DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

GHQ/SCAP Records (RG 331, National Archives and Records Service)

Description of contents

(1) Box no. 2828

(2) Folder title/number: (16)
Medical Treatise - Miscellneous
(Vitamins, Sulfa Drugs)

(3) Date: July 1946 - Jan. 1948

(4) Subject:

Classification	Type of record
752	t

(5) Item description and comment:
American Publications

(6) Reproduction: (Yes) No

(7) Film no. Sheet no.

(Compiled by *National Diet Library*)

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

ZEPHIRAN CHLORIDE

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

ZEPHIRAN

TRADEMARK REG. U. S. PAT. OFF. & CANADA

CHLORIDE

Brand of Benzalkonium Chloride Refined

Antiseptic and Germicide

No Iodine • No Phenol

No Mercury

or other Heavy Metals

ACCEPTED AMERICAN MEDICAL ASSN. Council on Pharmacy and Chemistry

WINTHROP CHEMICAL COMPANY, INC.

Pharmaceuticals of merit for the physician

NEW YORK 13, N. Y. • WINDSOR, ONT.

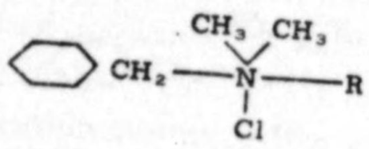
DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

CHEMICAL AND PHYSICAL PROPERTIES

Chemical Structure

Zephiran chloride is of special interest in that it belongs to a group of chemical compounds which have not been studied previously in regard to their germicidal properties.

Zephiran chloride is a mixture of high molecular, alkyldimethylbenzyl ammonium chlorides. The chemical structure of this nonmetallic organic compound is



in which R represents alkyl radicals ranging from C_8H_{17} to $C_{18}H_{37}$, as contained in the corresponding fatty acids of coconut oil. Inasmuch as these fatty acids occur in nearly constant proportion, and this relation is retained in the final product, essentially uniform composition is always assured. Zephiran chloride is freely soluble in water, forming a clear, colorless, almost odorless, solution. It is soluble in acetone and alcohol, insoluble in ether, and only sparsely soluble in benzene. The aqueous solution is slightly alkaline to litmus. The pH is approximately at the neutral point; it has an aromatic odor and upon shaking foams like soap. It has an acrid taste which, however, is hardly noticeable in higher dilutions.

Surface Tension

The surface tension of antiseptic compounds indicates to a degree the penetrating property of the solution. Preparations with low surface tension permit the antiseptic to disperse more readily into pores and crevices of the skin which may harbor microorganisms.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

The surface tension values of Zephiran chloride as determined by the tensiometer are given in Table 1.

Table 1

Dilution of substance	Temperature	Surface tension (dynes/cm.)
Zephiran chloride		
1:10	25.3	35.35
1:1000	25.3	37.39
Distilled water	24.75	72.75

A better method of evaluating surface penetration is by biologic means. White, Collins and Newman report bacteriologic studies made with full thickness skin biopsies which were taken from areas treated with Zephiran chloride tincture 1:1000 and cultured in an effort to determine whether the antiseptic had been carried deeply into the skin structure. In 51 cases where biopsy cultures were made from areas treated with Zephiran chloride, there was growth in but two instances and in these the organisms appeared morphologically altered. The controls or biopsy cultures of the untreated skin showed growth in every instance.

In addition to its low surface tension the detergent action of Zephiran chloride serves the useful purpose of removing dirt, skin fats, desquamating epithelium and superficial bacteria, and thus exposes the underlying skin to the germicide.

Stability

Many of the common antiseptic solutions deteriorate with age and lose their potency when subjected to repeated changes in temperature. The potency of Zephiran chloride kept at room temperature was found to be unchanged after several years of storage. Further tests of stability were performed by freezing Zephiran chloride in dry ice and storing in this state. Phenol coefficient determinations proved that there is no loss in efficiency. Storage at a temperature of 50°C over a period of weeks also caused no apparent loss in efficacy.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Compatibilities and Incompatibilities

Zephiran chloride is compatible with most substances with which it is likely to come in contact, as shown in the following table.

Zephiran Chloride Aqueous Solution 1:1000

*Compatible**

Acriflavine
Alcohol
Betain base 1%
Boroglycerin
Camphor
Carbowax 0.1% to 5%
Chlorobutanol 1:500
Cobefrin
Cocaine
Cresol
Dionin
Eosin
Ephedrine HCl
Epinephrine
(Adrenalin, Suprarenin)
Eserine sulfate
Fluorescein
Formaldehyde 1%
Fuchsin
Glycerin 5% to 15%
Homatropine 5%
Hydrazine hydrate
0.1% to 0.5%
Lime water U.S.P.
Nipagin M
Neo-Synephrine
Novocain
Oil of sassafras
1.5% to 2.5%
Penicillin
Pilocarpine
Polyethylene glycol
Pontocaine HCl
Procaine HCl
Resorcin
(cloudy when mixed)
Rose water
Scopolamine
Sodium carbonate
and sodium nitrite
Sulfadiazine sodium
Sulfanilamide
Suprarenin
Trisodium phosphate
Urea
Urethane
Zinc chloride
up to and including 1%

* Zephiran Chloride Aqueous Solution (1:1000 or higher dilution) may be used as solvent for small amounts of the substances listed as compatible. The term compatible applies only to the concentrations ordinarily used except for those substances where lower concentrations are listed.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Incompatible

Argyrol	Potassium permanganate
Benzyl ephedrine	Santomerse D
Boric acid 5%	Santomerse No. 3
Calogen	Saponin 0.1% to 0.5%
Caramel	Silicates
Citric acid	Silver nitrate 2%
Duponol	Sodium citrate
Iodine	Sodium tartrate
Neoprontosil	Sulfapyridine
Nipagin A	Sulfathiazole
Pantopon	Sulfathiazole sodium
Peroxide	Tartaric acid
Pilocarpine nitrate 3%+	Yellow oxide of mercury
Pine oil	Zinc peroxide
Potassium iodide	Zinc sulfate

Most antiseptics are relatively incompatible therapeutically with soap in that when mixed with high concentrations of soap their germicidal potency may be reduced and also their skin tolerance may become affected. Inasmuch as Zephiran chloride is a cationic detergent and soap is an anionic detergent, soap should not be mixed with Zephiran chloride. Soap should also be carefully rinsed from tissue before the antiseptic is applied. Zephiran chloride tincture largely inactivates the action of soap and is therefore recommended for use on intact skin which is generally scrubbed with soap and water preparatory to surgery.

Detergent and Emulsifying Properties

Walter states that Zephiran chloride aqueous solution for topical application possesses detergent, keratolytic, emulsifying and emollient properties. This unusual combination of properties can readily be demonstrated. The cleansing and wetting action is evident by contrasting the effect of washing off the grime which accumulates on the fingers while handling dusty books, first in tap water, then in a 1:1000 Zephiran chloride solution. The whorls of detritus removed during the preoperative preparation of the skin

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

illustrate the keratolytic properties. A milky emulsion is readily obtained by shaking human fat warmed to body temperature in Zephiran chloride solution. Dilute solutions have an emollient action on the skin which can be exhibited by wearing a dry glove on one hand and a glove wet with 1:5000 solution on the other; the satiny smoothness of the Zephiran chloride wet hand persists for several hours after removal of the gloves and thorough drying of the skin.

BACTERIOLOGY

High Germicidal Potency

Zephiran chloride solution exerts an antiseptic and germicidal action on bacterial organisms and fungi even in low concentration. The germicidal action has been shown to be most striking against virulent organisms such as hemolytic streptococci, pneumococci and staphylococci. The action of Zephiran chloride is relatively nonselective inasmuch as it acts with nearly equal proficiency upon most microorganisms.

Phenol Coefficients

A common criterion for determining the bactericidal efficiency of germicidal agents is the phenol coefficient. Inasmuch as conclusions drawn from phenol coefficients alone may be misleading as to the bactericidal efficiency of any chemical when applied to actual conditions, other available tests should be employed to determine the practicability of antiseptics when used on skin or infected tissue.

Tests carried out in conformity with the methods accepted by the Food and Drug Administration demonstrate that Zephiran chloride has a high bactericidal action, as shown by its phenol coefficients for various pathogenic and parasitic microorganisms.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Inasmuch as official standards of resistance have been established for Eberthella typhosa and Staphylococcus aureus only, arbitrary strains of predetermined phenol resistance were selected for testing with respect to the remaining organisms.

Table 2 represents phenol coefficient values as determined by Dunn.

Table 2
Phenol Coefficients

Organisms	20°C	37°C
Eberthella typhosa	250	429
Staphylococcus aureus	279	407
Escherichia coli	160	358
Streptococcus pyogenes	—	272
Streptococcus haemolyticus	435	579
Streptococcus viridans	384	434

In addition, phenol coefficients against Eberthella typhosa have been reported as follows: 150 at 20°C (Maier and Müller), 275 at 37°C (Heineman), and 250 at 20°C (Lawrence). Using Staphylococcus aureus as a test organism, phenol coefficients at 20°C were recorded as follows: 275 (Heineman), 200 (Maier and Müller), and 365 (Lawrence).

Definitely Germicidal in High Dilutions

Perhaps the simplest way of determining the germicidal activity of antiseptic substances under in vitro conditions is to find the highest dilutions capable of killing bacterial cultures in a given time. Care must be exercised to differentiate between bacteriostasis and actual killing power of the preparation. *In these tests subcultures were made as controls for bacteriostasis.*

Table 3 records the highest dilution capable of destroying organisms in ten but not five minutes as reported by Dunn.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Table 3

Highest dilution of Zephiran chloride destroying the organism in 10 but not in 5 minutes (average values).

Organisms	20°C	37°C
Staphylococcus aureus	1:20,000	1:35,000
Eberthella typhosa	1:20,000	1:70,000
Escherichia coli	1:12,000	1:40,000
Streptococcus haemolyticus	1:40,000	1:95,000
Streptococcus viridans	1:35,000	1:65,000
Cryptococcus hominis	1:24,000	1:70,000

Other reports have appeared suppiementing Dunn's work on dilution ratios. Using Staphylococcus aureus, Hoyt shows this organism killed at a 1:16,000 concentration in ten minutes at 20°C. Lawrence reports Staphylococcus aureus destroyed with a 1:19,000 dilution, Escherichia coli with a 1:23,000 dilution, and Eberthella typhosa at 1:26,000 at 20°C temperature.

Domagk, in his original report on Zephiran chloride, demonstrated that this antiseptic is effective against almost all pathogenic organisms in greater dilutions and in less time than cresol soap. The experiments consisted of the additions of 5 drops of 24-hour broth cultures to 5 cc. of the dilution of Zephiran chloride to be tested. After a given time a sample was transferred to the bouillon. Peptone broth with the addition of 1 per cent serum was used for the subcultures of streptococci; for gonococci a nutrient medium especially suited to the strain under investigation was used, and glycerine broth was used for diphtheria bacillus.

Table 4

Dilutions destroying the test organisms within from 2½ to 5 minutes

B. coli	1:2500 —1:10,000
B. typhosus	1:2500 —1:10,000
B. paratyphosus B.	1:5000 —1:10,000
B. dysenteriae	1:2500 —1:10,000
B. diphtheriae	1:25,000—1:50,000
Gonococci	1:25,000—1:50,000
Pneumococci	1:5000 —1:25,000
Staphylococci	1:5000 —1:25,000
Streptococci	1:25,000—1:100,000
B. abortus (Bang)	—1:10,000

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Bacteriostatic Tests

Maier reported on the "disinfectant spectrum" of Zephiran chloride as given in Table 5. He found that the germicidal range of the antiseptic reaches up to 1:100,000 and the bacteriostatic range up to 1:800,000.

Table 5
Test organism: Staphylococcus aureus. Incubation temperature 37°C. Time of contact: 24 hours.

Range	Concentration of Zephiran chloride	Original tubes	Subculture tubes
Germicidal	1:40,000	—	—
	1:60,000	—	—
	1:80,000	—	—
	1:100,000	—	+
Inhibition	1:200,000	—	+
	1:300,000	—	+
	1:400,000	—	+
	1:500,000	—	+
	1:600,000	—	+
	1:700,000	—	+
Inactive	1:800,000	+	+

— No growth. + Growth.

In a study of the bacteriostatic action of various wetting agents upon growth of tubercle bacillus in vitro, Freedlander reports that the most effective wetting agent is Zephiran chloride which produced complete inhibition of growth in a dilution of 1:80,000 and retardation of growth in a dilution as high as 1:400,000. None of the products tested showed a high bactericidal action against this resistant organism.

Fungicidal Action

In search for an antiseptic and fungicide suitable for the disinfection of swimming suits, Wallace investigated a group of available chemical agents in order to determine their germicidal and fungicidal activity on swimming suit materials. The test organisms employed were Escherichia coli, Staphylococcus aureus and Trichophyton interdigitale. Small squares of fabric were impregnated

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

with each of the three test organisms, respectively. They were then dried for from eighteen to twenty-four hours in order to fix the bacteria to the cloth fibers. The dried squares were then placed in disinfectant solutions for varying time intervals. Upon removal they were thoroughly washed in sterile water, to remove traces of disinfectants, and cultured. If no growth occurred on the plates within forty-eight hours, it was assumed that the disinfectant was satisfactory. These tests showed that Zephiran chloride aqueous solution 1:10,000 destroyed the test organisms in from four to six minutes.

Although the phenol coefficient is by no means an exact index of the fungicidal activity of a germicide as applied in actual practice, it serves as one of the criteria for evaluation of the in vitro activity of chemical antisepsis. Dunn in his extensive studies on Zephiran chloride employed a modified Rideal-Walker technic and determined a phenol coefficient of Zephiran chloride tincture 1:1000 on various fungi as outlined in Table 6.

Table 6
Average highest dilution destroying test organism in 10 but not 5 minutes (at 37°C.).

Test organisms	Average phenol coefficients*	Phenol	Zephiran chloride
Achorion schoenleinii	0.36	1:140	1:50
Actinomyces gedanensis	1.3	1:205	1:275
Cryptococcus hominis**	0.4	.....	1:70
Epidermophyton inguinale	0.44	1:167	1:73
Microsporon audouini	0.12±	1:320±	1:35
Monilia albicans	0.6	1:93	1:55
Saccharomyces cerevisiae	0.15	1:135	1:21
Trichophyton interdigitale	0.28	1:90	1:25

* Phenol coefficients based on Zephiran chloride tincture 1:1000.
** Phenol coefficients based on Zephiran chloride aqueous solution 1:1000.

Rapidity of Action

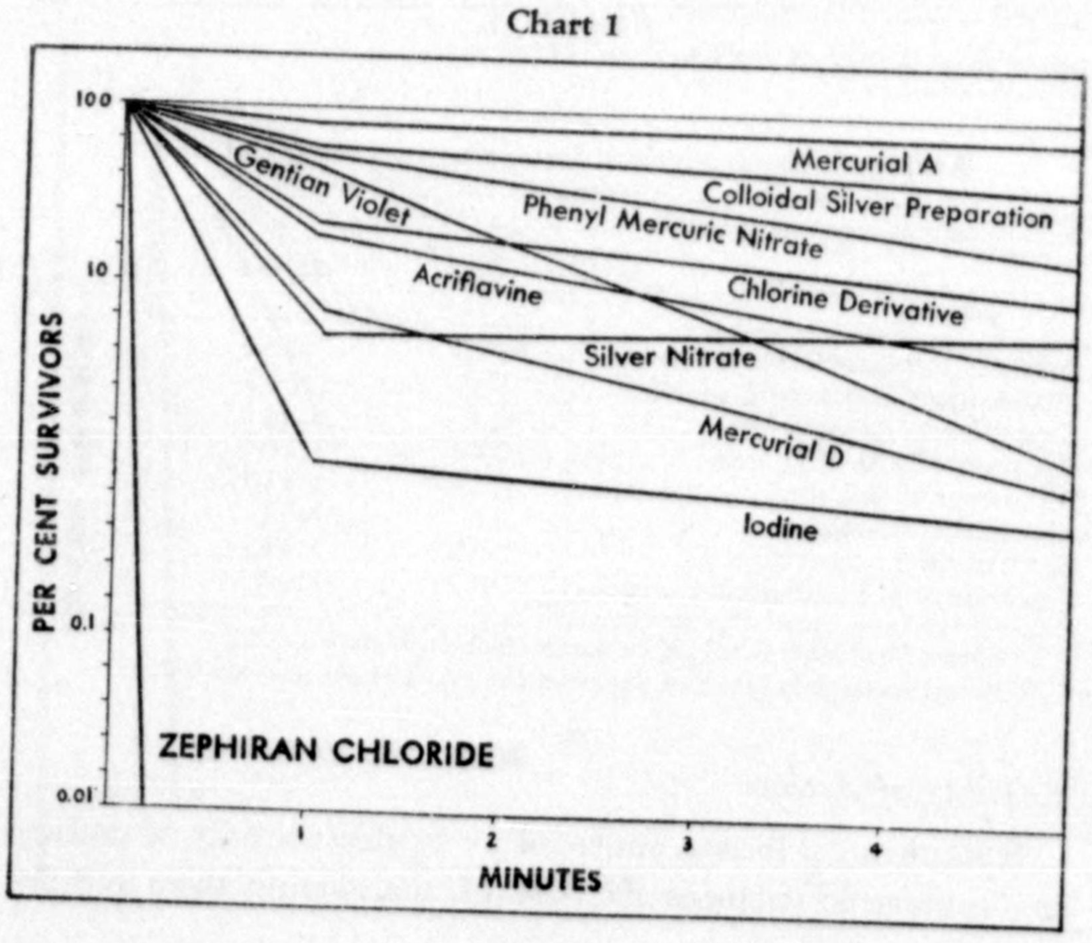
It is important that an antiseptic be capable not only of destroying pathogenic microbes but also of annihilating them rapidly.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Thompson, Isaacs and Khorazo, in an investigation in which a variety of antiseptics was studied for their rapidity of action, found that Zephiran chloride destroyed the test organism (Staphylococcus aureus) completely within less than one minute, whereas under identical conditions iodine, several of the mercurials, and silver preparations destroyed only a fraction of the organisms within five minutes. They state that "This disinfectant is characterized by its extreme rapidity of action, far surpassing in this respect all other disinfectants tested."

The subjoined chart is adapted from a graph in a laboratory study of some antiseptics by Thompson, Isaacs and Khorazo. It demonstrates disinfection rates of concentrations nonirritating to the eye. The figures for Zephiran chloride were obtained by a special method in which the antiseptic and organisms are kept in contact for approximately 0.3 seconds in a falling drop.

Chart 1



DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Germicidal Action in Organic Matter

When antiseptics are applied to infected surfaces the presence of serum may impair the bactericidal power of the preparation.

Thompson, Isaacs and Khorazo state that Zephiran chloride is affected less by the presence of organic matter than most other antiseptics.

To illustrate the efficacy of Zephiran chloride in the presence of 20 per cent serum under in vitro conditions Dunn reports phenol coefficients and dilution ratios for the organisms listed in Table 7.

Table 7

Germicidal action in the presence of 20 per cent serum

Test organism	Tests at 20°C		Tests at 37°C	
	Average phenol coefficients	Highest dilution destroying in 10 but not 5 min.	Average phenol coefficients	Highest dilution destroying in 10 but not 5 min.
S. aureus	54.2	1/3250	72	1/5500
Eberthella typhosa	23.0	1/1900	39.8	1/5750
E. coli	17.9	1/1250	31	1/3250
S. haemolyticus	63.6	1/5000+	61.5	1/8750
S. viridans	57.5	1/4000	48.9	1/5750

Anaerobic and Spore-Bearing Organisms

Most spores are highly resistant to destruction by chemicals. The anthrax spore, for instance, is capable of surviving in 5 per cent phenol for a period of from two to forty days. The presence of organic matter also diminishes the sporicidal effect of a germicide.

Spaulding has demonstrated the difficulty of sterilizing instruments grossly contaminated with blood and pus infested with Bacillus anthracis, Clostridium tetani, and Clostridium welchii. For want of a better procedure for the testing of the efficiency of antiseptics on spore-bearing organisms which may infest instruments, the phenol coefficient is generally employed, even though this procedure is inadequate as it does not take into consideration the presence of blood, dried organic matter, or other organic material present.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

According to Deskowitz Zephiran chloride was effective in destroying spore bearing organisms and anaerobes in the absence of serum at 37°C as listed in the following table:

Table 8

Organism	Zephiran chloride concentration	Time
Clostridium welchii	1:6000	10 min.
Bacillus subtilis	1:2500	95 min.

Dunn reports that spores of Bacillus subtilis failed to germinate for a period of several days when contained in subculture tubes, and in addition, noted that a two day culture of this organism was killed in less than fifteen minutes at a pH of 8.96.

These studies have been confirmed by Lawrence who found that a concentration of 1:500 to 1:600 Zephiran chloride solution destroyed a heavy suspension of a seven to ten day culture of Bacillus subtilis in less than five minutes' exposure. The tests were conducted at room temperature, using 0.5 cc. of inoculum to 5 cc. of Zephiran chloride dilution.

Bactericidal Test on Human Skin

The bactericidal efficacy of Zephiran chloride as a skin disinfectant was established by Walter in culturing full thickness skin biopsies taken from all regions of the body except the face and neck in over 70 surgical cases.

These full thickness biopsies, averaging 3 x 10 millimeters in size, were taken from one edge of the wound immediately after completing the skin incision. The specimens were transfixed with a silk suture and suspended in 1.5 liters of Ringer's solution to dilute the residual bactericide and to prevent its continued action prior to culturing. After incubation at 37°C for ninety-six hours, the cultures which showed no growth were inoculated with viable organisms to test for bacteriostasis; 73 per cent of the biopsies showed no growth after ninety-six hours.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Comparative Studies

The disinfectant efficiency of a group of popular antiseptics, as demonstrated by their phenol coefficients based on the usable or commercial concentrations, was established by Dunn (1938).

The action of various popular antiseptics commonly used was tested against Staphylococcus aureus and Escherichia coli. In the instance of Staphylococcus aureus, Zephiran chloride aqueous solution 1:1000 may be diluted thirty-five times and will still destroy the organism in less than ten minutes. It is interesting to note that undiluted commercial concentrations of several mercurial antiseptics failed to destroy the test organism within fifteen minutes. Although the complex mercurials are highly effective bacteriostatic agents, they are relatively ineffective as to their germicidal or killing power on pathogenic organisms.

Table 9

Highest dilutions destroying the organisms in 10 but not in 5 minutes.

Antiseptic	Microorganisms			
	Staphylococcus aureus		Escherichia coli	
	Highest dilutions	Phenol coefficients	Highest dilutions	Phenol coefficients
Zephiran chloride aqueous 1:1000	1:35	0.42	1:40	0.31
Zephiran chloride tincture 1:1000	1:60	0.75		0.167
Mercurial A				
Tincture 1:1000	1:2.5	0.031	1:5	0.045
Aqueous solution 1:1000.	Survival for 15 plus minutes			
Mercurial B				
Tincture (fresh)	1:5.5	0.063	1:70	0.64
Tincture (old)	1:3.5	0.041	1:25	
Aqueous solution 1:500.	Survival for 15 plus minutes			
Mercurial C	1:20	0.21		0.11
Mercurial D	1:3			
Antiseptic E	1:6	0.075	1:5.5	0.05
Antiseptic F	1:11.5	0.14	1:13	0.12

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

CLINICAL CONSIDERATIONS

Nonirritating to Skin and Mucous Membranes

Various concentrations of Zephiran chloride were applied to the shaved skin of rabbits and allowed to dry. A 1:100 solution was found to be safe and caused no irritation whatsoever. The effect of prolonged contact of Zephiran chloride in various concentrations was then tested on rabbit skin. Pads of gauze saturated with different concentrations were affixed to shaven areas of rabbits' ears and held in place for twenty-four hours. This experiment showed that a Zephiran chloride solution 1:1000 is the strongest concentration that may be allowed to remain in contact with the skin for twenty-four hours with minimum reaction.

Walter demonstrated the nonirritating effect of Zephiran chloride by applying sponges saturated in a 10 per cent Zephiran chloride solution and leaving them in the vagina of 5 patients following routine dilatation and curettage of the uterus. No irritation was observed. The lack of immediate irritation of the skin and the absence of protracted or cumulative effects following prolonged repeated use of Zephiran chloride solution were established by using the bactericide as an arm soak on surgical personnel on over 1000 occasions during an eighteen month period. However, as with most antiseptics, an occasional individual appears to be hypersensitive and may experience a skin irritation on prolonged contact.

Because of the efficiency of Zephiran chloride as a disinfectant and its rapidity of action coupled with its nontoxic and nonirritating properties, it is adaptable to nearly all phases of medicine and surgery where skin and mucous membrane antisepsis is required (Walter; Wright and Wilkinson; White, Collins and Newman; Gardner; Hauser and Cutter).

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

An extensive study on the use of Zephiran chloride as an inexpensive and reliable germicidal agent, especially for the armed forces, was carried out by Shumacker and Bethea who discussed its satisfactory use for multiple purposes in hospital and medical practice and the many advantages over some of the more commonly employed antiseptics.

Surgery

Zephiran chloride is particularly valuable as a germicide for use on skin preparatory to surgery. It has been used in thousands of applications, and published reports indicate that by the use of Zephiran chloride the incidence of infection in clean cases can be materially reduced as compared with the use of tincture of iodine. White, Collins and Newman reported that in 76 cases in which tincture of Zephiran chloride was used for the preparation of skin preparatory to surgery they had only one wound infection and there was reasonable doubt about skin contamination in this case. In a comparative study of 25 laparotomies performed by another service in the same hospital using tincture of iodine for skin disinfection, there was an infection rate of 28 per cent. They further remarked that no irritation was noted with Zephiran chloride even under adhesive plaster. Cutler and Zollinger reported on the use of Zephiran chloride previous to thyroidectomy and found the antiseptic satisfactory for preoperative preparation of the skin.

Recent contributions in the field of disinfection demonstrated that it is virtually impossible to disinfect skin to the point of sterility. Organisms may be harbored in skin crevices and may be enmeshed in sebaceous material inaccessible to the action of the antiseptic.

For the disinfection of unbroken skin Zephiran chloride tincture 1:1000 is suggested. The tinted solution, when applied to the skin, clearly defines the outlines of the operative field. The detergent action of Zephiran chloride is marked when used alternately

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

with alcohol for preparation of the field of operation; the skin is left smooth, clean, and of a ruddy hue.

Hauser and Cutter used Zephiran chloride in solution 1:1000 in their clinical experiments as a routine preparation of the skin in orthopedic procedures, including surgery for internal derangements of the knee, hallux valgus and reconstruction operations without infections.

Obstetrics and Gynecology

Zephiran chloride is preeminently useful for the disinfection of skin and mucous membranes in obstetric and gynecologic procedures. The tinted tincture may be applied to the intact perineum when a colored antiseptic is preferred. For vaginal instillations and douches Zephiran chloride aqueous 1:2000 is highly satisfactory. Zephiran chloride douches are recommended for the treatment of Trichomonas vaginalis. When used as a cleaning douche Zephiran chloride has the advantage that it does not stain clothing and effectively prevents the formation of unpleasant odors which may arise from the perineum. When it is advisable to irrigate the vagina prior to the insertion of radium, Zephiran chloride irrigations will remove products of disintegration of cancerous tissues and also avoid an increase in temperature which is frequently observed with the metallic type of antiseptics.

Genito-Urinary Infection

For bladder lavages Zephiran chloride aqueous solution 1:20,000 is recommended. While this dilution has been found satisfactory in a large number of cases, the individual susceptibility of the patient must be taken into consideration and the dilution adjusted up or down the scale. For retention bladder lavages, dilutions up to 1:40,000 may be employed. For urethral irrigations dilutions of 1:20,000 are recommended and the same considerations are to be observed as in bladder washes.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Eye Antisepsis

Zephiran chloride aqueous solution 1:2000 to 1:3000 has been found to be nonirritating to the conjunctiva. A concentration of from 1:2000 to 1:5000 may be used for preoperative preparation of the eye or for the treatment of suppurative ocular infections. *To prepare a 1:2000 subdilution of Zephiran chloride from the 1:1000 concentration add one volume of Zephiran chloride 1:1000 to one volume of physiologic salt solution or distilled water.*

Wounds

For the disinfection of superficial wounds, traumatic injuries, or as a first-aid prophylactic, Zephiran chloride tincture 1:1000, tinted or untinted, has been found valuable. For deep lacerations and cuts, where the application of alcohol is to be avoided, Zephiran chloride aqueous solution 1:1000 is suggested. For widely denuded areas and for wet dressings, concentrations of from 1:5000 to 1:10,000 are employed. Zephiran chloride solution may be applied to ulcerative processes without pain or discomfort to the patient. The untinted solutions do not stain the skin or linens.

Wright and Wilkinson report on the use of Zephiran chloride in 80 cases of deep and superficial lacerations of the scalp, face, neck and extremities at Harlem Hospital, New York. The technic was to apply Zephiran chloride tincture 1:1000 in the more superficial lacerations, and Zephiran chloride aqueous from 1:1000 to 1:5000 in the form of irrigations in the deep tissue injuries. In only one case, a deep laceration of the forearm, did infection result. They state: "The fact that Zephiran chloride is not irritating when used in proper concentrations, and does not damage the healing surfaces, makes it particularly efficacious in this type of injury."

Hauser and Cutter have used an aqueous solution 1:3000 of Zephiran chloride to cleanse chronic ulcers, osteomyelitis wounds

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Eye Antisepsis

Zephiran chloride aqueous solution 1:2000 to 1:3000 has been found to be nonirritating to the conjunctiva. A concentration of from 1:2000 to 1:5000 may be used for preoperative preparation of the eye or for the treatment of suppurative ocular infections. *To prepare a 1:2000 subdilution of Zephiran chloride from the 1:1000 concentration add one volume of Zephiran chloride 1:1000 to one volume of physiologic salt solution or distilled water.*

Wounds

For the disinfection of superficial wounds, traumatic injuries, or as a first-aid prophylactic, Zephiran chloride tincture 1:1000, tinted or untinted, has been found valuable. For deep lacerations and cuts, where the application of alcohol is to be avoided, Zephiran chloride aqueous solution 1:1000 is suggested. For widely denuded areas and for wet dressings, concentrations of from 1:5000 to 1:10,000 are employed. Zephiran chloride solution may be applied to ulcerative processes without pain or discomfort to the patient. The untinted solutions do not stain the skin or linens.

Wright and Wilkinson report on the use of Zephiran chloride in 80 cases of deep and superficial lacerations of the scalp, face, neck and extremities at Harlem Hospital, New York. The technic was to apply Zephiran chloride tincture 1:1000 in the more superficial lacerations, and Zephiran chloride aqueous from 1:1000 to 1:5000 in the form of irrigations in the deep tissue injuries. In only one case, a deep laceration of the forearm, did infection result. They state: "The fact that Zephiran chloride is not irritating when used in proper concentrations, and does not damage the healing surfaces, makes it particularly efficacious in this type of injury."

Hauser and Cutter have used an aqueous solution 1:3000 of Zephiran chloride to cleanse chronic ulcers, osteomyelitis wounds

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

and infected compound fractures with excellent results, and they found the compound a convenient and safe antiseptic for cleansing wounds in minor surgery.

Ear, Nose and Throat

Because of the good tolerance of the skin and mucous membranes to Zephiran chloride, it may be used in dilutions of 1:1000 to 1:10,000 in the form of irrigations in otitis media and suppurations of the antrums; also as throat swabs or wherever antisepsis is required.

Bacterial Skin Infections

In treating bacterial infections of the skin with wet packs or dressings, Zephiran chloride aqueous solution 1:5000 is suggested. For the treatment of fungous infections of the intact skin Zephiran chloride tincture 1:1000 is used. Indications: pyodermia, irritating eczema, folliculitis, trichophyton infections, impetigo contagiosa and furunculosis, etc.

Wright and Wilkinson employed Zephiran chloride aqueous solution 1:5000 in the form of wet dressings and irrigations in a group of patients with neglected lacerations, hand infections, human bites and cellulitis of the extremities. They state that it was found to be of much benefit in clearing up the infection following free incisions.

Burns

Following the tannic acid treatment of burns, a number of patients developed infection under the eschar. This type of infection is generally difficult to control by the usual methods employed and causes prolongation of disability and hospital care. In one of the large charity hospitals in New York the following routine was adopted:

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

After debridement of the eschar, aqueous Zephiran chloride 1:5000 in the form of wet dressings was applied. There resulted a rapid recession of temperature from 101°-103° to normal. Healing then rapidly resulted, first with healthy granulations, then good epithelium. In some of the cases the total skin involved in first, second and third degree burns varied up to 40 per cent. A solution of 1:10,000 aqueous Zephiran chloride is recommended for infants and children.

Sterile Storage and Decontamination of Instruments

A 1:5000 Zephiran chloride solution suffices for the sterile storing of instruments and apparatus such as bacterial filters, etc. Instruments and supplies which do not withstand sterilization by heat should be thoroughly cleansed and submerged in a 1:1000 aqueous solution for thirty minutes. The aqueous solution has also been used on optical instruments, rubber goods, paraffin mesh, or gutta percha tissues.

An anti-rust agent should be added to Zephiran chloride solutions which are to be used for the storage of metal instruments to prevent corrosion. Knife blades have been stored for months in Zephiran chloride solution containing an anti-rust agent without any evidence of corrosion and with little or no effect on the knife edge. Anti-rust Tablets–Winthrop are available for the purpose. Four tablets should be added to each quart of the antiseptic solution which should be changed at least once a week.

Caution: Zephiran chloride solution should not be used for the sterile storage of cystoscopes or other optical instruments, lacquered catheters or synthetic rubber goods.

Complete sterilization, including the destruction of all spores, is not possible merely by chemical means. While storage for at least thirty minutes in a 1:1000 solution of Zephiran chloride will destroy practically all pathogenic bacteria in their vegetative form, this is not a guarantee of the destruction of all spores.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Rubber Gloves

After the usual mechanical cleansing of rubber gloves used in operations, they are generally sterilized by exposure to steam under pressure. Gloves thus treated may be placed for sterile storage in a 1:5000 solution of Zephiran chloride.

For Use in Disinfection of Hands

With the ordinary methods of disinfecting the hands (washing with soap and hot water followed by rinsing in alcohol), the number of organisms slowly but steadily increases during the course of the operation. Particularly in surgeons who tend to perspire readily the exudate within the gloves becomes very rich in bacteria. Zephiran chloride possesses the advantage that even traces of the diluted Zephiran chloride adhering to gloves or the hands inhibit the growth of bacteria. Zephiran chloride does not make the hands raw or rough or the finger nails brittle, but leaves them soft, smooth and satiny. For the surgical disinfection of hands after the usual scrubbing with soap and water, they should be thoroughly rinsed with water and then immersed in a solution of Zephiran chloride tincture for from two to five minutes.

Comparative tests in the preoperative preparation of the hands were carried out by Hauser and Cutter. The hands of one group were scrubbed in soap and water for ten minutes, then soaked in alcohol and rinsed in sterile water; the other group washed for one minute in Zephiran chloride solution. The cultures in the soap and water group showed about 75 per cent positive reactions, while only 5 per cent of the cultures were positive in the Zephiran chloride group.

Interesting studies on the action of cationic detergents were carried out by Miller and his coworkers (1943). When hands were scrubbed or dipped for from one to three minutes in 1 per cent aqueous Zephiran chloride solution they appeared to have been sterilized completely. However, upon addition of soap to the

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

treated hands many organisms appeared in the culture plates, leading the authors to the conclusion that an invisible, non-perceptible film was formed on the hands which retained some of the bacteria under it, these being released when an anionic detergent, such as soap, was added. The inner surface of the film had apparently a low bactericidal power whereas the outer surface exerted a strong germicidal action. The durability of the film was unusual; it was found possible to use the hands for as long as three hours after initial application of Zephiran chloride without disruption of the film. The film resisted ordinary mechanical trauma as well as brief dips in water or blood, and also exposure to animal tissue, but it was disintegrated by continuous exposure to running tap water for from fifteen to thirty seconds and continuous dips in water or physiologic saline solution.

MODES OF APPLICATION

General Surgery

As a germicide for use on unbroken skin in the preoperative preparation of the surgical field, Zephiran chloride tincture 1:1000 is suggested. *Zephiran chloride is applied either by swab or spray in a manner identical to that employed for other antiseptics now in common use;* no special technic is recommended. As is the case with most antiseptics, soap should be thoroughly rinsed from tissues with water and the areas swabbed with alcohol before Zephiran chloride is applied. The following procedure has been found satisfactory and is essentially the approved method in many hospital operating rooms.

The site of operation is shaved and scrubbed with soap and water or with Zephiran chloride aqueous solution the day before the operation; the operative field is then prepared in the usual

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

manner. Zephiran chloride tincture 1:1000 tinted is suggested for this purpose. The tinted solution when applied to the skin leaves it an orange-amber color and clearly defines the outline of the operative field. The dye is readily removed from the skin or linens with soap and water.

Walter, of Peter Bent Brigham Hospital, Boston, has developed a technic of his own, which is as follows:

The site of the operative field is scrubbed for one minute with soap (10 per cent aqueous suspension to equal parts of coconut and olive oil soaps) and water until a stiff lather is produced; the lather is removed by shaving and the skin is then thoroughly rinsed with fresh tap water and dried with a towel. Whenever possible this preparation is carried out at least twelve hours prior to operative procedure. No dressing is applied during the interval. On the operating table the operative site is scrubbed with three changes of sponges saturated with 1:1000 Zephiran chloride aqueous solution alternated with three changes of sponges saturated with 70 per cent alcohol.

The detergent action of this combination is marked. The soapy aqueous solution emulsifies the skin fats and loosens the desquamating epithelium; the contrasting dry alcohol rolls the dirt off the skin. The skin is thus left smooth and clean and shows a rosy blush over the prepared area.

In regions where mechanical cleansing is difficult because of anatomic considerations, the following technic is employed:

A wet dressing of Zephiran chloride 1:1000 aqueous solution is applied two hours prior to operation; when the operative site has been exposed, Zephiran chloride tincture 1:1000 is applied.

Orthopedic Surgery

For the preparation of the operative field in orthopedics, the following technic has been recommended:

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Twenty-four hours prior to operating, the site of operation is cleansed with soap and water; the lather is shaved off, the skin thoroughly rinsed with tap water, and Zephiran chloride tinted tincture then applied. On the operating table Zephiran chloride untinted tincture is applied to that part of the previously prepared surgical area from which it is desired to remove the coloring; thus the skin resumes its normal flesh color and circulation in the extremities is more easily determined following the affixation of splints and casts.

Wright and Wilkinson suggest that in the preparation for open bone and joint operations the skin be prepared with alcohol, ether and Zephiran chloride 1:1000 for three successive days prior to operation.

FORMS AVAILABLE

ZEPHIRAN CHLORIDE CONCENTRATE 12.8% AQUEOUS SOLUTION

Must be diluted

Zephiran Chloride Concentrate 12.8% Aqueous Solution is a very economical form for preparing the various aqueous dilutions and tinctures that are commonly employed in the numerous branches of surgery.

Preparation of aqueous solution 1:1000

Zephiran Chloride Concentrate 12.8% . . .	1 oz.
Distilled water* q.s. ad	1 U. S. gal.

Preparation of stainless tincture 1:1000

Zephiran Chloride Concentrate 12.8% . . .	1 oz.
Acetone U.S.P.†	13 oz.
Alcohol U.S.P.	64 oz.
Distilled water* q.s. ad	1 U. S. gal.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Preparation of tinted tincture 1:1000

Add the contents of 1 vial of Zephiran Tint (28 grains) to 1 ounce of alcohol. When the dye is completely dissolved, add the following:

Zephiran Chloride Concentrate 12.8%	1 oz.
Acetone U.S.P.†	13 oz.
Alcohol U.S.P.	63 oz.
Distilled water* q.s. ad	1 U. S. gal.

* Physiologic salt solution may be substituted for distilled water.

† The acetone may be omitted (thereby achieving even greater economy) since Zephiran chloride is a wetting agent and possesses fat emulsifying and detergent properties.

ZEPHIRAN CHLORIDE AQUEOUS SOLUTION 1:1000

An efficient antiseptic and germicide for surgical and gynecologic procedures. Nonirritating and of pleasant odor.

Zephiran Chloride Aqueous Solution is recommended for the antisepsis of skin and mucous membranes and for use as a germicide and disinfectant in deep wounds. It has been successfully employed, in proper dilutions, for irrigations of body cavities, bladder lavages, urethral irrigations, vaginal douches, sterile storage of instruments and rubber articles, hospital utensils, scrubbing of hands, etc. It is stainless and of pleasant odor. For denuded and highly sensitive skin or mucous membranes dilutions of from 1:2000 to 1:5000 are suggested.

Because of the low concentrations of Zephiran chloride capable of destroying pathogenic organisms, dilutions of from 1:10,000 to 1:40,000 have been shown to be effective and safe for irrigations of inflamed body cavities.

ZEPHIRAN CHLORIDE TINCTURE 1:1000 STAINLESS

An efficient antiseptic of high germicidal, fungicidal and bacteriostatic potency.

Zephiran chloride tincture is an alcohol-acetone-aqueous 0.1 per cent solution of a mixture of high molecular alkyldimethyl benzyl ammonium chlorides. It contains 50 per cent alcohol and 10 per cent acetone by volume.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Zephiran chloride tincture stainless is recommended in all conditions in which a colorless antiseptic is desired as a germicide and disinfectant for use on intact skin. It is recommended for preoperative antisepsis of the skin and mucous membranes and as a first-aid prophylactic in traumatic injuries, lacerations, etc. Zephiran chloride tincture stainless may also be used as a germicide and disinfectant on hands and arms of surgeons following the usual routine scrubbing with soap and water.

ZEPHIRAN CHLORIDE TINCTURE 1:1000 TINTED

An efficient antiseptic and germicide for surgical and gynecologic procedures.

Zephiran chloride tincture 1:1000 tinted is precisely the same as the stainless solution except that an orange-amber coloring agent has been added which, when applied to the skin, clearly defines the outline of the operative field. The dye is readily removed from the skin or linens with soap and water, alcohol, or hydrogen peroxide 3 per cent.

The tinted tincture is recommended for all conditions in which skin antisepsis is desired. It is preeminently useful for preoperative preparation of the surgical field of the skin and as a first-aid prophylactic in traumatic injuries, lacerations, etc.

THE DYE

As a tinting agent for Zephiran chloride tincture 1:1000 an indicator dye has been employed, i.e., in acid mediums an orange-amber hue is maintained but in alkali mediums this rapidly fades to a light yellow. The intensity of the color of skin prepared with tinted tincture depends, therefore, upon the acidity or alkalinity of the skin. It also indicates whether a soap has been removed from the skin before the antiseptic is applied.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

ANTI-RUST TABLETS–WINTHROP

Each tablet contains 1.16 Gm. sodium carbonate (monohydrate), 0.5 Gm. sodium nitrite, and a small amount of boric acid (as a lubricant).

The addition of Anti-Rust Tablets–Winthrop to aqueous solutions of Zephiran chloride intended for the sterile storage of instruments of carbon steel or other corrosible metals tends to protect against rust formation and corrosion. The addition of 4 tablets to 1 quart of aqueous sterilizing solution should protect instruments against rust formation for one week. The solution should be changed at least once a week.

The efficacy of Anti-Rust Tablets–Winthrop as a means of retarding oxidation and corrosion is dependent upon several variable factors, such as the temperature of the sterilizing solution, surface area of solutions exposed to air, and the condition of the instruments. As a consequence these tablets are not offered as a completely effective protection against rust formation and corrosion under all conditions.

HOW SUPPLIED

Zephiran chloride is available in—

CONCENTRATE 12.8% Aqueous Solution in 4 oz. and 1 gal. bottles.

TINCTURE 1:1000 Tinted
TINCTURE 1:1000 Stainless
AQUEOUS SOLUTION 1:1000
} in 8 oz. and 1 gal. bottles.

ZEPHIRAN TINT (D & C Red No. 39) in vials of 28 grains, boxes of 4

ANTI-RUST TABLETS–WINTHROP, bottles of 50.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

ZEPHIRAN CHLORIDE — DILUTIONS EMPLOYED

SURGERY

As a germicide for preoperative disinfection of skin:	Zephiran chloride tincture 1:1000 stainless or tinted.
Minor wounds, lacerations, etc.:	Zephiran chloride tincture 1:1000.
Denuded skin and mucous membranes:	Zephiran chloride aqueous solution 1:2000 to 1:10,000 (1 part of 1:1000 to from 1 to 9 parts of water).
Deep infected wounds:	Zephiran chloride aqueous solution 1:3000 to 1:20,000 (1 part of 1:1000 to from 2 to 19 parts of water).
Surgeons' hand and arm soak:	Zephiran chloride tincture 1:1000 stainless.

OBSTETRICS AND GYNECOLOGY

As a germicide for preoperative disinfection of skin:	Zephiran chloride tincture 1:1000 or Zephiran chloride aqueous solution 1:1000.
Vaginal instillation and irrigation:	Zephiran chloride aqueous solution 1:2000 to 1:5000 (1 part of 1:1000 to from 1 to 4 parts of water).

UROLOGY

Bladder and urethral irrigation:	Zephiran chloride aqueous solution 1:5000 to 1:20,000 (1 part of 1:1000 to from 4 to 19 parts of water).
Bladder retention lavage:	Zephiran chloride aqueous solution 1:20,000 to 1:40,000 (1 part of 1:1000 to from 19 to 39 parts of water).

NOTE: ***Physiologic saline solution may be substituted for water.***

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

DERMATOLOGY

Fungous infections: Zephiran chloride tincture 1:1000.

For oozing and open infections: Zephiran chloride aqueous solution 1:2000 to 1:5000 (1 part of 1:1000 to from 1 to 4 parts of water).

Wet dressings: Zephiran chloride aqueous solution 1:5000 or less (1 part of 1:1000 to 4 or more parts of water).

MISCELLANEOUS

Eye, nose and throat: Zephiran chloride aqueous solution 1:3000 to 1:10,000 (1 part of 1:1000 to from 2 to 9 parts of water).

STERILE STORAGE OF INSTRUMENTS

Metallic instruments: Zephiran chloride aqueous solution 1:1000.

Rubber articles: Zephiran chloride aqueous solution 1:1000.

For the prevention of rust: To protect metal instruments stored in Zephiran chloride solution from rusting, Anti-Rust Tablets–Winthrop (from 2 to 4 tablets per quart) are added to the antiseptic solution.

For disinfection of utensils, operating tables, etc., use Zephiran chloride aqueous solution 1:5000 (1 part of 1:1000 to 4 parts of water).

NOTE: *Physiologic saline solution may be substituted for water.*

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Bibliography

Allen, J. H.: *Journal-Lancet*, 62:207, June, 1942.

Baker, Z., Harrison, R. W., and Miller, B. F.: *Jour. Exper. Med.*, 74:611, 621, Dec., 1941.

Cutler, E. C., and Zollinger, R.: *Surg., Gynec. & Obst.*, 67:69, July, 1938; *Am. Jour. Surg.*, 47:185, Jan., 1940. Atlas of Surgical Operations. New York, The Macmillan Company, 1939.

Deskowitz, M. W.: Unpublished report from the bacteriological laboratories of the College of Physicians and Surgeons, Columbia University, New York, May, 1937.

Domagk, Gerhard: *Deutsche med. Wchnschr.*, 61:829, May 24, 1935.

Dunn, Cecil G.: *Proc. Soc. Exper. Biol. & Med.*, 35:427, Dec., 1936; *Am. Jour. Hyg.*, 26:46, July, 1937; *Proc. Soc. Exper. Biol. & Med.*, 37:661, Jan., 1938; *Technology Rev.*, 40:271, Apr., 1938; *Am. Jour. Surg.*, 41:268, Aug., 1938.

Freedlander, B. L.: *Proc. Soc. Exper. Biol. & Med.*, 44:51, May, 1940.

Gardner, H. J.: *Roy. Melbourne Hosp. Clin. Rep.*, Dec., 1942, p. 55.

Harshbarger, K. E.: *Jour. Dairy Sci.*, 25:169, Feb., 1942.

Hauser, E. D., and Cutter, W. W.: *Am. Jour. Surg.*, 64:352, June, 1944.

Heineman, P. G.: *Jour. Am. Pharm. Assn.* (Scient. Ed.), 21:711, Aug., 1937.

Hirsch, M. M., and Novak, M. V.: *Proc. Soc. Exper. Biol. & Med.*, 50:376, June, 1942.

Hoyt, Anson, Fisk, Roy T., and Burde, Gerhard: *Surgery*, 12:786, Nov., 1942.

Krog, Andrew J., and Marshall, Charles G.: *Am. Jour. Pub. Health*, 30:341, Apr., 1940.

Lawrence, C. A.: Laboratory report (unpublished).

Lupton, Charles H.: *Virginia Med. Monthly*, 66:610, Oct., 1939; *Am. Jour. Surg.*, 57:122, July, 1942.

Maier, Eugene: *Jour. Bact.*, 38:33, July, 1939.

—— and Müller, E.: *Fortschr. d. Therap.*, 12:204, Apr., 1936.

Miller, B. F., Abrams, Richard, Huber, Dorothy Ann, and Klein, Morton: *Proc. Soc. Exper. Biol. & Med.*, 54:174, Nov., 1943.

—— and Baker, Zelma: *Science*, 91:624, June 28, 1940.

——, —— and Harrison, R. W.: *Proc. Soc. Exper. Biol. & Med.*, 42:705, Dec., 1939.

——, Muntz, J. A., and Bradel, S.: *Proc. Soc. Exper. Biol. & Med.*, 45:104, Oct., 1940.

Neter, Erwin: *Science*, 96:209, Aug. 28, 1942.

O'Brien, C. S., and Swan, K. C.: *Arch. Ophth.*, 27:253, Feb., 1942.

Sager, W. W.: *Med. Ann. District of Columbia*, 10:56, Feb., 1941.

Scobee, R. G.: *Am. Jour. Ophth.*, 25:184, Feb., 1942.

Shumacker, H. B., and Bethea, W. R.: *Surgery*, 14:931, Dec., 1943.

Smith, C. Souter: *Jour. Missouri Med. Assn.*, 36:72, Feb., 1939.

Spaulding, E. H.: *Surg., Gynec. & Obst.*, 69:738, Dec., 1939.

Swan, K. C.: *Journal-Lancet*, 62:79, Mar., 1942.

Thompson, R., Isaacs, M. L., and Khorazo, D.: *Am. Jour. Ophth.*, 20:1087, Nov., 1937.

Wallace, George: Report on Second Annual Swimming Pool Conference, June 4-5, 1940, State Dept. Pub. Health, Div. San. Eng., University of Illinois.

Walter, Carl W.: *Surg., Gynec. & Obst.*, 67:683, Nov., 1938.

Welch, H., and Brewer, C. M.: *Jour. Immunol.*, 43:25, Jan., 1942.

White, Charles S., Collins, J. Lloyd, and Newman, Howard E.: *Am. Jour. Surg.*, 39:607, Mar., 1938.

Wright, Louis T., and Wilkinson, Robert S.: *Am. Jour. Surg.*, 44:626, June, 1939.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Winthrop products are distributed through wholesale druggists. If your pharmacist has difficulty in obtaining them, he should send his order to New York 13 (170 Varick St.), or to the nearest commercial branch office: Atlanta 3 (152 Peters St., S.W.), Chicago 11 (445 Lake Shore Drive), San Francisco 7 (860 Second St.), or Windsor, Ont. (1019 Elliott St., W.). Prompt shipment will be made, and the merchandise charged through his wholesaler.

Address professional correspondence to the respective main office, or to the nearest of the following professional service offices:

Atlanta 3	1024 Candler Building
Baltimore 2	1628 O'Sullivan Building
Boston 16	441 Stuart Street
Buffalo 3	14 Lafayette Square
Chicago 1	180 N. Michigan Avenue
Cleveland 15	423 Republic Building
Fort Worth 2	908 Neil P. Anderson Building
Los Angeles 13	408 S. Spring Street
Memphis 3	46 N. Third Street
Minneapolis 2	1800 Rand Tower
New Orleans 12	806 Hibernia Bank Building
Philadelphia 7	626 Widener Building
San Francisco 4	One Eleven Sutter
St. Louis 8	3615 Olive Street
Seattle 4	Insurance Building
Honolulu (T. H.)	421 Damon Building
San Juan (P. R.)	Calle Fortaleza #352
Manila (P. I.)	670 Dasmariñas
Montreal (Que.)	Dominion Square Building
Kingston, Jamaica (B. W. I.)	141 Harbour Street
Port-of-Spain, Trinidad (B. W. I.)	#1 Chacon

WINTHROP

WINTHROP CHEMICAL COMPANY, INC.

Pharmaceuticals of merit for the physician

NEW YORK 13, N. Y. • **WINDSOR, ONT.**

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Ringworm

including

Athlete's Foot

U.S. PUBLIC HEALTH SERVICE · 1798 ·

Four common skin diseases caused by a fungus growth are: ringworm of the feet; ringworm of the scalp; ringworm of the body; and ringworm of the nail. The most common of these is ringworm of the feet. It is called athlete's foot. The most stubborn one to cure is ringworm of the nail. These four diseases are more annoying than dangerous. They are serious only when they cause breaks in the skin where other infections can enter. They all need prompt medical treatment.

Athlete's foot is caused by a low form of plant life called a fungus growth. Some of it is almost always on everyone's feet. It causes no trouble unless it grows. This fungus, like mold on food, grows in warm, moist, poorly ventilated places. The spaces between the toes make ideal places for a fungus growth, especially on feet that stay damp with perspiration. Two other things that help a fungus growth along are: bits of soggy dead skin between the toes and around the nails, and snug shoes that do not let air get to the feet.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

When this fungus on the feet grows, it causes athlete's foot. The symptoms are: increased sogginess between the toes, scaling, itching (in most cases), small blisters on the feet. When the disease continues and becomes worse, there can be larger blisters and raw places, swelling and redness. Some severe cases look and feel like ivy poisoning.

There are several forms of athlete's foot. Each one needs its own treatment. Let your doctor decide and tell you what to do. Athlete's foot can clear up in a short time if the right treatment is begun early and followed faithfully. Wrong treatment can make athlete's foot worse. A person can have this disease as often as germs on his feet find enough warmth and moisture for growth.

PREVENTION

Keep your feet dry and free from soggy dead skin. When you bathe, don't forget to soap between your toes; use a nail brush or orangewood stick under and around your nails - these are the places where dead skin collects. Rinse and dry your feet thoroughly, rubbing off any dead skin. Dust your feet well with talcum powder. If talcum fails to keep your feet dry all day, use petrolatum or zinc ointment instead; rub very little on your feet, not forgetting your toenails and the spaces between your toes. Wear stockings and shoes that are comfortably roomy. Change hose at least once each day.

RINGWORM OF THE SCALP

Ringworm of the scalp is contagious. It is spread in many ways, and usually to children. When a child has ringworm of the scalp, his brush and comb carry the infection; his hat may spread the disease to another child who tries it on; his barber could infect others if he failed to sterilize his shears or clippers. A dog or cat with ringworm can transmit the disease to a person.

Ringworm of the scalp causes a patch of hair to break off near the roots; this leaves a bald, mangy looking spot on the scalp. If your child gets this infection, take him to a doctor or hospital clinic at once; the illness can be stubborn if allowed to continue. It can be made worse by wrong treatment. It can spread to others unless cared for.

Report your child's condition, and the fact that he is being treated, to the school nurse or teacher. If one of the other pupils is spreading the disease, the teacher should know about it. If the infection has come from a dog or cat, see that the pet is cured by a veterinarian before allowing children to play with it.

RINGWORM OF THE BODY

Ringworm of the body is contagious. Children have it more frequently than adults. They get it by contact with a child who has it, or by handling cats or dogs that have ringworm. This type of ringworm occurs usually on the face or neck, but can appear on other parts of the body. The patches are generally ring or oval shaped; they are slightly raised, pink and scaly with a clear space in the center. Usually, one to four rings appear.

Although ringworm of the body is easier to treat than ringworm of the scalp, it needs the attention of a doctor. He will know the best treatment for each case.

To prevent another ringworm infection, be sure that any family pets with ringworm are cured by a veterinarian.

RINGWORM OF THE NAIL

Ringworm of the nail is the most difficult of all to cure. The fungus growth can work entirely through the nail, causing it to become discolored, pitted, grooved and

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

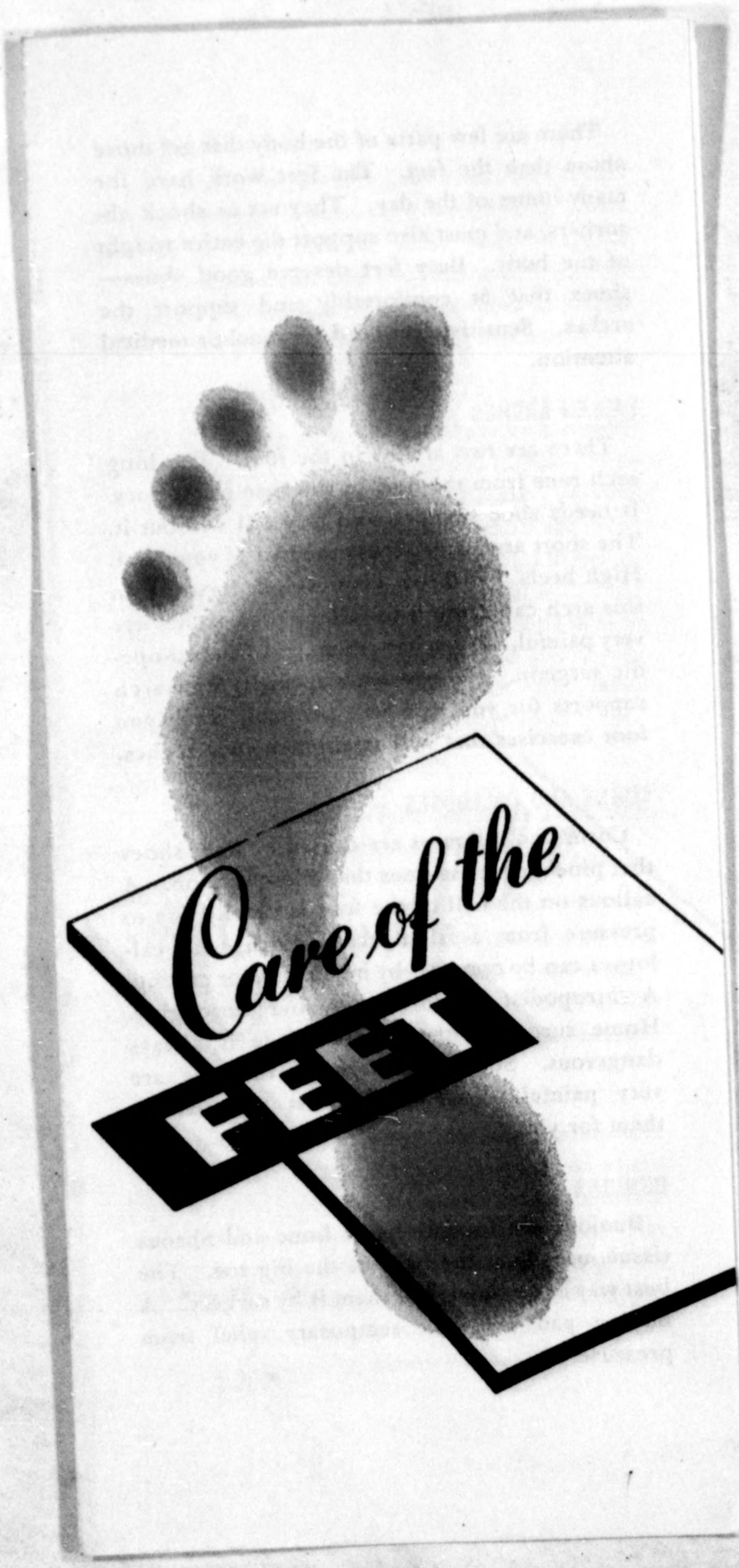
brittle. Do not delay a cure by trying to treat this infection yourself. Go to a skin specialist if there is one near you; if not go to a doctor or hospital clinic.

Ringworm of the nail is contagious.

JUNE 1947

FEDERAL SECURITY AGENCY
U. S. PUBLIC HEALTH SERVICE
Health Education Series No. 6

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013



DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

There are few parts of the body that get more abuse than the feet. The feet work hard for many hours of the day. They act as shock absorbers, and must also support the entire weight of the body. Busy feet deserve good shoes—shoes that fit comfortably and support the arches. Sensitive feet need personal or medical attention.

FALLEN ARCHES

There are two arches in the foot. The long arch runs from the heel to the base of the toes. It needs shoe support, and may fall without it. The short arch runs across the ball of your foot. High heels that throw your weight forward on this arch can cause it to fall. Fallen arches are very painful. If you have them, go to an orthopedic surgeon. He may order specially fitted arch supports for you, and will probably teach you foot exercises that will strengthen your arches.

CORNS AND CALLOUSES

Corns and callouses are caused by tight shoes that pinch, or loose ones that allow friction. A callous on the ball of the foot is usually due to pressure from a fallen arch. Corns and callouses can be removed by medication or cutting. A chiropodist can do it safely and thoroughly. Home surgery with a razor blade is always dangerous. Soft corns between the toes are very painful. Your chiropodist can remove them for you.

BUNIONS

Bunions are formations of bone and fibrous tissue, usually at the base of the big toe. The best way of getting rid of them is by surgery. A bunion pad will give temporary relief from pressure.

FOOT ODOR

To prevent unpleasant foot odor, bathe your feet and change hose at least once a day. Get a deodorant foot powder from your druggist. Dust it on your feet and between your toes after bathing. Having several pairs of shoes to change off with is helpful in overcoming foot odor.

SWELLING OF THE FEET

Swelling is a symptom which may be the result of mechanical causes or of certain diseases such as heart trouble and kidney disease. If your feet and ankles swell, by all means see your doctor. Sometimes feet swell from hours of standing or walking in the wrong shoes. They will swell and ache if your hose are too short in the feet. For relief, lie down and prop your feet high up on a pillow. For quick relief, wrap a wet hand towel around each bare foot.

VARICOSE VEINS

Varicose veins cause foot and ankle swellings. For this condition, see your doctor.

TOENAILS

Cut and file your toenails straight across and not too short. Rounding the nail at the corner may cause it to grow into the flesh. For an ingrowing nail, see your doctor or chiropodist.

ATHLETE'S FOOT

Athlete's foot is a distressing condition caused by a fungus growth. This growth thrives where it is warm and damp. If your feet perspire much the infection can start between your toes. For prevention dry your feet very thoroughly after bathing, then dust talcum powder between your toes. Use petrolatum or zinc ointment between your toes instead of powder if you prefer.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

FEDERAL SECURITY AGENCY
U. S. Public Health Service
Washington 25, D. C.
HEALTH EDUCATION SERIES NO. 5

U. S. GOVERNMENT PRINTING OFFICE 16—49243-1

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Punctule

CRYSTALLINE

PENICILLIN G POTASSIUM

IN OIL AND WAX

(ROMANSKY FORMULA)

Winthrop

Winthrop CHEMICAL COMPANY, INC.

PHARMACEUTICALS OF MERIT FOR THE PHYSICIAN

Punctule
TRADEMARK

CRYSTALLINE
PENICILLIN G POTASSIUM
IN OIL AND WAX
(Romansky Formula)

Winthrop

300,000 units per cubic centimeter

DESCRIPTION

PUNCTULE is a new injection unit consisting of a cartridge to which is attached a plunger with thumb rest. Penicillin in Oil and Wax-Winthrop is a sterile suspension of crystalline penicillin G potassium in a mixture of highly refined peanut oil and white wax. Each 1 cc. cartridge contains 300,000 units of penicillin. This product conforms to the specifications of Romansky who first suggested and administered penicillin in oil and wax.

PUNCTULE, A NEW CARTRIDGE PLUNGER UNIT FOR ADMINISTERING PENICILLIN IN OIL AND WAX

In order to avoid the task of drawing the heavy Romansky suspension into a syringe from an ordinary vial or bottle and to obviate the necessity of immediate and difficult cleaning of syringes and needles, special syringes and cartridges have been devised in the past for the administration of penicillin in oil and wax. However, there has been one serious objection to these devices, in that not all of them protect against unintentional and potentially dangerous puncture of a blood vessel. Furthermore, their use increases the cost of penicillin in oil and wax.

The accompanying illustrations depict a new device which enables the physician to aspirate in the usual manner and to inject the Romansky formula by means of a conventional form of syringe without the need of cleaning the syringe after the injection has been made. It will be observed that the medicament is contained within a glass cartridge which is long enough to receive one end of a plunger. The only additional item required is a needle with a double end, as illustrated (Fig. 1).

DIRECTIONS FOR USE

(1) Sterilize the 5 cc. syringe and the double-end needle. Meanwhile warm the Punctule cartridge thoroughly so that the wax and oil are completely liquefied. This is best done by immersing in hot water (about 45°C; 103°F). The warm material should flow freely when the cartridge is tilted back and forth. Make sure that it is kept warm up to the time of making the injection.

(2) Assemble the syringe and needle and place the plunger of the syringe at about the 5 cc. mark. Cleanse the rubber stopper of the Punctule cartridge with an antiseptic solution. Cleanse the skin with an antiseptic solution and then thrust the needle into the gluteal muscles. (The muscles of the thigh and upper arm may be used if desired.)

(3) Pull back the plunger of syringe (aspiration) and if no blood enters, continue pulling back on the plunger until it is released from the barrel (Fig. 2).

(4) Insert the Punctule cartridge into the barrel of the syringe and engage the rubber stopper of the Punctule cartridge on the needle end in the syringe by "pulling down" on the Punctule plunger (Fig. 3). Then push on thumb-rest of plunger and make the injection (Fig. 4).

(5) Withdraw the syringe and remove the needle. This releases the empty Punctule cartridge which may then be discarded.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

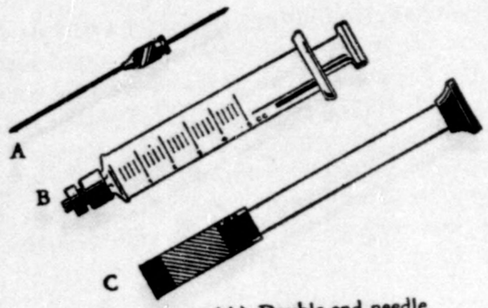


Fig. 1—Equipment: (A) Double-end needle. (B) 5 cc. Luer-Lok syringe. (C) Punctule.

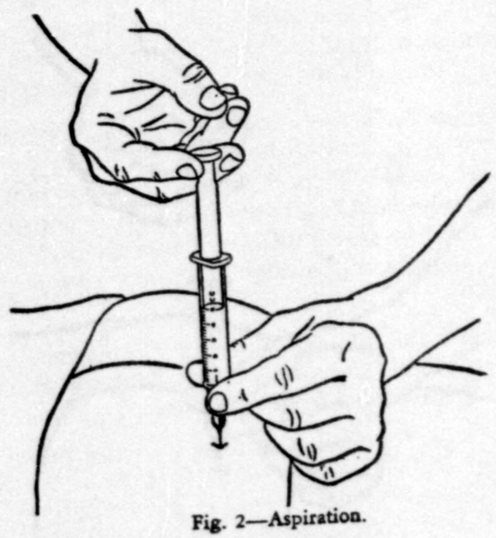


Fig. 2—Aspiration.

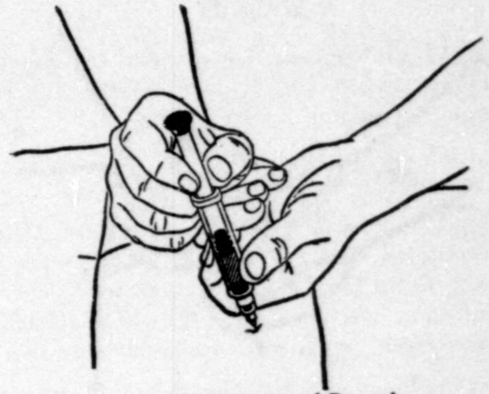


Fig. 3—Insertion of Punctule.

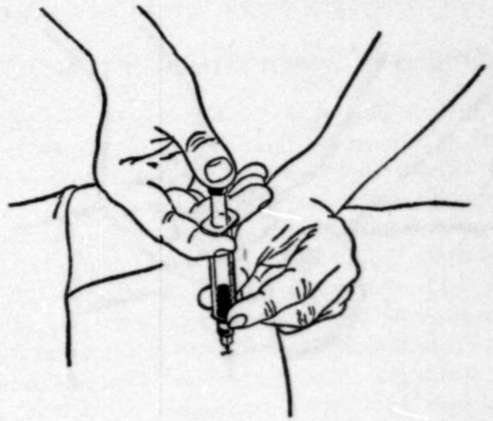


Fig. 4—Injection.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

STABILITY

Penicillin G in oil and wax when stored at room temperature retains its potency for eighteen months. The Punctule cartridges do not require refrigeration.

ACTION AND INDICATIONS

Following intramuscular injection, penicillin in oil and wax is slowly absorbed. The injection of 300,000 units in 1 cc. produces significant blood concentrations for from twelve to twenty-four hours. Smaller doses (100,000 to 200,000 units) give effective blood levels for from eight to twelve hours.[1]

Penicillin in oil and wax may be used for all the conditions for which penicillin in an aqueous solution is recommended. The principal difference between the two lies in the frequency of injection: Aqueous solutions must be injected once every two to three hours, whereas injection of oil and wax mixtures is necessary only every twelve to twenty-four hours.[2]

CONDITIONS IN WHICH PENICILLIN IS EFFECTIVE

Penicillin is indicated in the following infections and in complications caused by them:[3] Staphylococcus infections with and without bacteremia (acute and chronic osteomyelitis, carbuncles, soft tissue abscesses, meningitis, cavernous or lateral sinus thrombosis, pneumonia, empyema, carbuncle of kidney, wound infections, burns, endocarditis). Clostridia infections (gas gangrene, malignant edema). Hemolytic streptococcus infections with bacteremia and all serious local infections (cellulitis, mastoiditis with intracranial complications, i.e., meningitis, sinus thrombosis, etc., pneumonia and empyema, puerperal sepsis, peritonitis, endocarditis). Anaerobic streptococcus infections (puerperal sepsis, localized infections elsewhere). Pneumococcus infections of meninges, pleura, endocardium and all cases of pneumococcus pneumonia. Gonococcus infections. Cases of anthrax. Cases of chronic pulmonary suppuration in which surgical treatment is contemplated. Meningococcus infections failing to respond to sulfonamides. Cases of bacterial endocarditis due to susceptible organisms. Erysipeloid (swine erysipelas). Vincent's infection. Prophylactic use for the prevention of possible secondary infection following tonsillectomy and tooth extraction in cases with a history of rheumatic fever or in rheumatic heart disease, in congenital heart disease, and in other conditions in which secondary infection may occur (infected teeth or tonsils).

1. Romansky, M. J.: *Am. Jour. Med.*, 1:395, Oct., 1946.
2. Council on Pharmacy and Chemistry: *J.A.M.A.*, 132:23, Sept. 7, 1946.
3. Keefer, C. S., Herwick, R. P., Van Winkle, W., and Putnam, L. E.: *J.A.M.A.*, 128:1161, Aug. 18, 1945.

Penicillin has been established as an important antisyphilitic. It may also be of value in actinomycosis and diphtheria in conjunction with antitoxin but its position has not been definitely defined.

Penicillin is of questionable value in mixed infections in which the predominating organism is of the gram negative flora, i.e., ruptured appendix with peritonitis, liver abscesses, urinary tract infections due to Escherichia coli. It is also of questionable value in rat bite fever due to Streptobacillus moniliformis.

CONDITIONS IN WHICH PENICILLIN IS INEFFECTIVE

Penicillin is ineffective in all gram negative bacillary infections:[3] typhoid-paratyphoid, dysentery, Escherichia coli, Haemophilus influenzae, Bacillus proteus, Bacillus pyocyaneus, Brucella melitensis (undulant fever), Pasteurella tularensis (tularemia), Friedländer's bacillus.

Penicillin has also been found to be ineffective in the following diseases: tuberculosis, toxoplasmosis, histoplasmosis, acute rheumatic fever, lupus erythematosus, diffuse; infectious mononucleosis, pemphigus, Hodgkin's disease, acute and chronic leukemia, ulcerative colitis, coccidioidomycosis, malaria, poliomyellitis, blastomycosis, nonspecific iritis and uveitis, moniliasis, virus infections, cancer.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

CLINICAL EXPERIENCE

Gonorrhea.—In a series of 506 cases of acute uncomplicated gonorrhea Romansky[1,4,5] found approximately a 98 per cent cure rate after a single injection of 300,000 units of penicillin in oil and beeswax. Similar successful results have also been reported by Van Slyke and Heller[6] utilizing the same method of administration. Romansky and his coworkers[4] have pointed out that prostatitis subsided more rapidly after the single dose method and that other manifestations of the disease were relieved just as speedily as with the multiple doses of penicillin in saline solution. It is the opinion of all investigators in the field that penicillin in oil and wax provides a highly satisfactory treatment of gonorrhea.

Pneumococcus Pneumonia.—Initial clinical reports indicate that penicillin in oil and wax may also have value for the control of other coccus infections. Kinsman and others[7] had encouraging results in treating pneumonia with suboptimal doses. A four day treatment was successful in 12 patients who received 100,000 units every twelve hours for the first two days, but there were failures in the group given only 100,000 units per day through the course. Romansky[1] treated a total of 42 cases of pneumococcus pneumonia by single daily injections of 300,000 units of penicillin in oil and wax. Of the 42 cases, 38 required only four days of treatment, except for a group of 16 who received only one injection. Penicillin in oil and wax was given routinely for an additional day after the temperature had subsided to normal. Then the injection of this preparation was discontinued and sulfadiazine treatment was initiated with complete recovery. (This occurred during the early development of the Romansky formula and not enough was known about it to continue treatment. It is likely, however, that the results would have been satisfactory if the Romansky formula had been continued for a longer period of time.)

4. Romansky, M. J., Murphy, R. J., and Rittman, G. E.: *J.A.M.A.*, 128:404, June 9, 1945.
5. Romansky, M. J., and Rittman, G. E.: *New England Jour. Med.*, 233:577, Nov. 15, 1945.
6. Van Slyke, C. J., and Heller, J. R., Jr.: *Ven. Dis. Inform.*, 26:98, May, 1945.
7. Kinsman, J. M., Daniels, W. B., Cohen, S., McCracken, J. P., d'Alonzo, C. A., Martin, S. P., and Kirby, W. M. M.: *J.A.M.A.*, 128:1219, Aug. 25, 1945.

Furunculosis.—A total of 93 cases of Staphylococcus aureus infection were treated by Romansky.[1] Furuncles responded rapidly with a single daily dose of penicillin in oil and wax. Spontaneous evacuation of the pus occurred within the first forty-eight hours or resolution without drainage. Cases of furunculosis responded satisfactorily but in general the duration of treatment was longer. Patients with carbuncles also responded excellently to the single daily injections. Other infections, such as breast abscesses and early acute osteomyelitis due to staphylococcus, were also satisfactorily treated with the Romansky formula.

Pharyngitis.—Excellent results were obtained in cases of pharyngitis and tonsillitis due to beta hemolytic streptococci.[1] In only 1 of 8 cases studied were more than four injections required. Hamburger and Lemon[8] have shown that in 50 per cent of a group of beta hemolytic streptococcus carriers the organism was eliminated from the pharynx by single daily injections of the Romansky formula for five to eight days.

Impetigo.—In a group of 38 patients with impetigo treated by single daily injections of penicillin in oil and wax,[1] the response was particularly striking, for within twenty-four to forty-eight hours the lesions became dry. Thirty-three of the patients responded to injections given from one to four days.

Syphilis.—Kirby and others[9] reported on 35 cases of primary or secondary syphilis treated with 300,000 units once daily for eight days. Since relapse occurred in 3 patients, it was concluded that a 300,000 unit dose should be given every twelve hours in serious infections. Romansky and his coworkers[10] recently treated 75 patients with early syphilis using a single daily injection of 300,000 units of the Romansky formula for eight days. In 58 of these cases observed for from three to eighteen months results were satisfactory, 40

8. Hamburger, M., Jr., and Lemon, H. M.: *J.A.M.A.*, 130:836, Mar. 30, 1946.
9. Kirby, W. M. M., Liefer, W., Martin, S. P., Rammelkamp, C. H., and Kinsman, J. M.: *J.A.M.A.*, 129:940, Dec. 1, 1945.
10. Romansky, M. J., Rein, C. R., and Rittman, G. E.: *J.A.M.A.*, 132:847, Dec. 7, 1946.

having already attained seronegativity. Only two of the series with secondary syphilis were classified as failures.

TOLERANCE

Intramuscular administration usually causes muscle soreness beginning twenty-four hours after injection and lasting from one to ten days.

MANNER OF USE AND DOSAGE

Penicillin in oil and wax is used by intramuscular injection, preferably into the gluteus muscles. However, the muscles of the thigh and upper arm may also be used if desired. Penicillin in oil and wax should not be administered by the subcutaneous route, since the incidence of sensitizing reactions, with giant urticaria and angioneurotic edema, is excessively high. *Caution:* Penicillin in oil and wax should never be used intravenously.

The dosage of penicillin varies depending on the type and severity of infection. The objective in each case is to bring the infection under control as quickly as possible. In most cases a minimum of 300,000 units daily (contents of one Punctule cartridge) will be required.

In *serious infections* with or without bacteremia one injection of 300,000 units should be administered every twelve hours. Many physicians also use a "priming dose" of 50,000 or 100,000 units of penicillin in aqueous solution just before giving penicillin in oil and wax in serious infections.

After the temperature has returned to normal, the penicillin may be continued as long as there are any signs of active infection.

In *chronically infected compound injuries,* osteomyelitis and the like, the dosage should consist of 300,000 units daily. This dosage schedule may have to be increased, depending on the seriousness of the infection and the response to treatment. The best results are obtained in these cases when penicillin is combined with adequate surgical treatment.

In *gonorrhea,* one injection of 300,000 units has been found sufficient in the majority of cases. However, some experts recommend a second injection of 300,000 units after twelve or twenty-four hours. Others also administer a "priming dose" of 100,000 units of penicillin in aqueous solution, followed immediately by the injection of penicillin in oil and wax. The results of treatment should be controlled by culture of exudate. All patients failing to respond to the first course should be retreated.

In cases of *meningitis* penicillin does not penetrate the subarachnoid space in appreciable amounts so that it is necessary to inject penicillin in aqueous solution into the subarachnoid space or intracisternally in order to produce the desired effect. The dose is 10,000 units in 10 cc. of isotonic solution of sodium chloride once or twice daily, depending on the clinical course and the presence of organisms. In addition penicillin in oil and wax should be administered intramuscularly in doses of 300,000 units every twelve or twenty-four hours.

In *bacterial endocarditis* penicillin is the best agent available. Penicillin alone is as effective as penicillin combined with heparin. The treatment should be continued for three weeks or longer, depending on the individual case. The intramuscular route is the one of choice, although in a few instances it may be desirable to use the continuous intravenous route (using penicillin in *aqueous* solution) in order to obtain the maximum effect. For best results, 300,000 units of penicillin in oil and wax should be administered every twelve or twenty-four hours.

In *syphilis* recommendations for treatment with penicillin are tentative, being based on information now available, and are subject to revision if warranted by further experience. Penicillin may be administered alone or in combination with arsenoxide and bismuth. Arsenoxide enhances the therapeutic effect of penicillin and bismuth tends to reduce the incidence of infectious relapse within the first six to twelve months after treatment.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

If penicillin in oil and wax is used in any stage of syphilitic infection, the average daily dose for an adult should be 600,000 units, and the total duration of treatment from eight to fifteen days or longer, depending on the stage of the infection. For early syphilis a minimum total dose of from 4,800,000 to 6,000,000 units is advised.

Since the eventual value of penicillin therapy in syphilis will not be determined for several years, all patients so treated should be carefully followed up and observed frequently.

Address professional correspondence to the respective main office (170 Varick Street, New York 13, N. Y., or Windsor, Ont.) or to the nearest of the following professional service offices:

Atlanta 3	1024 Candler Building
Baltimore 2	1628 O'Sullivan Building
Boston 16	441 Stuart Street
Buffalo 3	14 Lafayette Square
Chicago 1	180 N. Michigan Avenue
Cleveland 15	423 Republic Building
Fort Worth 2	908 Neil P. Anderson Building
Los Angeles 13	408 S. Spring Street
Memphis 3	49 N. Third Street
Minneapolis 2	1800 Rand Tower
New Orleans 12	806 Hibernia Bank Building
Philadelphia 7	626 Widener Building
San Francisco 4	One Eleven Sutter
St. Louis 8	3615 Olive Street
Seattle 4	1002 Second Avenue
Honolulu (T. H.)	1327 Kamaile
San Juan (P. R.)	Calle Fortaleza #352
Manila (P. I.)	670 Dasmariñas
Montreal (Que.)	Dominion Square Building
Kingston, Jamaica (B. W. I.)	141 Harbour Street
Port-of-Spain, Trinidad (B. W. I.)	#1 Chacon

WINTHROP

WINTHROP CHEMICAL COMPANY, INC.

Pharmaceuticals of merit for the physician

NEW YORK 13, N. Y. **WINDSOR, ONT.**

Printed in U.S.A. 6-47 (8417)

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

New...PARENTERAL HIGH-POTENCY VITAMIN THERAPY

*Folbesyn**

VITAMINS

Lederle

The treatment of severe vitamin deficiency in debilitated patients unable to utilize oral medication has long constituted a problem for physicians. The parenteral administration of high-potency vitamins to aged and convalescent patients, as well as to individuals incapacitated by chronic exhausting disease, is now widely accepted therapeutic practice.

THIAMINE (B_1)

This component of the vitamin B complex is used to treat beriberi in all its forms (including cardiac beriberi), polyneuritis of pregnancy, polyneuritis of diabetes, alcoholic neuritis, pellagrous polyneuritis, anorexia of dietary origin, cardiac insufficiency, subcutaneous edema, certain forms of serous effusion, and the vitamin B_1 deficiency caused by excessive metabolism. Surgical patients receiving parenteral dextrose-saline solutions should be given thiamine.

RIBOFLAVIN (B_2)

This B complex factor is useful in the treatment of ariboflavinosis whether alone or associated with pellagra, and manifested by cheilosis, glossitis, seborrheic dermatitis, conjunctivitis, and dysphagia.

*Trade-mark

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

NIACINAMIDE

This member of the vitamin B complex, when used in conjunction with other B vitamins, is specific for the treatment of all the gastrointestinal, mental, and dermal manifestations of pellagra.

PYRIDOXINE (B_6) AND SODIUM PANTOTHENATE

The precise function in man of these vitamin B complex factors has not as yet been determined, but recent evidence has indicated their usefulness in aiding the utilization of other vitamins. Pyridoxine and thiamine have been found to relieve nausea and vomiting of pregnancy in many instances, especially when combined with appropriate diet and sedation.

ASCORBIC ACID (C)

This vitamin is used specifically for the prevention and treatment of scurvy as well as malnutrition resulting in dental caries, pyorrhea, anorexia, and secondary infection. There are also indications that routine administration of vitamin C to aid the healing of wounds is highly desirable. Surgical cases receiving glucose-saline solutions should be given ascorbic acid.

FOLVITE FOLIC ACID

This new B complex factor—first isolated and synthesized by *Lederle*—has recently been shown to be specific for the maturation of red blood cells, and has been found useful for the treatment of such macrocytic anemias as sprue, macrocytic anemia of pregnancy, macrocytic anemia of infants and children, macrocytic anemia of pellagra, and pernicious anemia. A combination of folic acid and liver extract may be superior to either alone in pernicious anemia.

ADMINISTRATION AND DOSAGE

Administration: FOLBESYN Vitamins *Lederle* should be prepared immediately before use. The diluent containing FOLVITE Folic Acid should be withdrawn aseptically from the ampul and injected into the vial containing the dried vitamins. It is essential that 2 cc. of diluent be added to the vial of dried material and that complete solution take place. *The final solution should not be allowed to stand for more than 1 hour since precipitation may take place.* Intravenous or intramuscular routes of administration may be used.

Dosage: 2 cc. daily; or more, in the judgment of the physician, if the depletion is severe.

PACKAGES

Each vial of FOLBESYN Vitamins *Lederle* contains: thiamine HCl (B_1), 10 mg.; riboflavin (B_2), 10 mg.; niacinamide, 50 mg.; pyridoxine HCl (B_6), 5 mg.; sodium pantothenate, 10 mg.; ascorbic acid (C), 75 mg.

Each ampul of FOLBESYN Vitamins Diluent *Lederle* contains: FOLVITE** Folic Acid, 3 mg. This diluent should be used only as a solvent for FOLBESYN Vitamins *Lederle*.

Single dose package contains 1 vial of FOLBESYN Vitamins *Lederle* and 2 cc. ampul of FOLBESYN Vitamins Diluent *Lederle*. Also in multiple package of 25 single dose units.

**Reg. U. S. Pat. Off.

LEDERLE LABORATORIES DIVISION • *American Cyanamid Company* • *New York 20, N. Y.*

4206-190-HL-4/47

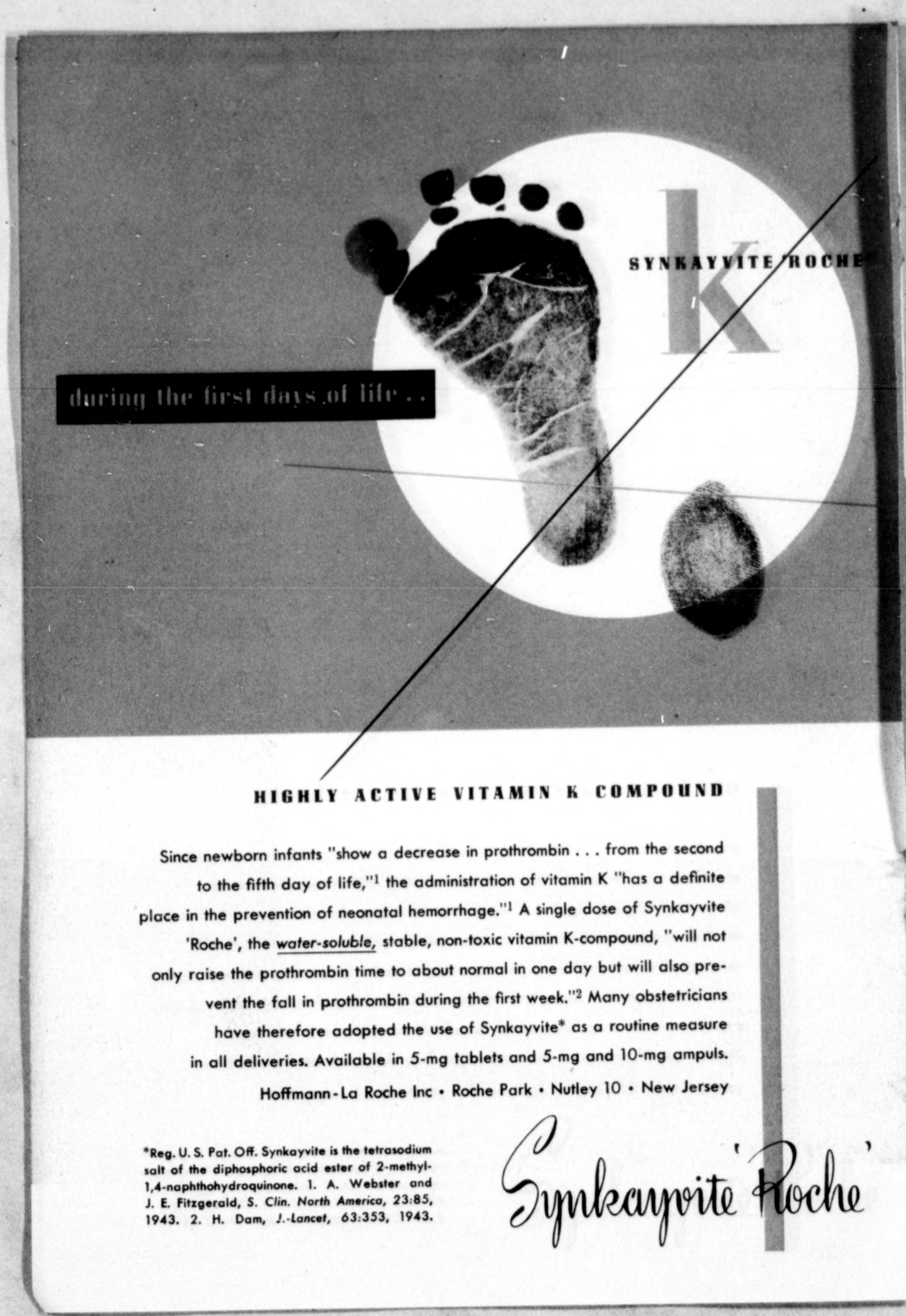
Printed in U.S.A.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

ROCHE REVIEW

PUBLISHED BY HOFFMANN-LA ROCHE INC AND ROCHE-ORGANON INC NOVEMBER, 1947

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013



HIGHLY ACTIVE VITAMIN K COMPOUND

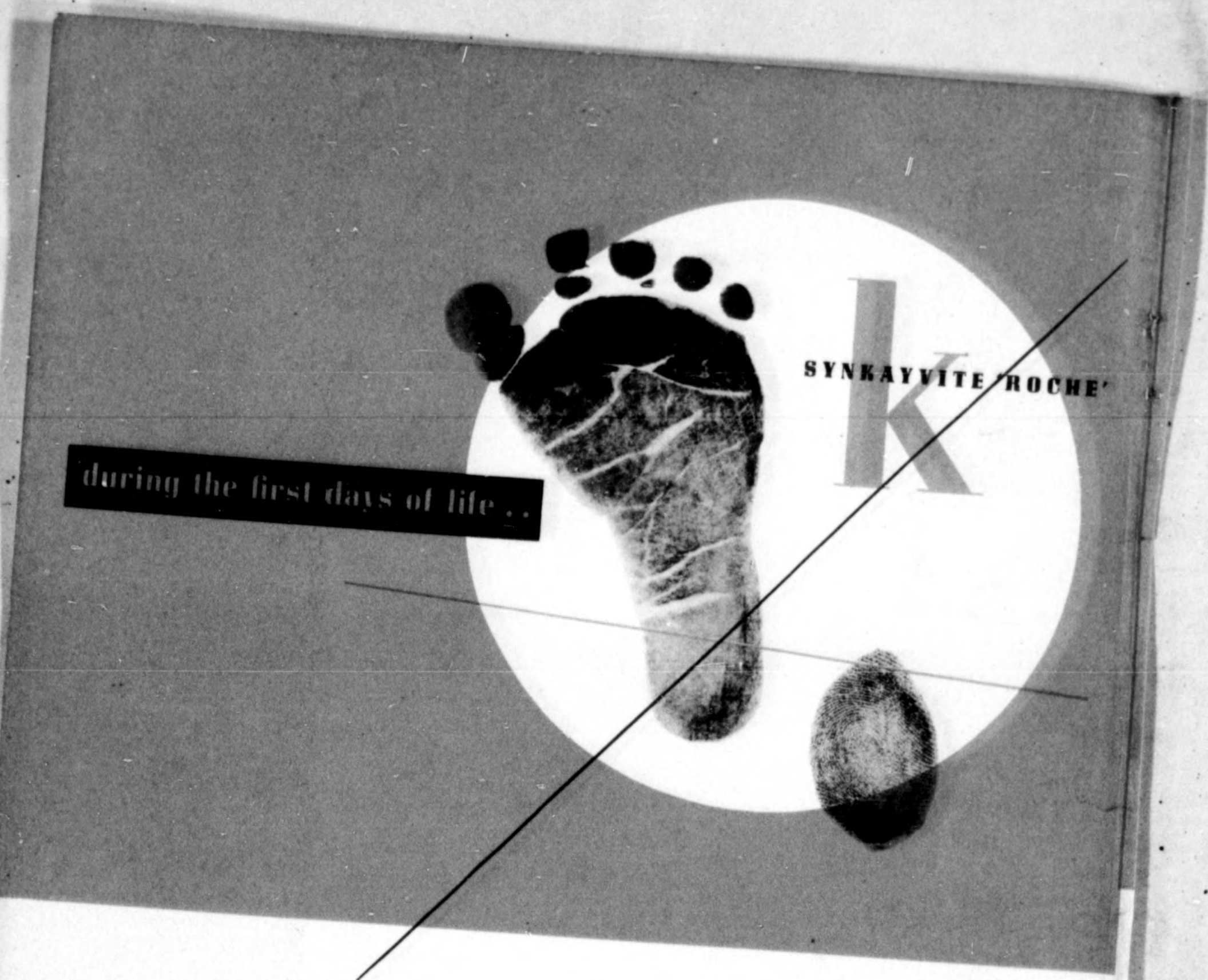
Since newborn infants "show a decrease in prothrombin . . . from the second to the fifth day of life,"[1] the administration of vitamin K "has a definite place in the prevention of neonatal hemorrhage."[1] A single dose of Synkayvite 'Roche', the *water-soluble,* stable, non-toxic vitamin K-compound, "will not only raise the prothrombin time to about normal in one day but will also prevent the fall in prothrombin during the first week."[2] Many obstetricians have therefore adopted the use of Synkayvite* as a routine measure in all deliveries. Available in 5-mg tablets and 5-mg and 10-mg ampuls.

Hoffmann-La Roche Inc • Roche Park • Nutley 10 • New Jersey

*Reg. U. S. Pat. Off. Synkayvite is the tetrasodium salt of the diphosphoric acid ester of 2-methyl-1,4-naphthohydroquinone. 1. A. Webster and J. E. Fitzgerald, *S. Clin. North America,* 23:85, 1943. 2. H. Dam, *J.-Lancet,* 63:353, 1943.

Synkayvite 'Roche'

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013



HIGHLY ACTIVE VITAMIN K COMPOUND

Since newborn infants "show a decrease in prothrombin . . . from the second to the fifth day of life,"[1] the administration of vitamin K "has a definite place in the prevention of neonatal hemorrhage."[1] A single dose of Synkayvite 'Roche', the *water-soluble,* stable, non-toxic vitamin K-compound, "will not only raise the prothrombin time to about normal in one day but will also prevent the fall in prothrombin during the first week."[2] Many obstetricians have therefore adopted the use of Synkayvite* as a routine measure in all deliveries. Available in 5-mg tablets and 5-mg and 10-mg ampuls.

Hoffmann-La Roche Inc • Roche Park • Nutley 10 • New Jersey

*Reg. U. S. Pat. Off. Synkayvite is the tetrasodium salt of the diphosphoric acid ester of 2-methyl-1,4-naphthohydroquinone. 1. A. Webster and J. E. Fitzgerald, *S. Clin. North America*, 23:85, 1943. 2. H. Dam, *J.-Lancet*, 63:353, 1943.

Synkayvite 'Roche'

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

ROCHE REVIEW

Vol. 12 NOVEMBER, 1947 No. 2

Editor: ELMER L. SEVRINGHAUS, M.D.
Associate Editor: J. Gregory, M.S.
Assistant Editor: M. J. Knowlton

General Article

The Visualization of Body Cavities; Rayopake as a Contrast Medium 39

Current Literature

Vitamin Deficiency and Gynecomastia 55
Androgens in Enuresis 55
Vitamin K in Postextraction Hemorrhage 56
Treatment of Amenorrhea 56
Androgens in Endocrine Blood Disorders 57
Ascorbic Acid Metabolism in Adolescents 57
Ascorbic Acid Reserves in Adults 58
Streptomycin Therapy 58
Progesterone in Migraine 58
Oral Penicillin in Acute Infections 59
Prostigmin in Multiple Sclerosis 59
Pyridoxine in Postanesthesia Vomiting 60
Vitamin K in Quinine-Induced Hypoprothrombinemia 60
Feeding of Premature Infants 60
Streptomycin in Tularemia 61
Diet for the Aged 61
Vitamin E in Heart Disease 62

Endocrine Section

Maternal Infections and Mongolism 64
Ossification 67

Features

Leaves from a Doctor's Diary 69
Miscellany 72

The ROCHE REVIEW, issued monthly by Hoffmann-La Roche, Inc. and Roche-Organon, Inc., brings to members of the medical profession authentic information, in quickly assimilable form, concerning therapeutic progress and the application of Roche preparations.

Copyright 1947, Hoffmann-La Roche, Inc.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

PROMPT HEMOGLOBIN BUILD-UP plus... NUTRITIONAL SUPPORT

℞

Cytora 'Roche-Organon' is "a hematinic plus"—a complete medication specially formulated for the prevention and treatment of hypochromic anemia and frequently associated nutritional deficiencies. Each Cytora tablet contains a well-balanced combination of iron, folic acid, liver, vitamin C and five B-complex factors; thus Cytora provides in a single tablet important factors utilized in erythropoiesis plus other dietary essentials so frequently needed by patients with hypochromic anemia and by patients during pregnancy and post-operative convalescence. Cytora is available in bottles of 100, 250, and 1000 tablets. ROCHE-ORGANON INC., Roche Park, Nutley 10, N. J.

CYTORA ·ROCHE-ORGANON·

T.M.—Cytora—Reg. U.S. Pat. Off.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

The Visualization of Body Cavities

Rayopake as a Contrast Medium

THE VISUALIZATION of various body cavities has become an important procedure since the discovery in 1895 of roentgen-rays, capable of penetrating the skin and other barriers to direct visualization. It was soon realized that although roentgenography was successful in showing the bones and certain other structures, some method of making the hollow viscera x-ray opaque must be found. According to Castiglioni[6], Cannon was the first to introduce the use of bismuth in the roentgenologic study of the gastrointestinal tract of animals, and Rieder of Munich (1904) and Beck of New York (1906) applied this method to human beings. Barium sulfate was later substituted for bismuth. The introduction of air into the peritoneal cavity in order to obtain a sharper outline of the digestive organs (Weber, 1915) and into the cerebral ventricles for the diagnosis of cerebral disease (Dandy, 1918) were further steps forward. Graham and Cole (1923) succeeded in visualizing the gall bladder with the use of tetraiodophenolphthalein. Various methods and opaque media have been developed for the roentgenography of the urinary tract (kidneys, ureters, and bladder) and the female genital tract. The latter two systems are those with which this paper is principally concerned.

DEVELOPMENT OF GENITOURINARY TRACT MEDIA

Rubin[17] states that Klose, in 1904, suggested the use of bismuth emulsion for outlining the lumen of the ureter and kidney pelvis, and Rindfleisch, in 1910, attempted to visualize the uterine cavity by injecting a bismuth emulsion into the uterus; although the value of x-ray opaque media in urology was recognized slowly, Voelcker and Von Lichtenberg had obtained satisfactory roentgenograms by injecting the bladder with colloidal silver, and later by using this medium for the visualization of the kidney and ureter. Colloidal silver was first used for visualization of the uterus by Dimier in 1913, and the same medium was used by Cary to determine tubal patency in 1914. Rubin himself independently reported the use of colloidal silver to demonstrate uterine tumors and to determine tubal patency at about the same time.

In 1924, the use of iodized oils was suggested, according to Neustaedter *et al.*[15], and several reports on these media appeared. Because of disadvantages of the iodized oils and other media used, which will be discussed later, attempts were made to develop new media which would accomplish the desired results without the undesirable side effects. Rubin[18] states

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

that "during the last decade, crystalline iodine compounds in aqueous solution have been used and have proven to be non-irritating, as they are tolerated by the blood stream when injected intravenously." However, because of their non-viscid nature, these compounds disappeared into the peritoneal cavity so quickly that roentgenography was difficult. Neustaedter *et al.*[15] attempted to use 50% glucose solution as a thickening agent, Rubin[18] tried stronger solutions, and Titus *et al.* recommended 25% acacia as a vehicle, according to Rubin. These substances proved either irritating or ineffective.

Rubin, however, in experimenting with various thickening substances, found that a 3½% concentration of polyvinyl alcohol added to 70% Rayopake* (diethanolamine salt of 2,4-dioxo-3-iodo-6-methyl tetrahydropyridine acetic acid) produced a substance which met the standards for an ideal opaque medium. This substance was at first known as Visco-Rayopake ('Roche'), but is now called Rayopake; the present formula differs only slightly from the original, containing 4.8% polyvinyl alcohol, 50% diethanolamine salt of 2,4-dioxo-3-iodo-6-methyl tetrahydropyridine acetic acid, and 0.01% benzalkonium chloride as a preservative. The iodine content is approximately 15%.

SPECIFICATIONS FOR AN IDEAL MEDIUM

According to Neustaedter *et al.*[15], the ideal radiopaque mixture "must possess at least five important features: *(1)* have a viscosity similar to that of oil; *(2)* be rapidly absorbed and excreted; *(3)* be non-injurious when entering the circulation; *(4)* render good delineation of the cavities of the pelvic organs; and *(5)* cause no pathologic changes in the tissues."

*Hoffmann-LaRoche Trade Mark, Reg. U. S. Pat. Off.

Rubin[17,18] also stresses the qualities of viscosity and density, radiopacity, rapid resorbability, and freedom from chemical irritation, and has stated that "until a radiopaque substance shall be available having the proper viscosity and density to demonstrate permeable tubal strictures and possessing that degree of resorption which leaves no residue within the tubal lumen after a few hours, thus preventing foreign body reaction, one would do well in instances of sterility to stop using lipiodol and other iodized oils whose chemical composition is more or less the same."

DISADVANTAGES OF PREVIOUS MEDIA

Neustaedter *et al.*[15], in reviewing the development of various opaque media, states that colloidal silver caused considerable irritation and produced roentgen plates which were difficult to interpret; sodium bromide excited severe chemical reactions; bismuth and barium sulfate were poorly absorbed and produced pathologic changes; and iodized oils were also slowly absorbed and caused irritation. Neustaedter *et al.* mention reports by others of peritoneal leukocytic infiltration and fibrin strands; calcification of a retained iodized oil mass in the tube months after injection; abscess formation and peritoneal irritation; oil peritonitis; oil embolism; foreign-body inflammation; and extremely slow absorption sometimes requiring 15 months.

Rubin[17] also mentions that bismuth produced roentgenograms which were difficult to interpret, and that the substance was impossible to remove from the ureters or tubes. Colloidal silver was likely to remain inspissated within the tubes, causing disagreeable sequelae. Sodium bromide and thorium citrate produced

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

pain and irritation. Lipiodol "demonstrated certain undesirable results which were inevitable by reason of its chemical properties" and "when trapped in tight places, such as at tubal strictures and stenoses, it was found to produce foreign body granulomata which resulted in permanent tubal occlusion where some degree of patency had existed before the lipiodol was injected." Since it often collected in pools in the peritoneal cavity instead of spreading thinly over the area available, it was likely to cause encystments, pseudotubercles, and adhesions.

In another paper, Rubin[18] stresses that the iodized oil was sometimes observed in the peritoneal cavity at laparotomy several years after its injection; even if this seemed to cause no ill effects, its presence was not considered desirable, as the shadows cast by it could be confused with ureteral calculus shadows.

Bernstein[1,2] sums up the disadvantages of the various opaque media studied before the development of Rayopake as follows: unsatisfactory opacity, tissue irritation, foreign body reaction caused by retarded absorption, insufficient viscosity, toxicity, and chemical instability. Norment[16] also stresses similar drawbacks.

Titus[20] calls attention to "the frequency of accumulating reports of oil emboli, fatal and otherwise, following the injection of iodized oil for hysterosalpingography." He states that iodized oil should not be used as the opaque medium, and recommends the use of one of the non-lipid, rapidly absorbed media.

Holm-Nielsen[11], in reviewing the recent literature and his own experiences concerning the use of iodized oils in the genital tract, states that the three most frequent complications are: recurrence of old adnexal inflammations, primary adnexal inflammation after salpingography, and diffuse peritonitis resulting from the examination. Injection of oil into the uterine veins is also said to be a hazard.

RAYOPAKE

Toxicity Studies

Rubin[18] states that toxicity studies on Rayopake in polyvinyl alcohol were carried out by Koppanyi, and summarizes the latter's results as follows:

> The acute toxicity of the contrast substance (diethanolamine salt of 2, 4-dioxo-3-iodo-6-methyl tetrahydropyridine acetic acid) and the vehicle (polyvinyl alcohol) were determined by intravenous injections on rabbits and dogs. It was found that doses of 3 gms. per Kgm. weight of the contrast salt were well tolerated and that the average acute fatal dose was 4 gms. per Kgm. of body weight. In determining the acute toxicity of the polyvinyl alcohol, it was found that, due to the extreme viscosity of the material it was impossible to administer more than 2 grams of polyvinyl alcohol per kilogram of body weight (5 per cent solution, 40 cc. per Kgm.). These doses did not prove fatal to either rabbits or dogs.
>
> Chronic toxicity experiments were carried out by daily intraperitoneal injections into dogs, rabbits and rats over a thirty day period. At the end of this time the animals were killed and microscopic sections of the organs were made. The daily dose of the contrast salt varied with the different animals.
>
> The results obtained in these studies do not reveal any outstanding toxic action of these substances on the liver, kidney, spleen, adrenals, pancreas or gastrointestinal tract. The few pathological changes which were observed could not be directly attributed to the substance injected. The kidneys of the albino rats which received large doses of the contrast media for over three weeks is the exception. Mild or severe renal irritation may be observed in this group. On the whole, it may be said that neither the contrast acid nor the polyvinyl alcohol produced, in moderate doses, either acute or chronic toxic effects.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

The compound when instilled for uterosalpingography is used in amounts ranging from 10 to 15 cc. The maximum amount of contrast acid given a patient is 8.25 gm. and the maximum amount of polyvinyl alcohol is 0.525 gm. Assuming that the average patient weighs as little as 50 kilograms, the amount of contrast acid a patient would receive by uterine instillation is 0.16 gms. per Kgm. and of the polyvinyl alcohol 0.01 gm. per Kgm. Recalling that an intravenous injection of 3 gms. per Kgm. of contrast acid and 2 gms. per Kgm. of polyvinyl alcohol is well tolerated, it is safe to conclude that patients tolerate the amount they absorb which is less than one fiftieth the maximum tolerated dose of contrast acid and less than one five-hundredth the tolerated dose of polyvinyl alcohol.

Rubin[19] corroborated these findings in his own studies on rabbits: there were no gross signs of irritation on laparotomy 24 to 72 hours after the medium had been injected into the peritoneal cavity, and none of the rabbits appeared to suffer any ill effects.

After testing the medium on 81 patients, Rubin concluded that "the properties inherent in visco-rayopake give promise of enlarging the scope of hysterosalpingography, enabling us to resort to it for other purposes than the determination of tubal patency. It shares all the advantages of lipiodol and other iodized oils but appears so far to have none of their disadvantages."

Advantages

Goldberger[10] states that Rayopake "is a superior contrast medium for hysterography . . . as it is radiopaque, easily and rapidly absorbed, is nonirritant, and has enough viscosity for properly filling and outlining the uterine cavity."

Bernstein[1] considers that Rayopake "has fulfilled the requisites for an adequate and satisfactory opaque medium for pelvic x-ray. Nontoxic, quickly absorbed, chemically stable and amply viscous, it is easily administered and does not gel or crystallize at room temperatures."

Norment[16], in discussing the requirements for an ideal opaque medium, states that one of the recent preparations which most closely approximates these standards is Rayopake. He stresses the value of hysterosalpingography and states that with the advent of a relatively nontoxic, rapidly absorbed dye such as Rayopake, the procedure becomes more readily adaptable to routine use. He noted no reactions of any type to Rayopake, which was often absorbed from the tissues within 60 minutes. "In our opinion, there is no longer any place for an oily contrast medium in hysterosalpingograms." Norment predicts that hysterosalpingography may become a routine procedure in gynecologic examinations.

Bernstein[2] believes that Rayopake has satisfied the requisites of an ideal opaque medium, and particularly stresses its rapid absorption and excretion. "As observed in the roentgen films, its renal excretion begins quickly. The dye may be observed in the kidneys and ureters within thirty minutes of intrauterine instillation, even while the pelvic shadows are still present. The renal shadows usually persist until the pelvic dye is completely absorbed, but often may disappear before this point. From serial studies of pelvic and renal tract shadow intensity, it may be concluded that the rates of pelvic absorption and renal excretion in the same patient are roughly proportional. These factors, however, may vary in different individuals because variations in peritoneal absorption and renal threshold undoubtedly play an important rôle. The complete disappearance of Visco-rayopake takes place rapidly."

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Montgomery and Lang[14] consider that the rapid absorption of Rayopake from the peritoneal cavity constitutes its most outstanding advantage. In addition, "the density of the shadows cast by Rayopake was highly satisfactory under the fluoroscope and also on the x-ray films. The excellent visualization of the tubes was made possible, of course, by the high viscosity of this fluid medium which causes it to remain in the tubal lumen long enough to permit x-ray films to be made."

Montgomery and Lang state that it is their impression that uterosalpingography has been generally regarded as a more accurate test of tubal patency than the carbon dioxide insufflation test, but that it has not been used as a routine procedure in some clinics because of the drawbacks inherent in the available media. They believe, however, that with such a medium as Rayopake available gynecologists need not hesitate to perform hysterosalpingography in all patients in whom uterotubal insufflation indicates obstruction.

In discussing the indications for and value of cystourethrography in the diagnosis of the cause of enuresis in children, Brodny and Robins[5] recommend the use of Rayopake, which they state is superior to oils and is especially valuable for voiding urethrograms, as it is easily voided in a steady stream and still casts a shadow with sufficient opacity for rapid exposure.

Lespinasse[12] also considers the use of Rayopake "remarkably successful" in visualization of the male urethra. It is stated to be nonirritating to the urethra and bladder mucosa or to the peritoneum; it produces superlative radiopacity; and it is water-soluble so that when it is used no foreign material remains.

Coe and Arthur[7] stress that Rayopake fulfills all the necessary requirements of a good contrast medium for cystourethrography (maximum opacity, minimum irritation, homogeneous nature, and suitable viscosity), in addition to which it need not be removed from the bladder and urethra after instillation, since it is miscible with urine.

Forsythe[8], in discussing the use of urethrograms in the diagnosis of prostatic abscess, states that he has used Rayopake as a contrast medium for this purpose and has been impressed with the excellent visualization of the urethra it affords, and the complete lack of irritation.

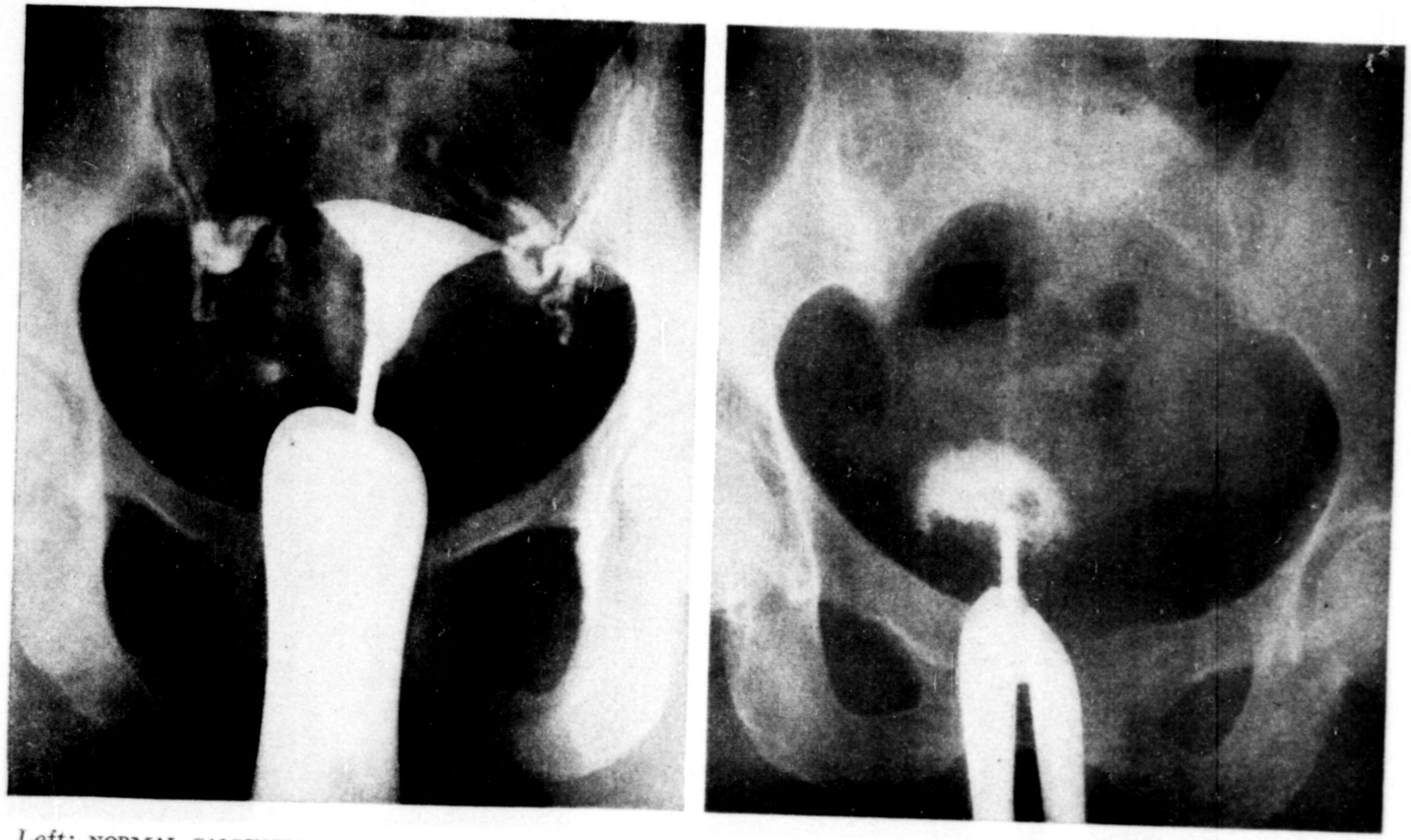
INDICATIONS FOR RADIOPAQUE MEDIA

Gynecologic Conditions

Rubin[17] considers that the principal use of radiopaque substances in gynecology is for demonstrating the outlines of the lumina of the fallopian tubes in order to determine the patency of the tubes in sterility studies. and the outlines of the uterus as a means of diagnosing uterine tumors. These uses were suggested in the work of Dimier (1913), Cary (1914). and Rubin (1914). When lipiodol was introduced as a contrast medium, hysterosalpingography became established as a method of gynecologic diagnosis, according to Rubin. "The primary object of all research in contrast media in gynecology has been from the beginning to arrive at a nonoperative method of establishing the fact of tubal patency or nonpatency in sterile women. A secondary aim was to diagnose the presence or absence of intrauterine tumors, which can as a rule be diagnosed by surgical exploration."

Rubin[18] later reported the use of Rayopake in 81 patients with various

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013



Left: NORMAL SALPINGOGRAM MADE WITH RAYOPAKE, SHOWING "PELVIC SPILL" OF CONTRAST MEDIUM FROM PATENT OSTIA. *Right:* SALPINGOGRAM MADE WITH RAYOPAKE, SHOWING EXTENSIVE CARCINOMA OF CORPUS UTERI; NOTE MOTH-EATEN, IRREGULAR APPEARANCE, IN CONTRAST TO THE NORMAL TRIANGULAR SHAPE OF UTERUS AT LEFT.

We are indebted to Dr. Warren[21] and the editors of the *Western Journal of Surgery, Obstetrics, and Gynecology* for permission to reproduce these figures.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

disorders and had satisfactory results. The conditions involved included sterility, submucous myomata, and checking the patency of the fallopian tubes after plastic operations on the latter.

Warren[21] reports the use of Rayopake in four patients two of whom "are representative of that group of individuals in whom accurate determination of the primary cause of their uterine bleeding is all but impossible from clinical observation alone." Dilatation and curettage are stated to be surgical procedures and as such are sometimes considered too radical for diagnostic use in nonemergency cases and may be dangerous in suspected carcinoma; and vaginal smears at best supply only contributory information, and provide no clue in nonhormonal bleeding. Thus Warren believes that hysterography fills a long-felt need and with the development of water-soluble compounds such as Rayopake, it may be considered in the category of simple, reliable radiographic technics attended by a minimum of risk.

The diagnoses in Warren's cases studied with the aid of Rayopake were adenomyosis uteri (confirmed at operation); endometrial polyp; and extensive carcinoma of the body of the uterus. One patient was studied roentgenographically after having undergone surgery for chronic bilateral salpingitis and chronic appendicitis and a pelvic "spill" of Rayopake from the left tube was seen.

Rubin[19], in discussing the desirability of performing a myomectomy rather than a hysterectomy in patients with uterine fibroids, states that one of the important indications for this is conservation of reproductive and menstrual function for women in the third and fourth decades of life, especially in those who have not borne children. He states that in cases in which carcinoma is even mildly suspected, roentgenography after injection of 2 or 3 cc of an x-ray opaque substance may be performed routinely; this procedure usually makes possible the differentiation between malignant and nonmalignant growths. Lipiodol is also often used to diagnose the presence of submucous fibroids or to study the amount of distortion of the uterine cavity by multiple fibroids, but several precautions must be taken; he therefore believes that the use of soluble Rayopake in fractional doses "is superior to the use of lipiodol, because it leaves no residue after a few minutes." This method is often the means of making an accurate diagnosis when other methods such as study of symptoms, use of uterine sound, and exploratory curettage have failed.

Goldberger[10] discusses the value of hysterography with Rayopake, on the basis of experience with 72 patients. He states:

> With the gradual development of contrast media for hysterography, diagnostic accuracy of intra-uterine lesions was obtained. At the outset, gross anatomic malformations were visualized. Later, filling defects and irregularities in the outline of the uterine cavity were recognized and correlated with the pathologic conditions found at operation. We can now depend on the hysterogram, in most cases, to such a degree as to influence and determine the procedure to be used in the cure of the patient. At the same time, the clinical interpretation of the gynecologic signs and symptoms must be carefully evaluated.
>
> Hysterography is indicated in cases where the history and physical findings do not reveal, but lead one to suspect the presence of an intrauterine pathologic lesion, such as an endometrial polyp, submucous fibromyoma, other intrauterine growths and malformations of the uterus. Hysterography is also of value in determining the nature and extent of a surgical procedure when intra- or extra-uterine tumors are present.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

In his group of patients, 22 complained of menorrhagia, and of these, 4 were shown to have submucous fibroids, 4 endometrial polyps, 1 adenomyosis, and 1 fundal carcinoma; in 11 there were no abnormal findings on hysterography. In another group of 12 patients with metrorrhagia, hysterograms showed no filling defects. Out of a group of 15 complaining of menometrorrhagia, there were 4 positive hysterograms (two showed submucous fibroids, one multiple fibroids, and one endometrial polyp); in 11 no gross pathologic changes were seen. In 8 cases of dysmenorrhea for which no cause or successful method of therapy had been found, hysterography showed submucous fibroids in 5 and polyps in 2 (one of these had polyps in each horn of a bicornuate uterus). In 8 cases of sterility, in which hysterosalpingography was performed, after tubal insufflation by the Rubin method (CO_2) had shown closed or diseased tubes, the opaque medium was useful in showing the site of occlusion and in demonstrating submucous fibromyomata in one. In 7 other patients with various gynecologic complaints, hysterography was helpful in locating unsuspected lesions and determining the types of treatment to be given.

"The conclusions that can be drawn from an analysis of these cases emphasize the value of hysterography in patients where the history, the clinical picture or the bimanual examination do not give sufficient evidence as to the exact diagnosis or indicate the method and extent of the curative procedure."

Bernstein[1] believes that visualization of the female genitalia is a practical and innocuous procedure by which a more accurate picture of numerous pelvic conditions can be obtained, and that with the use of Rayopake the simplicity and clinical safety of hysterosalpingography warrant its adoption for routine office and hospital use. On the basis of his experience in a series of 52 patients, he states:

> Many pathologic growths of the female generative tract were clearly defined by this method and, in many cases, unsuspected lesions were revealed. The alteration in size and contour of the uterine shadow indicates not only the extent and location of new growths, but also identifies the type of tumor by means of characteristic and representative patterns. Since the length, course, and patency of the Fallopian tube, as well as the presence of new growths, can be determined by x-ray, problems of sterility lend themselves particularly to its use. When employed with tubal insufflation as described by Rubin, complete knowledge as to both structure and function of the tube is obtained. In certain instances, tenuous peritubal adhesions causing obstruction to ovular migration, may undergo lysis following passage of the viscous radiopaque fluid. Salpingography served not only to differentiate between intrapelvic masses, but also between abdominal tumors and those of pelvic origin. In my experience this test has often been a guide to correct operative procedure and surgical conservatism.

Of the 52 patients, 38 were x-rayed routinely in the course of sterility studies after insufflation by the Rubin technic. Anomalies discovered included: infantile uterus (2); bicornuate uterus (2); ovarian cyst (2); dilatation and partial obstruction of the tubes (8); and bilateral closure of the tubes (11). In 27 patients tubal patency (one or both tubes) was found. Interestingly, 3 of the patients with bilateral tubal closure were found to be pregnant when the x-rays were made; Bernstein attributes the closure to uterotubal contraction or spasm which may be physiologic during pregnancy.

In the 14 patients who were not undergoing sterility studies, hyster-

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

ography was used to confirm findings made by pelvic examinations: these findings included 6 fibroids, 4 ovarian tumors, 2 hydrosalpinx, 1 uterine polyp, and 1 multiple carcinoma of the uterus and tube; menometrorrhagia had been the chief complaint in all cases.

Norment[16] states that the diagnosis of persistent uterine bleeding on the basis of cause presents a challenge to the physician, as it is often very difficult to determine whether bleeding is endocrine or mechanical in origin. It is sometimes easier to make a diagnosis of endocrine dysfunction than to determine the presence of a polyp or submucosal myoma, as simple endometrial curettage is often not reliable in ascertaining the presence or absence of these tumors. Two available methods of diagnosing these more accurately are, according to Norment, direct vision and injection of a radiopaque substance into the uterine canal. The disadvantage of the first method is stated to be that only one or two persons can observe the interior of the organ and nothing in the nature of a permanent record of the lesion can be made. Thus the use of a radiopaque substance and roentgenography is considered far more practicable.

Norment reports the use of Rayopake in the study of 20 patients; the medium outlined the parts with clarity and sharp demarcation. Examples of the conditions observed included: tubal obstruction in a woman complaining of severe dysmenorrhea and pain and tenderness in the left lower quadrant; tubal patency in a woman suspected of infertility; negative findings in a woman with menometrorrhagia suspected of having a uterine polyp, who later improved greatly on thyroid medication; uterine submucous fibroids in a woman with a low metabolic rate whose menometrorrhagia proved to be caused primarily by the thyroid disturbance; and ovarian cyst in a woman complaining of lower abdominal pain, tenderness, and dysmenorrhea.

Bernstein[2] also stresses the difficulties often encountered in the diagnosis and localization of various pathologic conditions of the female generative tract and the desirability of having an accurate method of diagnosis which will facilitate choice of surgical technic or conservative measures and enable specific preoperative measures to be taken when such are indicated.

"It would seem that the Fallopian tube, because of its unique anatomic setting and possibilities for x-ray visualization, could serve as a graphic index of changes occurring in adjacent structures. Thus, salpingography, supplemented, when desired, by stereoscopic studies, has proven to be a valuable aid in the visualization of adnexal masses, and warrants more widespread use. This simple x-ray test has proven safe, rapid, and inexpensive."

Bernstein's examples of the type of case in which salpingography with Rayopake provided valuable information include: tubal and uterine carcinoma (confirmed at operation) in an obese, hypertensive patient with coronary insufficiency, in which case, salpingography made possible adequate surgical preparation of a poor-risk patient; ovarian cyst in a patient complaining of abdominal pain and dysmenorrhea; bilateral tubal disease and left hydrosalpinx in a patient with headache, dyspnea, weakness, shortened menstrual cycle, dysmenorrhea, and bowel disturbances; and ovarian cyst in a patient whose condition had been previously diagnosed as fibroids of the uterus.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Marshak[13] has reported the successful use of Rayopake in the diagnosis of suspected ectopic pregnancy with a negative Friedman test and other findings which had led to postponement of laparotomy. He suggests that "further cases should be studied to determine the desirability of doing uterosalpingograms more routinely in suspected ectopic pregnancies."

Montgomery and Lang[14] used Rayopake in 79 patients to determine the patency or nonpatency of the fallopian tubes. The tubes were found to be closed in 54 (24 of whom had been sterilized by tubal ligation) and patent in 25. In 27 patients the tubes were shown by the Rubin CO_2 insufflation test to be completely closed, whereas use of the opaque medium demonstrated bilateral patency in 10 of these and unilateral patency in 4.

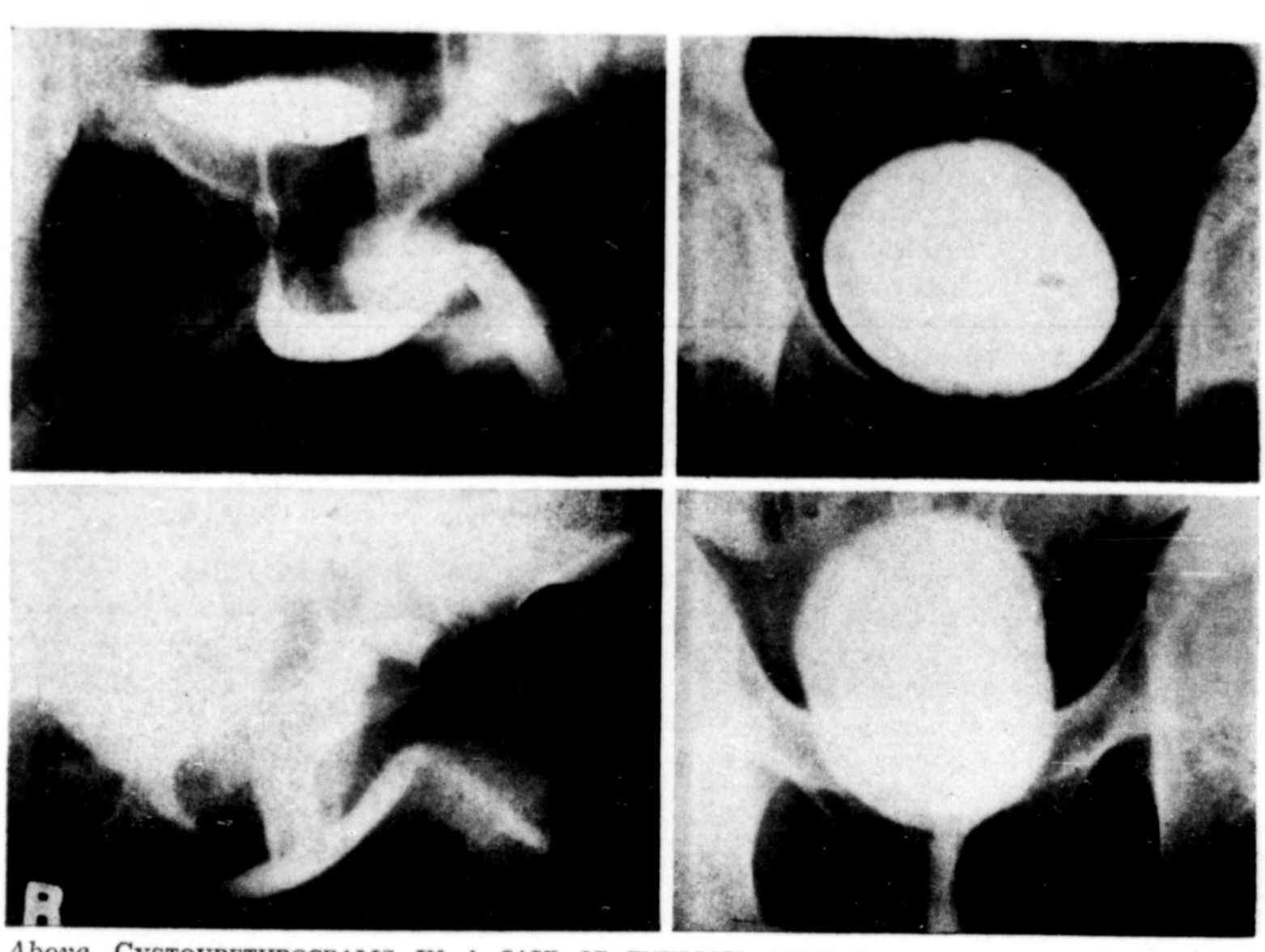
Wexler[22] has reported the use of Rayopake in determining the causes of uterine bleeding in four patients. One, in whom gynecologic examination had shown a "polyp," which was removed, was found, on hysterography, to have carcinoma of the cervix invading the uterus; one patient, in whom gynecologic examination had shown no positive finding because of obesity, was shown on hysterography (and subsequent operation) to have two fibroids; one woman with abnormal bleeding proved at hysterography to have several polyps; and in another woman with abnormal bleeding hysterography showed a hypertrophic endometrium, confirmed by therapeutic curettage. Wexler stresses the importance of the hysterogram in showing the absence of pathologic changes as well as their presence. In a series of 32 cases of uterine bleeding, 8 showed no demonstrable pathologic condition, 7 had submucous fibroids, 11 had polyps, and 5 had hypertrophic endometritis.

Urologic Conditions

Brodny and Robins[4] state that the rôle of the bulbo-urethral glands in gonococcic infection is not generally appreciated, probably because the diagnosis of bulbo-urethral adenitis is usually difficult. They therefore suggest urethrography (the roentgenologic visualization of the urethral canal with the aid of a contrast medium) "as a relatively simple procedure, that is valuable in the diagnosis and follow-up of bulbo-urethral adenitis, and that may add definite information to our knowledge of these glands if carried out in a large group of cases." They report a case of gonococcic infection of a bulbo-urethral gland, studied by urethrography for more than 4 years.

In a second paper, Brodny and Robins[5] evaluate cystourethrography as a method of investigating organic urologic disorders as causes of enuresis. Continence is stated to depend on four factors: an intelligence quotient adequate to appreciate the desirability of controlling the time and place of voiding; proper habit training; freedom from neurotic complaints and adequate emotional age; and a normal voiding mechanism. The latter factor is more important than is usually realized; one investigator found uropathy in 60% of 532 enuretic patients. Brodny and Robins believe that cystourethroscopy and endoscopy for the purpose of ruling out organic factors are complicated and have many disadvantages, but that cystourethrography is "unhampered by these difficulties and is adequate for the routine investigation of enuretic patients. This is a simple office or dispensary procedure which can be carried out without a general anesthetic. It is safe and relatively free from reaction. The size, shape, position, and abnormalities of the

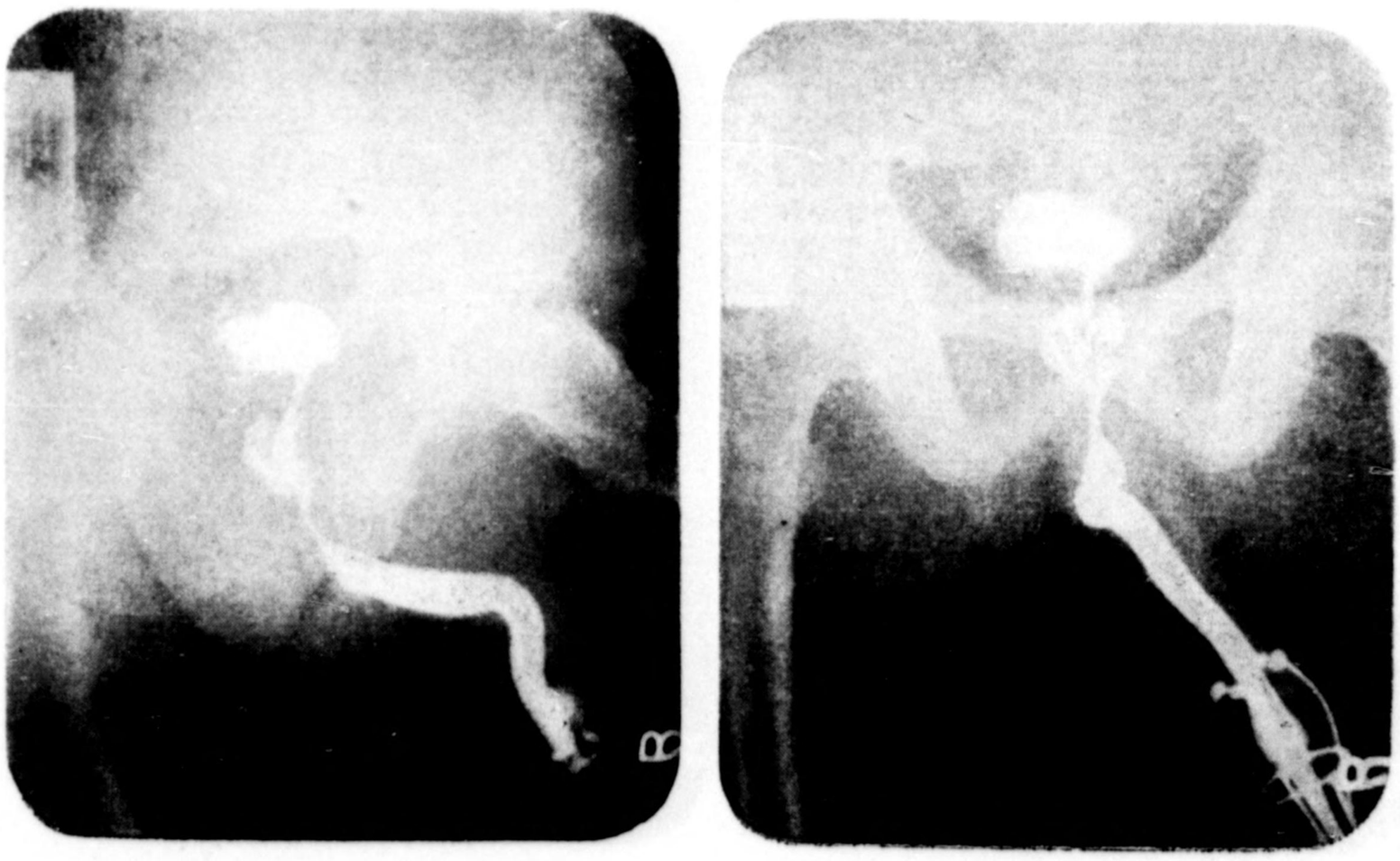
DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013



Above, CYSTOURETHROGRAMS IN A CASE OF ENURESIS, MADE WITH RAYOPAKE: *upper left,* RETROGRADE URETHROGRAM, oblique view; *upper right,* CYSTOGRAM; *lower left,* VOIDING CYSTOURETHROGRAM, oblique view; *lower right,* VOIDING CYSTOURETHROGRAM, anteroposterior view.

Below, CYSTOURETHROGRAMS SHOWING PROSTATIC CAVERNS OR DIVERTICULI.

We are indebted to Dr. Brodny for the loan of, and permission to reproduce, these figures; we are also indebted to the Editor of the Journal of the American Medical Association for permission to reproduce the above figures.



DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

bladder and urethra are accurately visualized, and progression or retrogression of lesions can be observed and compared." Brodny and Robins have used Rayopake in more than 125 examinations, with excellent visualization of the bladder and urethra. Some of the abnormalities often found include: dilated bladder (atonicity, caused by decompensation of the bladder musculature secondary to urethral obstruction or defective nervous conduction); diminished bladder capacity (hypertonicity, resulting from vesical and urethral inflammation or parasympathetic imbalance); deformities of the bladder (because of vesical neck obstruction or prostatic hypertrophy); ureteral reflux; urethral obstruction; stenosis of the glandular urethra; local congenital malformations; infections, causing compression and narrowing of the posterior urethra, enlargement of the verumontanum, and elevation of the bladder base; and neuromuscular dysfunction, causing spasticity or atonicity of the sphincters.

Forsythe[8] states that roentgenologic study has been found to be a valuable adjuvant in the diagnosis of prostatic abscess, which if undiagnosed may become very serious. Occasionally the procedure will also enable the differential diagnosis between abscess and carcinoma. He states that in the normal person "the oblique aerogram shows the catheter in the urethra entering the bladder neck straight. There is no soft-tissue shadow intruding into the bladder at the vesical outlet. The urethrogram shows a prostatic urethra measuring about 3 to 4 cm. in length. As the urethra is distended during the exposure, its walls will be apart. The internal and external sphincters are localized as points of slight narrowing. Often the verumontanum is seen as a rounded area of slightly decreased density near the external sphincter."

In cases of prostatic abscess, on the other hand, "the posterior urethra is found to be elongated and definitely narrowed. These changes often give a very rigid appearance to this portion of the canal. The mid-portion of the posterior urethra is frequently deflected anteriorly while, at the same time, there is posterior deflection of the urethra at the vesical outlet. In exaggerated cases the posterior urethra may show an S-shaped deformity. This we interpret as the urethra distorted by the pressure of the abscess within the prostate."

In another paper, Forsythe[9] discusses the value of cystourethrography in facilitating an accurate diagnosis of various types of prostatic disease. Other measures, such as rectal examination, residual urine determinations, and cystoscopy and urethroscopy are either undependable or are difficult and hard on the patient. Cystourethrography, however, offers less risk and less discomfort to the patient, and often provides more information than can be obtained by cystoscopy. Forsythe states that he has used Rayopake as a contrast medium in several hundred cases in which it was necessary to perform cystourethrography, and found it to be a very satisfactory medium producing no untoward reactions.

In simple bilateral prostatic enlargement, a definite soft-tissue shadow can be seen on the floor of the vesical outlet, or the bladder floor may appear elevated; elongation and lateral spread of the prostatic urethra can be seen. In middle-lobe enlargement, there is a broad soft-tissue shadow at the vesical outlet and the catheter is deflected anteriorly; the urethra appears only slightly elongated, but deflected anteriorly. In bi-

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

lateral and commissural enlargement there is a "horse-collar" type of intravesical intrusion, and the urethra is both elongated and deflected anteriorly. In subcervical enlargement the catheter may show a definite anterior deflection and the soft-tissue shadow is variable in size and has a slender base. In bilateral and subcervical enlargement there is a "trilobar" intravesical intrusion, the catheter is deflected anteriorly, and there is elongation and lateral spread of the posterior urethra. All of these deformities are accompanied by filling defects at the vesical orifice. When a median bar is present, the urethrogram shows a shortened posterior urethra with a prominent verumontanum and anterior deflection at the vesical orifice; no filling defect is seen at the outlet. Carcinoma is difficult to differentiate from posterior urethral stricture; prostatic calculi are usually easily seen; prostatic abscess has been discussed; and strictures and signs of neurogenic bladder are well defined.

Lespinasse[12] also discusses the advantages of a viscous medium such as Rayopake for urethrography in the male; he prefers the use of this substance to the use of rigid objects such as sounds or cystoscopes, because of the complicated structure and curvature of the urethra. He describes cystourethrographic findings similar to those of Forsythe in various prostatic disorders.

Coe and Arthur[7] state that they have been using cystourethrography as an aid in the diagnosis of lesions of the bladder, prostate, and urethra over a period of 10 years; Rayopake has been used as the contrast medium since 1939. They also describe the abnormalities seen by cystourethrography in various disorders, and conclude: "Cystourethrography when carefully executed and properly interpreted has added so much to the diagnosis and appraisal of methods of treatment that there is a growing demand for its use."

TECHNICS

Hysterosalpingography

Rubin[17] states that there are two methods of filling the uterus with opaque media: (*1*) immediate and full distention; (*2*) fractional filling. These may be done with or without fluoroscopic control. Fractional filling is stated to be especially designed to study defects in the uterine cavity, different rates of filling of the tubes, and uterine and tubal contractions. The injection is made by syringe with or without manometer or kymograph and manometer. The uterus should not be overdistended because this may wipe out the contrast otherwise given by the tumor. Rubin states that in general the amount of contrast medium injected determines to what extent the shadow outlines of the uterus and tubes are seen. Mistakes in interpretation of tubal patency are often caused by incomplete filling.

> In order to visualize the cervical canal the uterine cannula is inserted so that its tip does not exceed one-half to one cm. above the external os. To prevent leakage very tight obturation must be effected. However, the cervical canal may be demonstrable even though the tip of the uterine cannula is within the uterine cavity. Increased pressure will force the opaque fluid back into the cervical canal and distend it. This picture is obtained as a rule when the tubes are obstructed. To demonstrate tubal patency the uterine cannula passes beyond the internal os and frequently it is not necessary to grasp the anterior or posterior lip with bullet forceps to secure water tightness.

Bernstein[1] gives the following specific description of hysterosalpingography with Rayopake; this conforms very closely to the technic used by most investigators.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

The patient is given two drams of licorice powder the night before and an enema on the morning of the test. The patient is placed on a Squier genito-urinary x-ray table in lithotomy position, and a bimanual examination is performed to determine the cervico-uterine angle (for direction of canal) and the fundal size (for estimation of its capacity).

Aseptic technique is observed. The vulva and vagina are thoroughly cleansed with soap and water and the patient is draped with sterile towels.

The cervix, visualized through a non-opaque, bivalved speculum, is wiped dry and the external os is painted with tincture of iodine. A tenaculum forceps may be applied, but I found no advantage in this painful procedure, except in cases requiring traction for better cervical exposure, or, for a stenotic cervix resisting insertion of the cannula, or, where pressure against the cannula guard was necessary to prevent leakage.

A 20 c.c. syringe, containing 15 c.c. of viscorayopake, is fitted by means of a Luer metal tip to a uterine stem cannula with perforated end (as used in the Rubin insufflation test), or, when desirable, to a Colvin cervical stainless steel screw-tip cannula. The latter eliminates the danger of uterine perforation and, in some cases, has been found satisfactory in preventing backflow. Upward pressure of the syringe piston displaces air from the syringe and its contained opaque fluid. If the medium injected into the uterine cavity contains air bubbles, errors in diagnosis are prone to occur. The cannula is then cautiously inserted through the external os, following the line of the cervico-uterine axis, until the perforated tip lies within the cavity. If the Colvin device is used, the screw-tip is rotated until it becomes firmly fixed in the cervical canal. Excessive traction, or upward pressure on the cervix may cause uterine displacement producing shadow overlapping of the cavity outline. It is therefore advisable, before x-rays are taken, to replace the fundus so that it lies in a plane somewhat paralled to the x-ray plate.

With the cannula held in the cervix, the patient is moved into proper position under guidance of the x-ray technician, so that the x-ray tube and plate are in proper alignment with the pelvis. I have used, ordinarily, for a 20-centimeter body thickness, 50 milliamperes and 58 primary volts for a two-second exposure with the focal plate distance between thirty and thirty-six inches.

A flat plate or scout film is first taken. This often reveals calcified lymph nodes, phleboliths, or unabsorbed lipiodol used in previous tests, and is of value in excluding misleading shadows. Two c.c. of radiopaque fluid are then injected very slowly, and a second plate is taken. By delivering the viscous medium into the uterine cavity very gradually, with light or moderate pressure, the patient is spared unnecessary pain. Two c.c. injections are repeated until 6 or 8 c.c. of viscorayopake and four or five x-ray films have been used. At this point, the fluid contents of the uterine cavity may be removed by withdrawing the piston.

Montgomery and Lang[14] have found that 3 or 4 cc of Rayopake are sufficient to fill the uterine cavity, but that if the tubes are patent 10 to 15 cc must be injected. They used fluoroscopic control.

Warren[21] uses a tenaculum to grasp the lip of the cervix and exert traction downward and anteriorly. He finds that 1 or 2 cc of Rayopake usually suffice to fill the uterine cavity, while 10 to 15 cc are needed for radiographic study of the tubes.

In making hysterograms, Goldberger[10] uses, for the average patient, a distance of 30 centimeters from the source of irradiation, with 60 milliamperes, 115 primary volts, and 3 seconds exposure; these factors differ somewhat from those given by Bernstein. He gives two injections of 2 cc of Rayopake, making an x-ray exposure after each injection; these amounts and number of exposures may be varied in large uteri or when tubal visualization is also desired.

Cystourethrography

Coe and Arthur[7] give the following description of the technic for cystourethrography with Rayopake; the

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

only equipment needed, according to these authors, is a 30-cc syringe with 5 cm of soft rubber catheter firmly attached to the tip as an adapter.

A plain roentgenogram of the abdomen is taken first. The bladder is emptied of urine. The patient is placed in the right anterior oblique position; *i.e.*, with the left hip slightly elevated by use of a sandbag under the left hip. The right thigh is flexed and the left extended. The tube is centered directly over the symphysis pubis and a technique making use of the Potter-Bucky diaphragm is employed. The operator then inserts the soft rubber catheter adapter into the urethra with the right hand, forcibly extends the penis with the left hand, and at the same time exerts considerable pressure about the adapter to prevent the dye from regurgitating. Twenty cubic centimeters of the dye is slowly but steadily injected, the operator's hands protected with ⅛ inch of lead plate and the first exposure of a stereo pair is made. It is important to keep constant pressure on the plunger of the syringe at all times. While the plate is being changed the remaining 10 cc. is injected and the second exposure made. The antero-posterior roentgenogram is made by immediately placing the patient in the supine position and continuing the pressure on the plunger of the syringe. It is not necessary to mechanically remove the dye.

Lespinasse[12] has devised a special tip which obturates the urethral meatus and allows enough pressure to be produced to force the sphincter. This device has an intraurethral portion about 2 cm long, rounded at the distal end; it has no opening at the end, but has four openings, one on each side, about 1 cm from the end. Behind these is an olive-shaped enlargement. The tip is fitted with a Luer syringe socket.

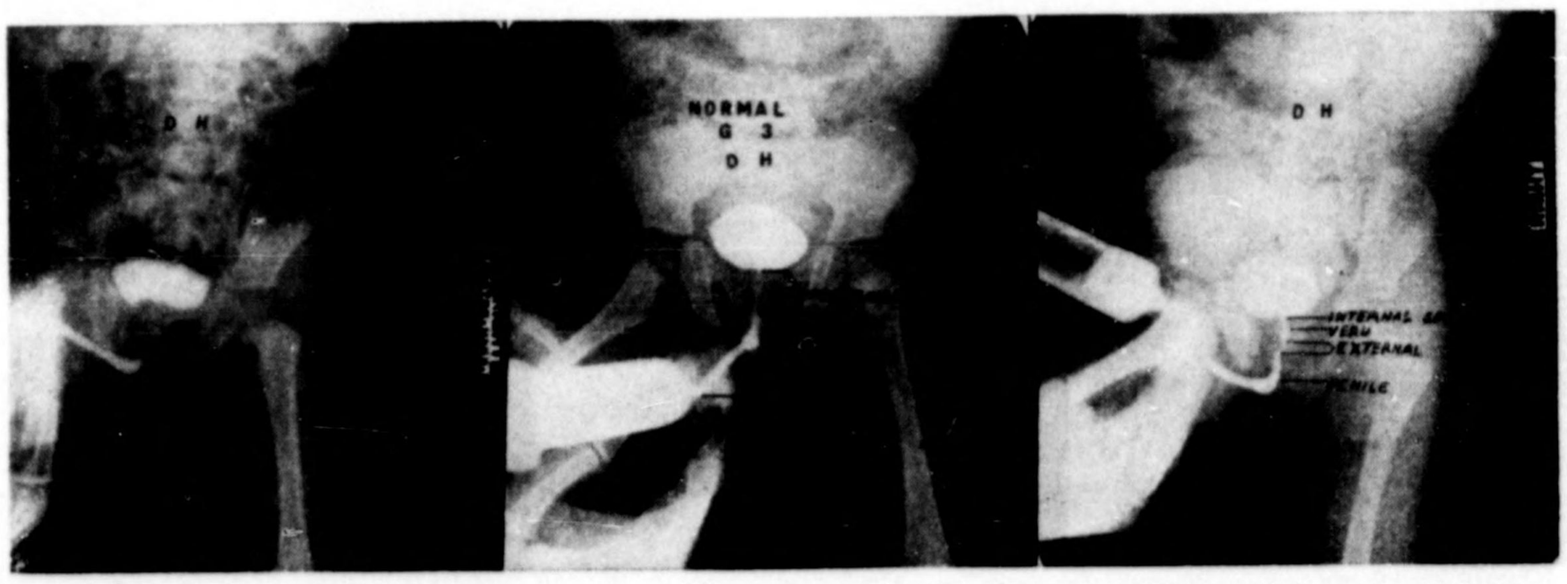
Brodny[3] has also reported an especially designed urethrographic instrument intended to eliminate the disadvantages inherent in the operator's holding the glans (exposure to x-ray; difficulty in retaining grasp on glans; and strain on operator to hold the syringe in place until the films have been developed and results checked). This instrument enables the glans to be held firmly and the meatus completely obturated during the injection.

CONTRAINDICATIONS

Hysterosalpingography

There are a few contraindications to hysterosalpingography which most investigators observe, although the procedure has been carried out, either by accident or intent, in a few cases in which it would ordinarily be contraindicated.

Goldberger[10] lists pregnancy, active uterine bleeding, gonorrhea, and other



NORMAL CYSTOURETHROGRAMS MADE WITH RAYOPAKE; showing bladder and urethra clearly outlined, and positions of posterior and anterior urethra, internal and external sphincters, and the verumontanum. (*We are indebted to Dr. Brodny and the editor of the Journal of the American Medical Association for permission to reproduce these figures.*)

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

infections of the genitourinary tract as the principal contraindications. Bernstein[2] states that moderate uterine bleeding is not strictly a contraindication to salpingography but that it is wise to defer the test until active bleeding (either menses or abnormal bleeding) has subsided. He also prefers to postpone the test during the interval phase of ovulation, the 6-month period post partum, and for 30 days after surgical procedures. He considers absolute contraindications to be acute pelvic infections, acute endocervicitis, gonorrhea, intrauterine or ectopic pregnancy, and cervical carcinoma. Epilepsy, petit mal, hysteria, and psychoneurosis are listed as conditions which may be unfavorable or hazardous for the test.

Cystourethrography

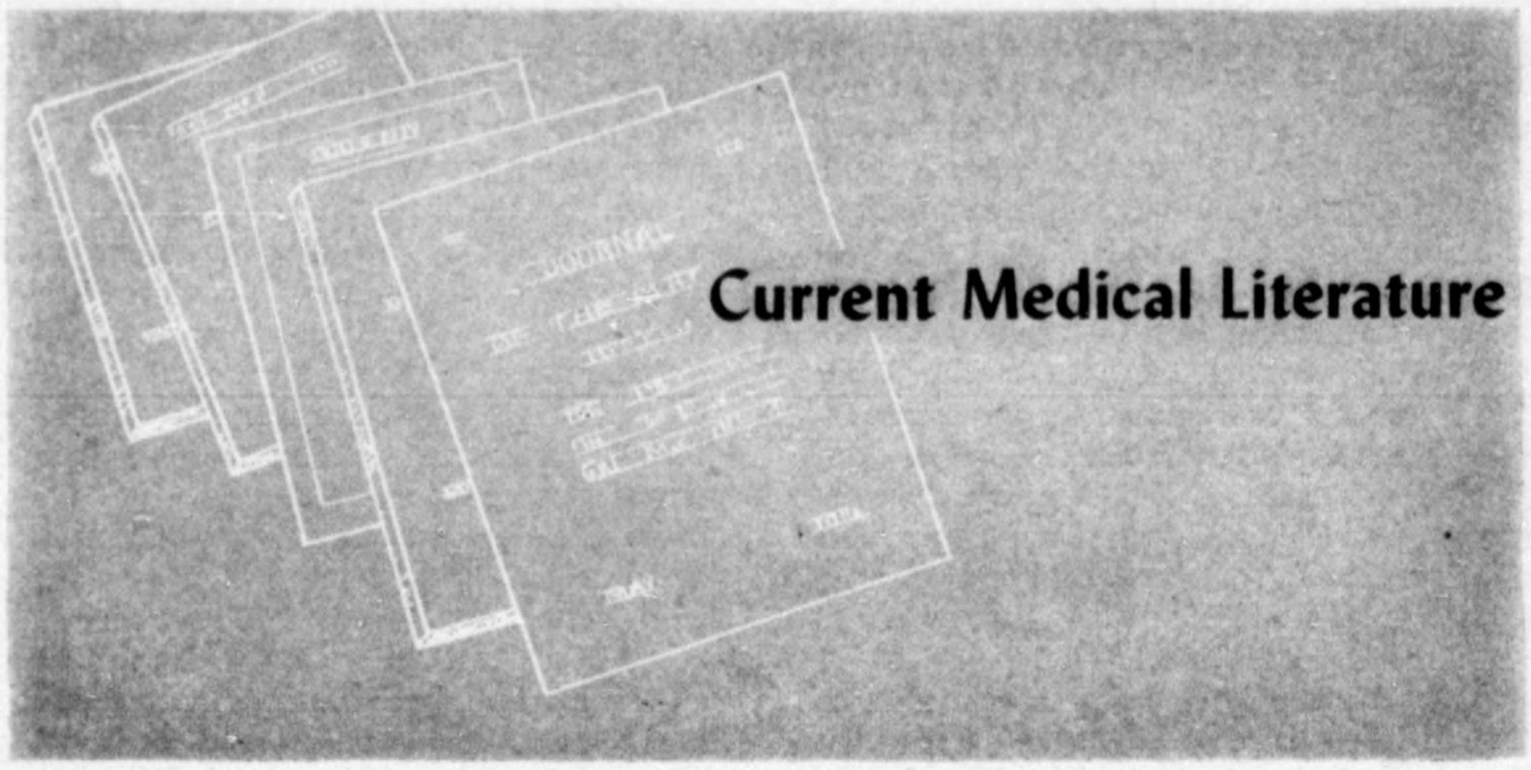
In discussing the use of urethrography in bulbo-urethral adenitis, Brodny and Robins[4] state that they do not recommend the procedure in the presence of acute or subacute urethritis since there is a danger of posterior urethral infection and complications. It is safe, however, in the chronic stage.

Rayopake is not recommended for retrograde pyelography or intravenous injection because of its high viscosity. It is not for use intraspinally, intracisternally, or within the cerebral ventricles.

REFERENCES

1. BERNSTEIN, P.: Hysterosalpingography, a routine aid in gynecological diagnosis, *Am. J. Obst. & Gynec.*, *48*:189, 1944.
2. BERNSTEIN, P.: Value of salpingography in surgical diagnosis, *Am. J. Surg.*, *70*:164, 1945.
3. BRODNY, M. L.: A new instrument for urethrography in the male, *J. Urol.*, *46*:350, 1941.
4. BRODNY, M. L., AND S. A. ROBINS: Urethrography in bulbo-urethral adenitis, *J. Urol.*, *43*:844, 1940.
5. BRODNY, M. L., AND S. A. ROBINS: Enuresis; the use of cystourethrography in diagnosis, *J. A. M. A.*, *126*:1000, 1944.
6. CASTIGLIONI, A.: A History of Medicine. Knopf, New York, 1941.
7. COE, F. O., AND P. S. ARTHUR: A new medium for cystourethrography, *Am. J. Roentgenol.*, *56*:361, 1946.
8. FORSYTHE, W. E.: Prostatic abscess with particular reference to the use of the urethrogram in diagnosis, *Urol. & Cutan. Rev.*, *46*:613, 1942.
9. FORSYTHE, W. E.: The cystourethrographic diagnosis of prostatic disease, *Urol. & Cutan. Rev.*, *47*:669, 1943.
10. GOLDBERGER, M. A.: The clinical evaluation of hysterography, *J. Mt. Sinai Hosp.*, *10*:241, 1943.
11. HOLM-NIELSEN, P.: Injuries caused by hysterosalpingography, *Acta obst. gyn. scand.*, *26*:565, 1946 (Abstr., *Internat. Abstr. Surg.*, 85:47, 1947).
12. LESPINASSE, V. D.: Urethrograms of the male urethra, *Quart. Bull., Northwest. Univ. M. School*, *19*:298, 1945.
13. MARSHAK, R. H.: The radiologic diagnosis of ectopic pregnancy, *New York State J. Med.*, *46*:317, 1946.
14. MONTGOMERY, J. B., AND W. LANG: Evaluation of a new contrast medium for hysterosalpingography, *Am. J. Obst. & Gynec.*, *51*:702, 1946.
15. NEUSTAEDTER, T., *et al.*: A new contrast medium for use in uterosalpingography; preliminary report, *Radiology*, *21*:568, 1933.
16. NORMENT, W. B.: The use of a new contrast medium (Visco-Rayopake) in the female generative tract, *Am. J. Obst. & Gynec.*, *49*:253, 1945.
17. RUBIN, I. C.: Use of soluble x-ray opaque media in gynecology, *M. Rec.*, *152*:212, 1940.
18. RUBIN, I. C.: A new soluble viscous contrast medium for hysterosalpingography, *J. Mt. Sinai Hosp.*, *7*:479, 1941.
19. RUBIN, I. C.: Progress in myomectomy; surgical measures and diagnostic aids favoring lower morbidity and mortality, *Am. J. Obst. & Gynec.*, *44*:196, 1942.
20. TITUS, P.: Oil embolism from hysterosalpingography, *Am. J. Obst. & Gynec.*, *53*:1067, 1947.
21. WARREN, J.: Hysterosalpingography with Visco-Rayopake; preliminary report, *West. J. Surg.*, *54*:294, 1946.
22. WEXLER, D. J.: The hysterogram in uterine bleeding, *News Letter, Suffolk County M. Soc.*, *24*:80, 1946.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013



VITAMIN DEFICIENCY AND GYNECOMASTIA

R. E. HIBBS (Cleveland Clinic, Cleveland, Ohio): *Am. J. M. Sc., 213*:176, February, 1947, presents a report on the appearance of gynecomastia associated with vitamin deficiency in men who were held prisoner by the Japanese during the war; about 10% of the 5000 inmates of the camp reported breast enlargement. Almost all of the men who were in the camp had suffered from malaria, dysentery, nutritional edema, pellagra, ariboflavinosis, beriberi, peripheral neuritis, scurvy, xerophthalmia, and corneal ulceration, in approximately that order, during the first 9 months of their imprisonment.

The first cases of gynecomastia were seen almost a year after the appearance of any new deficiency disease, during a period when the diet had greatly improved, allowing most of the men to gain 10 to 50 pounds during the months just before the onset of gynecomastia. A small tumor was palpable under both nipples, making the breast size comparable to that of an adolescent girl. The maximum size of 2.5 to 3.5 cm in diameter was reached in 2 or 3 months, and regression, which was spontaneous, was complete in another 3 months. "Improvement coincided with a shipment of Red Cross food and sufficient vitamins to provide each man with 1 vitamin capsule," containing 5000 U.S.P. units of vitamin A, 500 U.S.P. units of vitamin D, 333 U.S.P. units (1 mg) of vitamin B_1, 600 U.S.P. units (30 mg) of vitamin C, and 2 mg of vitamin B_2. Transitory hypertension occurred in about 60% of the personnel shortly after the disappearance of the gynecomastia (no attempt was made to correlate the cases of hypertension with those of gynecomastia), and adrenal dysfunction was suspected as the cause.

Hibbs concludes that "there appears to be a relationship between endocrine balance and adequate vitamin intake."

ANDROGENS IN ENURESIS

I. N. KUGELMASS (New York City), *New York State J. Med., 47*:1369, June 15, 1947, presents the theory that enuresis may be a Mendelian recessive trait because of the fact that the disorder usually appears "in the absence of local or systemic disease in one or more children of the same family with a predecessor's history of enuresis in childhood." The vast majority of children examined, according to Kugelmass, have no organic disease.

Since this familial weakness may result from immaturity of the sphincter mechanism, therapy in the form of methyl testosterone, in divided doses totaling 10 to 30 mg daily, was instituted and continued for a period of 1

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

to 3 months in a group of 75 children between the ages of 4 and 16 who had previously not responded to any form of therapy; boys outnumbered the girls in this group 3 to 1. If the oral medication had no effect within 2 weeks, it was supplemented by the weekly intramuscular administration of 10 mg of testosterone propionate. At the same time, fluid intake was restricted as much as possible. Excellent results were obtained, in that 59 children were cured by this means and 10 were improved, the remaining 6 receiving no benefit from the treatment. With improvement in bladder control effected by androgen, it was possible to remove restrictions on the fluid intake; at the same time, the dosage of testosterone was gradually decreased, without causing a return of symptoms for 6 months to 1 year.

VITAMIN K IN POSTEXTRACTION HEMORRHAGE

G. W. RAPP (Loyola University, Chicago, Illinois), *J. Am. Dent. A.*, 34:484, April 1, 1947, presents a comprehensive picture of the mechanism of blood clotting and emphasizes that disruption of this normal process of coagulation can be brought about by the use of analgesic preparations containing acetylsalicylic acid, acetophenetidin, and caffeine citrate which are so often used in dental practice and which cause hypoprothrombinemia in normal human beings. The incidence of delayed postextraction hemorrhages is stated to be directly related to the intake of these analgesics by patients. However, Rapp states that prolongation of the prothrombin time can be prevented by the use of vitamin K.

In arriving at these conclusions, Rapp conducted tests in 40 normal subjects. These subjects were divided into four groups of 10 persons, two of which groups received tablets containing 250 mg of acetylsalicylic acid, 160 mg of acetophenetidin, and 20 mg of caffeine citrate, under various dosage schedules, and the other two of which received similar analgesic tablets with 1 to 2 mg of menadione (synthetic vitamin K) at varying intervals. Hypoprothrombinemia was produced in the two groups receiving analgesic alone, while it did not occur in the groups in which menadione was administered. In a large group of dental patients receiving postoperative analgesics plus varying doses of menadione there was a postoperative hemorrhage incidence of only 1.6 to 4.5% as opposed to an incidence of 13.6% in a group receiving analgesics without menadione. Rapp concludes that hypoprothrombinemia which might arise from the use of acetylsalicylic acid preparations can be prevented by administration of vitamin K and that existing hypoprothrombinemia from the same cause can be corrected by the vitamin.

TREATMENT OF AMENORRHEA

L. M. RANDALL (Mayo Clinic, Rochester, Minn.), *Am. J. Obst. & Gynec.*, 53:453, March, 1947, in a report on the treatment of amenorrhea in young women, states that there are various factors which must be considered in the treatment of an amenorrhea patient. The first of these is nutrition; it is often found that menstrual disturbances occur in women who are underweight or overweight, in particular in those patients with anorexia nervosa. Treatment of this disorder is usually based on returning the weight to normal; when this occurs, the basal metabolic rate as a rule also returns to normal, as does the functional activity of the glands of internal secretion. If the nutritional state has been corrected and if menstruation still does not occur, cyclic estrogen therapy may be started, according to Randall, using any of the oral or parenteral forms of therapy.

Treatment as a rule will serve a threefold purpose: (*1*) it will prime the uterus and endometrium and will prevent further atrophy; (*2*) it may stimulate the pituitary by approximating the cyclic rise and fall of the body's estrogens under normal conditions (this will be more complete if both estrogens and progesterone are used); and (*3*) if there is no response in the uterus and

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

endometrium to adequate therapy, it may be assumed that the difficulty lies in an unresponsive Müllerian duct. In patients in whom the basal metabolism is low, thyroid extract is given to reestablish normal metabolism; at times, even if the basal metabolic rate is in the lower normal range (between —10 and zero), elevation of the rate to +5 may be attempted if properly controlled, since elevation to this degree may be necessary to bring about menstruation. Low-dosage roentgenotherapy to the pituitary gland or to the ovaries is also recommended for the treatment of amenorrhea. Rather than administer extrinsic gonadotrophins, Randall states that he prefers to stimulate the pituitary body itself into the production of gonadotrophins.

Randall reports on 87 patients with amenorrhea who were treated by combinations of these methods: of 17, whose amenorrhea resulted from functional ovarian failure, 10 (58.8%) had return of menstruation; of 37 whose amenorrhea was associated with failure of the pituitary body, 26 (72.2%) responded; of 15 in whom amenorrhea was related to anorexia nervosa, 8 (53.3%) were improved; and of 19 with primary amenorrhea, only 3 responded.

The first aim of treatment, according to Randall, is to provide the best environment for normal glandular function, and next to stimulate and maintain that function.

ANDROGENS IN ENDOCRINE BLOOD DISORDERS

G. WATKINSON, W. H. MCMENEMEY, AND G. EVANS (London, England), *Lancet, 1*:631, May 10, 1947, report two cases of a syndrome combining hypopituitarism, hypogonadism, and anemia which were treated with testosterone. A review of the literature indicated to the authors that the anemia in all previously published cases (8) had responded to liver and iron therapy, but the two cases presented here did not respond to this therapy until testosterone was added; the authors postulate that this indicates a direct relationship between the hypogonadism and anemia. Testosterone alone had no effect on the disorder; however, when 5 to 10 mg of testosterone per day was given in conjunction with liver and iron, the reticulocyte, hemoglobin, and red cell counts increased to normal.

As a result of the correlation of the findings of previous investigators with their own, Watkinson *et al.* conclude that androgens have a stimulating action on the blood formation, whereas estrogens have an inhibiting effect.

Two additional cases are presented in which testosterone produced no permanent improvement; one was a case of primary focal myelofibrosis in a female in whom no change was seen after treatment; the other, a case of achrestic anemia, was temporarily improved. According to Watkinson *et al.*, results were not so dramatic in these cases because hypogonadism or hypopituitarism was not present with the anemia.

ASCORBIC ACID METABOLISM IN ADOLESCENTS

C. A. STORVICK, M. L. FINCKE, J. P. QUINN, AND B. L. DAVEY (Oregon State College and U. S. Department of Agriculture), *J. Nutrition, 33*:529, May 10, 1947, present a report on ascorbic acid metabolism in adolescent children. Plasma ascorbic acid levels were first determined in 81 children between the ages of 11 and 18 before any vitamin C was given. Most of the levels (*i.e.*, in 71% of the girls and 42% of the boys) fell below the level of 0.60 mg which the Committee on Vitamins of the American Academy of Pediatrics has set as a standard for adequacy.

During the study comparison was made of the plasma ascorbic acid levels produced when the children were on their usual diet, when they were receiving "saturation" amounts of vitamin C, and when they were being given the daily allowance of ascorbic acid recommended by the National Research Council for each, according to age and weight.

On the basis of body weights, the requirements of ascorbic acid for tissue

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

saturation in children do not differ greatly from those for adults, although there are individual variations, according to Storvick *et al.*; they state further that their studies indicate that young adolescents may require more ascorbic acid per kg of body weight to maintain this saturation level than do younger children or adults. The amount recommended to provide an adequate plasma level, although not a saturation level, is that listed by the National Research Council (1945).

ASCORBIC ACID RESERVES IN ADULTS

J. E. HAINES *et al.* (Cornell University, Ithaca, New York), *J. Nutrition*, *33*:479, April 10, 1947, have studied the tissue reserves of ascorbic acid in 12 normal adults on three levels of intake in order to check the validity of the League of Nations' recommended daily intake of 33 mg and the National Research Council recommendation of 70-75 mg. At the beginning of the study, the patients were saturated over a period of 3 days with ascorbic acid (in the form of orange juice or tablets of synthetic ascorbic acid 'Roche') to a point where urinary excretion of a test dose of 400 mg of ascorbic acid exceeded 50% (250 to 387 mg) of the dose. The saturation period was followed by four 6-week periods during each of which a separate level of vitamin C intake was investigated, *i.e.*, 33, 50, 53, or 70 mg per day. A resaturation period followed these restricted-intake periods and during this resaturation period each subject was given 400-mg test doses of vitamin C each day until the urinary excretion again exceeded 50% of the test dose.

The findings of these tests were as follow: On the 70 mg per day allowance (National Research Council Standard), depletion of tissue stores of ascorbic acid was only slight; with 50 to 53 mg per day, depletion was moderate; and with 33 mg per day (League of Nations Standard), depletion was very definite, and it was not certain that maximum depletion had been reached within the 6-week period on this intake. Thus it could be seen that the National Research Council recommended allowance of 70 mg for women and 75 mg for men is not sufficient to maintain tissue saturation in adults (although it provides a wide margin of safety over the amount needed to prevent scurvy), and the League of Nations standard of 33 mg would allow distinct depletion of tissue stores.

STREPTOMYCIN THERAPY

H. C. HINSHAW (Mayo Clinic, Rochester, Minnesota), *Surg., Gynec. & Obst.*, *84*:579, April 15, 1947, in a general report on the clinical use of streptomycin in medicine and surgery, states that the drug may be used in treating many gram-negative bacillus infections which are not amenable to therapy with other antibacterial agents. The drug should be used in combination with penicillin for such infections as acute peritonitis, chronic suppurative pulmonary disease, and wound infections. Streptomycin is also effective alone in treating acute and chronic infections of the respiratory tract caused by organisms of the *Hemophilus* and *Klebsiella* groups, and may be considered specific in treating tularemia. Brucellosis and typhoid fever are only moderately responsive to streptomycin therapy.

The most promising possibilities for the use of streptomycin appear to be in the treatment of tuberculosis, since streptomycin is the only antibacterial that has any effect on the tubercle bacillus, according to Hinshaw. There are limitations, however, to its effect, and these seem to be imposed by the destructive and granulomatous changes produced in tuberculous tissue (on which streptomycin can have no effect) and by the fact that the drug cannot be depended upon to destroy tubercle bacilli in the human body.

PROGESTERONE IN MIGRAINE

I. SINGH, I. SINGH, AND D. SINGH, *Lancet*, *1*:745, May 31, 1947, report the use of progesterone in the treatment of 23 cases of migraine in women in whom estrogen was established as a causative

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

factor in precipitating migraine attacks. If pregnancy occurred, the migraine as a rule cleared up during the confinement only to return at varying intervals after delivery.

Singh *et al.* state that there is a definite relationship between the attacks of migraine and the time at which excretion of free estrogen in the urine would be expected, since most of the attacks occurred midway between menstrual periods or just before menstruation. They state that headache or migraine may be caused by estrogens in one or more of the following ways: (*1*) by causing temporary enlargement of the pituitary; (*2*) by their effect on blood vessels ("according to this hypothesis migraine is caused by arterial spasm followed by arterial dilatation within the distribution of the common carotid artery"); or (*3*) by retention of sodium and chloride in the body.

Progesterone (about 5 mg) was effective in relieving or preventing attacks of migraine in the 23 cases studied; other disorders or associated symptoms, such as lassitude and languor, loss of appetite, lack of concentration, and vague headaches, were also alleviated by progesterone therapy.

ORAL PENICILLIN IN ACUTE INFECTIONS

W. S. HOFFMAN AND I. F. VOLINI (Cook County Hospital and Loyola Medical School, Chicago, Illinois), *Am. J. M. Sc.*, *213*:520, May, 1947, present a report of the results of their use of the optimal dosage of penicillin established by them in a previous study (*i.e.*, 200,000 units of penicillin initially, followed by 100,000 units every 3 hours) in a series of 49 patients with lobar pneumonia and 81 patients with miscellaneous infections. In 77% of the cases of pneumonia, amelioration of symptoms and subsidence of fever occurred within 48 hours, sometimes within 12 hours. Reasons for failure in the remaining 23% were listed as "(*a*) inadequate absorption of penicillin; (*b*) the presence of a penicillin-insensitive organism, such as a virus; (*c*) penicillin-resistant pneumococci; or (*d*) overwhelming complications." Similar results were obtained in the patients with various infections, although those with hemolytic streptococcic infections responded rapidly, and those with staphylococcic infections more slowly. Plasma penicillin levels (under this regimen) were 0.06 unit per cc or higher during most of the 3-hour interval between doses. Sensitivity of the organism to penicillin and not the severity of the infection is stated to be the criterion in determining the dosage.

"Urticaria occurred in 3.8% of 130 therapeutic cases and only in 0.86% of the 580 total subjects used for either assay or treatment. When purified preparations were used, only 2 spurious cases of urticaria developed."

In using various penicillin preparations, Hoffman and Volini found that crude calcium penicillin in capsules gave the poorest results, whereas among the other preparations there was actually little difference.

PROSTIGMIN IN MULTIPLE SCLEROSIS

H. KABAT (Kabat-Kaiser Institute, Washington, D. C.), *Permanente Foundation M. Bull.*, *5*:1, March, 1947, reports the treatment of 29 patients, suffering from multiple sclerosis of almost 10 years' duration, by the use of Prostigmin* Methylsulfate 'Roche' (neostigmine methylsulfate, U. S. P.), and muscle re-education. The initial intramuscular dose was usually 1 mg of Prostigmin with 1/200 or 1/150 gr. of atropine sulfate per day and was gradually increased so that at the end of 1 month the patients were each receiving 2 or 3 mg of Prostigmin daily with 1/100 gr. of atropine sulfate, and supplementary doses of 15 to 30 mg of Prostigmin Bromide 'Roche' three times a day with 1/200 gr. of atropine sulfate (if necessary with the larger oral dose). An intensive and carefully supervised course of muscle re-education was also carried out.

The treatment was "highly effective in bringing about improvement in neuromuscular function in these patients": the rapidity with which improvement was brought about depended upon the

*Reg. U. S. Pat. Off.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

severity of the involvement. Prostigmin decreased or eliminated fatigue, relaxed spastic muscles, and facilitated voluntary innervation, in addition to being of value in decreasing intention tremor, in improving co-ordination, and in bringing about improvement in control of urination. All of the patients were benefited to some degree by treatment.

PYRIDOXINE IN POSTANESTHESIA VOMITING

W. BERGMANN (Yuma, Colorado), *Canad. M. A. J., 56*:554, May, 1947, presents a short report of the use of pyridoxine for the relief of postanesthesia vomiting in a series of 12 consecutive cases, with 12 cases to serve as controls. One injection of 100 mg of pyridoxine was given to each patient before operation and it was found that none of the patients so treated vomited, whereas all in the control group vomited several times or were nauseated although none had received any more anesthesia nor were their operative procedures any more lengthy.

After the first series, Bergmann increased the dosage to 100 mg of pyridoxine before operation and an equal dose one hour after operation. Patients receiving pyridoxine were ambulatory 2 or 3 days after operation, while those in the control group became ambulatory 3 or 4 days after operation.

VITAMIN K IN QUININE-INDUCED HYPOPROTHROMBINEMIA

L. A. PIRK, AND R. ENGELBERG (Nutley, N. J., and New York, N. Y.), *Am. J. M. Sc., 213*:593, May, 1947, report confirmation of their previous findings to the effect that quinine sulfate will cause hypoprothrombinemia unless vitamin K is given to prevent this. Inasmuch as Quick, in a recent report, had stated that elevated prothrombin time had not occurred after administration of quinine sulfate, Pirk and Engelberg repeated their tests, using both their method of determination (Russell viper venom) and Quick's method (thromboplastic tissue extract). They concluded that the difference in results could be attributed to the fact that their method was more sensitive than the one employed by Quick, inasmuch as a consistent and definite rise in prothrombin time was found when the levels in 5 patients were tested by means of Russell viper venom, while no change was seen when these same levels were tested by means of thromboplastic tissue extract. Prothrombin levels were elevated by as much as 12.3 seconds after several days' administration of quinine sulfate.

The thrombinopenic effect of 0.33 Gm of quinine sulfate was counteracted by the concomitant oral administration of 5 mg of vitamin K; in all instances the prothrombin levels under this regimen remained at a level which was considered normal for the subject on the basis of control-period prothrombin determinations.

FEEDING OF PREMATURE INFANTS

H. E. GORDON, S. Z. LEVINE, AND H. MCNAMARA (New York Hospital and Cornell University Medical College, New York City), *Am. J. Dis. Child., 73*:442, April, 1947, present a report on the feeding of 88 premature infants. Vitamin K was given routinely to all infants after birth. Within the first week of life, all were also receiving vitamins A, C, and D.

Three feeding procedures were used during the study: the first consisted in the administration of breast milk; the second in the use of evaporated milk, carbohydrate, and water; and the third in the mixture of half-skimmed milk powder, carbohydrate, and water. The mixture to be given to each infant was carefully arranged according to a rotation system based on sex, weight at birth, plurality of birth, and race. Actually, in the final analysis, it was found that there was little difference within the group receiving each formula and the results were therefore analyzed only on the basis of which mixture had been used. If an infant became ill or died, his record was not included in the study; the result of this policy was that only 16 infants who had received human milk, 39 who had received evaporated

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

milk, and 33 who had received half-skimmed milk (total of 88) were reported on. From these it was found that the average gain in weight was greatest in infants who were fed half-skimmed milk; here the gain in weight was 15.7 Gm per kg per day, as compared with 12.5 Gm in infants fed breast milk and 14.1 Gm in infants fed evaporated milk. When the groups were divided into smaller and larger infants according to weight at birth, the differences were even more noticeable among the groups of smaller infants; birth weight was listed as between 1022 and 1621 Gm and the gain under administration of half-skimmed milk was 17.3 Gm per kg per day as compared with 11.7 Gm in infants receiving human breast milk, and 14.9 Gm in those receiving evaporated milk.

In addition, 14 infants who weighed less than 1000 Gm at birth gained at a rate approximating that of "smaller" infants mentioned above on the same diet of half-skimmed milk.

STREPTOMYCIN IN TULAREMIA

L. FOSHAY (University of Cincinnati, Cincinnati, Ohio), *Am. J. Med.*, *2*:467, May, 1947, presents a report on the use of streptomycin in the treatment of tularemia. Thirty-seven patients, 10 of whom were of the typhoidal clinical type and 14 of whom had tularemic pneumonia (illustrating the average severity of the infections), were given 0.64 to 29.5 Gm of streptomycin by intramuscular injection over a period of 2 to 17 days; individual doses were given every 3 or 4 hours. In a few dangerously ill patients, part of the total dosage was given by continuous intravenous or subcutaneous drip. In some cases the disease was already in its one hundred twenty-third day at the time that treatment was instituted; Foshay postulates that results would have been better had treatment been started sooner in such cases.

Regardless of the stage at which streptomycin therapy was begun, the temperature usually fell to normal within 3 days after streptomycin was administered. "Primary lesions that were in the non-ulcerated papular stage at the onset of therapy usually healed without ulceration, and in about one-third to one-half of the usual healing time," preventing secondary pyogenic infection of ulcers and reducing the frequency of suppuration of buboes.

Foshay refers to the fact that many investigators are using a rather high dosage of streptomycin in treating tularemic patients and states that although experience is limited, evidence indicates that a low dosage such as 0.5 Gm per day for 2 days followed by 0.25 Gm per day for 4 days, or 0.5 Gm per day for 6 days may be considered adequate dosage for a case of usual severity, with or without tularemic pneumonia.

DIET FOR THE AGED

J. MEYER (University of Illinois, College of Medicine, Chicago, Illinois). *Geriatrics*, *2*:149, May-June, 1947, presents a report on diet for the aged. According to Meyer, the diet for the aged should not be much changed from that to which the individual has become accustomed. As a rule, "the majority will eat enough calories to supply their energy needs"; although some will eat too much and others not enough, this is true of any age, and overnutrition or undernutrition can be corrected by the physician when such a condition becomes apparent. Meyer states that extra amounts of vitamins, in particular vitamins B-complex and C, should be given to supplement the diet. Although the daily allowance has been stated by other investigators to be 5000 I.U. of vitamin A, 1.8 mg of vitamin B_1, 75 mg of vitamin C, 2.7 mg of riboflavin, and 18 mg of niacin, Meyer suggests that, because of increased intake of carbohydrate, the vitamin B-complex requirement is greater than normal in the aged.

Meyer states that prohibition of alcohol, coffee, or tobacco is not necessary if the individual is accustomed to their use and if he or she indulges in moderation. A basic diet for the aged (recommended by Sebrell) is described.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

VITAMIN E IN HEART DISEASE

W. SHUTE, E. SHUTE, AND A. B. VOGELSANG (Ontario, Canada), *M. Rec.*, *160*: 91, February, 1947, present in tabular form case reports of 84 patients suffering from anginal pain, and signs and symptoms of heart disease other than precordial pain, who were treated with large doses of vitamin E; Ephynal* Acetate 'Roche' was one of the vitamin E preparations used in the study. Many types of cardiac involvement and all degrees of functional impairment are, according to Shute *et al.*, represented. The dosage of vitamin E ranged from 150 to 600 mg (in terms of alpha-tocopherol) and resulted in improvement in the patient's exercise tolerance and relief from anginal pain in the majority of cases. In a number of instances of hypertension, the blood pressure was reduced to a nearly normal level.

A. B. VOGELSANG, E. V. SHUTE, AND W. E. SHUTE (Ontario, Canada), *M. Rec.*, *160*:163, March, 1947, present a second paper containing 28 short reports of cases of rheumatic heart disorders treated with vitamin E (one of the preparations used was Ephynal* Acetate 'Roche'). The dosage ranged from 150 to 400 mg of vitamin E (alpha-tocopherol or mixed tocopherols) and resulted in improvement in a high percentage of cases, although larger doses of vitamin E combined with adjuvant drugs such as digitalis would, according to the authors, have improved the final figures a great deal.

W. E. SHUTE, E. V. SHUTE, AND A. B. VOGELSANG (Ontario, Canada), *M. Rec.*, *160*:230, April, 1947, in the third of a series of articles dealing with the use of vitamin E in heart disease, report the treatment of 66 patients with hypertensive heart disorders by the use of various vitamin E preparations, one of which was Ephynal* Acetate 'Roche'. Therapy consisted in the administration of 175 to 1000 mg of vitamin E. The percentage of improvement was high, although better results may be obtained with more prolonged and intensive therapy, according to the authors, since a number of patients were still showing improvement at the time of the report.

A. B. VOGELSANG, E. V. SHUTE, AND W. E. SHUTE (Ontario, Canada), *M. Rec.*, *160*:279, May, 1947, present general remarks on three previous reports in which case histories of heart disorders treated with vitamin E had been reported, and sum up the percentages of cure obtained.

Of 84 patients treated with 150 to 600 mg of alpha-tocopherol in whom anginal pain was a common symptom, 6 (7%) had complete relief, 38 (45%) had great improvement, 37 (44%) had some improvement, 2 (3%) had no improvement, and one (1%) died.

Of 28 patients with rheumatic heart disease who were given 150 to 400 mg of alpha-tocopherol, none showed complete relief, 15 (53%) showed definite improvement, 12 (43%) showed some improvement, and 1 (4%) showed no improvement.

In the hypertensive heart disease group were included 66 patients to whom 175 to 600 mg of alpha-tocopherol was given, with results as follows: none reported complete relief of symptoms, 28 (42%) reported considerable relief, 28 reported some improvement, 2 (3%) reported no improvement, and there were 8 (12%) deaths.

In summary, Vogelsang *et al.* state that most patients with anginal disorders experience prompt relief with vitamin E therapy; rheumatic patients are helped considerably, although little improvement in valvular lesions can be expected. Hypertensive hearts are benefited, and, at times, the hypertension itself is decreased. Arrhythmias are occasionally regulated. Any electrocardiographic changes noted were slight, but the authors state that any changes would probably not be apparent for 6 months to 1 year. Few toxic reactions were reported and these were mild.

Vogelsang *et al.* conclude that although they recommend this form of therapy, "vitamin E is a mode of treatment, not a 'cure'."

* Reg. U. S. Pat. Off.

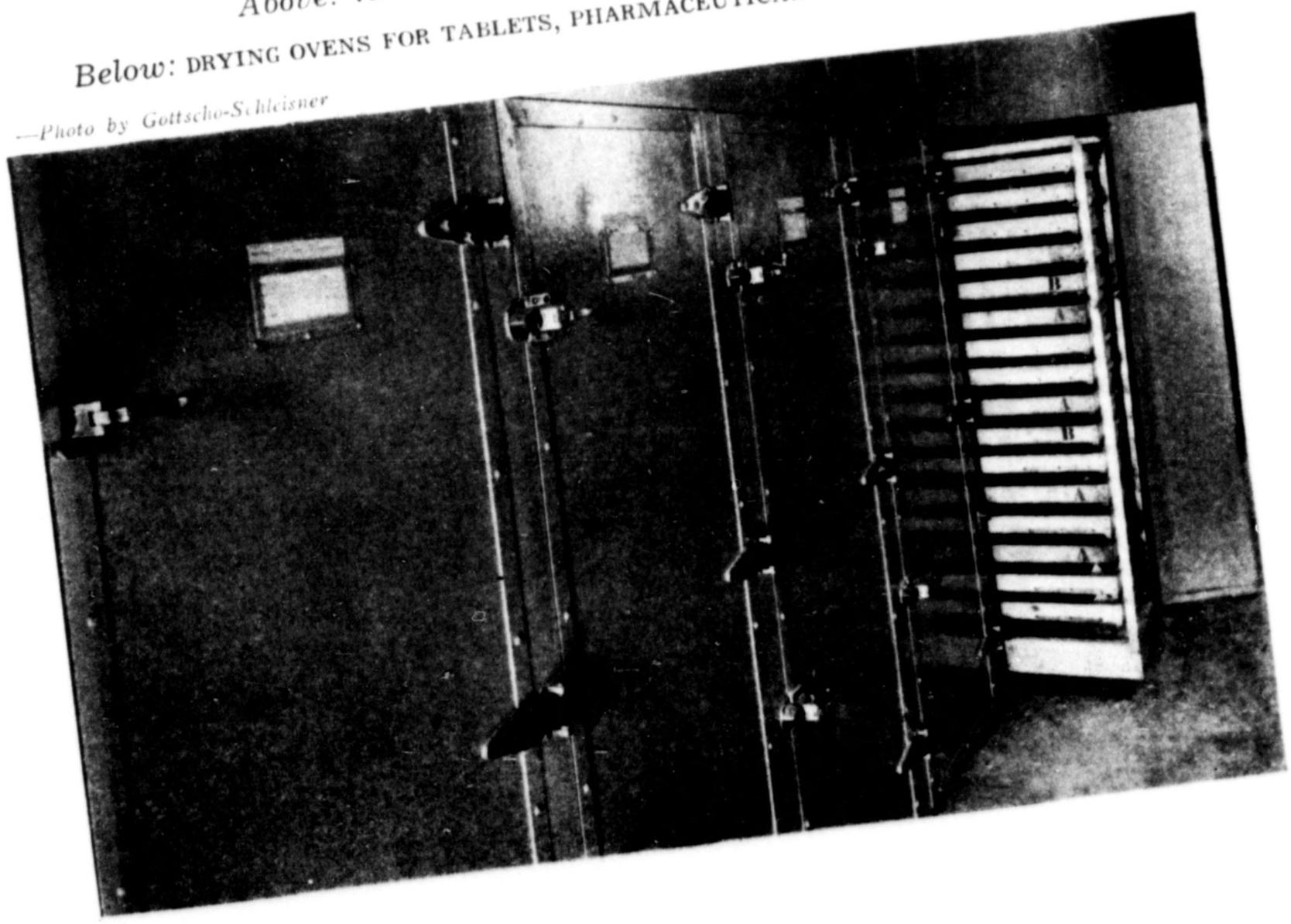
DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

—Photo by Gottscho-Schleisner

Above: VIEW OF RESEARCH BUILDING, ROCHE PARK.

Below: DRYING OVENS FOR TABLETS, PHARMACEUTICAL BUILDING, ROCHE PARK.

—Photo by Gottscho-Schleisner



DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Maternal Infections and Mongolism

In the July-August 1947 issue of the Roche Review there appeared an article on mongolism. One of the causative factors of mongolism which is currently receiving wide attention, and which was unfortunately omitted from our recent article, is the effect of rubella (German measles) and other infectious diseases on the fetus, when contracted by the mother during the second or third month of pregnancy. Some of the data which have been collected on the subject are presented here, and this material, although not bearing directly on the subject of mongolism, is given to show the evolution of the theory that virus or other infections during pregnancy can produce an effect as devastating as that which is found in mongolism.

From Australia in 1941 came a report by Gregg[8] on the appearance of congenital defects in 78 infants whose mothers had had a virus infection, diagnosed as rubella, during the first few months of pregnancy. All of the infants had congenital cataracts and 44 had, in addition, a congenital heart disturbance. Gregg postulated at that time that this exanthematous disease has a destructive effect on the embryonic cells which results in these malformations.

Swan *et al.*[11] followed up Gregg's article by reporting 49 cases in which the mother had contracted rubella during pregnancy; 25 mothers had had rubella during the first 2 months and all of the infants born to these mothers had a congenital defect of either the heart or eye or of both. In addition, four out of eight infants born to mothers who had had rubella during the third month of pregnancy also showed defects; when the infection occurred after the third month, only two out of 16 showed any malformation. One of the infants was a mongolian idiot; others showed mental retardation and microcephaly.

In a report on the effect of diseases of the mother on the fetus, in which he reviews the literature on the subject, Bull[3] states that a mechanism has been postulated for the formation of anomalies in infants whose mothers had rubella during pregnancy. Inasmuch as the embryonic cells are very susceptible to virus infections, and since the cells of the heart and eye are in their formative period between the first and second months of pregnancy, it is believed that infections in the mother during that period, although seemingly trivial, may bring about striking malformations in the child. Bull states that it is possible

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

that these changes result from involvement of the hyaloid artery or others with resultant impairment of nutrition of the lens fibers and formation of cataracts.

Erickson[5] has reported 11 cases of unilateral or bilateral cataract with associated disorders, including nine cases of heart defects and two cases of mental retardation, in infants born to mothers who had rubella early in pregnancy. Because of the tremendous susceptibility of the embryonic cells to virus infection, it is plausible that other more severe virus infections in the mother may be responsible for more devastating defects in the infant. He also suggests that girls be deliberately exposed to rubella at an opportune time during childhood in order to avoid likelihood of contracting the disease during pregnancy.

Altmann and Dingmann[2] report an additional case in which unilateral cataract and congenital deafness were found in a child born to a mother who had contracted rubella during the second month of pregnancy. No other malformations were present and Altmann and Dingmann stated at that time that it is possible that many cases of congenital deafness of hitherto undetermined origin may be caused by a rubella infection in the mother during the first stage of pregnancy.

Long and Danielson[10] describe in detail six cases of malformation at birth which seemed to be related to the contraction of rubella by the mother during the first 2 to 6 weeks of pregnancy. All six children had cardiac defects; three had bilateral cataracts associated with bilateral microphthalmos, and the remaining three had unilateral microphthalmos with an unusual type of cataract in the smaller eye. One child was also mentally deficient.

It is suggested that the rubella virus has undergone a change in recent years and is now more toxic than it was formerly; the reason for this postulate is that since rubella is such a common disease, having certainly infected pregnant women before, it is surprising that it is only recently that congenital abnormalities have been correlated with infection during the early months of pregnancy.

Greenthal[7] adds two cases to the list of those which confirmed Gregg's findings of congenital defects in the infant apparently caused by rubella during the first few months of pregnancy. In one infant there was congenital deafness and in the other there were congenital cataract, heart murmur caused by a patent intraventricular septum, and physical and mental retardation.

In 1945, Adams[1] reported two additional cases of rubella during pregnancy which resulted in abnormalities and malformations in the infant. In one infant, there were bilateral cataracts and a heart defect which was considered to be a patent intraventricular septum; in the other, there were complete cataract of the left eye, a heart defect (also interpreted as a patent intraventricular septum), and gross mental deficiency. Both mothers had had rubella early during pregnancy, one during the sixth week and the other during the fourth week of gestation.

At variance with these findings is the report by Fox and Bortin[6] on 11 women who had rubella during pregnancy; two of the infants born to these women showed signs of abnormality; one, a stillborn infant, was hydrocephalic; the other had sinus disease, otitis media, and hydrocephalus, which receded spontaneously, leaving the child normal at the time the report was made. Fox and

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Bortin state, however, that further investigation is indicated, although their findings do not justify consideration of termination of pregnancy.

Ingalls and Davies[9] state that thus far it has been impossible to correlate the production of mongolism with any specific cause; however, the discovery that maternal rubella, a comparatively minor infection, can produce such major defects as congenital blindness, heart disease, or deafness in the infant has brought about a change in the outlook. The authors present seven cases of mongolism which were associated with intercurrent infectious diseases during pregnancy. In six out of seven cases, the mother became infected during the second month of pregnancy, which, according to Ingalls and Davies, is "provocative," inasmuch as mongolism has long been associated with deformities such as cleft palate, syndactylism, and imperforate anus "which date from about the same period of fetal life." The diseases which infected the mothers during pregnancy were influenza, rubella, mumps, mastoiditis, pleurisy, grippe, and acute purulent otitis media and sinusitis (with vomiting).

According to Ingalls and Davies, even if intercurrent infectious diseases during pregnancy are proved to be a causative factor of mongolism, they will probably account for only a small percentage of the cases. However, when a sufficient number of cases has been assembled, the figures should be submitted to statistical analysis. Ingalls and Davies express the hope that their report will prompt physicians to provide further information from their personal experiences.

An editorial in the *Journal of the American Medical Association*[4] mentions the paper by Ingalls and Davies and states that all that is possible should be done to exclude maternal infections during pregnancy.

REFERENCES

1. ADAMS, F. H.: Rubella in pregnancy and congenital malformations, *J. Lancet*, 65:197, 1945.
2. ALTMANN, F., AND A. DINGMANN: Congenital deafness and cataract following rubella in the mother, *Arch. Otolaryng.*, 42:51, 1945.
3. BULL, C.: The effect on the fetus of diseases of the mother during pregnancy, *Arch. Pediat.*, 62:289, 1942.
4. EDITORIAL: Mongolism and infections in pregnancy, *J. A. M. A.*, *134*:1096, 1947.
5. ERICKSON, C.: Rubella early in pregnancy causing congenital malformations of eyes and heart, *J. Pediat.*, *25*:281, 1944.
6. FOX, M. J., AND M. M. BORTIN: Rubella in pregnancy causing malformations in newborn, *J. A. M. A.*, *130*:568, 1946.
7. GREENTHAL, R. M.: Congenital malformations in the infant caused by rubella early in pregnancy, *Arch. Pediat.*, 62:53, 1945.
8. GREGG, N. M.: Congenital cataract following German measles in mother, *Tr. Ophth. Soc. Australia*, *3*:35, 1941.
9. INGALLS, T. H., AND J. A. V. DAVIES: Mongolism following intercurrent infectious disease in pregnancy, *New England J. Med.*, *236*:437, 1947.
10. LONG, J. C., AND R. W. DANIELSON: Cataract and other congenital defects in infants following rubella in the mother, *Arch. Ophth.*, *34*:24, 1945.
11. SWANN, C., *et al.*: Congenital defects in infants following infectious diseases during pregnancy, with special reference to relationship between German measles and cataract, deaf-mutism, heart disease and microencephaly, and to period of pregnancy in which occurrence of rubella is followed by congenital abnormalities, *M. J. Australia, Sydney*, *2*:201, 1943.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Ossification

In 1942, an article on anthropometric measurements and endocrine diagnosis, including material on ossification centers and indices, appeared in the ROCHE REVIEW. In order to bring this article up to date, we are publishing here a few abstracts of papers which would seem either to revise some of the data which appeared in the previous article or to add new material to it.

D. W. Leonard, *Am. J. Roentgenol.*, 55:716, 1946, reports the use of a revised ossification index for the detection of endocrine disorders in childhood. Actually, according to Leonard, the only exception which he found to the ossification index originally proposed by him was in the maximum age for normal appearance of the ulna; this has resulted in a change of the age limit for appearance of ossification in the distal ulnar epiphysis from the seventh to the eighth year.

The normal age extremes for the first appearance of ossification centers as listed by Leonard are given in the table below.

Leonard emphasizes that in order to obtain accurate figures the age of the child must be listed as that age which has already been completed; *e.g.*, a child should not be listed as 2 years old until he has passed his second birthday.

According to Leonard, this index has been used as an aid in diagnosing hypothyroidism, pituitary deficiency, rickets, and dwarfism, although in no case should the index alone be used to establish diagnosis, but rather it should be taken in conjunction with the entire clinical picture. It is a "simple expedient" in the initial study of a subnormal child.

D. W. Leonard, *J. Pediat., 26*:379, 1945, has also suggested an ossification index for the bones of the foot. From a survey of the literature and from his own experience, he has arbitrarily set the ossification index for the normal foot as follows: Ossification centers for the calcaneus, talus, and cuboid are usually present at birth; that for the tibia makes its appearance during the first year (average age, 4 months), as does that for the cuneiform III (lateral) (average age, 5 months); that for the fibula is seen sometime between the eighth and

	Earliest	*Majority*	*Latest*
Capitate	Birth	2½ mo.	6 mo.
Hamate	Birth	3½ mo.	7 mo.
Radius (epiphysis)	6 mo.	1 yr.	2 yrs.
Triquetrum	1 yr.	2¼ yrs.	4 yrs.
Lunate	2 yrs.	4 yrs.	5 yrs.
Navicular	4 yrs.	5 yrs.	6 yrs.
Lesser Multangular	4 yrs.	5¼ yrs.	7 yrs.
Greater Multangular	4 yrs.	5¼ yrs.	7 yrs.
Ulna (epiphysis)	5 yrs.	6¾ yrs.	8 yrs.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

seventeenth months (average age, 1 year); that for the cuneiform I (medial) is seen from the twelfth to the thirty-eighth month (average age, 2 years); the ossification center for the cuneiform II is seen from the seventeenth to the fortieth month (average age, 2 years and 4 months); and that for the navicular appears from the ninth to the forty-seventh month (average age 2 years and 9 months).

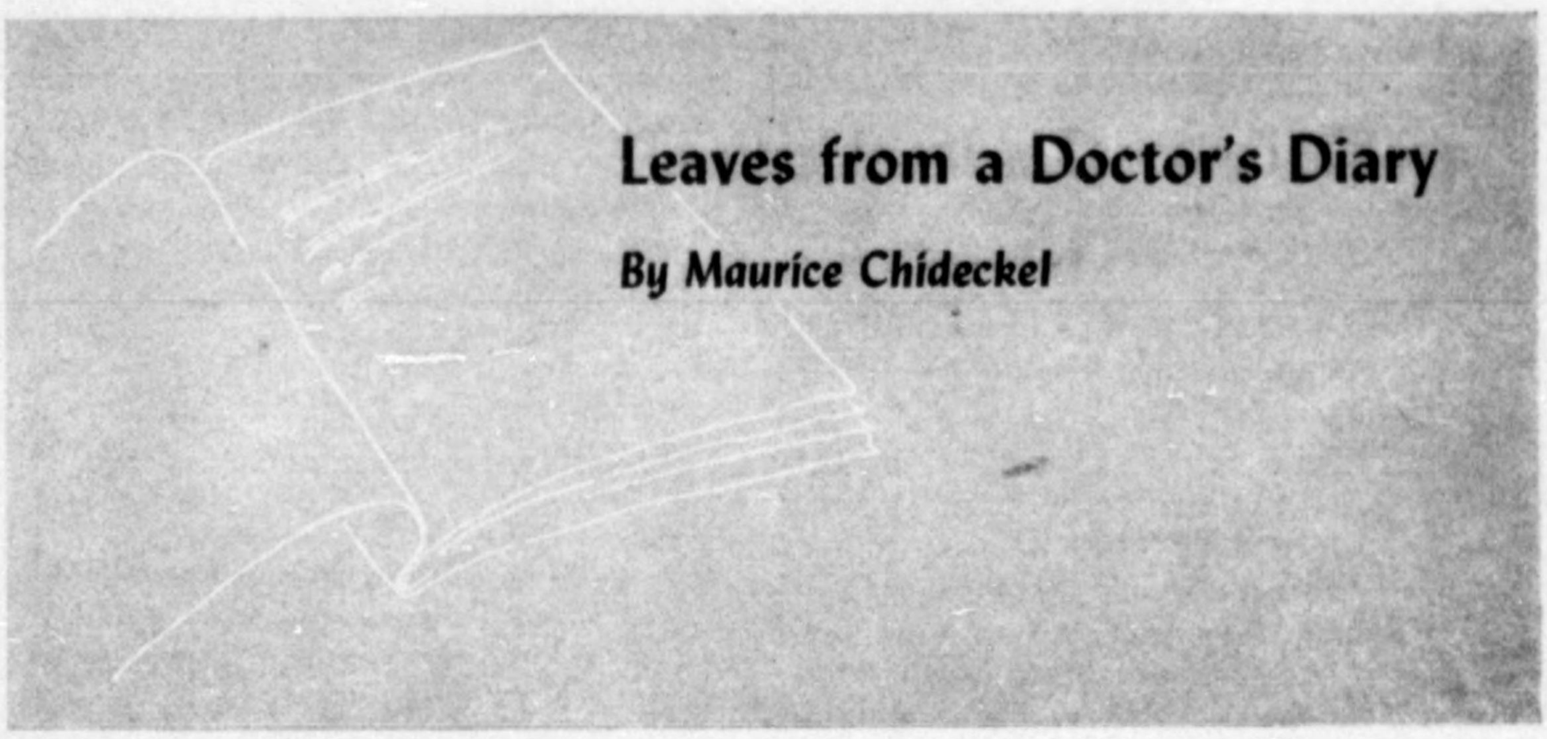
This index has been used as a guide in the treatment of clubfoot. If the centers of ossification are delayed, the use of restraining splints is continued until such time as the centers appear in order to prevent a relapse to the patient's former status. If ossification is delayed for so long a period that muscular and ligamentous structures will suffer seriously from lack of use (which can be determined in advance by a very close watch on bone formation), a decision to treat by surgical means may be reached at an early date, thereby shortening the total period of disability. A large percentage of children with clubfoot show a delayed ossification, and Leonard states that it has been suggested that thyroid substance will speed up ossification during the period that the bones are being held in their normal position. Use of the ossification index as a guide should be continued throughout treatment.

P. V. Woolley and R. W. McCammon, *J. Pediat.*, 27:229, 1945, report the use of serial roentgenograms of the long bones for the detection of congenital myxedema. The authors contend that the growth and status of the radius may be used as an indication of the bone age of the child. In congenital myxedema, roentgenograms have indicated that a hard, calcified epiphyseal plate is always found; this plate differs from those found in rickets, scurvy, syphilis, or lead poisoning, and is found only in myxedematous patients.

The authors present three cases in which roentgenograms of the radius aided in the diagnosis of cretinism. When treatment with thyroid substance was instituted, there was immediate resumption of growth and replacement of the abnormal line by newly calcified bone; treatment, if adequate, starts growth at an accelerated rate, but this later slows down to parallel the normal curve. Woolley and McCammon state in conclusion that they did not attempt to use this standard in patients over the age of 2, inasmuch as bone growth is considerably slower after that age and "other norms for thyroid function are easily applicable to older children."

We are indebted to Dr. Donald Leonard and the publishers of the *American Journal of Roentgenology* for permission to reproduce this index.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013



Leaves from a Doctor's Diary

By Maurice Chideckel

October 1. . . . You must pay homage to Dr. G., for he has unbounded pride in himself and he is broadly tolerant of other's views, if they coincide with his. Hear him talk about other men of our calling and you can't help concluding that medical ethics has had its day. "Don't talk to me about that man Brady," he said to a group of doctors in the clinic. "This man should not be allowed to practice. Imagine diagnosing a foreign body in the larynx as congenital laryngeal stridor." "You never examined the child's larynx," came from one of the group. "The little patient is in the hospital now. It proved to be a cyst of the tongue." Dr. G.'s lips quivered. "Not so loud. You are the most unethical creature I know." Reminds me of the story of the two thugs who broke into a clothing store and carried off several dozen suits. One suit was marked $150. Says one robber to the other: "Look at the price. Highway robbery."

October 6. . . . Ethics. The diagnosis of pellagra was established in a 3-year-old child. No nicotinic acid was prescribed. The busy gentleman attending him ordered the mother to have the child bask in the sun. "Tell the mother," said Dr. Alvin to me, "that exposure to the sun aggravates the condition. Tell her not to take the little boy to that doctor. He either didn't look, or didn't know." "Why don't you tell her?" I asked. "Oh," he responded, "it's unethical." Brings to mind my good old student days when we all took a modified Oath of Hippocrates. Aloud: "I shall never commit an abortion." In an undertone: "But I shall send her to one who does." Or the married (but not to each other) couple who were motoring at night on a dark isolated road. Said the lady to the gentleman: "I am a faithful wife. I never cheat. But I shan't stop you if you do."

October 10. . . . Did something go wrong with the mental make-up of Dr. Price? He invited himself to give "an informal talk," and he leaped from one subject to another. He began with the scientific triumph of folic acid, then said he didn't like the name, since it is a derivative of spinach, liver, and cereals. He assured us that he has cured many cases of burning tongue and mouth with folic acid. Suddenly he wanted to know why so many brilliant medical students prove failures in practice—financial failures at least—and why those who pass their medical examination by the skin of their teeth are often eminently successful, financially speaking. In a depressed tone he quoted: "The race is neither to the swift, nor the battle to the strong." His face became red and he

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

screamed: "The progress of medicine disseminated in popular form has brought disaster to the human race, to the doctor and the layman, for both fear death. Fear is what kills. Those peoples who are out of reach of scientific medical progress are much happier and live longer." O.K., Doc. Let's turn the calendar back a few hundred years. How about going back to the medicine of Galen? Or better still, back to the Middle Ages. Wasn't it a beautiful era?

October 14. . . . Passing events.

At the psychological conference they discussed Freud's analysis of Dostoyevsky's epileptiform seizures. The convulsions of the author of "Crime and Punishment" and "The Brothers Karamazov" were, according to Freud, psychogenic in origin, representing his identification with his murdered father. His gambling and drinking arose from the sense of guilt and the need for punishment. I know unnumbered gamblers and drunkards whose fathers were not murdered, who have no sense of guilt, yet drink and gamble and have no seizures.

October 17. . . . Well, Tightwad thinks this world is a splendid place to live in. For a while I feared for his sanity. He danced the rumba in the corridor of the hospital. Cause of celebration—an infant with calculous cholecystitis after scarlet fever; and a missed abortion, a mummified fetus that remained long in the uterus of a syphilitic woman. "Great life, wonderful world," he kept repeating.

October 20. . . . They say that lovemaking is the only activity that is aided, encouraged, and stimulated by darkness. What havoc it worked in the case of Elmer Kooknit. On a park bench, sitting next to Leona Pamelach, with his eyes closed, he saw a world of grandeur, of loveliness, and of unsurpassed beauty. (The main story was told to me by Leona.) "You are so beautiful," he spoke in ecstasy. "Ah, you shine, you shine—" Here his vocabulary failed him. "You shine more, more than an ordinary shine." As he was talking with unopened eyes, Leona stole away to answer an urgent call of Nature. The vacant seat was soon occupied by another young woman. Near her stood her boy friend, a truck driver of no mean dimensions. Elmer now displayed extraordinary vitality, for both his hands reached out, in the dark, for forbidden zones. The powerful large hands of the truck driver were on Elmer's neck. Then came brutal blows and kicks in the abdomen. I saw Elmer at the hospital that night with a ruptured diaphragm. The rent was so large that there was a hernial protrusion of the stomach into the pleural cavity. The greatest problem I have to face now is shock.

October 22. . . . Minor events of a week.

Jack Blair consulted colleague Black about his wife's sterility. The living, kicking mind of the doctor is always ready to find the cause of anything, and remove it. "In a year you shall have a baby," he promised his patient. For a week he read up on the causes of low fecundity in women and on the factors affecting fertility. Minor causes must first be searched for—say erosion of the cervix. He examined the lady and found there was no cervix because there was no uterus.

Of course, itching is a manifestation of anxiety just as blushing and blanching are signs of shame and fear. There sat brother Paul and scratched himself vigorously. I asked him why he doesn't scratch himself at home. He retorted with the old chestnut, "If it itches on Broadway do you expect me to scratch myself on Park Avenue?" His poetry-quoting patient, Jonas by name, whom he treated for osteoarthritis of the cervical spine, had cashed a check with him. One-fifth, a hundred dollars, went for professional services; the other four-fifths went to the patient. The

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

check came, or rather rushed, back marked "No Account." Jonas, when threatened with arrest, said: "I am your friend! Now listen:

Lose not the friendship of a friend
in vain,
The same lost friendship you may
scarce regain.
Friendship once broken, like a china
bowl
Can never, never be again made
whole."

"I should never have trusted him," murmured the doctor. "It's wise to sometimes modify thought with an afterthought. Too late." He turned to me. "You know, so many oddities cluster around us professional men that I often wonder if we are really sane. As businessmen our I.Q. does not exceed that of a child of five."

October 24. . . . Sudden and unheralded death, result of coronary occlusion, in a young man of 21. And Tightwad is insane with joy. Such a rarity.

Acute bacterial endocarditis. Penicillin. Recovery. And Tightwad suffers from melancholic depression. He so anxiously and impatiently awaited the confirmation of the diagnosis by necropsy.

But there was the woman of 26 with two appendices, double cervix, and double uterus, and she is pregnant in each womb. And Tightwad is distributing cigarettes, completely recovered from his melancholia.

October 27. . . . They called me to an asthma emergency. By the time I arrived he felt better. I took him to my office for intradermal skin tests. Either because the serum was contaminated or because of extreme sensitivity to the material, I was faced with a dire emergency. I was thinking, after I had succeeded in warding off the threatened fatality, of the pride that we physicians take in parrying the scythe of death. Don't we sometimes bring the scythe with us when we treat the patient?

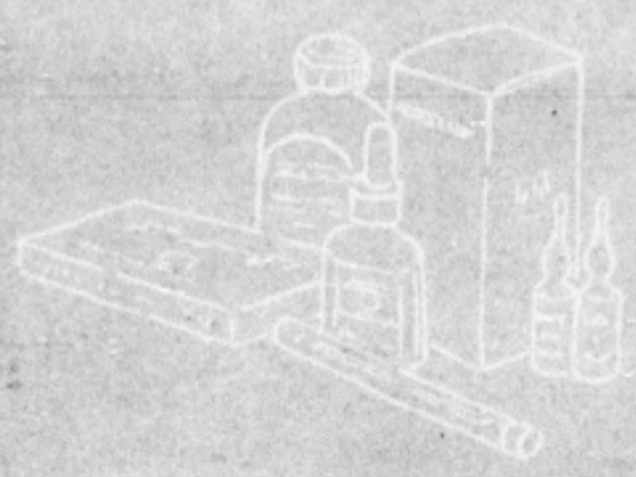
Allergy. John Miller is allergic to lipstick, though not to that of his wife. Dr. Allan discussed the advisability of sympathectomy. "Yes, I'll be needin' it," said John. "Needing what?" "Sympathy. The old lady got wise."

October 29. . . . The hemopoietic activity of folic acid was demonstrated in the case of young McIntire who was suffering from megaloblastic anemia. The patient responded well to folic acid therapy though he did not react to parenteral liver treatment. His father, reminded of the bill, requested that I stop at his house when I pass by. "Make it two o'clock," he said. I was there at the appointed hour. "He was expecting you," his wife informed me. "He sure was. He left."

October 31. . . . Eccentric Colleague Gleason came home highly agitated. He had just read the Pearl report that between the ages of 30 and 50 one out of five heavy smokers dies before his time. He had also read about the investigations of Hoag and Larson, who found that a noninhaling smoker excretes in his urine one-tenth as much nicotine as is excreted by the inhaling smoker who smokes the same number of cigarettes a day. "I am doomed," he moaned. "Doomed, I say. I am an incessant smoker. What chance do I stand?" He lit a cigarette and puffed at it nervously. His wife's piano-playing irritated him. "You should have the bust of Beethoven on top of the piano, not that of Bach. Beethoven at least was deaf." She rose, put on her coat, and smiled. "So you are going shopping again," he whined, "spending some more money." She told him that she was going shopping only to buy what she needed, and she needed plenty. "And I'll buy you a carton of cigarettes." He looked pitifully at me after she left. "Do you think she read the Pearl report too? Lately she has been buying me too many cartons of cigarettes. My God. Do you think—?"

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Miscellany



SYNTROPAN IN GASTRIC DISORDERS

Kunstler (New York State J. Med., **47**:1248, 1947), in a discussion of the treatment of the gastritis-peptic ulcer syndrome, states that antispasmodics act on smooth muscle, affecting rhythm and spasm to a noticeable extent, and should be the medication of choice in this disorder. He recommends in particular the use of Syntropan ('Roche') and adds that this should be given in large enough dosage to exert its full effect.

Syntropan, the Roche antispasmodic, is the phosphate salt of 3-diethyl-amino-2, 2-dimethyl-propanol tropic acid ester.

Tablets: 50 mg, tubes of 20, bottles of 100; 100 mg, bottles of 100 and 1000.

Powder: 5-Gm and 25-Gm vials.

ANDROGENS IN ANGINA PECTORIS

Lesser (J. Clin. Endocrinol., **6**:549, 1946) in a report on the use of testosterone propionate for the treatment of angina pectoris, states that improvement in the amount of exercise which could be tolerated and in the severity of attacks was noted after treatment with this hormone. Excellent results were obtained in 100 patients (92 men and 8 women) who were treated by 25-mg injections of testosterone propionate twice a week for the first 2 weeks and once a week thereafter for a total of 12 injections. No response was elicited when placebos were given as controls.

Neo-Hombreol* is the Roche-Organon brand of testosterone propionate.

Ampuls (1 cc): 5, 10, and 25 mg; boxes of 3, 6, and 50.

PROSTIGMIN AS TEST FOR PREGNANCY

Natenshon (West J. Surg., **54**:149, 1946) reports the use of Prostigmin* as a test for pregnancy; 1 cc of Prostigmin Methylsulfate, 1:2000, was given to 56 patients on each of 3 successive days. In 37, menstruation occurred and no evidence was found of pregnancy. In the remaining 19, no flow occurred and all but three underwent either delivery or abortion; the other three were not seen again by the author. Natenshon concludes: "The procedure has been found to be simple, inexpensive, and almost 100 per cent accurate, provided the usual limitations are observed."

Prostigmin Methylsulfate 'Roche' (for injection).

Ampuls (1 cc): 1:2000 (0.5 mg), boxes of 12 and 50; 1:4000 (0.25 mg), boxes of 12.

* Reg. U. S. Pat. Off.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Roche Specialties

Allonal*—Non-narcotic hypnotic-analgesic tablets containing allyl-isopropyl barbituric acid plus acetophenetidin. Prompt, smooth action, notably free of undesirable by-effects. Valuable in insomnia associated with pain or nervous tension. Boxes of 12 and 50 tablets.

Berocca* Compound—Tiny, high-potency tablets containing the essential factors of the vitamin B group in a well-balanced formula. Well-tolerated and easy to take, assuring maximum patient co-operation. Bottles of 30, 100, 250, and 1000 tablets.

Berocca* -C—An injectable, stable solution containing, in each 2-cc ampul, 20 mg thiamine hydrochloride, 6 mg riboflavin, 40 mg niacinamide, 6 mg pyridoxine hydrochloride, 6 mg sodium pantothenate, and 100 mg ascorbic acid; may be used intramuscularly or subcutaneously (given slowly, full-strength) or intravenously if diluted 20 times. Ampuls (2 cc); boxes of 6, 25, and 100.

Cal-C-Tose*—Delicious, chocolate-flavored vitamin supplement. Contains vitamins A, B_1, B_2, C, D, and niacinamide, plus dibasic calcium phosphate and iron. Especially useful for children, pregnant and nursing women, and convalescents. Powder, available in 12-oz and 5-lb cans.

Citro-Thiocol*—Well-balanced prescription for the control of cough; ingredients are blended into a pleasant-tasting aromatic syrup. Available in 4-oz, 16-oz, and 1-gallon bottles.

Digalen*—Dependable digitalis medication containing the cardioactive glycosides of whole-leaf digitalis free from fats, resins, and inert substances. Oral tablets of ½ and 1 cat unit (0.4 and 0.8 U. S. P. XII digitalis unit); boxes of 4 vials, 25 tablets per vial. Oral liquid; 30-cc vials (1 cc= 1 cat unit). Injectable ampuls, 2 cc (1 cat unit), boxes of 6 and 12.

Elixir Alurate*—Pleasant-tasting liquid sedative-hypnotic containing ½ gr of Alurate (allyl-isopropyl-barbituric acid) per fluidram. Prompt action; rapid elimination, minimizing unpleasant after-effects. Available in 6-oz and 1-gallon bottles. Alurate is also available in tablet form.

Ephynal* Acetate—Alpha-tocopherol acetate—highly stable, potent vitamin E compound. Useful in threatened abortion and neuromuscular disorders. Oral tablets: 3 mg, bottles of 30 and 100; 10 mg, bottles of 50 and 250; 25 mg, bottles of 50, 250, and 1000; and 50 mg, bottles of 30, 100, and 500.

Imadyl* Unction—Skilfully blended histamine ointment for the rapid relief of arthritic, rheumatic, and neuralgic pain through vasodilation and local analgesia. Available in 1½-oz tubes and 1-lb jars.

Larostidin*—Histidine monohydrochloride, for ambulatory peptic ulcer therapy which does not usually require prolonged adherence to a strict dietary regimen. Ampuls (5 cc); boxes of 6 and 25.

Pantopon*—Highly purified injectable whole opium. Smooth balanced

* Reg. U. S. Pat. Off.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

action. Less likely than morphine to cause nausea, smooth muscle spasm, constipation, or pruritus. Ampuls, 1 cc (1/3 gr), boxes of 6 and 12; hypodermic tablets, 1/3 gr., tubes of 20; oral tablets, 1/6 gr., bottles of 20; powder, 1/8-, 1/4-, 1/2-, and 1-oz vials.

Per-Os-Cillin* —Penicillin calcium combined with special long-acting buffers for efficient oral penicillin therapy. Easy to take, stable, well-tolerated. Tablets, 50,000 and 100,000 units, vials of 12.

Prostigmin* —Parasympathetic stimulant of many uses—postoperative abdominal distention and urinary retention, myasthenia gravis; experimentally in poliomyelitis, rheumatoid arthritis, glaucoma, pregnancy diagnosis, etc. Ampuls (1 cc), 1:2000 (0.5 mg), boxes of 12 and 50; 1:4000 (0.25 mg), boxes of 12. Oral tablets, 15 mg, tubes of 20, bottles of 100. Ophthalmic solution.

Spasmalgin* —Spasmolytic, analgesic, and sedative, having this three-fold effect as a result of the combination of its three constituents, Atrinal (1/60 gr), Papaverine (1/3 gr), and Pantopon (1/6 gr). Tablets, tubes of 20 and bottles of 100; ampuls, 1 cc, boxes of 6.

Synkayvite* —Stable, highly active, nontoxic, water-soluble vitamin K-compound. Administered orally without bile salts, or parenterally. Oral tablets, 5 mg, bottles of 40, 100, 500, and 1000; ampuls, 5 and 10 mg, boxes of 6, 25, and 100.

Syntrogel* —Outstanding antacid of prompt action and prolonged effect. Does not cause alkalosis or rebound of acid secretion. Bottles of 50, 100, 250, and 1000 tablets.

Syntronal* —Dependable sedative-antispasmodic containing 50 mg of Syntropan and 15 mg of phenobarbital per tablet. Valuable in spastic disorders of gastrointestinal and urinary tracts, and spastic dysmenorrhea. Bottles of 30, 100, and 1000 tablets.

Syntropan* —Non-narcotic antispasmodic with a dual action—musculotropic and neurotropic. Minimum of by-effects. Oral tablets; 50 mg, tubes of 20, bottles of 100; 100 mg, bottles of 100 and 1000. Powder, 5-Gm and 25-Gm vials.

Syrup of Thiocol* —Syrup of Thiocol is a cough remedy of long-established therapeutic merit; does not contain sedatives or narcotics. Available in 6-oz and 1-gallon bottles.

Vi-Penta* Drops—Easy-to-take multivitamin drops containing vitamins A, B_1, B_2, C, D, and niacinamide plus dibasic calcium phosphate and iron. Added to liquid foods, the drops do not significantly alter the flavor. Available in 15-cc and 30-cc vials, and 60-cc packages.

Vi-Penta* Perles 'Roche'—Tiny, easily swallowed capsules containing the same vitamins as the Drops. Boxes of 25 and 100, bottles of 250.

Vitaminets* —Efficacious, economical, vitamin-mineral tablets so palatable that they may be chewed. Contain liberal amounts of 9 essential vitamins and 5 important minerals. Bottles of 30, 100, and 250.

*Reg. U. S. Pat. Off.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Roche-Organon Specialties

Cytora*—A modern hematinic containing folic acid, liver, iron, vitamin C, and B-complex factors, for the treatment of hypochromic anemias. Bottles of 100, 250, and 1000 tablets.

Dimenformon*—Pure crystalline alpha-estradiol, biologically standardized. It is chemically identical with the estrogenic hormone. Among its effects are increased stratification of the squamous layers of the vaginal epithelium, hypertrophy of the myometrium, enlargement of the mammae, and development of the female secondary sex characteristics. Tablets, 0.1, 0.2, and 0.5 mg; boxes of 30, 60, and 250.

Dimenformon Benzoate 'Roche-Organon'—Biologically standardized follicular hormone, the pure crystalline benzoic acid ester of alpha-estradiol, in oil solution. The physiologic properties of Dimenformon Benzoate are similar to those of Dimenformon. Dimenformon Benzoate, however, is intended for parenteral use. Ampuls (1 cc): 0.1 and 0.166 mg, boxes of 6, 50, and 100; 0.333 and 1 mg, boxes of 3, 6, 50, and 100; and 1.66 mg, boxes of 5, 50, and 100. Vials (10 cc), 0.333 mg and 2 mg per cc.

Dimenformon Dipropionate 'Roche-Organon'—Pure, crystalline dipropionic acid ester of alpha-estradiol, in oil solution. Possesses the same degree of therapeutic activity as Dimenformon Benzoate, but its action is of more prolonged duration. Ampuls (1 cc): 0.1 mg and 0.2 mg, boxes of 6 and 50; 0.5 mg, 1 mg, 2.5 mg, and 5 mg, boxes of 3, 6, and 50.

Di-Pro Ampuls*—Combination of Dimenformon Benzoate (2.5 mg per ampul) and Progestin (12.5 mg per ampul), for the shortened treatment of secondary amenorrhea. Boxes of 2 ampuls of each or 6 ampuls of each.

Doca*—Oil solution containing in each cc 5 mg of pure, synthetic, crystalline desoxycorticosterone acetate. The use of Doca is followed by improvement in sodium and chloride retention, increased potassium excretion, increased plasma volume and total plasma content of sodium and chloride, increase in body weight and blood pressure, and improved appetite and strength. Ampuls (1 cc), 5 mg; boxes of 3, 6, and 50. Vials (10 cc), 5 mg per cc; supplied singly.

Liquaemin*—Sterile isotonic solution of the highly purified sodium salt of heparin. Used in conditions in which prolongation of the blood coagulation time is indicated, especially postoperatively to avert the danger of thrombosis. Available in 10-cc rubber-capped vials, each cc containing 10 mg of sodium heparin (equivalent to 1100 Toronto units), and 0.45% phenol as a preservative.

Lynoral*—Ethinyl estradiol, synthetic estrogen closely related to alpha-estradiol, for oral administration. Indicated for use in control of meno-

* Reg. U. S. Pat. Off.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

pausal symptoms, symptomatic treatment of prostatic carcinoma, infantilism, menstrual disturbances resulting from estrogen deficiency, and juvenile and senile vaginitis. Tablets, 0.05 mg; bottles of 30, 60, 250, and 1000. Elixir, 0.03 mg per 4 cc, 4-oz and 1-pint bottles.

Menformon*—Highly purified estrogen, physiologically standardized. Menformon possesses physiologic properties similar to those of naturally occurring estrogenic hormone. May be used in menopausal and menstrual disorders. Vials (25 cc), 10,000 I.U. per cc, and 25,000 I.U. per cc, boxes of 2 vials.

Menformon Dosules 'Roche-Organon'—Highly purified estrogen in an improved, hydrophilic ointment base. May be used alone, in conjunction with, or after, more intensive (parenteral) estrogenic medication. They may also supplement or partly replace parenteral treatment. Dosules, 2000 I.U. and 5000 I.U.; boxes of 10 and 25.

Neo-Hombreol*—Synthetic testosterone propionate, the potent crystalline male sex hormone derivative, in oil solution for parenteral administration. For use in the male climacteric, early prostatic hypertrophy, impotence, hypogonadism, cryptorchidism, castration, various nervous and mental disturbances associated with male sex hormone deficiency, and certain disorders in the female. Ampuls (1 cc), 5, 10, and 25 mg; boxes of 3, 6, and 50. Vials (10 cc), 10, 25, and 50 mg per cc.

Neo-Hombreol (M) 'Roche-Organon'—Methyl testosterone, synthetic androgenic hormone preparation which is effective when given orally or percutaneously. Methyl testosterone has the same physiologic effects as testosterone propionate. Tablets, 10 mg; boxes of 15, 30, and 100; 25 mg, boxes of 15 and 100. Dosules (2 Gm), 4 mg, for cutaneous application; boxes of 25.

Progestin 'Roche-Organon'—Synthetic crystalline progesterone, identical with the pure corpus luteum hormone, in oil solution. Indicated in threatened and habitual abortion, and has been used with some success in menorrhagia, metrorrhagia, amenorrhea, dysmenorrhea, and premenstrual tension. Ampuls (1 cc): 1, 2, and 5 mg, boxes of 6 and 50; 10 mg, boxes of 3, 6, and 50. Vials (10 cc), 5, 10, and 25 mg per cc

Progestoral*—Pregneninolone (anhydro-hydroxy-progesterone), orally effective progestogen. It is a synthetic crystalline substance closely related chemically to progesterone, and can be used in the same conditions as the latter. Tablets: 5 mg, boxes of 20, 40, 100, and 250; 10 mg, boxes of 10, 20, 40, 100, and 250.

Thyroxine 'Roche-Organon'—The natural hormone of the thyroid gland synthesized by the Harington and Barger method. Crystals; 100-mg vial. Ampuls (1 cc), 1 mg; boxes of 6, 12, and 100. Tablets, 1 mg; vials of 30, bottles of 100. Ophthalmic solution, 7½-cc vial, 2 mg per cc.

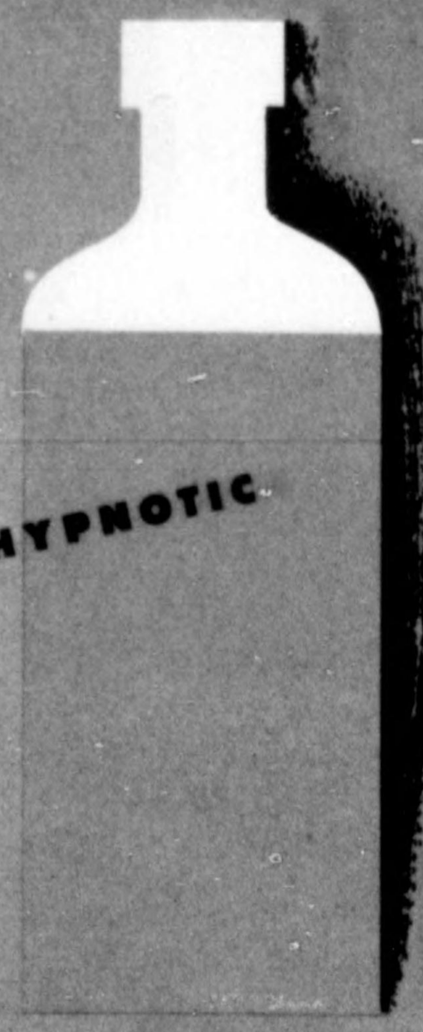
* Reg. U. S. Pat. Off.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Alurate

DEPENDABLE LIQUID SEDATIVE—HYPNOTIC

. . . alone or combined



FOR SIMPLE INSOMNIA

Elix. Alurate 'Roche' . . . . . 120 cc (℥ iv)
Sig. 8 cc (ʒ ii) at bed time p. r. n.

FOR MENOPAUSAL NERVOUS TENSION

Sod. Bromide . . . . . 12 Gm (ʒ iii)
Tr. Hyoscyamus . . . . . 12 cc (ʒ iii)
Elix. Alurate, q.s. . . . . 120 cc (℥ iv)
M. Sig. 4 cc (ʒ i) in water three times a day.
(Dispense with "Shake Well" label)

FOR SPASTIC DYSMENORRHEA

Syntropan . . . . . 2 Gm gr. xxx
Elix. Alurate . . . . . 90 cc (℥ iii)
Elix. Aromatic, q.s. . . . . 180 cc (℥ vi)
M. Sig. 8 cc (ʒ ii) in water as required.

FOR ANOREXIA IN NERVOUS PATIENTS

Elix. Thiamin HCl
Elix. Alurate, aa . . . . . 90 cc (℥ iii)
M. Sig. 8 cc (ʒ ii) three times a day before meals.

FOR NEURITIC PAIN

Sod. Salicylate . . . . . 15 Gm (ʒ iv)
Elix. Alurate, q.s. . . . . 120 cc (℥ iv)
M. Sig. 4 cc (ʒ i) every 4 hours.

FOR SPASTIC COLITIS

Tr. Belladonna . . . . . 12 cc (ʒ iii)
Elixir Alurate, q.s. . . . . 180 cc (ʒ vi)
M. Sig. 4 cc (ʒ i) every 3 to 4 hours as required.
(Dispense with "Shake Well" label)

HOFFMANN • LA ROCHE INC • NUTLEY 10 • N. J.

Elixir Alurate 'Roche' containing ½ gr of Alurate (allyl-isopropyl-barbituric acid) per fluidram, is available in 6-oz, 1-pint and 1-gal bottles.

elixir alurate 'ROCHE'

T. M.—Alurate—Reg. U.S. Pat. Off.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

FOR THREATENED AND HABITUAL ABORTION In the treatment of habitual abortion, "vitamin E should be used because it appears to offer great hope in salvaging pregnancies that would otherwise habitually abort."* Ephynal Acetate —the Roche vitamin E preparation (α-tocopherol acetate)—is particularly suitable for the treatment of habitual and threatened abortion because it is stable, of unvarying potency and purity, and well tolerated even in large doses and over long periods of time. Its freedom from side reactions is of signal value in all disorders amenable to vitamin-E therapy. Available in tablets of 3, 10, 25, and 50 mg.

HOFFMANN-LA ROCHE INC • Roche Park • Nutley 10 • New Jersey.

*A. T. Hertig & R. G. Livingstone,
New England J. Med., 230:798, 1944

ephynal acetate

'ROCHE'

T.M.—EPHYNAL—REG. U. S. PAT. OFF. Printed in U. S. A.

NEO-SYNEPHRINE

Elixir

WINTHROP

Winthrop CHEMICAL COMPANY, INC.

PHARMACEUTICALS OF MERIT FOR THE PHYSICIAN

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

NEO-SYNEPHRINE HYDROCHLORIDE

Elixir

NEO-SYNEPHRINE* hydrochloride is a synthetic sympathomimetic drug which has approximately the same field of usefulness as epinephrine and ephedrine. However, Neo-Synephrine hydrochloride rarely produces the undesirable side effects of epinephrine and ephedrine such as tremor, pallor, perspiration, palpitation or collapse. In contrast to epinephrine or ephedrine the pressor effect of Neo-Synephrine hydrochloride is obtained without increase in the heart rate, increase in the irritability of the heart, or production of extrasystoles or other arrhythmias. Furthermore, Neo-Synephrine hydrochloride does not produce nervousness and apprehension, nor does it lose its effectiveness after repeated administration.

DESCRIPTION

Neo-Synephrine hydrochloride is laevo-α-hydroxy-β-methylamino-3-hydroxy ethylbenzene hydrochloride. Chemically it is closely related to epinephrine and ephedrine. In contrast to epinephrine which is readily decomposed, Neo-Synephrine hydrochloride is relatively resistant to decomposition by boiling, exposure to light and air and contact with alkaline solutions.

Neo-Synephrine Hydrochloride Elixir contains 0.1 per cent (1 mg. per cubic centimeter) of Neo-Synephrine hydrochloride in a pleasantly flavored vehicle, alcohol content 8 per cent.

*Neo-Synephrine, trademark reg. U.S. Pat. Off., Sterling Drug, Inc., brand of phenylephrine originated by Frederick Stearns & Company.

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

ACTION

The pressor and antiallergic actions of Neo-Synephrine when administered by mouth are essentially the same as when injected parenterally except that much larger doses are necessary.

Tainter and Stockton[1] demonstrated that oral administration of Neo-Synephrine hydrochloride in total doses of from 120 to 300 mg. caused an increase in blood pressure which was sustained for two or more hours. Keys and Violante[2] state that Neo-Synephrine hydrochloride is effective when taken by mouth but relatively large amounts are necessary. In the basal state the threshold oral dose is from 40 to 60 mg. in the average young adult. The oral dose is about fifty times the subcutaneous dose; that is, 250 mg. orally are roughly equivalent to 5 mg. subcutaneously. With this dose the pulse rate is decreased about 20, the systolic pressure is increased 30 mm., while the diastolic pressure is increased about 20 mm. in normal human beings. After oral administration the effects are slower but last longer than after subcutaneous injection.

CLINICAL USE

Hypotension. — Capaccio and Donald[3] in a report on idiopathic orthostatic hypotension indicate that the treatment is largely symptomatic. They state that Neo-Synephrine hydrochloride has advantages over other drugs used for this treatment in that it is effective, has practically no side reactions and does not develop a tolerance. The dose used, starting at 150 mg. per day and decreasing to 60 mg., enabled the individual to carry on a useful life. Gregory[4] states that in orthostatic hypotension Neo-Synephrine hydrochloride produces the greatest benefit of any of the sympathomimetic drugs. There were no central nervous symptoms following the administration of 50 mg. every two hours. Hines,[5] in his discussion of the differential diagnosis of orthostatic hypotension, points out the advantage of Neo-Synephrine hydrochloride over ephedrine. In smaller than the aforesaid doses, Neo-Synephrine hydrochloride may be used in the treatment of the more mild cases of hypotension.

Asthma, Hay Fever, Bronchitis. — In the symptomatic treatment of moderately severe attacks of bronchial asthma Falk[6] reported that a capsule containing 5 grains of aminophylline with ¼ grain of Neo-Synephrine hydrochloride and ½ grain of phenobarbital sodium administered every two to three hours, as necessary, is of value. Others have reported similar findings. In the management of the asthmatic attack, Holt and McIntosh[7] found Neo-Synephrine hydrochloride elixir to be very effective in children, 1 teaspoonful doses being used for children 8 years of age. Occasionally, sedatives such as the soluble barbiturates were added to allay nervousness.

For the treatment of bronchial coughs in adults Neo-Synephrine hydrochloride elixir with codeine is efficient. Iodides and ammonium chloride may be added if expectorants are desired.

There are also reports which indicate that in many individuals hay fever symptoms are decreased following the oral use of Neo-Synephrine hydrochloride.

1. Tainter, M. L., and Stockton, A. B.: *Am. Jour. Med. Sc.*, 185:832, June, 1933.
2. Keys, A., and Violante, A.: *Jour. Clin. Invest.*, 21:1, Jan., 1942.
3. Capaccio, G. D., and Donald, C. J.: *J.A.M.A.*, 110:1180, Apr. 9, 1938.
4. Gregory, R.: *Am. Heart Jour.*, 29:246, Feb., 1945.
5. Hines, E. A., Jr.: *Minnesota Med.*, 22:318, May, 1939.
6. Falk, O. P. J.: *Trans. Am. Therap. Soc.* (1939), 39:72, 1940.
7. Holt, L. E., Jr., and McIntosh, R.: Diseases of Infancy and Childhood. New York, D. Appleton-Century Co., 11th ed., 1940, page 922.

Fatigue.—Kotalik, Maison and Pfeiffer[8] described a significant increase in work capacity following intramuscular injections of from 5 to 10 mg. of Neo-Synephrine hydrochloride. Larger doses given orally have the same effect. Persons of around 50 years of age complaining of low backaches and easy fatigability, and with systolic blood pressures of 110 or less, have responded well to 40 or 60 mg. of Neo-Synephrine hydrochloride per day. Any pathology relative to the cause of backaches should be ruled out. Subjective symptoms often disappear, with blood pressure changes being almost nil. Occasionally, however, there may be a rise of a few millimeters in systolic pressures.

CAUTION

In patients with hypertension, heart disease, diabetes or hyperthyroidism, Neo-Synephrine hydrochloride should not be used or with caution only.

DOSAGE

Average dose for adults and children is 1 or 2 teaspoonfuls three or four times daily by mouth.

HOW SUPPLIED

Neo-Synephrine Hydrochloride Elixir is supplied in bottles of 8 fl. oz.

8. Kotalik, G. C., Maison, G. L., and Pfeiffer, C.: *Am. Jour. Med. Sc.*, 206:503, Oct., 1943.

Address professional correspondence to the respective main office (170 Varick Street, New York 13, N. Y., or 1019 Elliott Street West, Windsor, Ont.) or to the nearest of the following professional service offices:

Atlanta 3	1024 Candler Building
Baltimore 2	1628 O'Sullivan Building
Boston 16	441 Stuart Street
Buffalo 3	14 Lafayette Square
Chicago 1	180 N. Michigan Avenue
Cleveland 15	423 Republic Building
Fort Worth 2	908 Neil P. Anderson Building
Los Angeles 13	408 S. Spring Street
Memphis 3	46 N. Third Street
Minneapolis 2	1800 Rand Tower
New Orleans 12	806 Hibernia Bank Building
Philadelphia 7	626 Widener Building
San Francisco 4	One Eleven Sutter
St. Louis 8	3615 Olive Street
Seattle 4	1002 Second Avenue
Honolulu (T. H.)	421 Damon Building
San Juan (P. R.)	Calle Fortaleza #352
Manila (P. I.)	670 Dasmariñas
Montreal (Que.)	Dominion Square Building
Kingston, Jamaica (B. W. I.)	141 Harbour Street
Port-of-Spain, Trinidad (B. W. I.)	#1 Chacon

WINTHROP

WINTHROP CHEMICAL COMPANY, INC.

Pharmaceuticals of merit for the physician

NEW YORK 13, N. Y. **WINDSOR, ONT.**

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Printed in U.S.A. 3-47 (8420)

DECLASSIFIED E.O. 12065 SECTION 3-402/NNDG NO. 775013

Demerol

HYDROCHLORIDE

Analgesic · Spasmolytic

Sedative

FOR ORAL AND
INTRAMUSCULAR
ADMINISTRATION

1

WINTHROP

WINTHROP CHEMICAL COMPANY, INC.