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ALLERGIES AND OTHER REACTIONS DUE TO DRUGS AND COSMETICS*

by

Charles W. Whitmore**

I. INTRODUCTION

THE social and economic problems in bringing a drug or cosmetic to the market place are large and complex.¹ A new drug may take several years and millions of dollars to develop. The economic health of one or more drug companies may be involved, as well as the economic welfare of their employees. The drug may bring materially improved health or well-being to a sizeable segment of the population, and it may even save or prolong their lives if it performs as expected; conversely, the drug may cause harm to the public and the drug house alike if it performs in a manner other than that anticipated.

No drug or cosmetic is, or ever will be, completely free from adverse reactions; yet decisions still must be made.² Should the product be produced at all? Should the conditions under which it is to be used be restricted? As long as human beings exist, mistakes in judgment will be made occasionally. In that event, who is, or should be, held liable?³

The attorney working in the field of products liability for drugs and cosmetics needs certain basic factual information regarding the drug or cosmetic involved in his particular case. Some of this information is as follows:

1. Is the particular drug or cosmetic capable of producing the type of reaction which occurred in the case?

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¹ See Ladimer & Newman, *Clinical Investigation Medicine—Legal, Ethical, Moral Aspects* (1963).

² See Larrick, *No Absolute Safety*, NSA J. Am. Pharm. Ass'n 217 (1964).

³ See 2 Frumer & Friedman, *Products Liability* § 28 (1964); 6 *Lawyers' Medical Cyclopedia* §§ 45.7-45.8 (1958); Schwartz, *Problems of Proof in Claims For Recovery For Dermatitis*, 41 Mich. L. Rev. 893 (1943).

2. Was adequate pre-marketing testing of the drug or cosmetic carried out, and were Food and Drug Administration requirements met?
3. With what frequency does the particular drug or cosmetic produce reactions of the type occurring in the particular case, and was the manufacturer aware of this incidence of reactions?
4. Did the particular drug or cosmetic in fact produce the untoward reaction?
5. Was adequate information regarding the use and safety of the drug or cosmetic placed in the hands of the physician, patient or consumer?

II. DRUG EVALUATION—PRE-MARKETING

New drugs generally are released to the market after thorough scientific study and approval by the Food and Drug Administration of the product itself, the materials used therein and the results obtained in the scientific study regarding both toxicity and effectiveness. The steps involved in pre-marketing scientific evaluation usually include the following:⁴

1. Chemical compounds are selected for laboratory study at random or on the basis of their molecular structure, relating them to other compounds of known pharmacological activity and toxicity.
2. The chemical compounds are then tried on small laboratory animals whose genetic and physiological patterns are known, and the pharmacological and pathological results are assessed.
3. If the initial results are interesting in relation to the results obtainable with known existing drugs, an elaborate series of tests are conducted over a long period with a large number of animals of various types and suitabilities. These tests involve a study of the amount of the compound required to produce the desired pharmacological or therapeutic effect and the amount required to produce death of the experimental animals—thereby establishing a margin of safety or tolerance. The structural and functional effects of the drug on the liver, brain, blood, kidney and all other organs are observed. The effect on the fetus during pregnancy is studied, as is post-natal growth and development during long-term administration of the drug.⁵
4. If the drug proves both to be safe and to have interesting thera-

⁴Modell, *Safety in New Drugs*, 190 *J. Am. Med. Ass'n* 141 (1964).

⁵Commission on Drug Safety, Report on Conference on Prenatal Effects of Drugs (1963); *Drug Pairs Increase Teratogen Danger*, *Antibiotic News*, Sept. 2, 1964, p. 3, cols. 1-3.

peutic and pharmacological effects in animals, it remains to be discovered whether it is safe and has similar effects in man.

5. If preliminary trials in normal human subjects show both safety and the expected pharmacological effects, then the drug may be tested in selected human cases of the pathological state which it is expected to benefit.
6. If the initial human trials appear safe and rewarding therapeutically, the study is expanded to encompass hundreds or even thousands of cases under rigid scientific controls over a period of months or years.
7. If these extensive clinical trials are successful and if the drug can be commercially produced and marketed satisfactorily, and assuming the blessing of the Food and Drug Administration is obtained, the drug reaches the open market and becomes available for use by physicians generally.

One of the primary purposes of drug evaluation prior to marketing is to detect any reactions which may result from the use of a given drug under study. Some of the more serious types of reactions which drugs may produce are set out below:

Table I: *Types of Reactions to Drugs*⁶

1. Allergic:
 - a. Anaphylactic shock and death
 - b. Generalized skin rashes
 - c. Serum sickness
2. Blood:
 - a. Aplastic anemia (failure to form white blood cells)⁷
 - b. Reduced white blood cell count (leucopenia)
3. Cardiovascular reactions:
 - a. High blood pressure
 - b. Low blood pressure
 - c. Peripheral vascular insufficiency
4. Endocrine-metabolic reactions:
 - a. Aggravation or precipitation of diabetes mellitus
 - b. Hypothyroidism
5. Eye:
 - a. Cataract formation
 - b. Damage to the retina of the eye
 - c. Visual-function disturbances

⁶ Year Book of Drug Therapy 1963-1964 Series, 495-617 (Beckman ed. 1964).

⁷ Huguley, *Agranulocytosis Induced by Dipyrone, a Hazardous Antipyretic and Analgesic*, 189 J. Am. Med. Ass'n 938 (1964).

6. Gastro-intestinal:
 - a. Intestinal ulceration and hemorrhage or perforation
 - b. Liver damage with jaundice
 - c. Pancreitus
7. Kidney:
 - a. Acute or chronic toxic kindey damage⁸
8. Neurological:
 - a. Convulsive seizures
 - b. Disorders of motor function or sensation
 - c. Nerve deafness
9. Pediatric:
 - a. Congenital abnormalities
 - b. Intra-uterine death of the fetus or abortion
 - c. Post-natal respiratory distress
10. Psychiatric:
 - a. Drug addiction
 - b. Precipitation of psychotic or confusion states

III. DRUG EVALUATION—POST-MARKETING

Despite all of the precautions that are observed prior to marketing, use of drugs both can and does result in unanticipated effects or reactions after mass marketing. This is because the total picture regarding the many effects which a given drug may produce becomes clear only after an extended period of use by many thousands of patients. We are constantly dealing with compounds which have increasing biologic activity. These compounds are increasingly capable of producing both desirable and undesirable effects.

Among other problems, a whole new list of genetic variations is being discovered, including enzyme, chemical and hormonal abnormalities. Some of the persons whose abnormality is unknown to them metabolize or handle certain drugs differently than the "normal" person. These genetic differences account for some of the variations in tolerances or reactions to drugs.⁹

Indispensable to an intelligent evaluation of a given drug after it has been marketed, of course, is the availability of accurate statistics on its actual performance, including the incidence of reactions produced by it. In this regard, certain characteristics of various types of information-gathering systems are deserving of notice:

⁸ *Analgesic Abuse and the Kidney—a Commentary*, 190 J. Am. Med. Ass'n 238 (1964).

⁹ La Du, *Pharmacogenetics*, Oct. 26, 1964 (Unpublished, Symposium on Cutaneous Toxicity, Sponsored by Committee on Cutaneous Health of Cosmetics of AMA and Society of Toxicology).

Table II: *Information-Gathering System Characteristics*

1. Clinical statistics:
 - a. Hospital level:
Reflect only reactions occurring while in the hospital or severe enough to require hospitalization; do not represent a normal population cross section.
 - b. Office level:
Reflect only reactions occurring while under medical care or severe enough to require medical attention; do not represent a normal population cross section.
2. Industry statistics:
Reflect only reactions severe enough to mature into complaints to the company; frequently available from only the individual manufacturer.
3. Insurance statistics:
Reflect only reactions severe enough to mature into actual claims.
4. Local or regional:
Difficult to correlate with drug or cosmetic distribution and to determine incidence therefrom.
5. National:
National-level systems of any type are in their infancy.

Traditionally, both the drug and cosmetic industries have relied largely on insurance-claim statistics and on industry complaint-file statistics involving the incidence and types of reactions. The drug industry, in addition to utilizing these sources, has also looked to some local-area, clinical reaction-incidence statistics, but in the past it generally has not aggressively sought out post-marketing reaction information. With respect to drugs, however, a number of new information-gathering programs have been instituted to provide a better picture of the incidence of reactions at both the local and national levels.¹⁰ From the standpoint of the consuming public, the

¹⁰ (1) American Medical Association—Registry on Adverse Reactions.

a. Purpose:

To acquire and disseminate information on possible reactions to drugs which had not been previously suspected, and serious reactions to any drug even if they are known to occur; to evaluate the reports of adverse reactions to drugs with the help of impartial experts; and to inform the profession promptly of the nature and significance of reactions to potentially toxic drugs and other agents.

Solicits reports from hospitals and individual physicians, and reviews 500-600 periodicals for reports of adverse reactions.

b. Responsible Official:

Department of Drugs
American Medical Association
535 North Dearborn Street
Chicago, Illinois 60610

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most important area is being undertaken for study first, because it is in the drug area that the most severe reactions occur.

- (2) Chemical-Biological Activities.
The Chemical Abstracts Service
American Chemical Society
Ohio State University
Columbus, Ohio
 - a. Purpose:
To provide a convenient key to all references concerning the biological activity of organic compounds, covering 312 bioscience journals.
 - b. Responsible Official:
Director
Chemical Abstracts Service
Ohio State University
Columbus, Ohio
- (3) Drug Information Center (Proposed) (Federation of American Societies for Experimental Biology, 9650 Wisconsin Avenue, Washington, D. C. 20014).
 - a. Purpose:
To establish by coordinated effort a drug-information clearing house to serve government agencies, scientific groups, professional societies, trade associations, universities and others.
 - b. Responsible Official:
Dean, College of Pharmacy
University of Minnesota
Minneapolis, Minnesota 55414
- (4) *Drugs in Use*.
 - a. Purpose:
Drugs in Use is a service offered to drug companies by Mr. Paul de Haen. To provide in condensed and organized form references to significant drug data taken from clinical observations and published in the literature. Covers (1) single chemical entities, their salts and derivatives, including antibiotics and enzymes, and also (2) combination drugs which are sold in the United States. Abstracts from 199 Journals.
 - b. Responsible Official:
Mr. Paul de Haen
11 West 42d Street
New York, New York 10036
- (5) Food and Drug Administration—Adverse-Reaction Reporting Program.
 - a. Purpose:
To obtain information promptly on the untoward effects of drugs (especially newer drugs) from monthly reports received from participating hospitals. Until 1963 involved only 30 hospitals. Planned to include 1000 hospitals. Recent agreement with American Medical Association to exchange information.
 - b. Responsible Official:
Director
Division of Research and Reference
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20025
- (6) IPAD Working Group on Adverse Drug Reactions (Intergovernmental Procurement Advisory Council on Drugs, Defense Supply Agency, Cameron Station, Virginia).
 - a. Purpose:
To provide Food and Drug Administration with uniform reporting system of adverse drug reactions from the medical facilities of the Army, Navy, Air Force, Veterans Administration and Public Health Service.
 - b. Responsible Official:
Bureau of Medicine and Surgery
Navy Department
Washington, D. C. 20025
(Continued on page 82)

IV. COSMETIC EVALUATION—PRE-MARKETING

New cosmetics and dermatological medicinals containing no active therapeutic ingredients have been traditionally evaluated scientifically in animals and man only for allergic sensitization capacity and primary irritancy potential regarding the skin and eyes. The Food and Drug Administration has usually required 200 human test subjects.

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- (7) ISI Drug Alert.
- a. Purpose:
To provide a weekly comprehensive listing to all published reports concerning the clinical use of drugs. This listing is in the form of an index, arranged alphabetically by trademark name or nonproprietary name. Cross reference between trade and generic name provided.
- b. Responsible Official:
Institute for Scientific Information
325 Chestnut Street
Philadelphia, Pennsylvania 19106
- (8) Medical Literature Analysis and Retrieval System (MEDIARS).
- a. Purpose:
Designed for use by the National Library of Medicine to perform various functions of literature analysis and retrieval.
Provides abstracts covering 2,500 bioscience periodicals, of which sixty-five per cent are in foreign languages.
- b. Responsible Official:
Chief, Bibliographic Services Division
National Library of Medicine
Bethesda 14, Maryland
- (9) Pharmacy Drug Information Services.
- a. Purpose:
To enable pharmacists to be trained as drug-information specialists; to contribute to rational drug therapy and to enable the pharmacist to serve the physician as a "consultant" or "informant"; and to provide the means for developing a plan to audit drug therapy in major teaching hospitals under a program to improve the evaluation and use of drugs.
International Pharmaceutical Abstracts to cover 448 periodicals.
- b. Responsible Official:
Executive Secretary
American Society of Hospital Pharmacists
2215 Constitution Avenue, N. W.
Washington, D. C. 20007
- (10) Philadelphia Registry for Drug Reactions (Greater Philadelphia Committee for Medical-Pharmaceutical Sciences, 3401 North Broad Street, Philadelphia, Pennsylvania 19140).
- a. Purpose:
To establish a metropolitan drug-reaction registry that could serve as a model for other cities, and to collect "meaningful information" from the five teaching hospitals in Philadelphia.
- b. Responsible Official:
Chairman, Subcommittee on Drug Reaction Registry
Women's Medical College
Philadelphia, Pennsylvania
- (11) RINGDOC.
- a. Purpose:
This service is an outgrowth of the Documentation Ring set up by a group of pharmaceutical companies in Europe to supply their need for information about new drugs. To provide in abstract form references to articles of pharmaceutical interest, including pharmacologic as well as clinical reports. The abstracts cover a wide range of subjects.

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The cosmetic industry today, however, with its constant striving for enhanced cosmetic values, has embarked to a considerable degree upon the development of cosmetics which "do something" from an aesthetic, therapeutic or prophylactic standpoint.¹¹ Moisturizers, drying agents, bleaches, dyes, hormones, bacteriostatic agents, antibiotics, vitamins and other ingredients of an "active" nature are being added to cosmetics. This trend, of course, begins to require testing not only for toxic and harmful effects locally to the skin, but also for systemic absorption through the skin and for therapeutic effectiveness.¹²

A. Predictive Testing Of Cosmetic And Dermatologic Pharmaceuticals¹³

There are no tests that absolutely guarantee safety. This question can be resolved only after sufficient trial by many users over a long period. Predictive procedures in their present form are imperfect tools. At best, they can only be considered as rough screening devices which can identify the "bad actors," either irritants or sensitizers.

Predictive tests may be falsely negative or falsely positive. In false negative tests, the product passes the test, but trouble is encountered under the conditions of use. The false negative develops usually be-

b. Responsible Official:

Managing Director
Derwent Publications, Ltd.
Rochdale House, Theobalds Road
London, W. C. 1, England

- (12) Scientific Group on the Evaluation of the Safety and Efficacy of Drugs (World Health Organization, Geneva, Switzerland).

a. Purpose:

To collect information concerning the safety and efficacy of new drugs as they are introduced from national health authorities in member countries. No clearing-house for such information has been established, but data is apparently becoming available on a limited basis directly from cooperating nations.

b. Responsible Office:

Division of Biology and Pharmacology
World Health Organization
Geneva, Switzerland

A detailed compilation of current adverse drug-reaction reporting programs is available on request from the Pharmaceutical Manufacturers Association, Washington, D. C.

¹¹ Certain inherent differences between drugs and cosmetics are worthy of note:

Drugs: Taken for relief of pain, discomfort or disease under medical supervision. When is the risk of reaction worse than the disease being treated? What is the permissible reaction rate?

"Over-the-counter" drugs: Taken for relief of pain, discomfort or disease. No medical supervision. Permissible reaction rate?

Cosmetics: Used for beautification. No disease relief involved. No medical supervision. Reaction rate permissible? Reaction rate that will interfere with sales?

¹² LeVan, *The Cosmetic Industry and the Clinical Investigator*, The Evaluation of Therapeutic Agents and Cosmetics 142-49 (Sternberg & Newcomer eds. 1964); Conley, *Toxicity Problems of Cosmetics*, 166 J. Am. Med. Ass'n 638 (1958).

¹³ Rostenberg, *Predictive Procedures for Eczematous Hypersensitivity*, 20 A.M.A. Archives of Industrial Health 181 (1959).

cause of inappropriate sampling or inaccurate conclusions from the data. The false positive test, on the other hand, means that the material causes trouble under the conditions of testing, but not under use conditions. False positives arise because of inappropriate biological techniques.

The two independent variables in predictive testing are the biological and the statistical variables. By the biological variable is meant the degree to which the predictive technique fails to simulate the conditions under which the product will be used. Included in the statistical variable are two somewhat independent questions, namely: (1) How much confidence can one have that the outcome of the given experiment was not due to chance alone? (2) What extrapolations can be made from the results on the test sample to the larger universe of potential users?

With regard to the biological variable, it appears obvious that for the predictive technique to simulate use conditions, at least two factors must be controlled: (1) The population on which the test is to be conducted must be reasonably representative of the population for whom the product is designed, and (2) the conditions under which the test is applied must be a reasonable facsimile of the conditions under which the product will be used. It is at times very difficult and sometimes impossible to control the second factor. This does not imply that predictive procedures should not be used, but it does emphasize that the further the divergence between the predictive techniques and the use conditions, the less confidence one can have in the prediction. For example, the limitations of predictive techniques with respect to the projection of results of patch tests on the relatively limited numbers of the patch-test group to the larger numbers of potential consumers are not well appreciated.¹⁴

¹⁴ These limitations are shown by the following table:
Statistical Calculations: Maximum Anticipated Reactions in General Public From Analysis of Prophetic Patch-Test Data:

| Test Population (Sample Number of Individuals) | Per Cent Anticipated Reactions in General Public Per Number of Positive Reactions in Test Population | | |
|--|---|-------------------|-------------------|
| | None (Per Cent) | One (Per Cent) | Two (Per Cent) |
| 30,000 | 0.01 | ... | ... |
| 10,000 | 0.03 | 0.05 | 0.06 |
| 5,000 | 0.06 | 0.09 | ... |
| 1,000 | 0.3 | 0.45 | ... |
| 200 | 1.5 | 2.2 | 2.9 |
| 100 | 3.0 | 4.4 | 5.8 |
| 50 | 5.8 | 8.8 | ... |
| 20 | 13.9 | 20.8 | 27.0 |
| 10 | 26.9 | 38.2 | ... |

See Spoor, *Skin Reaction to Cosmetics—Classifications and Diagnosis*, 60 N.Y. State J. Med. 1940 (1960).

Conventionally, statisticians employ the ninety-five per cent and the ninety-nine per cent confidence levels. If 200 persons are tested and no reactors are found in the challenge test, it is not likely that more than fifteen reactors will be encountered out of every 1000 persons using the material. By the phrase "with a ninety-five per cent likelihood" it is meant that, if, for example, 100 groups of 1000 persons each used the material, in ninety-five of the groups there would be fifteen or fewer reactors, but it is possible that in five groups there would be more than fifteen reactors. In a similar manner, the likely number of reactors could be computed at a ninety-nine per cent confidence level, meaning that the prediction would likely be wrong only once in 100 times.

If a manufacturer wished to be certain that he would not encounter more than one reactor out of every 1000 users and he wished to predict this result at a ninety-five per cent confidence level, a sample of 3,000 individuals would be required with no positives. Such a sample, however, would not ordinarily be feasible, from the standpoint of either the cost to the manufacturer or the facilities and test population available to the average investigator.

Most of the testing procedures currently in use are oriented toward the two variables mentioned above (biological and statistical). Thus, they are designed to simulate closely use conditions and to result in a high degree of statistical veracity. Some of these testing procedures are described in the margin.¹⁵

¹⁵ *Predictive Testing Procedures Commonly Employed Today for Cosmetics or Drugs To Be Applied to the Skin*

- (1) Landsteiner guinea-pig test:
 - a. Subject—white male guinea pig, weighing 300-450 gm.
 - b. 0.1 per cent solution of suspension in saline injected in subject intracutaneously.
 - c. Injection made every other day or three times a week until ten have been given.
 - d. First injection—0.05 ml. solution; subsequent injections—0.1 ml. solution.
 - e. Injections made in a 3-4 cm. area on upper back or flank.
 - f. Readings made after each of the ten injections.
 - g. After tenth injection, two weeks' rest.
 - h. Final test conducted with 0.05 ml. solution.
 - i. Comparison of average of first ten readings with eleventh reading.
- (2) Draize human technique:
 - a. 200 persons (100 men, 100 women) of a wide age range.
 - b. 0.5 ml. or 0.5 gm. applied by patch to arms or back.
 - c. Patch removed after twenty-four hours, and site read.
 - d. Rest for twenty-four hours.
 - e. Patches repeated until ten have been made; areas randomized.
 - f. Ten to fourteen days of rest.
- (3) Schwartz-Peck human technique:
 - a. Standard patch test for forty-eight hours, with use of both the new and old formula on 200 subjects.
 - b. Site read for three days.
 - c. Rest period of ten days.
 - d. Repeat standard patch test with both formulae.

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In light of this background, a relatively safe pre-marketing testing procedure has been suggested. The procedure outlined below is designed to produce statistics that form an adequate basis for valid predictions concerning the incidence of reactions; to meet the requirements of the Food and Drug Administration; and, at the same time, to be feasible for the manufacturer with limited funds and facilities.

An outline of a possible pre-marketing testing program is as follows:

1. Closed patch test: forty-eight hours, 200 subjects.
2. Use accepted comparable product for control testing.
3. Read tests on third, fourth and fifth days.
4. Repeat tests on same subjects ten to eighteen days later.
5. Use tests (paired comparison) with old and new products—same subjects, daily for one month.
6. If no dermatitis: trial sale of 5,000 to 10,000 packages in one community during one month.
7. If one case of dermatitis: retest on 200 new subjects.
8. Even if no reactions in 30,000 subjects, reaction rate of 0.01 per cent is likely—no tests guarantee safety.

Two hundred subjects is the minimum control group generally accepted by the Food and Drug Administration in line with its policy of requiring testing adequate to make statistically valid predictions as to the probable incidence of reactions when the product is distributed to the general public. Trial sale of 5,000 to 10,000 units of the drug is suggested in order to verify predictions made on the basis of the patch tests under conditions that closely simulate sale to the general public. If one reaction occurs, further tests are indicated; thus, in that event, retesting on 200 new subjects is suggested.

A relatively new technique has been under development for several years by Drs. Albert Kligman and William L. Epstein¹⁸ for patch

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- e. A use test for four weeks by the same 200 persons with both formulae on opposite sides of the body.
 - (4) Shelanski-Shelanski human technique:
 - a. Standard patch test for twenty-four hours.
 - b. Rest for twenty-four hours.
 - c. Repeat steps a and b, using same sites for fifteen applications.
 - d. Rest for two to three weeks.
 - e. Standard patch test for forty-eight hours.
 - (5) Traub-Tusing-Spoor human technique (combined patch and use test):
 - a. Initial patch.
 - b. Three-week use test on appropriate subjects.
 - c. Two weeks' rest.
 - d. Challenge patch.

¹⁸ Kligman, Calnan & Epstein, *Methods of Evaluating Contact Sensitizers*, The Evaluation of Therapeutic Agents and Cosmetics 157-70 (Sternberg & Newcomer eds. 1964).

testing, prior to marketing, for cutaneous irritancy and sensitivity with a much smaller number of individuals than the 200 persons currently required by the Food and Drug Administration. This test makes no attempt to reproduce use conditions, but pushes the tolerance for the drug or cosmetic to the worst possible cutaneous exposure and demonstrates what the compound may do under the most unfavorable circumstances. It provides a maximization of potential situations likely to be encountered, and it is felt that a compound can be initially assessed regarding its irritating or sensitizing capacity with the use of about twenty-five subjects.

Dr. Kligman's technique, simplified to its basic elements, includes irritating the skin initially in one of several possible ways. Most recently he has stabilized on the use of sodium lauryl sulfate, although satisfactory irritation can be produced by ultra-violet light or by slight freezing of the skin surface. The patch test is then applied to the irritated skin and covered with an occlusive plastic film.

Paraphenylenediamine under these circumstances will sensitize twenty-five out of twenty-five, and so will the insecticide malathione. Nevertheless, both of these compounds have been used extensively with nothing like the disastrous results suggested, because the actual use conditions are substantially different from those of the test conditions.

Substances which show no reactions with Dr. Kligman's maximization technique would necessarily have to be rated as compounds which have substantially less capacity to irritate or sensitize than those showing twenty-five reactions out of twenty-five. This system perhaps provides a grading standard of sorts for various classes of compounds and their *potential* irritancy or sensitization capacity.

C. Types Of Cosmetic Reactions And Their Usual Causes¹⁷

Use of various cosmetics can cause a variety of allergic reactions.¹⁸ The most common allergic reactions to cosmetic products are of the

¹⁷ Dermatoses due to Environmental and Physical Factors, 206-24, (Rees ed. 1961) (hereinafter referred to as Rees); Kinmont, *Skin Reactions to Cosmetics Preparations*, 15 J. Soc'y Cosm. Chem. 3 (1964).

¹⁸ In the following table, there appears information concerning reactions to and other characteristics of various cosmetics and related products.

(1) Soaps and Detergents

1. Not cosmetics in legal sense.
2. 4.5 billion pounds used in United States during 1954 (seventy-five per cent detergents).
3. Defatting and dehydrating.
4. Allergy is rare.
5. Common allergies caused thereby—"housewives' eczema," "winter itch."
6. Dry skin is irritable and vulnerable.
7. Aggravates dry and senile skin, atopic and contact dermatitis.
8. Keratin water loss is vital.

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dermatitis variety. Apparently the incidence of this type of reaction is even more common than reports indicate. Dermatitis can arise from

Rees, *op. cit. supra* note 17, at 211; Suskind, *Cutaneous Effects of Soaps and Synthetic Detergents*, 163 J. Am. Med. Ass'n 943 (1957).

(2) *Hair Dyes*

1. May cause dermatitis (local and general), ocular disturbances, pain, headache.
2. One and one-half per cent sensitive on first exposure; two and one-half per cent sensitive on total exposure.
3. Least likely to cause reaction—synthetic coal-tar dyes (paraphenylenediamine and paratolylenediamine).
4. More likely to cause reaction—vegetable and heavy-metal dyes.
5. Food and Drug Administration restrictions—patch test each time; forbidden near eyes.
6. "Rinse"—a euphemism.

Rees, *op. cit. supra* note 17, at 212; Committee on Cosmetics of AMA, 27 *Hygeia* 318, 354 (1949).

(3) *Cold Permanent Waving*

1. Involves physical, chemical and morphologic changes.
2. Alkaline (usually ammonium) salts of thioglycolic acid.
3. Surface-active agent also (allergy).
4. Gums and resins (clouding agents).
5. Perfumes and coloring (allergy).
6. Neutralizers (peroxides, perborates, bromates, citric acid).
7. Usual reaction: alkali burn.
8. Remarkably safe (if used properly).

Rees, *op. cit. supra* note 17, at 214; Lehman, *Health Aspects of Common Chemicals Used in Hair-Waving Preparations*, 141 J. Am. Med. Ass'n 842 (1949).

(4) *Depilatories*

1. Types:
 - a. Calcium thioglycolate (four to ten per cent) cream; newest, most popular—softens keratin.
 - b. Sodium or calcium sulfide (acts like thioglycolate).
 - c. Waxes.
 - d. Electrolysis.
 - e. Others (mercaptans, xanthates).
2. Direct irritation or infection.

Rees, *op. cit. supra* note 17, at 215-16; Schwartz, Tulipan & Birmingham, *Occupational Diseases of the Skin* (1957).

(5) *Face Creams*

1. Many ingredients (including hormones, bleaches, etc.).
2. Most common offenders—perfume, alkalinity, emulsifying agents or oil-phase ingredients.
3. Dermatitis is rare.

Rees, *op. cit. supra* note 17, at 215-16; Schwartz, Tulipan & Birmingham, *Occupational Diseases of the Skin* (1957).

(6) *Deodorants*

1. Most common ingredients—aluminum chloride, sulfate, and phenolsulfonate (mild antibacterial).
2. Deodorant soaps—hexachlorophene ("Phisohex," "Dial"), tetramethylthiuramdisulfide ("Lifebuoy"), actamer or bithionol (similar to hexachlorophene) antibacterial.
3. Others: antibiotics (Neomycin), oxidizers, benzoic acid, hexamine, oxyquinoline—antibacterial.
4. Antiperspirant—none?
5. Most likely reactions: retention cysts, furuncles and irritation.
6. Dermatitis not uncommon.
7. Possible cross-sensitivity with inhibitors in rubber and fabric—tetramethylthiuramdisulfide.
8. Antibiotic sensitivity—rare.
9. Zirconium salts—granulomas (rare).

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three different mechanisms: (1) acquired allergy, which is the most common mechanism; (2) chemical or physical irritation; and (3)

Rees, *op. cit. supra* note 17, at 215-16; Schwartz, Tulipan & Birmingham, *Occupational Diseases of the Skin* (1957).

(7) *Neomycin: Dermal Delayed Sensitivity*

1. Used as deodorant and preservative.
2. Patch tests often negative.
3. Intradermal test: 0.05 ml., 1:1000 or 1:100 solution.
4. Popular reactions—forty-eight hours.
5. Controls negative.
6. Apparently rare (ten cases reported).

Rees, *op. cit. supra* note 17, at 217; Epstein, *Contract Dermatitis From Neomycin Due to Dermal Delayed (Tuberculin-type) Sensitivity—Report of Ten Cases*. 113 *Dermatologica* 191 (1956).

(8) *Zirconium Deodorant Granulomas*

1. Rare but important.
2. Protracted and disabling.
3. Allergic granulomas.
4. Intradermal tests positive (1:1000 to 1:10,000 solution).
5. Criteria of allergy fulfilled (rare, delayed, weak concentration, controls negative).

Rees, *op. cit. supra* note 17, at 217; Shelley & Hurley, *The Allergic Origin of Zirconium Deodorant Granulomas*, 70 *British J. Dermatology* 75 (1958).

(9) *Hair Tonics and Lotions*

1. Frequently cause dermatitis.
2. Usually contain antiseptic, rubifacient, oil, perfumed alcohol.
3. Resorcinol, betanaphthol, salicylic acid, capsicum and cantharides are both sensitizers and primary irritants in sufficient strength.
4. Wetting agents (sodium lauryl sulfate, triethanolamine) may sensitize.
5. Perfumes may cause trouble.
6. Newer commercial anti-seborrheic shampoos (*e.g.*, sulfides, hydroxy quinolines) may be irritating.

Rees, *op. cit. supra* note 17, at 218; Schwartz, Tulipan & Birmingham, *Occupational Diseases of the Skin* (1957).

(10) *Suntan Preparations*

1. PABA (paraaminobenzoic acid) and esters.
 - a. Direct sensitization (Baer and Melzer).
 - b. Cross-sensitivity (PPDA, aniline dyes, sulfa, local anesthetics).
- a. Photosensitization (Satulsky).
2. Common ingredients—digalloyl trioleate, menthyl salicylate and anthranilate, and many others.
3. Psoralens abused (suntan pills).
 - a. Furocoumarin—parsnip, celery.
 - b. Photodynamic absorption (?).
 - c. Thick horny layer and increased pigment.
 - d. Carcinogenic (?).

Rees, *op. cit. supra* note 17, at 219; Sagarin, *Cosmetics: Science and Technology* (1957); Becker, *Use and Abuse of Psoralens*, 173 *J. Am. Med. Ass'n* 1483 (1960).

(11) *Perfumes*

1. Found in most cosmetics.
2. Three chief sources: vegetable, animal (ambergris and musk) and synthetic.
3. Complete composition (alcohols, terpenes, aldehydes, esters, ketones, phenols, acids, anhydrides, nitrogenous substances, hydrocarbons).
4. Contact penetration and exposure to light of required wave length.
5. Essential oils (penetrate keratin easily).
6. Common offenders: oil of bergamot (berlock dermatitis), methyl heptene, carbonate (synthetic violet and jasmine), and linalool (a terpene alcohol).
7. Fairly common offenders (photosensitizers).

Rees, *op. cit. supra* note 17, at 219; Schwartz, Tulipan & Birmingham, *Occupational Diseases of the Skin* (1957).

(Continued on page 90)

photosensitivity.¹⁹ A full appraisal of the patient's medical history is the key to diagnosis, but a "re-use" test or patch test is used to confirm the preliminary diagnosis.²⁰

For convenience, the most important types of tissue reactions and their usual causes are set forth below in tabular form.

Table III: *Types of Tissue Reactions to Cosmetics*²¹

1. Dermatitis (irritative and/or allergic).

Usual cause: lotions, dyes, perfumes, creams, powders, lac-

(12) *Skin Lighteners and Bleachers*

1. Mercury (ammoniated five per cent or chloride 0.5 per cent).
 - a. Used for centuries.
 - b. Temporary lightening only.
 - c. Qualified approval by Food and Drug Administration.
 - d. Discoloration from prolonged use.
 - e. "Poisons" (?)—tyrosine, tyrosinase.
 - f. Irritant and sensitizer.
2. Zinc peroxide anhydrous ointment.
3. Monobenzyl-ether of hydroquinone—five per cent lotion, twenty per cent cream (capricious).
4. Ascorbic acid (ineffective and unstable).

Rees, *op. cit. supra* note 17, 221; Sagarin, *Cosmetics: Science and Technology* (1957).

(13) *Lipstick and Cheilitis*

1. Dermatitis (cheilitis) is usually from perfume or dye.
2. Not uncommon.
3. Hypersensitivity (allergy).
4. All dyes must be FDA-approved.
5. Fluorescent dyes (halogen derivatives of fluorescein) penetrate and photosensitizers.
6. Negative lipstick patch tests may become positive after sun exposure.

Rees, *op. cit. supra* note 17, at 219; Schwartz, Tulipan & Birmingham, *Occupational Diseases of the Skin* (1957).

(14) *Nail Preparations*

1. Most common reaction—patchy dermatitis of face and neck.
2. Chiefly caused by resin content of nail lacquer.
3. Sixteen principal types of synthetic resins.
4. Most common offender—sulfonamide-formaldehyde resin.
5. FDA-certified dyes may cause trouble (fluorescent dyes include eosin, erythrosin, fluorescein, and rhodamine B; nonfluorescent offenders include Lithol red, Methanil yellow, Bordeaux red, and Alizarine).
6. Dry brittle nails—lacquers, removers, soaps, detergents.
7. Destructive changes—resins, acrylics.

Rees, *op. cit. supra* note 17, at 222; Schwartz & Peck, *Cosmetics and Dermatitis* (1946); Sutton, *Diseases of the Skin* (11th ed. 1956).

¹⁹ *Allergic Contact Dermatitis—Definition*

1. Incubation period necessary (five days or more).
2. Sensitivity becomes generalized.
3. Substance reacts in weak concentration.
4. Patch test positive on distant sites.
5. Patch test negative on control subjects.
6. Sun exposure also necessary in photoallergy.
7. Hyposensitization or tolerance often occurs spontaneously.

Rees, *op. cit. supra* note 17, at 210; Schwartz & Peck, *Cosmetics and Dermatitis* (1946).

²⁰ Rees, *op. cit. supra* note 17, at 209; Nelson, *Clinical Appraisal of Dermatoses Due to Cosmetics*, 163 J. Am. Med. Ass'n 740 (1957).

²¹ Rees, *op. cit. supra* note 17, at 206; Spoor, *supra* note 14.

- quers, wavers, preservatives, dentifrices, cleansers, soaps, detergents.
2. Folliculitis.
Usual cause: depilatories.
 3. Hair damage; conjunctivitis.
Usual cause: alkalis (*e.g.*, hair wavers, straighteners), bleaches, shampoos.
 4. Local swelling.
Usual cause: hormone cream.
 5. Nail damage.
Usual cause: base coat (formaldehyde resin), nail builders (acrylics).
 6. Photosensitivity.
Usual cause: suntan agents, perfumes, lipstick dye.
 7. Pigment changes.
Usual cause: mercury, hydroquinone, perfumes (post-inflammatory).
 8. Sweat-gland abscesses; granulomas.
Usual cause: aluminum salts, zirconium salts.

V. POST-MARKETING PERFORMANCE OF COSMETICS

Unlike the drug industry, the cosmetic industry has not yet initiated large-scale, information-gathering programs. It largely has relied on insurance-claim and industry complaint-file statistics involving the incidence and types of reactions to evaluate the post-marketing performance of its products.

An analysis of certain of these statistics provides some basis upon which to quantify the incidence of allergic reactions to cosmetic preparations. For example, Dr. Rees has published data concerning the incidence of reactions to the marketed products of one large cosmetic manufacturer.²² The figures are of the complaint-file type. Dr. Rees indicates that a total of 448 reactions (0.0004 per cent) were reported out of sales of 113 million units of 150 different cosmetic products. Almost fifty per cent (236) of the reactions were caused by depilatories, lotions or eye products. The incidence of reactions to the use of cleaners, creams, shampoos, hair rinses and deodorants was significantly lower. Reactions to wave lotions, powders, lipsticks and perfumes were the least common. No reactions from use of nail polish were reported. The incidence of reactions to the

²² Rees, *op. cit. supra* note 17, at 207; Masters, *Allergies to Cosmetic Products*, 60 N.Y. State J. Med. 1934 (1960).

various products as reported by Dr. Rees is set forth in the margin.²³

Robert Goldemberg compared Shulton consumer irritation-complaint statistics to unit sales by the cosmetic industry. He reported that, on an industry-wide basis, from 1957 to 1961 there was an average of .204 consumer complaints of reactions per 100,000 units sold. Approximately .065 complaints per 100,000 units sold were of such a nature that the complainant required medical attention. These statistics are presented by product class in the table in the margin.²⁴

In addition to the basic lack of source material, there exists a wide statistical variation among the various sources of information which currently are available. To illustrate this statistical variation, a survey made by Dr. F. Reiss²⁵ may be compared with the number of reported

²³ *Reported Frequency of Reactions To 113 Million Units of Cosmetics Sold*

| AGENT | % | AGENT | % |
|----------------|--------|-----------------------|---------|
| Depilatories | 0.004 | Hair Products | 0.0003 |
| Cleansers | 0.002 | Shampoos | 0.0002 |
| Wave Lotions | 0.001 | Make Up | 0.0001 |
| Hormone Creams | 0.001 | Powders | 0.00007 |
| Lotions | 0.0005 | Medicated Creams | 0.00005 |
| Eye Products | 0.0005 | Suntans | 0.00005 |
| Creams | 0.0004 | Lipstick | 0.00002 |
| Deodorants | 0.0003 | Colognes and Perfumes | 0.00002 |
| Rinses | 0.0003 | Nail Polish | 0.00000 |

Rees, *op. cit. supra* note 17, at 208; Masters, *supra* note 22.

²⁴ *Comparison of Shulton Consumer Irritation—Complaint Rates to Unit Sales*

| Product Category | Unit Sales 5 yrs. (millions) | Allergic Reactions per 100,000 Units Sold | | Required Med. Att'n | |
|--------------------|------------------------------------|---|----------------|---------------------|--------------|
| | | Total 1961 | 5 yrs. 1961 | 1961 | (per 5 yrs.) |
| Alcoholic perfumes | 100 | 0.037 | 0.043 | —0— | 0.018 |
| Antiperspirant | 10-20 | 0.340 | 0.350 | 0.034 | 0.110 |
| Bath products | 10-20 | 0.033 | 0.023 | —0— | 0.006 |
| Deodorants | 20-50 | 0.282 | 0.464 | 0.060 | 0.174 |
| Emulsions, general | 10-20 | 0.110 | 0.087 | 0.022 | 0.019 |
| Hair, general | 5-10 | 0.044 | 0.051 | 0.044 | 0.025 |
| "Medicated" items | 1-5 | 2.408 | 5.577 | 0.230 | 0.908 |
| Shaving products | 20-50 | 0.122 | 0.118 | —0— | 0.021 |
| Sunscreens | 5-10 | 1.323 | 0.729 | 0.265 | 0.307 |
| OVERALL RATES* | 275 | | 0.204 | | 0.065 |

Goldemberg, *Cosmetics and the General Population—Safety Aspects*, Proceeding of the Scientific Section, No. 38, The Toilet Goods Ass'n (1962).

* Note: Of the 560 irritation complaints received in the five-year period 1957-1961, 129 resulted from the "medicated items category." Omitting these 129 complaints, the overall irritation rate for the purely cosmetic and toiletries items drops from 0.204 to 0.157 per 100,000 units sold.

²⁵ *Tabulation and Analysis of Replies to Questionnaires Sent by Dr. F. Reiss to 2969 Dermatologists in 1958*

| | No. of Cases | Per Cent of Total | No. of Cases per Physician Reporting |
|-----------------------|-----------------|----------------------|---|
| Permanent Wave Lotion | 3764 | 25.2% | 3.9 |
| Lipstick | 2137 | 14.4% | 2.2 |
| Hair Dye | 3549 | 23.8% | 3.7 |
| Nail Lacquer | 5447 | 36.6% | 5.7 |
| Total | 14,897 | 100% | 15.5 |

Reiss, *Cosmetic Dermatitis—A Survey of Its Incidence*, 116 *Dermatologica* 419 (1958).
(Continued on page 93)

insurance claims through the National Bureau of Casualty Underwriters.²⁸

Tabulation and Analysis of Replies to Questionnaires Sent by Dr. F. Reiss to 2969 Dermatologists in 1958

| Size of Cities No. of Population | Total No. of Patients Examined | Patch Test | | Number of Positive Cases | | | |
|--|--------------------------------------|------------|------|--------------------------|---------------|--------------|-----------------|
| | | % | No. | Perm. Wave | Lip- stick | Hair Dyes | Nail Lacquer |
| Over 1,000,000 | 4531 | 2634 | 58.1 | 884 | 650 | 1370 | 1627 |
| 500,000-1,000,000 | 2106 | 1134 | 53.9 | 587 | 254 | 462 | 813 |
| 250,000-500,000 | 2006 | 1024 | 51.0 | 596 | 247 | 424 | 739 |
| 100,000-250,000 | 2467 | 1229 | 50.0 | 626 | 285 | 424 | 732 |
| 50,000-100,000 | 1024 | 567 | 55.4 | 277 | 145 | 287 | 315 |
| 25,000-50,000 | 1697 | 1034 | 61.2 | 392 | 354 | 287 | 664 |
| 10,000-25,000 | 751 | 492 | 65.5 | 249 | 128 | 170 | 204 |
| Below 10,000 | 715 | 360 | 50.4 | 153 | 84 | 125 | 353 |

Reiss, *Cosmetic Dermatitis—A Survey of Its Incidence*, 116 *Dermatologica* 419, 422 (1958). Replies were received from only 956 of the 2969 Dermatologists to whom questionnaires were mailed.

Sales figures in dollars for the above cosmetics for 1956, as published in the *Drug Trade News* of August 12, 1957, can be related to the number of units sold. It should be noted, however, that units of nail lacquer and lipstick are repeatedly used, whereas hair dyes and permanent waves represent packages used only once. The values in dollars were:

| | |
|-----------------------------|--------------|
| Home permanents and refills | \$86,510,000 |
| Hair tints and dyes | \$20,670,000 |
| Lipsticks | \$71,330,000 |
| Nail polish and enamel | \$26,170,000 |

²⁸ *Products-Liability Insurance Claims*

| Policy Year | Sales of Covered Entities | Number of Indemnity Claims |
|---|---------------------------|-------------------------------|
| <i>Class 1015—Drug Dealers and Stores—Wholesale</i> | | |
| 1956 | \$465,419,000 | 15 |
| 1957 | 541,963,000 | 15 |
| 1958 | 561,650,000 | 29 |
| 1959 | 537,762,000 | 40 |
| 1960 | 572,569,000 | 14 |
| Total | \$2,679,363,000 | 113 |
| <i>Class 1055—Drugs, Medicine and Pharmaceutical Products</i> | | |
| <i>N.O.C. (Manufacturers)</i> | | |
| 1956 | \$767,846,000 | 203 |
| 1957 | 767,393,000 | 237 |
| 1958 | 1,134,226,000 | 203 |
| 1959 | 1,184,346,000 | 380 |
| 1960 | 1,138,077,000 | 175 |
| Total | \$4,991,888,000 | 1,198 |
| <i>Class 1056—Cosmetics (Manufacturers)*</i> | | |
| 1956 | \$250,254,000 | 201 |
| 1957 | 207,548,000 | 241 |
| 1958 | 213,532,000 | 240 |
| 1959 | 274,621,000 | 297 |
| 1960 | 388,359,000 | 351 |
| Total | \$1,334,314,000 | 1,330 |
| <i>Class 1057—Cosmetics, Hair or Skin Preparations</i> | | |
| <i>N.O.C. (Manufacturers)**</i> | | |
| 1956 | \$193,152,000 | 501 |
| 1957 | 220,362,000 | 602 |
| 1958 | 133,025,000 | 485 |
| 1959 | 91,953,000 | 1,153 |
| 1960 | 122,360,000 | 493 |
| Total | \$760,852,000 | 3,234 |

(Continued on page 94)

Dr. F. Reiss' survey reflects replies from about one-third of the skin specialists in the nation in 1958. This survey shows 14,000 reactions in 1958 to a limited number of cosmetic preparations. In contrast, the number of insurance claims during that year was less than 1,000 for a large number of products, including all those covered by Dr. F. Reiss' survey. The actual number of cases, however, must have numbered between 15,000 and 50,000, considering that many consumers must have sought either medical advice from non-specialists or no medical advice at all.

Thus, it appears that in the cosmetic field the testing procedures currently in use are not entirely adequate. Furthermore, the Food and Drug Administration does not impose as stringent requirements on that industry as it does upon the drug industry. Moreover, the evaluation of cosmetic products is complicated by the dearth of statistics concerning post-marketing performance and by the wide statistical variation among the various sources of information that are available.

These apparent deficiencies, however, do not necessarily mean that the cosmetic industry has failed to engage in thorough testing procedures before marketing new products. There are some checks and balances in the cosmetic field. The major manufacturers who sell products nationally on a large scale simply cannot afford to take chances on a new product. In contrast to drugs, the cosmetic must have direct consumer patronage and acceptance. Bad reputation from just one product can affect sales of all other products on which survival as a profitable corporation depends. From a commercial point of view, it would be a self-defeating proposition for these corporations to sell a product which they knew to be harmful to the public in any way. Aside from the ethics and the question of corporate reputation, the manufacturers must also consider "product liability" insurance rates. For these excellent economic reasons, thorough safety testing of new products is conducted by nearly every major corporation in the cosmetic field, as well as by most smaller ones.

National Bureau of Casualty Underwriters—unpublished statistical data (1956-60).

* Included in this class are the following: face, toilet, bath and baby powder; rouge and lipstick; toilet water and bath salts; finger nail and toenail cream or polish; cuticle or polish remover; facial packs; hair tonics; creams or lotions other than specific-purpose creams or lotions.

** This classification includes but is not limited to hair rinses or packs, hair dyes, depilatories, skin bleaches, freckle removers, deodorants, reducing creams, eye shadow, eyebrow pencil, mascara, hair bleach and suntan lotion.

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