COUNCIL ON PHARMACY AND CHEMISTRY

REPORT OF THE COUNCIL

The Council has authorized publication of the following report. The outline in this report is offered as an objective, a pattern and not a regulation. However, it has been adopted for publication with the belief that it will be of help to manufacturers and scientists who undertake the investigation of new drugs.

Austin Smith, M.D., Secretary

LABORATORY AND CLINICAL APPRAISAL OF NEW DRUGS

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A new drug should pass through several phases of investigation before it is declared suitable for distribution in commerce. It should be studied in the laboratory and in the clinic, the details of the study depending on the nature of the ingredients and the intended uses, but all investigations should follow a general plan which will permit a thorough understanding of the usefulness and toxic properties of the drug.

In considering new drug applications in the enforcement of the Federal Food, Drug and Cosmetic Act, the Food and Drug Administration is concerned primarily with evidence of safety. The Council on Pharmacy and Chemistry is concerned not only with the evidence of safety but also the evidence adduced to support the claims made for new drugs. Too frequently this evidence is found inadequate and the sponsors of new preparations, if they wish to provide the missing data, may find it necessary to repeat some of the more time consuming and expensive procedures and at other times find it advantageous to proceed along entirely new lines of thought. If the manufacturer has adequate facilities for laboratory and clinical appraisal, he can usually obtain the desired information within a reasonable period. Frequently however such facilities are not immediately available and much effort must be spent in searching for appropriate channels for investigation. If a comprehensive outline had first been prepared and then closely followed, loss of time and expenditure of needless effort might have been avoided.

At the same time it is an advantage for physicians and allied scientists to know by what standards a new drug has been evaluated. When the physician is urged to use this agent, he should have available such evidence as will satisfy his questions concerning safety and efficacy.

The activities of the Council on Pharmacy and Chemistry of the American Medical Association in this field have recently been described.[1] Certain phases of the activities of the Food and Drug Administration which bear on this problem have also been published or are in press.[2]

The Council on Pharmacy and Chemistry has provided for almost forty years a set of rules to guide manufacturers for the submission of articles for inclusion in New and Nonofficial Remedies. At periodic intervals it has enlarged on these rules to provide criteria such as those found acceptable for the evaluation of skin disinfectants and contraceptives.[3] Usually the criteria have been concerned with one special agent or class of agents. The Federal Food, Drug and Cosmetic Act provides that applications for new drugs shall contain "full reports of investigations which have been made to show whether or not such drug is safe for use," and the Food and Drug Administration provides a form in which are set forth suggestions concerning the scope and character of these reports.

If the utmost of possible benefits with a minimum of possible dangers is to result when a new drug is introduced for experimental trial and later in commerce, it is necessary to develop methods of appraising the therapeutic usefulness and potential harmfulness of new drugs and to organize these methods into a logical system which, if followed, will give reasonable assurance that the new preparation will not be offered to the medical profession or to the public before the extent of its usefulness or the potentialities for harm are understood. The present paper outlines the principles which have been helpful in making such an appraisal of new drugs.

PRELIMINARY OBSERVATIONS

The preliminary experimental observations with a new agent give the clue to the possible field of usefulness. In dealing with chemotherapeutic agents, these preliminary observations consist usually of tests of the efficacy of the agent in combating or preventing some experimental infections. In the case of drugs that might be termed "symptomatic agents," the preliminary observations should include tests of the possible pharmacodynamic actions of the drug. These observations "set the sights," so to speak, and indicate the course to be pursued in subsequent and more detailed investigations.

LABORATORY OBSERVATIONS

Assuming that a new drug has shown promise in the preliminary tests, more extensive inquiry must now be made into the mechanisms of its action and its

The authors wish to express their appreciation of the helpful comments offered by Dr. Torald Sollmann, Dr. P. J. Hanzlik and Dr. A. L. Tatum.

1. Smith, Austin: Membership, Activities, Method of Operation, Attainments of the Council, J. A. M. A. **124**: 433 (Feb. 12) 1944.
2. Woodard, Geoffrey, and Calvery, Herbert O.: Acute and Chronic Toxicity, Industrial Med., January 1943. Calvery.[4] Van Winkle.[6] Draize, Woodard and Calvery.[5]
3. Contraceptive Agents, Report of Council on Pharmacy and Chemistry, J. A. M. A. **123**: 1043 (Dec. 18) 1943; Criteria for Evaluation of Skin Disinfectants, ibid. **121**: 593 (Feb. 20) 1943.

toxicity. In order for the clinician to use a drug intelligently he must know the manner in which its effects are brought about. The plan of procedure and the details of the tests to be employed should be formulated in accordance with the type of agent to be investigated, e. g. single chemical entity, complex extract, hormone, serum or vaccine. The conditions in which the drug is thought to be useful and the observations made in the preliminary testing will also modify the plan of investigation and the details of the test procedures. Nevertheless we feel that the following general types of study should prove to be applicable to most new drugs, keeping in mind that these are suggestive and not necessarily exhaustive:

(A) *Biochemistry.*—General properties of drug, including solubility, stability; studies of absorption, reabsorption, fate, distribution and excretion of the drug; quantitative data on these points where possible; mode of detoxification (excreted unchanged, oxidized, reduced, acetylated?); effect on enzymes, blood and tissues; chemistry of body fluids and tissues; production of toxic products during course of metabolism.

(B) *Pharmacodynamics.*—Local: Tests of irritation on skin, eye, alimentary canal; intradermal irritation, sensitivity or anesthesia; tests of protoplasmic depression or toxicity, and reversibility of effects on cilia, nerve trunks, mucosa; hemolysis, antihemolysis and blood pigment changes.

Systemic: Action on blood pressure, respiration, muscles, nervous system, cardiac functions, secretions, temperature, voluntary activity, organ perfusion, isolated tissues; effects of vasomotor agents, proteins, fats, metals, solvents and other agents on the actions of the drug; cumulative effects; development of tachyphylaxis; quantitative and qualitative differences in action in different species of animals.

(C) *Experimental Functional Pathology.*—Effects in experimentally induced pathologic states, e. g. smooth muscle spasm, hypodynamic hearts, fibrillations and arrhythmias, hypertension, respiratory depression, edema, shock, burns, anemias.

(D) *Chemotherapeutic.*—Effects in preventing specific experimental infections; effects in combating experimental infections or actions of toxins; antagonists of chemotherapeutic agents, e. g. pus, serum, tissue products; distribution in inflammatory states, e. g. meningitis, dermatitis; minimal effective dosage (ED50).

The data obtained from these studies will serve as a guide in the clinical application of the product and doubtless will also show evidence of undesirable or potentially harmful effects. If such effects are not observed, a careful search must be made for them. This involves the very important study of the toxicology of the preparation. Woodard and Calvery,[2] Calvery [4] and Draize, Woodard and Calvery [5] have set forth in considerable detail the approach to the study of the acute and chronic toxicity of drugs and other chemical agents. Certain of the principles which they have formulated bear repetition here, and the original publications can be consulted for more detailed discussions.

Depending on the conditions for which the product may be used, on its biochemical and pharmacodynamic actions and on the methods of its use, adequate studies of its toxicity must be made. The following outline sets forth in general terms the scope that these studies should embrace:

4. Calvery, Herbert O.: Safeguarding Foods and Drugs in Wartime, Am. Scientist **32**: 103-119, 1944.

5. Draize, John H.; Woodard, Geoffrey, and Calvery, Herbert O.: Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes, to be published.

(A) *Acute Toxicity.*—Dosage response curves in three or more species; objective symptoms; statistical calculations for comparative studies; simultaneous comparative determinations of other substances; variations in toxicity with method of administration.

(B) *Subacute Toxicity.*—Large daily doses to one or more species for six to twelve weeks; microscopic pathology.

(C) *Chronic Toxicity.*—Three or more species; at least one species for the life of the animal; several dosage levels graduated to produce from no effect up to pronounced lesions, and possibly shortening life span; microscopic pathology; effects on voluntary activity, e. g. running or other performance as evidence of more subtle functional changes.

(D) *Local Effects.*—Sensitization; skin irritation; mucous membrane irritation; photosensitization.

(E) *Special Studies.*—Reproduction; distribution and storage; effect of diet; effect of environment; kidney and liver function tests.

In selecting animals for investigation of new drugs it is important to use several distinct species, since it is well known that qualitative as well as quantitative differences exist between animal species in their reactions to drugs. Some species are wholly unsuited for demonstration of certain effects; e. g. methemoglobin is not readily produced in rodents and if the drug is suspected of causing this reaction rats, rabbits and guinea pigs are not suitable test animals. Rabbits are not usually satisfactory animals for blood pressure studies and often react atypically; e. g. histamine produces a rise of pressure instead of a fall. Emetics cannot be tested in rodents, since vomiting does not occur in these species. Many other examples could be cited, but these suffice to demonstrate the need for careful selection of suitable test animals.

Each investigator, including those concerned with clinical as well as laboratory investigations, should realize from the beginning where each specialty fits in the over-all plan of study; e. g. chemistry, pharmacology, physiology, pathology. He should keep a careful record of all data and not be guided solely by impressions. The records should include actions not seemingly connected with the immediate project and dramatic response; for example, micturition, defecation, vomiting, pulse, respiration.

After completion of the experimental studies, a critical review of the accumulated data should be made. The purpose in this review is to reach a decision as to whether clinical trial of the drug is justified. It is difficult to set forth criteria on which this decision should be made, since the judgment of the investigators must always be an important factor. However, without any claim for completeness, the following points should be considered:

1. Has the drug definite and desirable pharmacodynamic or chemotherapeutic actions?

2. Are its actions constant and reproducible?

3. Are these actions observed in different species of animals?

4. Is the mechanism by which its actions are produced a desirable one, or are the actions the result of an ultimately undesirable reaction of the animal?

5. Are the effects obtained in animals in which experimentally produced pathologic or functional changes comparable to human diseases have been made?

6. What is the therapeutic index of the compound (ratio of effective dose to toxic dose: ED50/LD50)?

7. Are the undesirable side actions of sufficient importance and severity to militate against its clinical use?

8. Is there an adequate margin of safety in its use?

CLINICAL OBSERVATIONS

When sufficient information regarding the experimental actions of a new drug has been obtained to permit a logical decision to be reached that clinical trial is indicated, such studies may be commenced cautiously. The primary objectives to be reached in clinical investigation are twofold: (1) to determine the therapeutic efficacy and (2) to detect all signs of clinical intolerance or toxicity. The secondary, but nevertheless important, objectives are (1) to establish the effective dosage range for different age groups and conditions, (2) to determine the type and extent of collateral treatment necessary to obtain the maximum benefit from the drug, (3) to determine the best method of minimizing any undesirable side actions incident to the use of the drug and (4) to determine the contraindications and precautions to be observed in the use of the drug. Each clinical investigator should keep these objectives clearly in mind throughout his investigation in order that nothing may be overlooked.

Frequently the pharmaceutical manufacturer concerned with the development of a new product has neither the facilities nor the personnel to investigate the drug adequately. This is particularly true of clinical investigations. This work must be undertaken by others in cooperation with the manufacturer. The selection of the investigator is important, and it is a waste of time and money and may even be dangerous to place the investigation of the safety and efficacy of a new drug in the hands of incompetent or poorly trained individuals. Furthermore, it is important to select the investigator who has proper qualifications and training in the particular phase of the problem requiring study. A good pharmacologist is not necessarily a competent pathologist; a specialist in internal medicine may not be in a position to evaluate a product offered for nasal or sinus infections. Furthermore, not all specialists in clinical medicine are capable of conducting acceptable clinical investigations. The caliber and training of each investigator should be carefully considered before putting a problem in his hands. Clinical investigation of a new drug presents many very difficult problems. The heterogeneity of the persons under observation, the difficulty of securing adequate controls, the many extraneous and uncontrollable factors, the constant presence of subjective effects influenced by conscious or unconscious bias and many other unique conditions hamper the investigator in his efforts to secure the truth. Regardless of these, it is possible to suggest certain factors to be given consideration in conducting clinical investigations:

(*a*) *The Selection of Individuals to Be Observed.*—Cooperation from subject; absence of complicating factors; age; sex; emotional and psychic factors.

(*b*) *Diagnosis.*—Objective proof of diagnosis if possible, such as isolation and identification of infecting organism; x-ray evidence or other informative laboratory data; accurate description of lesion; differential diagnosis.

(*c*) *Control Observations.*—Preliminary control observations on the individuals; concurrent observations of untreated controls; alternation of treatment; alternation of treated and control subjects; post-treatment, control observations.

(*d*) *Observation During Treatment.*—Repeated physical and laboratory examinations; hematology; urinalysis; blood chemistry; x-ray; functional tests; precise objective measurements of improvements alleged to be produced by drug; determination of concentration of drug in blood, urine and other body fluids and the correlation of levels so observed with the dosage and the effect.

(*e*) *Number of Subjects.*—Sufficient number of treated individuals to minimize chance or other uncontrollable factors from influencing results; sufficient number of untreated control subjects. The results should be subjected to statistical analysis in order to determine their reliability.

(*f*) *Carefully Planned Administration of Drug.*—Controlled variation in dosage, frequency, method and duration of administration; effect of other drugs, and so on.

(*g*) *Criteria of Benefit.*—Establishment of criteria whereby the effects of the drug may be evaluated; objective tests; subjective observations; comparison with control treatments; comparison with natural course of disease.

(*h*) *Separation of Subjective and Objective Observations.*—Use of "blind tests" (neither investigator nor subject knows which of several samples being administered is control or test product) or other methods to eliminate conscious or unconscious bias on part of observer and subject; careful separation of symptomatic reactions from objective findings; psychologic appraisal of subject.

(*i*) *Duration of Observation.*—Treatment to continue until any intrinsically undesirable or harmful manifestations have had time to develop as well as until sufficient time has elapsed to demonstrate beneficial effects; comparison of rapidity of cure or improvement with that of other methods of treatment.

(*j*) *More Than One Clinical Investigation.*—Several different investigators working independently; conclusions to be made independent of one another's results.

When the investigator is satisfied that he has a therapeutic agent which may be given satisfactorily by one route he should not by conjectural reasoning alone decide that it may be given safely and effectively by some other route. For example, if a product is safe and efficacious for oral use it may not be so when administered by rectum or by injection.

If it is decided to have several persons working on the clinical aspects of the problem, each one should provide a complete picture of the phase under investigation and not just a piecemeal study. Above all, it should be realized that summaries of case histories unless accompanied by the full report from which the summaries were derived are of little significance. A multiplicity of fragmentary case reports provide less information than a few complete and detailed reports of cases carefully and critically studied.

On completion of the clinical investigations it should be possible to provide definite answers to the questions implied in the statement of the objectives which were set forth at the beginning of this section. If these answers are not forthcoming from the data, more investigation is necessary. However, with the fulfulment of the objectives it is now necessary to decide whether the new drug has sufficient merit to be used in the alleviation of human suffering and in the treatment, prevention or cure of disease. At the same time thought should be given to providing adequate warnings against use in certain pathologic conditions or against unsafe dosage or methods or duration of administration or application.

EVALUATION OF RESULTS

Two factors enter into the decision with regard to the merits of the drug: 1. Is it efficacious? 2. Is it dangerous? Neither of these factors can be separated one from the other and considered alone. This has been emphasized by Van Winkle[6] in discussing the evaluation of new drug applications submitted under the new drug provisions of the Federal Food, Drug and Cosmetic Act. It has been emphasized that there is no arbitrary standard of safety; it is a relative matter in which the toxicity of the drug must be weighed against the therapeutic benefits which its use will bring about. Drugs with potentialities for harm and with only slight therapeutic effectiveness may be too dangerous for use, whereas another drug with the same potentialities for harm but with exceptional therapeutic usefulness may be relatively safe. Therefore, in evaluating the results of the clinical and experimental studies of a new drug, the following factors should be considered:

1. For what conditions is the drug to be offered?
2. How effective is it in these conditions?
3. Is it superior to other drugs and methods of treatment?
4. What is its inherent toxicity?
5. Does its toxicity outweigh the therapeutic advantages, keeping in mind the seriousness of the conditions for which it is being offered?
6. If there are other drugs equally or more effective in the same conditions, is the new drug less toxic or does it offer advantages in ease of administration, duration of action and so on?
7. How extensive will the use of the drug be; are its applications limited?

SUMMARY

A study of this outline for the therapeutic and toxicologic appraisal of new drugs may leave the impression that the task which has been set is far too complex and difficult, requires too much time and expenditure of energy and money and can be circumvented by briefer and less thorough investigations. While this may be true in a few isolated instances, it is not true in the majority of cases of really new drugs. Recent history contains too many instances of disastrous results that have followed incomplete or inadequate investigations on new drugs. This outline is an objective toward which investigations of new agents should be directed. It need not apply in full to all cases, but the reasons for omitting any part should be that the omitted parts of the program are not necessary and not merely that they are troublesome. It should also be borne in mind that new methods and new criteria may be developed and these should, of course, be applied when indicated.

Finally it is necessary to exercise sound judgment in deciding whether a product deserves recognition, and the only basis on which such a judgment can be made is by a careful appraisal of the data obtained through a systematic study. Investigations of new therapeutic agents are perhaps the most exacting of all scientific investigations since human health, and even life, may depend on the thoroughness of these investigations. Furthermore, failure to interpret correctly the results of the tests conducted and criteria for their evaluation may be disastrous.

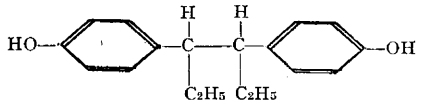
6. Van Winkle, Walton, Jr.: The Safety of New Drugs, Stanford M. Bull. **2**: 103-107, 1944.

NEW AND NONOFFICIAL REMEDIES

The following additional articles have been accepted as conforming to the rules of the Council on Pharmacy and Chemistry of the American Medical Association for admission to New and Nonofficial Remedies. A copy of the rules on which the Council bases its action will be sent on application.

AUSTIN SMITH, M.D., *Secretary.*

HEXESTROL.—Meso-3,4-*di*-parahydroxyphenyl-n-hexane. $C_{18}H_{22}O_2$ (M.W. 270.36). Hexestrol may be represented by the following structural formula:



It may be prepared from anethole in ether solution by (*a*) treating with anhydrous hydrogen bromide to form anethole hydrobromide, (*b*) conversion of the anethole hydrobromide to 3,4-dianisylhexane by means of metallic magnesium, aluminum, copper or zinc turnings and (*c*) hydrolysis of the 3,4-dianisylhexane to form hexestrol. The product thus obtained may be purified by recrystallization from dilute alcohol.

Actions and Uses.—Hexestrol is used for the same conditions for which estrogenic substances are employed. It is claimed to cause a lower incidence of toxic symptoms than those which follow diethylstilbestrol administration.

Dosage.—As is the case with all estrogenic substances, the dosage of hexestrol must be adjusted to the individual case. As a guide the following dosages may be satisfactory: For menopausal symptoms, 2.0 to 3.0 mg. daily by mouth until symptoms are under control, and then 0.2 to 1.0 mg. daily as a maintenance dose; or by injection, 1.0 mg. in oil three times weekly with similar lowering for maintenance of control. For gonorreal vulvovaginitis the drug may be given orally in 3.0 mg. doses three times daily for seven days; senile vaginitis and kraurosis vulvae, 2 to 3 mg. daily by mouth, or 1 mg. in oil three times weekly by injection; suppression of lactation, 15.0 mg. one to three times daily for two or more days, or 15.0 mg. in oil daily for two or more days by injection.

Tests and Standards.—

Hexestrol occurs as an odorless white crystalline powder which melts at 185-188 C. It is freely soluble in ether; soluble in acetone, ethanol and methanol; slightly soluble in benzene and chloroform; practically insoluble in water and in dilute mineral acids. It may be dissolved in vegetable oils and in dilute solutions of sodium or potassium hydroxide. When recrystallized from diluted alcohol, hexestrol appears in the form of thin, platelike crystals of irregular, serrated outline.

Dissolve about 10 mg. of hexestrol in 10 cc. of dilute alcohol and add three drops of 1 per cent ferric chloride solution: a yellowish green color develops which changes to yellow. Add a few drops of 50 per cent solution of antimony pentachloride in dry alcohol, free chloroform to a very dilute solution of hexestrol in the same solvent: a red colored solution is produced. Dissolve 10 mg. of hexestrol in 5 cc. of concentrated sulfuric acid: no color is produced (distinction from diethylstilbestrol, which yields an orange color).

The hexestrol diacetate obtained in the assay given below melts at 137-139 C.

Dry an accurately weighed specimen of hexestrol to constant weight at 100 C.: the loss does not exceed 0.5 per cent. Ignite an accurately weighed specimen of hexestrol after the addition of concentrated sulfuric acid: the sulfated ash residue is not more than 0.05 per cent. Dissolve 0.1 Gm. of hexestrol in 10 cc. of warm normal sodium hydroxide solution: the solution is clear and colorless; dilute to 20 cc. with distilled water and add 5 drops of 10 per cent sodium sulfide solution: the darkening produced does not exceed that of a control to which has been added 0.02 mg. of lead.

Transfer to a suitable flask about 0.5 Gm. of dried hexestrol, accurately weighed, and add 2 cc. of acetic anhydride and 4 cc. of dry pyridine. Boil the mixture under a reflux condenser for fifteen minutes; cool, add 50-60 cc. of distilled water and shake the flask and contents thoroughly. Stopper the flask and place it in the cold for one to one and one-half hours. Collect the precipitate on a suitable filter and wash it with four 20 cc. portions of distilled water. Dry the precipitate at 75-80 C. overnight, cool and weigh: the weight of the dry hexestrol diacetate obtained, when multiplied by 0.7628, corresponds to a hexestrol content of not less than 98.5 per cent and not more than 100.5 per cent.

LOESER LABORATORIES, INC., NEW YORK

Ampul Solution Hexestrol in Oil 1 mg. per cc.: 20 cc. Prepared with 0.5 per cent chlorobutanol.

THE WM. S. MERRELL COMPANY, CINCINNATI

Tablets Hexestrol: 0.2 mg., 1.0 mg. and 3.0 mg.

PENICILLIN (See THE JOURNAL, Oct. 7, 1944, p. 367). The following dosage form has been accepted:

SHARP & DOHME, INC., PHILADELPHIA

'Lyovac' Penicillin Sodium: 20 cc. vials containing 100,000 Oxford units.