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MANUAL OF MEDICAL THERAPEUTICS

20th Edition

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Preface

The Washington University School of Medicine *Manual of Medical Therapeutics* was originally prepared in 1943–1944 and has been revised each year or two by residents, fellows, and staff members. It has served as a guide to a course in medical therapeutics given to the fourth-year medical students during their rotation on Ward Medicine. The increasing popularity of the *Manual* outside the Washington University Medical Center precluded publication by the Department of Medicine; therefore, recent editions have been published by Little, Brown and Company. However, the character of the *Manual* has not changed; it still reflects the approach to therapeutic problems taken by the majority of physicians on the staff of the Washington University–Barnes Hospital Medical Center.

All chapters have been updated and, where appropriate, new material added. The chapters on renal disease, pulmonary disease, antibiotics and infectious diseases, chemotherapy of malignant diseases, and arthritis have been considerably revised and contain material not previously discussed in the *Manual*. It is hoped that the approaches to therapy outlined will be useful not only to the students and house officers for whom it is written but also to other physicians.

The physicians responsible for the revision of the various chapters in this edition are listed in the table of contents. Unfortunately paucity of space prevents the listing of past and present house officers who have made contributions to the *Manual* and of the members of the Department of Medicine who have critically reviewed the various sections. Particular thanks are due to Dr. H. James Wedner. It is impossible to thank sufficiently Mrs. Marjorie Davis, Mrs. Nancy Grimshaw, Miss Pearl Heuer, Miss Ruth Roberts, and Miss Sharon Vitt for their heroic secretarial efforts.

The *Manual of Medical Therapeutics* is yet another reflection of the compassionate, scholarly, and meticulous approach to care of the sick patient that is taken and taught by Carl V. Moore, M.D., Head of the Department. The results of his comments and keen editorial suggestions are evident throughout.

M. G. R.

Contents

Preface *vii*

1. **GENERAL CARE OF THE PATIENT** *1*
   (Topical Therapy of the Skin by Lester T. Reese, M.D.)
2. **FLUID AND ELECTROLYTE DISTURBANCES** Dennis D. Taggart, M.D. *35*
3. **RENAL DISEASE** Dennis D. Taggart, M.D. *65*
4. **CORONARY HEART DISEASE AND RHEUMATIC FEVER** *93*
   Hall E. Harrison, M.D.
5. **CONGESTIVE HEART FAILURE** Hall E. Harrison, M.D. *117*
6. **CARDIAC ARRHYTHMIAS** *143*
   Jerome Cohen, M.D., and Robert Kleiger, M.D.
7. **HYPERTENSION** Joan Blondin, M.D., and Owen Kantor, M.D. *167*
8. **PULMONARY DISEASE** *183*
   Robert M. Bruce, M.D., and Russel N. Hirst, Jr., M.D.
9. **ANTIBIOTICS AND INFECTIOUS DISEASES** J. Joseph Marr, M.D. *209*
   (Tuberculosis and Mycotic Infections by Timothy J. Sullivan, M.D.)
10. **HEPATITIS AND CIRRHOSIS** Joseph L. Kinzie, Jr., M.D. *263*
11. **GASTROINTESTINAL DISORDERS** Joseph L. Kinzie, Jr., M.D. *277*
12. **ANEMIA AND BLEEDING DISORDERS** James W. Turner, M.D. *295*
13. **CHEMOTHERAPY OF MALIGNANT DISEASE** *323*
    Stanley Lowenbraun, M.D.
14. **THYROID DISEASE** Joseph E. Loewenstein, M.D. *347*
15. **DIABETES MELLITUS** Laurence S. Jacobs, M.D. *363*
16. **ARTHRITIS AND RELATED DISORDERS** *381*
    Bevra H. Hahn, M.D., and Isaias Spilberg, M.D.
17. **MEDICAL EMERGENCIES** James R. Couch, M.D. *403*

APPENDIXES

I. Trade Names and Generic Names of Drugs *451*

II. Nomogram for Calculating the Body Surface Area of Adults *454*

Index *457*

1

General Care of the Patient

ORDERS FOR PATIENTS

A. Hospital orders

1. Organized, clear, and complete orders that cannot be misinterpreted should be written (as soon as possible) after admission of the patient. Each order should be dated, with the time of the order recorded, and signed by the physician.
2. Previous orders should be canceled specifically before new orders are written.
3. All orders should be canceled once weekly and a new set of orders written.
4. Careful consideration should be given to any PRN order. Pain severe enough to warrant administration of a narcotic generally also warrants examination of the patient by the physician. If it is decided to order a PRN narcotic, a definite time limit (maximum of 48 hours) should be specified.
5. **Writing orders:** A constant categorization of orders should be used to insure that no important therapeutic measure will be overlooked. One possible categorization of orders would be:
   a) Statement of diagnosis and the patient's condition.
   b) **General measures**—e.g., activity permitted, type of diet, fluids, intake and output, bowel care, weighing of patient, etc.
   c) **General observations:** Vital signs (T-P-R and blood pressures), checking of specific signs of mental status, etc.
   d) **Precautions**—e.g., isolation technique, measures to decrease confusion of patient (e.g., by leaving a light on at night), and a statement of all drugs to which the patient is allergic.
   e) **Tests and preparation required**—e.g., NPO after midnight, enemas, save urine or stool for house officer.
   f) **Equipment required at bedside**—e.g., airway, drugs, monitor, etc.
   g) **Symptomatic treatment** (e.g., for pain, fever) : Physical measures and drugs (orders for laxatives and enemas should be indicated and not written automatically).
   h) **Medications for specific therapeutic purposes**—e.g., antibiotics, diuretics, hormones, vitamins, fluid, fluid orders, etc.
   i) **Conditions for which the physician should be notified**—e.g., increasing fever, change in mental status.

j) **Measures to prevent or treat complications**—e.g., skin, eye, or mouth care, frequent turning, and padding to prevent decubitus ulcers, restraints if appropriate, respiratory care, use of footboard for patients with lower extremity paresis, social service consult.

B. **Orders written for drugs to be taken at home** should contain explicit instructions in language fully understood by the patient or his family.

C. **Prescriptions** should include name of patient, date, name of drug, dosage, amount dispensed, clear instructions about how medication is to be taken, number of times the prescription may be refilled, whether it is to be labeled, and signature of the physician. Wherever possible:

1. Use generic rather than trade name.
2. Write dose in metric units.
3. Give clear instructions in the SIG for administering the drug.
4. In almost all instances have name of the medication recorded on the label. Prescription should be marked: Label as such.
5. Indicate that prescription may be refilled, if that is your wish, one or two times, but not more often.
6. Instruct patients to bring all their medications when visiting the physician. On occasion, by dispensing the exact amount of a medication to last to the next appointment, one can assess the consistency with which the patient is taking his medication.

II. ADVERSE DRUG REACTIONS AND DRUG INTERACTIONS

Adverse drug reactions, i.e., any undesired or unintended effects caused by a drug, occur in 10–20% of hospitalized patients; the rate increases proportionately to the number of drugs dispensed. Most drug reactions are toxic or side reactions (rather than allergic), are pharmacologically mediated, and are in large part dose-related. To reduce their number:

A. Take a careful history of previous drug reactions and record it both in the patient's chart and on the order sheet.

B. Use as few drugs as possible.

C. Pay careful attention to drug dose, particularly in relation to age, size, and metabolic and renal status of the patient.

D. **Look up every drug you prescribe;** learn the adverse effects, contraindications, interactions with other drugs, mode of metabolism, and how excreted.

E. Report suspected drug reaction to the FDA or AMA.

Drug interactions are complicated (e.g., interaction of Coumadin and phenobarbital). As each new medication is added, the physician must assure himself that there is no likelihood of harmful interaction with a medication the patient is already taking. A brief outline of drug interactions is found in *Drug Letter* 12:93, 1970. The effects of one drug may exaggerate the toxic effects of another. Adjust drug dosage according to the patient's changing condition—e.g., alteration of digitalis dosage in patients developing hypercalcemia.

III. FLUIDS

Fluid intake should be specified for all patients. Fluid balance and electrolyte and acid-base problems are discussed in Chapter 2.

A. When neither fluid restriction nor administration of extra fluids is necessary, leave an order for fluids ad lib.

B. In case of dehydration, 3000–5000 ml of fluids should be given each 24 hours until dehydration is corrected. The responsibility for adequate fluid ingestion may be delegated to the nurse.

C. If sodium intake is restricted and large quantities of water are allowed, dilutional hyponatremia may result. Water restriction and not hypertonic salt administration is the usual treatment of choice.

D. Fluids must be given parenterally if the patient cannot take them orally. The rate of intravenous infusion should be monitored by central venous pressure in patients with expanded extracellular fluid volumes and compromised cardiac function.

E. Careful input and output records should be charted on patients with congestive heart failure, renal failure, liver failure, dehydration, and severe vomiting or diarrhea.

F. Thiamine deficiency may be precipitated during refeeding of starved patients. Thiamine requirement is roughly 1 mg/1000 calories. If actual thiamine depletion has occurred, as in patients with accelerated metabolic requirements (e.g., hyperthyroidism), several times this amount should be given. Severely debilitated patients should receive about 5 mg/day. Ascorbic acid in doses of 100–300 mg/day should also be given. Preparations of B complex vitamins with vitamin C for administration in intravenous fluids include Folbesyn, Solu-B with C, and Vi-Cert. Folic acid can be administered after appropriate evaluation.

G. For hyperalimentation one may use such preparations as Aminosol 5% in 5% D/W, 750 ml; and 50% D/W, 350 ml, adding desired vitamins, potassium, etc. This necessitates a large central venous catheter.

IV. HOSPITAL DIETS

provide adequate nutrition for the patient, but selection of an appropriate diet, so important in many disease states, is often neglected. Sick people frequently have poor appetites and often select inadequate diets. Dietary manuals (e.g., the Barnes Hospital Dietary Manual) that describe routine and special diets should be consulted. A dietitian may tailor a diet to meet specific needs.

A. Liquid diet

1. **A clear liquid diet** contains water, sugar, and salt; only such foods as broth, tea, coffee, strained fruit juice, and carbonated beverages are allowed. It is inadequate in protein, vitamins, and minerals. It is usually the first diet ordered after surgical procedures and after oral feedings have been withheld for gastrointestinal disease.

2. **A full liquid diet** requires no chewing but does require normal gastrointestinal function for digestion and assimilation. It allows the foods listed above plus milk, eggnog, ice cream, cereal, gelatin, and strained cream soups. It is inadequate in protein, thiamine,

niacin, iron, and phosphorus. Larger servings are usually given at mealtimes, and between-meal supplementary feedings can be ordered.

3. ***Liquid diets are indicated for:***

   a) Acutely ill patients for whom the effort of eating may be exhausting.

   b) Patients with constricting lesions of the esophagus or pylorus.

   c) Patients in whom intestinal bulk must be kept at a minimum (e.g., those recovering from abdominal operations or severe gastroenteritis, etc.)

   d) Vitamin supplements must be given to patients on liquid diets.

B. **Soft diet** contains foods of low residue; easily assimilated proteins and carbohydrates are given. Such foods include refined cereals, white bread, crackers, well-cooked vegetables, cooked fruits, ground meats, eggs, cottage cheese, starch desserts, spongecake, bananas, applesauce, and the foods listed under Liquid Diet. This diet is useful for patients unable or unwilling to chew. It is recommended as a transition from liquid to regular diet, and in those situations in which easily digested foods are required. Fried foods, raw fruit, and highly seasoned foods are excluded. Caloric, vitamin, and protein requirements are fulfilled.

C. **Regular diet** has no restrictions except for foods requiring a long time for digestion, such as fried foods and some raw vegetables.

D. **Special diets** such as diabetic, ulcer, and low-salt diets require a specific order to the dietitian.

E. **Tube feedings** may be given to patients who cannot or will not take feedings orally. Their use in selected debilitated or malnourished patients allows the administration of high-calorie, high-protein mixtures. Precise diets can be given, and fluid and caloric intake maintained. Small flexible plastic tubes may be left in place for prolonged periods of time with essentially no danger of irritation to the mucous membranes or ulceration of the esophagus. When ordering tube feedings, one should specify the protein and salt content, number of calories, and volume to be administered each 24-hour period. The mixture is then prepared basically from milk solids and Dextri-Maltose, to which have been added vitamins and minerals. **Remember:**

   1. **Aspiration** of gastric contents is an ever-present danger, in comatose patients with absent gag reflex, for example, the high incidence of this complication may preclude use of a feeding tube. Risks may be reduced by elevating the patient's head during, and for a short time after, administration of the feeding; by suctioning the stomach prior to each feeding (to ensure that gastric distention and retention have not developed); and by limiting the volume of feeding to 300 ml (e.g., 250 ml formula followed by 50 ml water) every 3 hours.

   2. **Diarrhea** may occur. Preventive measures include frequent rinsing of the feeding cylinder, irrigation of the feeding tube, and avoidance of excess volumes of water in the feeding mixture. Therapeutic measures for diarrhea are outlined in Section VI, Treatment of Diarrhea. Addition of 30–60 ml Kaopectate and/or 4 ml paregoric to each feeding will frequently control the diarrhea.

3. **Dehydration, azotemia, and hypernatremia** may develop following administration of an excessive solute load and inadequate water. This complication is most common in obtunded patients receiving high-protein (or high-carbohydrate and high-salt) feedings who are unable to express their sensation of thirst. Hyperosmolarity may appear rapidly, especially if renal function is compromised, and reflects the discrepancy between fluid intake and obligatory solute excretion by the kidney. Large volumes of urine of high specific gravity may be excreted as the dehydration worsens. To preclude such developments, adequate amounts of water must be given, the amount depending on protein catabolism, insensible water loss, and state of renal function. Generally speaking, 2000–2500 ml of fluid daily (including the volume of tube feeding plus additional water) will provide sufficient water if the feeding mixture contains less than 100 gm protein, 10 gm salt, and 2500 calories.

V. TREATMENT OF CONSTIPATION

A. General comments

1. Physiologic bowel action is preferable to the use of cathartics. Therefore, where appropriate, activity, a diet adequate in fiber content, the use of stimulants of the gastrocolic reflex (e.g., coffee or warm water), and establishment of a proper "habit time" should be employed. Bedside commodes are preferable to the use of bedpans whenever possible. Be alert to the possibility that constipation may be a symptom of an underlying disease.

2. If these measures are ineffective, emollient or bulk-forming laxatives and/or enemas may be useful. Cathartics which act by adding water content to the stool or by stimulating mobility are also available. Choose the preparation to be used after deciding which mechanism of action is appropriate.

3. Chronic use of cathartics is contraindicated. Aside from perpetuating another drug dependence, the prolonged use of strong laxatives may result in (a) excessive fecal loss of fluids, sodium, and potassium, occasionally with volume depletion sufficient to cause secondary aldosteronism and a hypokalemic alkalosis, and (b) spastic colitis and clinical and roentgenologic manifestations that have been mistaken for ulcerative colitis.

B. Indications for laxative use

1. Bedridden patients, especially elderly patients, who frequently become constipated.

2. Patients for whom straining (Valsalva maneuver) at the stool may be dangerous—e.g., after myocardial infarction or central nervous system hemorrhage; patients with hernias.

3. Patients in whom desiccation of stool is undesirable—e.g., patients with diverticulitis, hemorrhoids, etc.

4. Patients who have had constipating substances or medications—e.g., barium for gastrointestinal examination.

5. As a complement to certain drug therapy—e.g., prior to and following the administration of antihelmintics.

C. **Contraindications** include undiagnosed abdominal pain, symptoms or signs suggestive of acute appendicitis, intestinal obstruction, and chronic constipation. Orders for laxatives should not be written as routine orders for all hospital patients.

D. **Preparations**

1. **Emollient laxatives**

a) **Mineral oil** (liquid petrolatum) lubricates the feces and is essentially unabsorbed. Regular ingestion may inhibit absorption of carotene and fat-soluble vitamins and is discouraged in elderly, debilitated, or dysphagic patients, as lipoid pneumonia results if the oil gains access to the lungs. Dose: 15–45 ml, usually given at bedtime.

b) **Dioctyl sodium sulfosuccinate** (Colace and Doxinate), a surface-active wetting and dispersing agent, allows penetration of the fecal mass by water and fats. The resultant soft stool decreases the need for straining at defecation. The drug should not be given with mineral oil, since absorption of the oil may be promoted. Dose: 240 mg Doxinate or 50–200 mg Colace daily.

2. **Bulk-forming agents** include polysaccharides and alkaline derivates that dissolve or swell in water to form an emollient gel or viscous solution that serves to maintain the feces soft and hydrated and stimulates peristalsis by a reflex mechanism. These agents should always be given with generous amounts of water to prevent esophageal obstruction. Preparations include methylcellulose and psyllium (Metamucil). Dose: methylcellulose 1–1.5 gm BID–QID; psyllium 4–10 gm in a glass of water BID–TID.

3. **Stimulant cathartics**

a) **Castor oil** acts upon the small intestine, causing prompt, rapid evacuation of the bowel. It is usually used only when the bowel is being prepared for special examinations. Dose: 15–30 ml.

b) **Diphenylamine cathartics** (Bisacodyl), a structural analog of phenolphthalein, stimulates peristalsis in the large bowel; it may be administered orally or per rectum. Dose: 2 or 3 tablets (5 mg each). Rectal suppository, 10 mg, generally acts in 15–60 minutes.

c) **Anthraquinone cathartics,** extract of cascara sagrada, and extract of senna (Senekot), stimulate the colon and usually produce a single bowel evacuation 6–10 hours after administration. Senekot is useful in patients chronically using cathartics. Dose: 4–12 ml cascara, generally given at bedtime; 1 tablet of extract of senna once or twice daily.

4. **Saline cathartics** are relatively nonabsorbable salts which retain water in the lumen of the colon by osmotic forces:

Milk of magnesia Dose: 15–30 ml at bedtime.

Magnesium sulfate Dose: 15–30 ml of a 50% solution.

Magnesium citrate solution Dose: 200 ml of standard solution.

Sodium or potassium salts Dibasic sodium phosphate, 4 gm; sodium sulfate, 15 gm; dibasic potassium phosphate, 4 gm.

Magnesium sulfate and magnesium citrate are generally used only in preparation for a special examination because of their

strong action. Since 20% of the magnesium ions may be absorbed, **magnesium cathartics are contraindicated in patients with renal failure.**

E. **Enemas** are used where immediate bowel evacuation is indicated, e.g., in preparing patients for certain surgical procedures, sigmoidoscopic examination, and x-ray studies, in patients with paralytic ileus, and in many chronic disease states. Types of enemas include:

1. Tap water or saline: 1000–2000 ml. An effective enema for removal of desiccated stool may be made by adding 10 ml of 1% solution of dioctyl sodium sulfosuccinate to 90 ml tap water.
2. Oil retention: 200 ml of olive oil.
3. Magnesium sulfate, glycerin, and water: 60 ml of each.
4. Soapsuds enema.
5. Fleet disposable enemas induce prompt, complete emptying of the left colon, and are useful in preparing patients for sigmoidoscopic examinations.

VI. TREATMENT OF DIARRHEA

A. General considerations

1. Diarrhea can be caused by a variety of etiologic factors including: infections, nonspecific inflammatory diseases, ulcerative colitis, regional ileitis, tumors, drugs (e.g., digitalis), radiation, toxins, neurologic disorders, in association with other diseases as Graves' disease, Addison's disease, diabetes mellitus, portal hypertension, anemia, allergic, metabolic, humoral (e.g., secretin), defective gastric or pancreatic digestion, malabsorption, or laxative abuse. Diagnosis should be established in all but self-limited diarrheal episodes. Diarrhea can cause a number of electrolyte abnormalities, which should be treated as discussed in Chapter 2.
2. Diarrhea may be symptomatically treated by putting the gastrointestinal tract at rest by administering only liquids and foods low in bulk, or withholding oral feeding entirely. For fulminant and acute self-limited diarrhea, such as those of bacterial or viral origin, opiates are usually the drugs of choice, in the absence of contraindications.

B. *Antidiarrheal agents*

1. Bulk-forming agents.
2. **Adsorbents:** Kaopectate (hydrated aluminum silicate [kaolin with pectin]): 60–90 ml QID.
3. **Narcotic agents:** Realize the dangers and observe the necessary precautions if used in patients with asthma, chronic lung disease (danger of viscous plugs), benign prostatic hypertrophy, or acute angle closure glaucoma.
   a) **Paregoric** (camphorated tincture of opium): 4–8 ml after each liquid stool or QID.
   b) **Opium and belladonna:** 0.5–1 ml tincture of powdered opium (30 mg) and 15 mg belladonna in capsule TID or QID.
   c) **Codeine:** 16–64 mg BID or QID.
   d) **Morphine** should be reserved for selected patients who have

severe diarrhea that fails to respond to conservative measures. Small doses which would not provide significant analgesia, are usually effective. It should not be used in chronic diarrheal states.

e) **Diphenoxylate hydrochloride** (Lomotil) is a meperidine congener. It effectively inhibits excess gastrointestinal propulsion; 2.5 mg are approximately equivalent in antidiarrheal efficacy to 4 ml paregoric. Although its effects on the bowel are similar to those of morphine, diphenoxylate possesses low analgesic activity and is free of parasympatholytic actions and addiction potential when used in the dosage range described below. It is narcotic-exempt. Side effects are uncommon (nausea, dizziness, vomiting, and rarely pruritus and skin rashes). The drug is contraindicated in patients with advanced liver disease. Respiratory depression may be increased by phenothiazine derivatives or imipramine type antidepressants. Each Lomotil tablet or 5 ml liquid contains 2.5 mg diphenoxylate and 0.025 mg atropine sulfate (a subtherapeutic amount added to discourage deliberate overdosage). Dose: 5 mg TID or QID until initial control of diarrhea is effected, then maintenance dosage of 2.5 mg BID or TID.

VII. TREATMENT OF FEVER

A. General comments

1. The cause of fever should be established as rapidly as possible. Acute infections are the most common cause of elevated temperatures, but numerous diagnostic problems are engendered by those fevers due to chronic granulomatous disease, malignant disease, collagen-vascular disease, drug sensitivity, etc.

2. Temperature elevation may cause increased tissue catabolism, dehydration, congestive heart failure, acute brain syndromes, and convulsions (rare in adults). Tachycardia may be deleterious to patients with heart disease, especially tight mitral stenosis, and with artificial heart valves.

3. The type and severity of fever may provide important clues in establishing the diagnosis or in assessing the efficacy of antibiotic therapy. The routine administration of salicylates or other antipyretics is to be discouraged when the cause of the fever is obscure, unless it is imperative that the temperature be lowered. It is often difficult to decide when to treat a fever. In very acutely ill febrile patients, antibiotics are given after appropriate bacterial cultures have been obtained (see Chapter 9, Antibiotics and Infectious Diseases); the fever is treated only if the deleterious effects listed above are felt to be threatening to the patient or if the patient's discomfort is extreme.

B. Treatment A hypothermic blanket may be effective; however, rectal temperatures must be monitored closely, and shivering may be a problem. The blanket should generally be discontinued when the rectal temperature has decreased to about 38°C (100.4°F); a further fall in body temperature can be expected. Tepid sponge baths with water-alcohol mixtures are less effective in adults than in children. Salicylates are the drugs of choice, however.

Analgesic-antipyretic drugs may be divided into three classes:

1. Salicylates.
2. Para-aminophenol derivatives: phenacetin, acetaminophen.
3. Pyrazolon derivatives: antipyrine, aminopyrine, phenylbutazone.

All the above are effective antipyretic agents and are discussed in the following section. All act mainly on the CNS to produce antipyresis of pathologically elevated body temperatures. Salicylates may be given orally, intravenously, or rectally. Patients with Hodgkin's disease, other lymphomas, or gram-negative sepsis are occasionally very sensitive to salicylates and develop hypothermia and hypotension after small doses. Although this complication is rare, it is wiser to use other antipyretic agents in patients experiencing a marked fall in temperature after administration of small doses of aspirin. Since salicylates cause a prolongation of prothrombin time, patients taking coumarin drugs should be given acetaminophen rather than aspirin.

VIII. RELIEF OF PAIN

A. General comments Numerous drugs are available; all increase the capacity to tolerate pain. The drug or combination of drugs to administer will depend on many factors, especially the nature of the pain, its severity, chronicity, and etiology, and the personality of the patient. Nonnarcotic preparations should be used whenever possible.

B. Nonnarcotic preparations

1. Salicylates Aspirin is the most commonly used analgesic-antipyretic drug. Its mechanism of action is not yet entirely defined, but probably involves both CNS effects and blockade of impulse generation in peripheral pain-mediating chemoceptors. It is useful in relieving the discomfort of pain from many sites and is the mainstay of treatment in acute rheumatic fever, rheumatoid arthritis, and degenerative joint disease. Uricosuric effects may be marked in dosages of 5–6 gm daily, but with smaller doses urate retention and hyperuricemia occur. Aspirin should not be given concurrently with coumarin because it prolongs the prothrombin time; it should be given with caution to people with liver disease, a history of peptic ulcer, and coagulation disorders (e.g., hemophilia).

a) Preparation and dosage Acetylsalicylic acid (aspirin) is the preparation of choice. Sodium salicylate, buffered preparations, and enteric-coated tablets (which are often poorly absorbed) do not reduce gastric irritation significantly. Usual dosages of aspirin for relieving pain or reducing fever are listed below; dosage of aspirin for treatment of rheumatic fever and arthritis is discussed in those respective chapters. Very low albumin levels will decrease the dosage requirement of aspirin.

Orally 0.3–1.0 gm (5–15 grains) every 3–4 hours.

Rectally One or two 0.3-gm suppositories every 3–4 hours.

Intravenously Sodium salicylate 0.5 gm may be added to fluids and infused intravenously over 4–8 hours; generally, the dosage should not exceed 1.0 gm/24 hours. Rapid infusions may cause

thrombophlebitis, and extravasation may lead to soft-tissue sloughs.

b) Toxic effects The toxicity of aspirin when given in high dosage is significant; the major problems are upper gastrointestinal distress, tinnitus, and decrease in auditory acuity. Idiosyncratic reactions are very rare and the symptoms usually mild, but severe and fatal reactions may occur. Because asthma is the major allergic manifestation of aspirin sensitivity, caution is required whenever aspirin is prescribed for patients with asthma.

i) Salicylism is characterized by dizziness, tinnitus, decreased auditory and visual acuity, sweating, thirst, nausea and vomiting (due to CNS effects as well as local gastric irritation), confusion, and rarely by an erythematous skin rash. Symptoms subside when dosage is reduced.

ii) Irritation of the gastric mucosa is common, and in the majority of patients small amounts of blood are regularly lost into the intestinal tract. Peptic ulceration, blood loss sufficient to cause iron-deficiency anemia, and even massive bleeding may occur. Although antacids are frequently given to patients receiving sustained doses of aspirin, there is no clear-cut evidence that they will prevent these complications.

iii) Severe toxic symptoms include central nervous system manifestations (restlessness, incoherent speech, anorexia, diplopia, hallucinations, stupor, convulsions, coma) and bleeding (due to hypoprothrombinemia, and corrected by administration of vitamin K_1). Although individual sensitivity varies greatly, CNS manifestations are uncommon at serum salicylate levels below 20 mg/100 ml.

Protein and formed elements (white blood cells, red blood cells, casts) may appear in the urine and then disappear when salicylates are discontinued. Since approximately half of salicylate excretion is renal, severe toxic symptoms may develop when renal function is impaired. Aspirin administration may rarely induce bone marrow failure.

Acute salicylate poisoning is discussed in Chapter 17.

2. Para-aminophenol derivatives

a) Preparations

i) **Phenacetin** is a common constituent of a number of proprietary analgesic mixtures. Although the drug does not have anti-inflammatory properties, its antipyretic and analgesic actions are essentially the same as those of aspirin. Prothrombin is not affected.

ii) **Acetaminophen** is the major metabolite of phenacetin, and its pharmacologic actions are essentially identical. The usual dosage for adults is 300–600 mg every 4–6 hours; preparations include Tylenol or Tempra tablets (325 mg) (5 grains), and Tylenol elixir or Tempra syrup (125 mg/5 ml).

b) Side effects and toxic reactions Most side effects are rare. Methemoglobinemia, hemolytic anemias (particularly in patients with glucose 6-phosphate dehydrogenase deficiency), skin rash,

hepatic injury, vascular collapse, and drug fever may occur.

A number of reports have suggested an association between "analgesic abuse" and renal disease. Circumstantial and epidemiologic evidence seem to relate chronic ingestion of large amounts of analgesic compounds to chronic interstitial nephritis and to a unique susceptibility to pyelonephritis, with a high incidence of renal papillary necrosis.

Most reports suggest phenacetin as the offending agent, but whether nephrotoxicity is due to phenacetin per se, to metabolites of phenacetin, or to certain impurities occasionally present is not known. Clinically, analgesic nephropathy has been reported to occur in patients ingesting large amounts of the drug over a number of years—at least 1–3 gm daily for a total intake of 5 kg or more. Azotemia and polyuria (due to decreased concentrating ability) are the major manifestations; pyuria, bacteriuria, and acidosis associated with progressive renal insufficiency may occur.

3. **Pyrazolon derivatives** Antipyrine and aminopyrine are not recommended as routine analgesics because agranulocytosis and even aplastic anemia may follow their administration. Phenylbutazone is generally not employed as an analgesic except for pain associated with inflammatory diseases; the same hematologic complications may occur. Its use is discussed in Chapter 16.

4. **Propoxyphene (Darvon)** is a nonnarcotic analgesic structurally related to methadone, with potency similar to codeine. It is better tolerated than codeine, and side effects (nausea, vomiting, epigastric distress, dizziness, drowsiness, pruritus, skin rashes) are minimal. It has been associated with hypoglycemia and pulmonary edema. Oral dosage is 32–65 mg every 4–6 hours. Combinations of propoxyphene and salicylates are more effective than is either agent alone.

5. **Pentazocine (Talwin)** is a nonnarcotic analgesic which produces significant analgesia 15 to 20 minutes after intramuscular injection; 30 mg are usually as effective as 10 mg of morphine. Drug addiction does not occur with oral administration, although mild withdrawal symptoms may occur after continual use. Because it is a narcotic antagonist, it must be given with caution to patients receiving narcotics. Adverse effects include oversedation, dizziness, nausea, vomiting, euphoria, and respiratory depression. Dosage is 30 mg IM, IV, or subcutaneously; or 50 mg orally (one-third as effective). Its primary clinical usefulness is in those patients who require chronic administration of analgesics.

C. Narcotics

1. **General comments** These drugs are used for the treatment of severe pain and for the control of severe cough and diarrhea. Dyspnea caused by acute left ventricular failure is frequently relieved by morphine. About a dozen narcotics are commonly employed. Morphine is the most active and is the standard against which the efficacy of other analgesics is measured.

2. ***Pharmacologic actions,*** in addition to analgesia, include respiratory and circulatory depression, sedation, alteration of mood, bronchospasm, increase in sphincter tone, atony of the bowel, nausea, vomiting, antidiuresis, addiction, and rarely true allergic reactions,

which may account for episodes of "sudden death" or pulmonary edema among addicts (*Amer. J. Med.* 45:555, 1968). Tachyphylaxis usually occurs. There are probably no major differences in adverse effects when given in equianalgesic doses, but patients will usually tolerate one drug better than another.

3. Clinical use and precautions

a) Narcotics should not be used when other drugs or physical measures will provide relief of pain. They should not be prescribed for longer than 24–48 hours at a time except in patients with far-advanced malignancy. They are most effective parenterally. They should be used cautiously in patients who experience euphoria as well as relief of pain, for these individuals may be particularly susceptible to habituation or addiction. More stable individuals do not develop physiologic dependence until after the drug has been given for two weeks or longer, but habituation may occur more quickly. Hazards of addiction should not preclude long-term administration of narcotics to patients with terminal malignancy.

b) Narcotics should not be used in certain acute disease states (e.g., suspected surgical abdomen) in which the pattern and degree of pain are important diagnostic signs. Patients with suspected acute head injuries should not be given narcotics, for their administration will prevent accurate assessment of neurologic changes.

c) Narcotic-induced vomiting may be frequently circumvented by giving a small dose (to depress the vomiting center) before the planned therapeutic dose. Side effects may also be reduced by keeping the patient recumbent.

d) **Narcotics depress the respiratory center,** the effect being directly proportional to the dose. Therapeutic doses diminish the tidal volume, respiratory rate, and minute volume. Bronchospasm may occur. The response to hypercapnia, but not to hypoxia, is depressed.
Narcotics should be used cautiously in patients with pulmonary insufficiency and in patients who are taking phenothiazine derivatives.

e) Narcotics increase the sphincter tone in the gastrointestinal tract, biliary tree, ureters, and urinary bladder. They should be given with great care to patients with biliary colic, fulminant ulcerative colitis, and prostatic hypertrophy. Transient elevation of serum amylase may follow the administration of morphine. Narcotics markedly decrease propulsive contractions in the bowel.

f) Narcotics impair reflex activity from receptors in the aortic arch, carotid sinus, and pulmonary vessels, and may occasionally produce orthostatic hypotension, syncope, peripheral vasodilatation, and circulatory collapse.

g) Narcotics should be used with extreme caution in patients with hypothyroidism, Addison's disease, hypopituitarism, anemia, reduced blood volume, heart trauma, asthma, and severe malnutrition or debilitation. In patients with increased intracranial pressure narcotics may further elevate the CSF pressure.