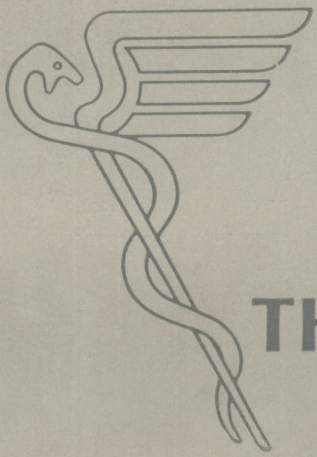

1976
YEAR BOOK OF
DRUG THERAPY

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Drug Therapy

1976

Edited by

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YEAR BOOK MEDICAL PUBLISHERS, INC.
35 EAST WACKER DRIVE • CHICAGO

Printed in U.S.A.

Library of Congress Catalog Card Number: CD38-23

International Standard Book Number: 0-8151-3289-1

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The material covered in this volume represents literature reviewed up to August, 1975.

Introduction

New Developments

The past year has been fruitful for the development of new drugs, new uses for drugs already available and new diagnostic and therapeutic technics.

Mebendazole has been found to be the first really effective drug for the treatment of trichuriasis. Colchicine, for centuries the drug of choice for podagra, has now been found to be useful in controlling Mediterranean fever and has also shown considerable promise in the treatment of psoriasis. Glucagon is of therapeutic value for diverticulitis. Potassium sorbate is a new, effective antifungal agent. Dihydroergotamine has been found useful in combating hypotension. A new β-adrenergic stimulator, terbutaline, relieves bronchospasm with fewer cardiac effects. Zinc effectively relieves acrodermatitis enteropathica, a real breakthrough. Molluscum contagiosum is controlled by methysergide. Metronidazole shows promise in the treatment of Crohn's disease. A new drug, bromocriptine, is useful in controlling acromegaly. Chorea may be helped by trifluoperazine. Propranolol is proving to be useful in relieving glaucoma. Phenoxybenzamine, an α-blocker, relieves nonocclusive bowel ischemia. Phenylpropanolamine is useful in preventing retrograde ejaculation.

Drugs have been altered to give improved action. Para-aminosalicylic acid has been recrystalized with ascorbic acid to give a better-tasting preparation useful in treating elevated cholesterol and triglyceride levels. Testosterone has been shown to be effective when given orally. It is absorbed from the intestine by the lymphatic circulation.

There are many other interesting developments in therapeutics that signify an encouraging trend toward more and better agents and procedures to treat disease.

D.G.F.

General Information

Chloramphenicol-Containing Drugs: Report from Spain. The possible development of aplastic anemia after treatment with chloramphenicol has led to repeated warnings against its indiscriminate use. Sergio Erill, Patricio du Souich and Jesus A. Garcia-Sevilla[1] (Univ. of Barcelona) examined the principal pharmaceutical specialties containing chloramphenicol sold in Spain, particularly the information included in their package inserts. Practically all the formulations recorded in a 1973 publication were examined. Of the 198 chloramphenicol-containing products listed, 13 could not be obtained. The 185 specialties that were analyzed included 169 brands sold by 71 different companies.

Eighty-two agents were to be taken orally, 43 were suppositories, 32 were injectables and 28 were topicals. Only 11 contained chloramphenicol as a single active ingredient. In 51 other products, chloramphenicol was the only antibiotic present. One other antibiotic was present in 78 compounds and two others in 34, whereas 11 compounds contained combinations of chloramphenicol and three or four other antibiotics. Excluding topicals, the usual recommended mean daily dose of chloramphenicol was 15 mg/kg, but in 11 instances it exceeded 30 mg/kg. Eight package inserts did not include a recommended dosage. Indications were not mentioned in 3 instances. The most common indications given were bronchitis and pneumonia. Side effects were not mentioned in 132 of the 185 leaflets. Dose-related bone marrow depression was mentioned 28 times and aplastic anemia 22 times. Contraindications were mentioned in only 53 leaflets, whereas 8 claimed there were no contraindications for the product. Further warnings or other advice about usage was given in 36 leaflets, in 28 under a specific heading. Periodic hematologic tests were recommended in 35. Long-term treatment was cautioned against in 30 leaflets.

These findings emphasize the need for better information and instructions about use in chloramphenicol products. There is evidence that this is a widespread problem. A change in the availability of drug combinations containing chloramphenicol and an improvement in the information accompanying them are urged.

► [What a terrible situation! The thousands of travelers to Spain from the United States, as well as other countries, may be exposed there to a dangerous drug, often without knowing it. It is absolutely essential that physicians warn their patients about taking any foreign medication unless they know the contents or seek expert advice from a reputable physician.—Ed.] ◄

Drugs—Remarkably Nontoxic. Hershel Jick[2] (Boston Univ.) has found that drugs, though responsible for considerable morbidity and

(1) J. Clin. Pharmacol. 15:401–404, May–June, 1975.
(2) N. Engl. J. Med. 291:824–828, Oct. 17, 1974.

mortality, are remarkably nontoxic and as benign as one could reasonably expect. The short-term effects of drugs have been studied in some 19,000 medical inpatients in the Boston Collaborative Drug Surveillance Program. About 30% of hospitalized medical patients manifest at least one adverse drug reaction during hospitalization. Drug-attributed deaths occur in 0.29% of such patients, an annual total in the United States of about 29,000 such deaths. The average medical inpatient receives about nine different drugs per hospitalization. At least 75,000,000 adults take drugs regularly. The rate of life-threatening reactions in hospital patients is about 3%, but the rate per course of drug therapy is only 0.4%. The rate of drug-attributed death per course of drug therapy is currently about 3 per 10,000. Over a third of 46 such deaths have been attributed to hyperkalemia or pulmonary edema. One third of these 46 patients had advanced cancer, and another third had advanced alcoholic liver disease. Hospitalizable illness results from an estimated 1 of every 500 long-term outpatient drug treatments per year.

These estimates ignore drug use in pediatric and surgical practice. Rare adverse drug effects are generally not identified, and the study does not provide for the identification of "delayed" adverse drug effects. Nevertheless, it appears that, despite some alarming gross numbers, most drugs are remarkably nontoxic. Drugs with risks grossly out of proportion to their benefits are not in current use. If the amount of drug toxicity is to be reduced substantially, the number of drugs that people take must be decreased. There appears to be little need for alarm about the problem of drug toxicity, but a need remains to quantitate the toxicity that does occur, to identify the populations at highest risk and to uncover any drugs whose toxicity may be unwarranted in relation to the benefits derived from them.

► [General surveys of this type gather many interesting data and confirm what many have long realized, that in skilled hands, under proper observation, hazard from drugs is far less than many risks faced daily by our society. Most drug deaths occur among seriously ill patients, who require heroic measures in attempts to save or prolong life and who in previous decades would have died from their disease. There is altogether too much loose thinking about drug hazards. Certain concerned groups have become so alarmed that they are making efforts to control drug therapy so completely that medical progress and good therapeutic practice would be inhibited.—Ed.] ◄

Use and Abuse of Intravenous Solutions are discussed by Donald G. Vidt[3] (Cleveland Clinic). Intravenous fluids are used to maintain normal body composition when normal food or fluid intake is impossible, and to correct acute and chronic disturbances of fluid and electrolyte balance. Simple solutions suffice when maintenance problems exist for only several days. High-calorie solutions may be given when patients cannot take nutrition or fluids orally for 3–6 days. If oral feedings must be deferred for weeks or longer, total parenteral nutrition is necessary.

Sufficient nutrients exist in intravenous saline solution to support the growth of gram-negative bacteria. Solutions may be contaminated by airborne microbes. The major hazard of adding drugs to intrave-

(3) J.A.M.A. 232:533–536, May 5, 1975.

nous fluids is microbial contamination. Further, interactions of active drugs with components of solutions are complex and often poorly understood. Drug availability is also a consideration when drugs are added to intravenous solutions. More research is needed to learn the role of particulate matter in lung damage. Volume control sets carry many hazards, including omitted drug doses and admixture errors. Polyvinyl chloride in containers may adversely affect solutions stored in them. The use of high-percentage glucose solutions for total parenteral nutrition may lead to several clinical problems.

The open system with tube containers should be opened only in an aseptic environment to reduce the possibility of microbial contamination. Addition of drugs to intravenous fluids should be discouraged except in emergencies. Only one drug should be added to a fluid, and all additions should be noted in the patient's permanent drug file. Critical attention should be paid to the administration equipment used for intravenous solutions, especially volume control sets. Hospitals should consider establishing a continuous admixture monitoring system and quality control program, which would help indicate sources of contamination and be useful in planning inservice education and training programs pertaining to intravenous therapy preparation and administration.

► [A wise suggestion is given for the proper use of intravenous solutions. Excessive use of such solutions is common. Furthermore, the practice of adding several drugs to such infusions is almost routine in hospital practice. There certainly needs to be a tightening up of technics.—Ed.] ◄

Metabolism of Drugs by Microorganisms in the Intestine is discussed by Peter Goldman, Mark A. Peppercorn and Barry R. Goldin[4] (Harvard Med. School). The metabolism of both exogenous and endogenous compounds can be attributed not only to host enzymes but also to the enzymes of the host's bacterial microflora.

An interesting example is found with salicylazosulfapyridine (SAS), composed of a sulfa drug and a salicylate. Whether it is the intraluminal content of 5-aminosalicylate, the release of sulfapyridine in the colon or the presence of undegraded SAS in the colon that is related to the mechanism of action of SAS is not clear.

Alterations in the flora may alter the distribution of a drug and its metabolites so as to influence its effectiveness. Caffeic acid metabolism can be attributed to a variety of intestinal bacteria and caffeic acid metabolites in the urine can be used as a probe of the activity of various constituents of the flora. There is no obvious correlation between the metabolic transformations made by bacteria in culture and those attributable to the bacteria when associated with a germ-free rat.

It is not clear whether the conversion of dopamine to m-hydroxyphenylacetic acid (m-HPAA) that occurs in conventional animals proceeds through dopac or through m-tyramine. The time course of the appearance of m-HPAA after feeding dopamine suggests that an active conversion of dopamine to m-tyramine occurs in the gastrointestinal tract. Neomycin reduces the urinary excretion of m-tyramine and m-HPAA in patients taking L-dopa, indicating reduced conver-

(4) Am. J. Clin. Nutr. 27:1348–1355, November, 1974.

sion of dopamine to m-tyramine as the result of suppression of the intestinal flora by the antibiotic. The pharmacokinetic argument implicating the flora in the transformation of dopamine to m-HPAA is applicable to food-deprived as well as to fed animals.

Study of the metabolism of both exogenous and endogenous compounds by the flora offers an opportunity to elucidate the effects of these compounds on the host and the possibility that the effects may change with alterations in the flora.

► [This is an important observation. It is forgotten all too often that there may be a considerable difference in drug action between the oral and percutaneous doses of the same drug. Perhaps a variable portion of drug metabolism usually attributed to the liver or other tissues is actually the effect of bacterial enzymes. This subject needs more study. – Ed.] ◄

The Placebo Effect: Neglected Asset in Care of Patients. According to Herbert Benson and Mark D. Epstein[5] (Boston), the placebo effect is a neglected and berated aspect of patient care, the value of which must be recognized so that provision can be made for its incorporation and proper use in evolving health care delivery systems. Any system that fragments the physician-patient relationship will lessen the effects of this asset. Although the placebo effect is disdained in medicine today, throughout much of medical history it was the most a physician could offer his patients.

Most controlled drug studies have failed to assess the placebo effect itself as a therapeutic intervention by not incorporating nontreatment controls. The placebo effect is considered merely as a variable to be controlled and hence is ignored. The existence of the placebo effect in treatment of a variety of diseases is well substantiated. Reactions to placebos may involve practically any organ system.

The placebo effect seems to be derived from a combination of factors involving the patient, the physician and the relationship between the two. The psychologic state of the patient affects his responses to both active and nonactive drugs. The milieu in which drugs are given may also affect the patient's response. The physician exerts much influence on the course of treatment as a result of his own biases, attitudes, expectations and methods of communication. The actual interaction of the physician and patient is probably more responsible for the effect than is the contribution of each.

The placebo effect usually enhances the patient's well-being and is thus an essential aspect of medicine. More emphasis on the potency of the placebo and its positive effects is needed. Research and instruction in efficient methods of establishing the appropriate doctor-patient relationship conducive to the placebo effect should be initiated. The placebo effect must be allowed to survive if medicine is to provide optimal care for patients.

► [A timely, sensible article on placebo therapy is offered here. It must be remembered that physicians have been honored and accepted by society for many centuries for their role in relieving the maladies of mankind. Since extremely few specific remedies were available, it must be obvious that some other factor was operating. I have been amused by the often quoted statement, attributed to Laurence J. Henderson, the biochemist; he reputedly said in regard to medicine in the early years of this century

(5) J.A.M.A. 232:1225–1227, June 23, 1975.

that a patient seeing a physician "had a 50–50 chance of benefiting from the contact." If that were so, it is doubtful if medicine would have survived as a useful profession. What most scientifically trained people fail to realize is the fact that human belief overcomes many obstacles. Therefore, if a physician can instill the necessary confidence, the patient often does the rest.—Ed.] ◄

Effects of a Procaine Preparation (Gerovital H3) in Hospitalized Geriatric Patients: Double-Blind Study. The action of procaine hydrochloride as an anesthetic and vasodilator is well known, but its effect on the aging process is more controversial. Israel Zwerling, Robert Plutchik, Margaret Hotz, Ruth Kling, Leo Rubin, Joel Grossman and Barbara Siegel[6] conducted a 12-week study on the effects of Gerovital H3, a procaine hydrochloride preparation, on geriatric inpatients. Each 5-ml ampule contains 100 mg of 2% procaine plus benzoic acid and potassium metabisulfite; the pH is buffered to 3.3. Nineteen patients with varying levels of organic brain dysfunction were studied 4 weeks after the withdrawal of all drugs. A 5-ml injection of Gerovital H3 was given intramuscularly 3 times a week for 6 weeks; a double dose of 10 ml was then injected for 6 weeks. Control subjects received saline injections. Nine drug and 10 control patients completed the first 6 weeks of study, and 6 drug and 7 control patients completed the second 6 weeks. The mean age of drug patients was 74 years and of controls, 72 years. The respective average hospitalizations were 28 and 33 months.

The Geriatric Rating Scale, Geriatric Interpersonal Evaluation Scale and Brief Psychiatric Rating Scale were utilized. At 6 weeks, there were no significant differences between the groups. At 12 weeks, the only significant difference was greater hostility in the drug group, probably reflecting random variation. No significant differences in change of scores were found for any laboratory values, psychologic measures or psychiatric ratings at 12 weeks. Depressive items were comparable in the two groups. Side effects were also comparable, the most common in both groups being agitation, confusion and difficulty in walking, which are typical in geriatric populations. Overall, there were only small, apparently random differences between the drug and control subjects.

Gerovital H3 had no apparent therapeutic efficacy in this sample of hospitalized geriatric patients with organic symptoms, in agreement with most previous studies. No antidepressant effect of the drug was observed, and there were no changes in ward behavior, cognitive functioning or memory. Gerovital H3 had no ameliorative effect on either psychologic or physiologic functioning among these hospitalized geriatric patients.

► [This needed study supports what medical investigators have long believed. Whether such subjective data will have any impact on those who use Gerovital H3 remains to be seen. Past experience with such agents has shown that they continue to be used as long as a gullible patient is available or until their use is prohibited by law.—Ed.] ◄

Snake Venom Poisoning in the United States: Experiences with 550 Cases. According to Findlay E. Russell, Richard W. Carl-

(6) J. Am. Geriatr. Soc. 23:355–359, August, 1975.

son, Jack Wainschel and Arthur H. Osborne[7] (Univ. of Southern California), snake venom poisoning is a medical emergency requiring immediate attention and considerable judgment. In the United States, about 45,000 snakebites occur annually, of which nearly 8,000 are inflicted by venomous snakes. About 20% of such bites show no evidence of envenomation. About 20 types of snakes in the United States are venomous.

The lethal fractions of snake venoms are certain peptides that seem to have specific receptor sites. The role of these peptides in snake venom poisoining is often overlooked by physicians. Snake venoms also are rich in enzymes, some of the more important being proteinases.

Snake venom poisoning represents multiple poisonings, perhaps involving three or more toxic reactions that may occur simultaneously or sequentially. The venoms of rattlesnakes and many vipers produce deleterious local tissue changes, blood cell changes, defects in coagulation and injury to the vascular intima. The early cardiovascular collapse seen in occasional patients bitten by rattlesnakes is due to a decreased circulating blood volume and perfusion failure. Pain immediately follows the bites of most North American rattlesnakes. Bleeding and clotting times are usually prolonged.

Treatment must be instituted immediately to be effective, but no first aid measure is a substitute for antivenin or medical care. A constriction band is placed if the patient is seen within 30 minutes of a rattlesnake or cottonmouth bite. Incision through the fang marks and suction are indicated in viper bites. In rattlesnake bites, longitudinal incision through the fang marks is followed by suction for 1 hour after the bite. In severe envenomation, a tight tourniquet may be applied proximal to the bite and left in place until antivenin is started. Antivenin is best given intravenously. In rattlesnake bites, polyvalent crotaline antivenin is the antitoxin of choice. An antivenin for North American coral snake venom is also available. A broad-spectrum antimicrobial agent is given if there is severe tissue involvement. Isolation-perfusion of the extremity and intra-arterial infusion of antivenin have given indifferent results.

The wound is cleaned and covered with a sterile dressing and the injured part immobilized in a physiologic position. Follow-up care includes debridement as necessary, soaks of the wound in Burow's solution and daily painting of the wound with an aqueous dye. An antimicrobial ointment can be applied at bedtime. Fasciotomy should be discouraged.

► [This conservative approach has merit. All too often, unfortunately, antivenin is not readily available. Treatment for shock, electrolyte balance, analgesics for pain and a tetanus toxoid booster are all useful supportive measures.—Ed.] ◄

(7) J.A.M.A. 233:341–344, July 28, 1975.

Drug Action

Cardiac and Pulmonary Effects of Acebutolol. Sympathetic stimulation of the airways may vary considerably with time and between persons, and asthmatics may be more dependent than others on sympathetic stimulation to maintain bronchial patency. A consistent increase in sympathetic stimulation improves the conditions for testing the pulmonary effects of β-adrenoceptor blocking agents. C. R. Kumana, C. M. Kaye, Monica Leighton, Paul Turner and John Hamer[8] (London) used vigorous exercise to assess the pulmonary effects of single intravenous doses of acebutolol, propranolol, practolol and placebo. Studies were done in 6 healthy subjects aged 20–22, 3 of each sex. The intravenous treatments included propranolol, 0.1 mg/kg, practolol, 1 mg/kg, acebutolol, 1 mg/kg, and placebo. The 10-minute treatments were given in a double-blind manner. Subjects were exercised for 3 minutes on a bicycle ergometer before and 2, 3, 4 and 6 hours after each treatment. Cycling was against a fixed load of 1,050 or 750 kpond m per minute, producing pretreatment exercise heart rates of 158 per minute or higher.

All three active agents markedly reduced the exercise heart rate. Propranolol and acebutolol produced similar reductions; practolol resulted in a more persistent response. Resting and exercise peak flow rates fell only after propranolol and acebutolol. Only propranolol reduced the timed forced expiratory volume significantly. The declines in plasma propranolol and acebutolol were similar and more rapid than the fall in practolol. At 2, 3 and 4 hours, when acebutolol and propranolol produced equivalent cardiac β-blocking activity, their mean plasma concentrations were in a ratio of about 8:1. At 2 hours, when practolol and acebutolol gave rise to nearly equivalent cardiac β-blockade, their mean plasma concentration ratio was 3:1.

These findings suggest that propranolol is not cardioselective and that acebutolol is not as cardioselective as practolol.

► [Further evaluation of β-blocker activity and the relative merit of those β-blockers used clinically is presented. Practolol exerts more cardiac β-blocking action than propranolol. Acebutolol resembles propranolol.—Ed.] ◄

Disposition of Acetylmethadol in Relation to Pharmacologic Action was investigated by Robert F. Kaiko and Charles E. Inturrisi[9] (Cornell Univ.). The prolonged opiate effects of the narcotic analgesic acetylmethadol have stimulated interest in its use in the maintenance therapy of opiate dependence. It has a longer duration of action than methadone, and its use would reduce the need for treatment outside the clinic, thus reducing illegal drug distribution. Studies were

(8) Lancet 2:89–93, July 19, 1975.
(9) Clin. Pharmacol. Ther. 18:96–103, July, 1975.

done on 12 men; 8 were outpatients receiving an average dose of 50 mg acetylmethadol 3 times weekly for 4–25 weeks and 4 were inpatients.

Plasma acetylmethadol levels were highest (mean, 0.06 μg/ml) 4 hours after oral administration of 50 mg of the drug. Plasma levels declined rapidly, the drug being undetectable by 48 hours in all subjects. Noracetylmethadol levels were maximal at 4 and 8 hours, and the levels declined slowly. Dinoracetylmethadol levels rose slightly after 4 hours and did not decline on subsequent sampling. Pupillary constriction was maximal at 8 hours, the mean peak constriction being 1.8 mm, compared with 0.3 mm at 48 hours. The apparent half-life of acetylmethadol elimination from the plasma was 7 hours; the value for noracetylmethadol was 48 hours. The subject with the lowest urinary pH had the highest renal clearance of all three compounds, whereas the patient with the highest pH had the lowest renal clearance values.

The relatively long duration of opiate effects of acetylmethadol results from biotransformation to active and persistent metabolites. The plasma noracetylmethadol level is a more reliable correlate of the sustained effect of acetylmethadol than is the drug dosage. Factors that influence biotransformation should be considered in use of acetylmethadol for the treatment of opiate dependence.

► [The hope is to find a long-acting compound that will block heroin. Acetylmethadol shows promise. In view of the profound effect of metabolism on the drug, as well as urinary pH effects, much more work must be done before it can be used successfully clinically.—Ed.] ◄

Increased Rate of Alcohol Removal from Blood with Oral Fructose and Sucrose. Oral and intravenous fructose has been shown to accelerate the metabolism of alcohol in man but it is not readily available and is costly, whereas sucrose is abundant and relatively inexpensive. Jack Soterakis and Frank L. Iber[1] (Tufts Univ.) compared the effects of oral sucrose, fructose and glucose on the removal of alcohol from the blood in 8 male chronic alcoholics aged 25–53. Each was abstinent for at least 1 week before study and none had evidence of gastrointestinal or metabolic disease. All had normal liver function. On 3 consecutive days after overnight fasting, sugar solutions were given in lemon-flavored solutions of 2 Gm glucose and fructose per kg body weight and 4 Gm sucrose per kg. The solutions were ingested over 1 hour. After 30 minutes, 1 Gm intravenous alcohol per kg was given over 60 minutes.

Comparable blood alcohol levels were present at 1 hour after ingestion of the various sugars. At 3 hours the alcohol level was significantly higher with glucose than with the other sugars. The alcohol removal rate was greatest with fructose ingestion at 25.4 mg/100 ml per hour, compared with 23.9 mg for sucrose and 19.1 mg for glucose. Serum fructose levels were quite similar with fructose and sucrose ingestion. All patients had moderate diuresis on each study day. One had transient abdominal cramps after ingesting fructose.

The acceleration of the alcohol removal rate observed with both fructose and sucrose in these studies was quantitatively modest. Most

(1) Am. J. Clin. Nutr. 28:254–257, March, 1975.