THE YEAR BOOK *of* DRUG THERAPY

(1957-1958 YEAR BOOK *Series)*

EDITED BY

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THE YEAR BOOK PUBLISHERS

INCORPORATED

200 EAST ILLINOIS STREET

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THE PRACTICAL MEDICINE YEAR BOOKS

This volume is one of the 15 comprising the Practical Medicine Series of Year Books founded in 1900 by G. P. Head, M.D., and C. J. Head, and published continuously since then. The complete list follows:

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EDITORIAL

I despair of the world about us—meaning, of course, only that segment of it concerned with the use of drugs in treating disease. For this small but so important bit is being distorted out of all semblance of relationship to scientific thought and procedure, and utterly vulgarized and cheapened too, by the money-mad rush of some of the pharmaceutical companies. These companies are traducing the objective independence of the medical man, and I give solemn warning that unless such practices cease we will see our whole noble structure, so painstakingly erected through sound and honest endeavor, go toppling over—to be swept down into the river of greed.

As I write these lines there lay before me recent numbers of 3 journals of high national repute containing prominently in their front advertising sections a 4-page spread in several colors introducing a new drug whose use is urged as a skeletal muscle relaxant. I know nothing directly of the merits or demerits of this compound, but I do know that its proponents insult me as a man of science and a physician when they ask that I accept their drug for use in practice while offering only the following in substantiation of their claims:

(a) One (1) reference to an article that appeared in a leading journal of laboratory research and had no other aim than to show that the compound, like some other members of the chemical group to which it belongs, is recoverable from the plasma of the dog after oral and intravenous administration.

(b) One (1) reference to a 21-line abstract that appeared in another laboratory journal in which it was stated that the compound had been compared with other members of its group with respect to some central nervous system effects after oral administration to rats, one sentence stating also that little toxicity had been found on administration to dogs and mice.

(c) Three (3) references to publications that are said to be "pending."

(d) Three (3) references to what are described as "personal communications."

(e) Nothing else!

This is not the way in which the great contributions were

announced that brought medicine to its present position of high if grudging esteem; no, nor the little ones either. Far from it. And no medical journal should dare to carry within its covers, and thus by inference approve, advertising copy in which there is offered a list of references whose value in substantiation of the claims being made is entirely spurious.

Had I not already so many irons in the fire, and getting on in years to boot, I should like to lead a crusade against the evils that are enveloping us in the cloud of misrepresentation, obfuscation, specious double talk and downright deceit billowing out of some of the pharmaceutical houses. From the front offices, that is. I am a pharmacologist and many of my friends in pharmacology are on the staffs of pharmaceutical houses; good men, all of them—excellent scientists. But it is not they who dictate the promotional policies of their organizations. It is the advertising and sales management officials who are seeking to take over the practicing methods of medical men and tell them what to do and how to do it so that certain of the pharmaceutical houses may make more money. Never has the welfare of mankind been threatened by a group with more effrontery.

Something must be done about it. I call for someone in the medical profession to dedicate himself to the cause.

HARRY BECKMAN

Method to Block Constitutional Reactions Produced by House Dust Extract with Antihistaminic Drugs Orally is presented by Enrique Drassinower[1] (Lima, Peru). Severe constitutional reactions have been observed during desensitization with autogenous as well as stock house dust extracts in patients with allergic manifestations of the respiratory tract and with a high hypersensitivity to house dust. The constitutional reaction is probably the result of an antigen-antibody response. Several previous methods of antihistaminic therapy have been unsuccessful, including 50 mg. Pyribenzamine® orally 20 minutes before injection of the pollen extract, 3 doses of 50 mg. Thephorin® orally 20 minutes before injection, 25 mg. injected with the extract and 50 mg. orally 60 minutes after injection.

In a study of 16 patients (10 children), 2 doses were effective orally. The optimal time for administration of the antihistamine is 20 minutes before and 35 minutes after injection of house dust extract. The antihistamines used were Hista-Clopane® (in capsules containing 25 mg. Histadyl® and 12.5 mg. chlorhydrate of cyclopentamine), Neohetramine® in 50 mg. tablets, Thephorin in 25 mg. tablets or Tagathen® in 25 mg. tablets. For each patient the antihistamine used was that which proved most effective in blocking the constitutional reactions and gave the least side effects. Several antihistamines were tried in some patients.

By giving the antihistamine orally 20 minutes before and 35 minutes after the injection of house dust extract, the antigen dosage could be increased, permitting a satisfactory maintenance dose to be determined. Constitutional and local reactions to the extract were reduced or eliminated. Doses of the antihistamine should be adjusted in each patient according to age, weight and degree of hypersensitivity to the antigen. The same method can be used for desensitization with other antigens such as molds and pollen.

Observations on Iodide Sensitivity are presented by La-

(1) Ann. Allergy 15:150-157, Mar.-Apr., 1957.

mar B. Peacock and Hal M. Davison[2] (Atlanta, Ga.). For more than 100 years, inorganic iodide compounds have been used to treat bronchial asthma, particularly the perennial allergic type. Potassium iodide is absorbed from the small intestine and carried in the extracellular compartment. It is concentrated in salivary glands, mucous glands of the stomach, thyroid and lactating breasts. Serum iodine can be raised from normal levels of 12 μg. to 22,000 μg./100 ml. The elevated levels are thought to act on the mucous glands of the respiratory tract, producing an increased excretion of lower viscosity, resulting in an over-all expectorant action. The mucus produced is easier to break loose and does not stick as easily to the bronchial tree.

Reactions to iodides may be those due to acute and chronic overdosage. These include a taste of iodine in the mouth due to excessive amounts in the saliva, ptyalism, excessive serous discharge from the mucous glands of the nose, swelling of all the salivary glands with tenderness and pain, acneiform lesions of the skin, injection of the conjunctivas, edema of the eyelids, frontal headache and gastric upset. These are normal reactions to overdosage. The second group of symptoms are those of true hypersensitivity with mild symptoms of conjunctivitis, coryza, pharyngitis and enlarged lymphatics, fever, eosinophilia and papular rash. Many cases have been reported in which death followed intravenous administration of compounds containing iodine for x-ray studies.

Of 502 patients with asthma treated with iodides, 81 (16.1%) had reactions. In 68, reactions were sufficiently severe to warrant discontinuance of the drug. The reactions were of the physiologic type due to overdosage. No patient had signs or symptoms of true hypersensitivity such as arteritis, eosinophilia, proteinuria, jaundice, polyneuritis or bullous iododerma.

Since organic iodides generally are less toxic and cause less reaction, 29 patients with known reactions to inorganic iodide were given 10-20 drops of an organic iodine solution 3 times daily; 24 had good relief from asthmatic symptoms without reaction to the drug, 4 were helped but had a reaction to the drug, and 1 had no benefit but had a reaction. Rather than avoid all iodide compounds in patients who react to them, organic iodides should first be tried.

(2) Ann. Allergy 15:158-164, Mar.-Apr., 1957.

The technic for administration of inorganic iodides has been the same for 35 years. Fowler's solution, 1½ drams, saturated solution potassium iodide, 4 drams, and elixir of peptenzyme to make 4 oz. are prescribed, 1 dram in water 3 times a day after meals. One prescription lasts 10 days. A series of prescriptions is given in which the elixir of peptenzyme remains constant, Fowler's solution is decreased by ½ dram each prescription down to zero, then again increased to 1½ drams, and the potassium iodide solution is increased by 1 dram each prescription to a maximum of 16 drams or to tolerance and then decreased by 1 dram each prescription to 4 drams.

Allergic Reactions to Blood Transfusion: Their Prevention with Injectable Chlor-Trimeton®. Allergic reactions to blood transfusion are not infrequent, and persons with allergic disorders are about 4 times as likely to be sensitive to pooled plasma as nonallergic patients. Allergic posttransfusion reactions occur in 1-3% of persons receiving blood. Among possible causes of allergic transfusion reactions are passive transfer of sensitivity from an allergic donor to a normal recipient, similar transfer of "H substance," receipt from a donor's blood of a specific allergen (often food) by a patient with a matching hypersensitivity, sensitization to blood of a specific donor and factors which are not routinely sought on typing such as M and N sensitivity. The commonest allergic manifestations in order of decreasing frequency but of increasing importance are urticaria, angioedema, respiratory difficulty due to asthma or edema of the glottis or larynx, headache, epigastric distress, loss of sphincter control and severe or fatal anaphylactic shock.

C. Rowell Hoffmann[3] added 20 mg. Chlor-Trimeton in solution to each of 108 pt. blood given to 46 patients known to have previous allergies and of whom 17 had had previous transfusion reactions. These patients also received 109 blood transfusions which had no added antihistamine. No atopic reactions occurred among the 46 when Chlor-Trimeton was added to the blood, whereas 13 reactions occurred when blood was given alone without added antihistamine. The only side effect was drowsiness in some patients.

Proper procedures and precautions can reduce incidence of allergic reactions to blood transfusions. Blood should be

(3) Surgery 41:491-495, March, 1957.

taken only from fasted donors to avoid introduction of substances from food ingested by the donor to which the recipient might be sensitive. Donors with histories of allergy should be excluded. The clinical laboratory can skin test the recipient to the blood serum at the time of cross-matching and exclude blood which gives a positive reaction. Chlor-Trimeton, 20 mg., or some other antihistamine can be added to the blood given to patients with a history of allergy or transfusion reaction.

► [In three earlier articles (1955-56 YEAR BOOK, pp. 17-19) it was reported that tripelennamine (Pyribenzamine®) reduced the incidence of both allergic and pyrogenic reactions, whereas diphenhydramine (Benadryl®) and chlorprophenpyridamine (Chlor-Trimeton) did not apparently affect the incidence of pyrogenic reactions. Pyribenzamine and Chlor-Trimeton had been added to the blood just before administration, as in the present studies, whereas the Benadryl had been added to stored blood 1-3 weeks previously; could this have accounted for the difference in protective action?—Ed.]

Use of Antihistamine Agent in Preventing Serum Reactions Following Injection of Tetanus Antitoxin. Serum sickness is a systemic reaction occurring usually within 2 weeks after introduction of a foreign serum, and usually runs a course of about 2 days. Manifestations are due to interaction between antigens of the injected serum and specific antibodies produced by the recipient. The commonest are skin eruptions, pruritus, fever, lymphadenopathy, abdominal pain, nausea, vomiting, polyarthritis and often edema of the eyelids, face and ankles. Hypersensitive patients may die.

Serum sickness reactions usually can be controlled with epinephrine, antihistamines, sedatives and cortisone or ACTH, but suitable prophylaxis has not been developed. Increasing immunization with tetanus toxoid has reduced the necessity for prophylactic tetanus antitoxin injections in recent years, but serum reaction to tetanus antitoxin continues to be a major problem. In an attempt to overcome this problem, A. O. Singleton, Jr. and Harry M. Little, Jr.[4] (Univ. of Texas) gave Phenergan®, the N-dimethylaminopropyl derivative of phenothiazine, to patients receiving tetanus antitoxin.

The first 250 patients received tetanus antitoxin alone. The next 250 patients received tetanus antitoxin, plus 12.5 mg. Phenergan at time of injection, 12.5 mg. the next night and 25 mg. each night thereafter for 7 days. Incidence of serum

(4) Surgery 40:784-786, October, 1956.

sickness was 11.2% when tetanus antitoxin was given alone and 7.2% in the group receiving Phenergan. The severity of the reactions, when they occurred, was unaffected. Statistical analysis showed that the same results could have occurred by chance alone. Therefore, decrease in incidence of serum sickness reaction after prophylactic Phenergan has no statistical significance.

Molar Sodium Lactate in Acute Epinephrine-Fast Asthmatic Patients. Epinephrine is the most potent and valuable bronchial antispasmodic agent for symptomatic relief of bronchial asthma, but tolerance or "fastness" often develops. This presents a difficult therapeutic problem, and many methods have been tried unsuccessfully.

J. S. Blumenthal, E. B. Brown and G. S. Campbell[5] (Univ. of Minnesota) treated 22 patients with 120-150 cc. intravenous molar sodium lactate. All had severe allergic asthma and were extremely tolerant of epinephrine or showed epinephrine fastness.

Results were good. Marked relief from symptoms occurred within 10 minutes to 2 hours. Neither epinephrine nor any other drug was used to obtain relief, and results apparently were due to the endogenous drug. Results frequently were dramatic when relief was needed urgently. The rapidity of response indicates that some mechanism beyond the systemic pH might be involved, possibly local tissue acidosis.

Animal and clinical experiments indicate that the action of epinephrine is correlated with the blood pH. Epinephrine fastness may in part be due to general or local acidosis. This condition may be corrected by elevating the pH, often with dramatic relief from epinephrine-resistant asthmatic states. Increasing the dose of epinephrine over that usually given may result in adequate response, but administration of sodium lactate is the treatment of choice, except in patients in whom sodium is contraindicated.

► [Contraindications to the use of molar sodium lactate are discussed in an article in the section on arrhythmias.—Ed.]

Prophylaxis of Acute Asthmatic Attack in Infants and Children by Use of Symptomatic Medication. Jerome Glaser and Marilyn F. Smelzer[6] (Rochester, N.Y.) studied 389 children, aged 10 or less, with bronchial asthma. Of these, 320

(5) Ann. Allergy 14:506-510, Nov.-Dec., 1956.
(6) Pediatrics 19:680-684, April, 1957.

(82.2%) showed prodromal symptoms of the asthmatic attack; these symptoms were respiratory in nature in about 92%. The commonest symptoms were nasal discharge, sneezing, cough and watering of the eyes. If the child had prodromal symptoms, regardless of their nature, the parents were given the following instructions.

INSTRUCTIONS FOR PROPHYLAXIS IN ASTHMATIC ATTACKS.—I. *Immediately,* at the first sign of an impending cold or asthmatic attack, which in this case is ..... proceed as follows in an attempt to prevent the condition from progressing and developing into asthma:

A. Put the child to bed in a room as free as possible from house dust, feathers, wool, animals of all kinds with fur or feathers, and free from odors, particularly fresh paint, tobacco smoke, burning leaves, cooking, etc.

B. The following medications are to be started *simultaneously* and repeated every 4 hours the first 24 hours when the child is awake and thereafter as may appear desirable:

(1) An antihistamine

(2) Nose drops: ..... drops into each nostril

(3) One teaspoon of the cough mixture No. .....

These medications must be started *as soon as possible* as delay of even an hour mitigates against the best results.

II. Insert an aminophylline suppository every night at bedtime and repeat every 12 hours thereafter until the danger of an asthmatic attack is passed.

III. If the above measures fail to prevent or minimize the cold or asthmatic attack, then with the next episode, along with items *(1), (2)* and *(3)* above, an antibiotic should be given. This will be prescribed by your doctor or from this office.

The antihistamine was given in liquid form to children unable to swallow tablets or capsules. The nose drops could be any vasoconstricting preparation of the physician's choice. The cough medication contained ephedrine or some similar sympathomimetic preparation. Successful dosage of antihistamines depends quantitatively on Benadryl®—4 mg./kg./24 hours usually is adequate.

Adequate co-operation by the parents was obtained in about 174 cases (54%). Among these 174 patients, results were satisfactory in 96.4%. The chief source of failure was inability of the parents to comprehend, despite repeated explanation, that the directions had to be followed exactly.

If the regimen plus antibiotics should fail, addition of hormone therapy (prednisone, prednisolone, adrenocorticotropin) should be considered in a prophylactic procedure.

Medihaler® Therapy for Bronchial Asthma: New Type of