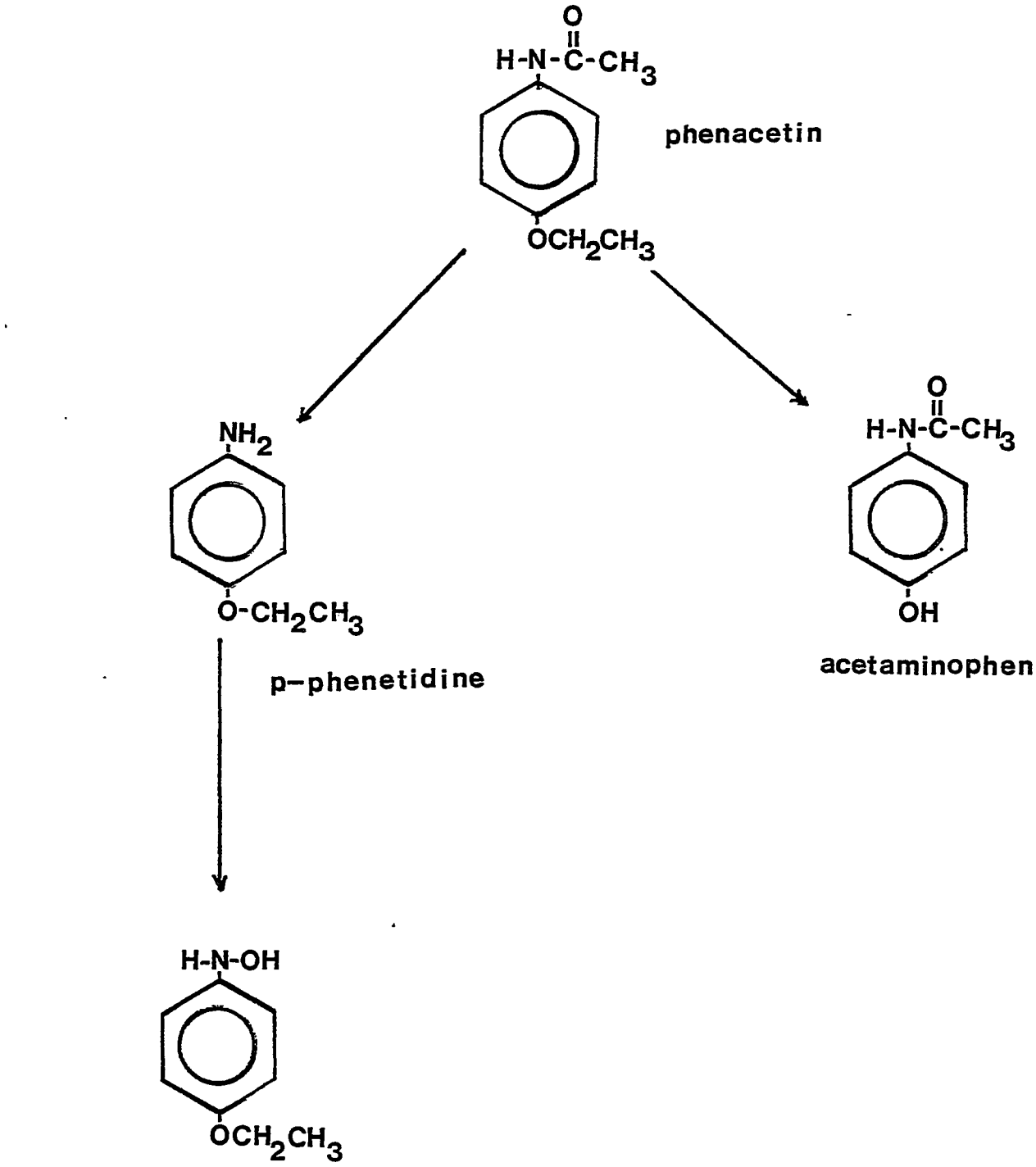

Figure 1: Phenacetin Metabolism in Man (Peterson & Rumack, 1978)

1.2 Therapeutic Use

Acetaminophen is a non-narcotic antipyretic/analgesic that is used not only in adults, but also in children and infants. It has been classified as an "Aspirin^{R} substitute" since its therapeutic properties are similar to those of A.S.A. (acetylsalicylic acid, Aspirin^{R}) (Yaffe, 1981). Both drugs are equally effective as antipyretics. They lower body temperature by altering the response of the hypothalamus to pyrogens (by interfering with the synthesis and release of prostaglandins from the anterior hypothalamus). The effect on this heat-regulating center is to cause a lowering of the set point in the hypothalamus thus activating mechanisms of heat loss -- cutaneous vasodilation and sweating (Lovejoy, 1978) (Figure 2).

The analgesic effect appears to be the result of the ability to inhibit the biosynthesis of prostaglandins and the most abundant precursor of prostaglandin, arachidonic acid (Meredith & Goulding, 1980). However, unlike A.S.A., acetaminophen's analgesic effect is not associated with anti-inflammatory activity in the usual therapeutic doses (Hinson et al., 1980). This is due to different sensitivities of central and peripheral prostaglandin synthetase enzymes in the anterior hypothalmus. Acetaminophen is a potent inhibitor of central prostaglandin synthetase while A.S.A. inhibits both central and peripheral enzymes.

Acetaminophen has many advantages over A.S.A. Acetaminophen does not inhibit the clotting process, nor does it cause gastric irritation or erosions, when taken in therapeutic dosage (325 - 650 mg, 4 to 6 times daily) (Meredith & Goulding, 1980). It is remarkably free from side effects, with allergic reactions such as skin rashes (Koch-Weser, 1976) and drug fever occurring only rarely.

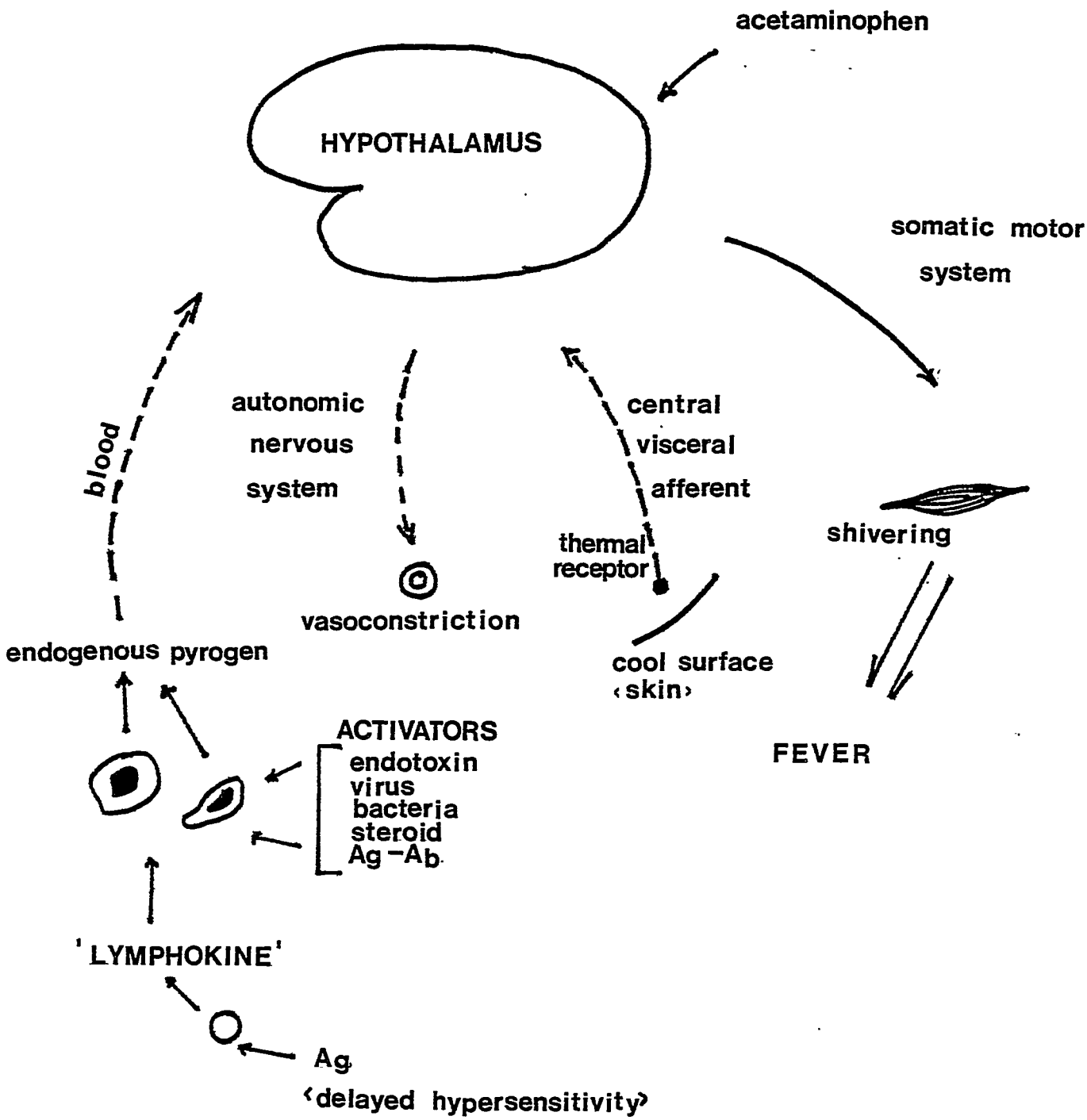

Figure 2: Antipyretic Action of Acetaminophen (Lovejoy, 1978) (cell types shown are: lymphocytes with nongranular cytoplasm, monocytes, with oval or indented nucleus, and granulocytes with multilobed nucleus)

Acetaminophen is commonly used to treat headaches, migraines, neuralgias, and dysmenorrhea and to reduce fever (Savides and Oehme, 1983). It is considered one of the safest of all minor analgesics in therapeutic dosage and is now more widely used than A.S.A. in many countries (Mitchell et al., 1974).

1.3 Pharmacokinetics of Acetaminophen

1.3.1 Absorption

Oral administration of acetaminophen to fasting subjects results in rapid and complete absorption, with peak plasma levels occurring in 20 to 45 minutes (Rumack & Matthew, 1975). Absorption is complete within 4 hours (Prescott, et al., 1971).

Acetaminophen is not absorbed to any extent from the stomach but is almost totally absorbed from the small intestine (Heading et al., 1973) (Figure 3). Since absorption for most drugs is much faster from the small intestine (K_A) than from the stomach (K_A*), the rate of gastric emptying (K_g) affects the overall rate of absorption into the systemic circulation. Therefore, the rate of absorption can be influenced by factors which alter gastric emptying, including: ingestion of food, certain drugs (eg: narcotic analgesics) (Clements, et al., 1978) and posture (Nimmo & Prescott, 1978; Hayes, 1981). Delayed gastric emptying results in lower peak plasma levels at later times. The extent of absorption, however, is not affected.

1.3.2 Distribution

Acetaminophen is relatively lipid soluble and appears in most body fluids. The volume of distribution is 0.9 - 1.0 L/kg (Forrest et al., 1982). Plasma protein binding of acetaminophen and its

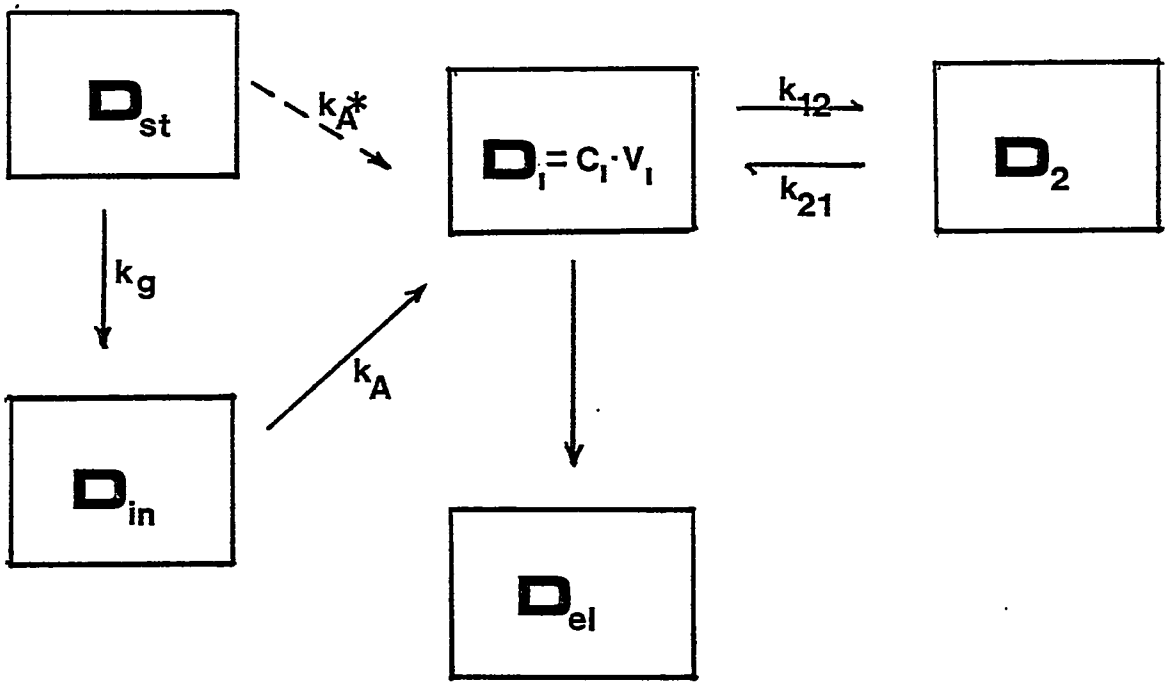

Figure 3: Modified two-compartment Pharmacokinetic model used to describe the gastric emptying pattern of acetaminophen in man (Clements, et al. 1978).

k_{12}, k_{21} - rate constants for transfer into and out of the second body compartment
k_{el} - elimination rate constant from the central compartment
k_g - 1st order rate constant for gastric emptying
k_A^* - rate constant for absorption from the stomach
k_A - rate constant for transfer of drug from the small intestine to systemic circulation
D_{st}, D_{in}, D_1, D_2, D_{el} - quantities in the stomach, small intestine, compartment 1 and 2 and quantity of eliminated drug, respectively.

glucuronide metabolite is low at therapeutic doses (10 - 15%) (Gazzard et al., 1973; Meredith & Goulding, 1980). Acetaminophen sulfate is appreciably bound to serum proteins (greater than 50%) (Morris & Levy, 1984).

Acetaminophen distributes very poorly into human milk. Berlin and associates (1980) found that the fraction of an acetaminophen dose available to an infant through breast milk is less than 1%. Neither acetaminophen nor its metabolites were detected in the urine of nursing infants. This evidence suggests that maternal ingestion of acetaminophen in usual therapeutic doses does not present a risk to the nursing infant. Although acetaminophen is able to cross the placental barrier and enter the fetal circulation, there are no reported teratogenic effects, adverse or maternal effects associated with the use of acetaminophen in therapeutic dosage.

1.3.3 Elimination

1.3.3.1 After Therapeutic Dosing

Acetaminophen is extensively metabolized in the body (Figure 4). Following oral administration, up to 20% of a dose is converted via first pass metabolism to inactive products (Oie, 1975; Ameer & Greenblatt, 1977; Rawlins et al., 1977). The remaining 80% of the dose reaches the systemic circulation where it is metabolized to inactive products in the liver and then excreted in the urine, mainly as the glucuronide and sulfate conjugates (Levy & Yamada, 1971; Mitchell et al., 1974; Mrochek et al., 1974). Only 2 - 5% of a therapeutic dose is excreted unchanged. The remaining 4 - 7% of an acetaminophen dose is transformed via the P_{450} mixed function oxidase enzyme system to a reactive metabolite (Seller & Freedman, 1981; Clements et al., 1983).

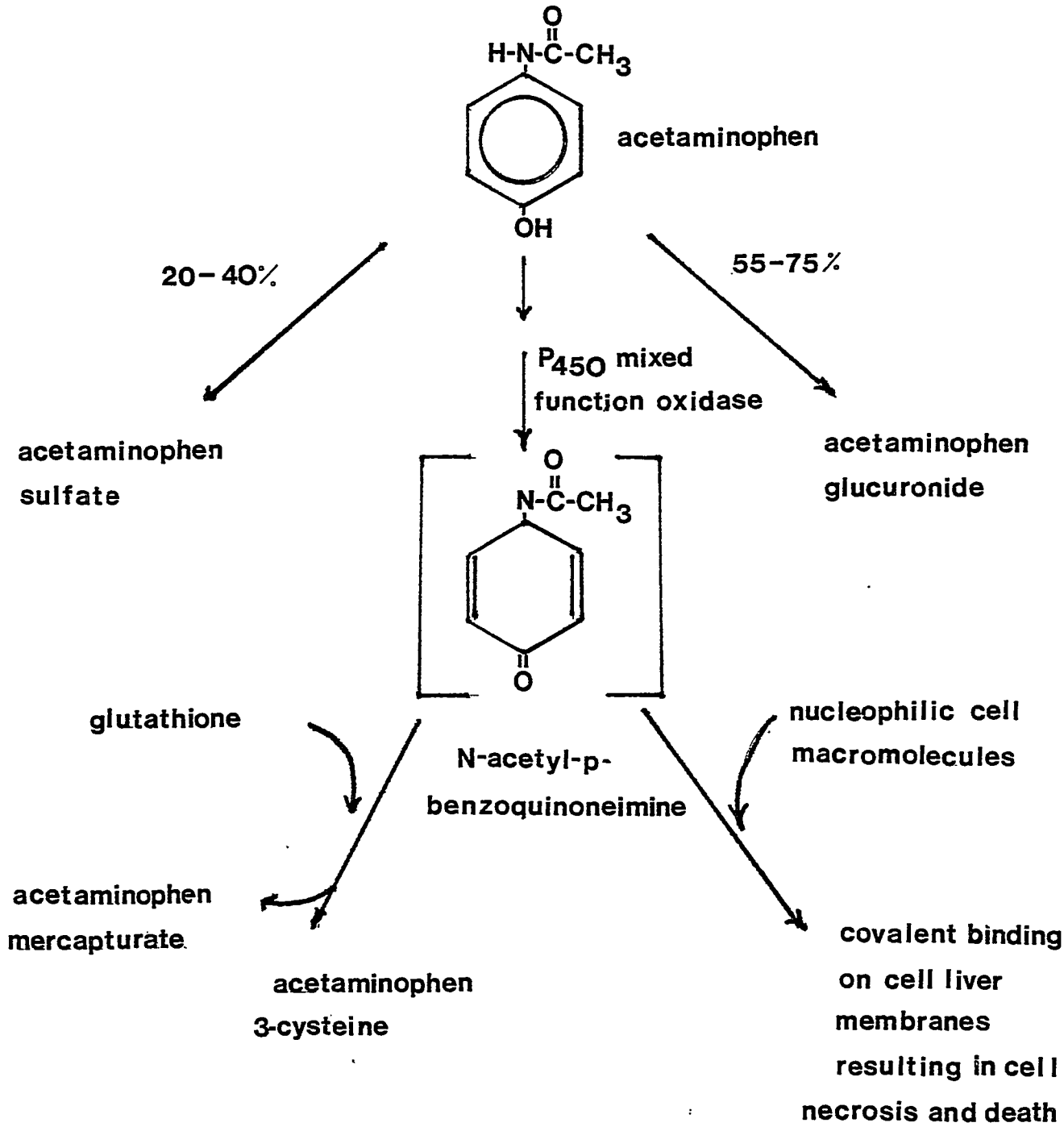

Figure 4: Metabolism of Acetaminophen in Man (Savides & Oehme, 1983)

This highly reactive arylating agent, thought to be N-acetyl-p-benzoquinoneimine, (Miner & Kissinger, 1979; Clements et al., 1983) is quickly detoxified by reaction with glutathione to form cysteine and mercapturic acid conjugates.

Excretion of acetaminophen metabolites is rapid and almost exclusively via the kidney, with 90% of a therapeutic dose appearing in the urine within 24 hours (Mitchell et al., 1974). Relative proportions of metabolites excreted in urine after a therapeutic dose of acetaminophen in man are: acetaminophen glucuronide - 55-75%, acetaminophen sulfate - 20-40%, acetaminophen cysteine and mercapturic acid conjugates - 5-10%, and unchanged drug - 1-4% (Levy & Yamada, 1971).

The plasma elimination half-life (t 1/2) of acetaminophen varies considerably among individuals; the range is 2-4 hours for adults (Miller et al., 1976). Half-life is shorter in children (1.9-2.2 h), somewhat longer in neonates (3.4-3.6 h) and cirrhotic patients (2.1-3.8 h) (Levy et al., 1975; Benson, 1983). The half-life is not prolonged in patients with impaired renal function (Ameer & Greenblatt, 1977). However, in anephric patients, there is accumulation of glucuronide and sulfate metabolites (Lowenthal et al., 1976).

1.3.3.2 Following Acute Overdosage

After a toxic dose of acetaminophen is ingested, changes in metabolism occur. As the dose ingested approaches four grams, sulfate conjugation becomes saturated. With ingestion of greater than 10 grams, the fraction of the dose conjugated with sulfate drops dramatically, from 30 to 9% (Prescott, 1983) and glucuronidation becomes saturated. With both of these pathways saturated, a greater fraction is metabolized via the P_{450} pathway, thus increasing the

percentage of cysteine and mercapturic acid conjugates produced (Howie et al., 1977; Slattery & Levy, 1979). If glutathione stores are depleted by 70% or more, the reactive, toxic metabolite (N-acetyl-p-benzoquinoneimine) begins binding irreversibly to liver macromolecules and/or cell membranes (Mitchell et al., 1974). Centrilobular hepatic necrosis and cell death result. Other vital organs may also be affected, including the heart and kidneys (Hinson, 1983).

With overdose, there is often an increase in half-life (t 1/2) which is directly related to the extent of liver damage (up to 7 hours for severe hepatic injury) (Prescott et al., 1971). If liver damage does not occur, t 1/2 increases only slightly.

1.4 Toxicity

Acetaminophen is a remarkably safe agent when used in therapeutic doses. The major concerns with respect to toxicity are related to acute overdosage -- most often the result of attempted suicide (Volans, 1976). The drug is usually taken on impulse for manipulative purposes and most individuals are completely unaware of the possible consequences. There is wide variation between individuals in susceptibility to the toxic effects of acetaminophen, but in an adult, serious toxicity can result after ingestion of 20-30 - 325 mg tablets (6-10 grams).

1.4.1 Symptoms of Toxicity

The symptoms of acute acetaminophen poisoning have been categorized and divided into three phases (Rumack & Matthew, 1975):

1) The first phase occurs within the first 24 hours. This stage is clinically deceptive because there is often no acute distress. Some