fungistatic property, (3) thymol and oil of cinnamon show excellent fungistatic action in any of the bases used but particularly in vanishing cream or cold cream, (4) ointments of thymol or oil of cinnamon or a combination of both in either cold cream or vanishing cream are superior to any of the ointments tested including three commercial ointments.

The favorable results of the *in vitro* reactions of thymol and oil of cinnamon seem to indicate that a clinical trial is warranted. The following specific formula and certain modifications of it are suggested.

Thymol	2.5 Gm.
Oil of cinnamon	1.0 cc.
Cold cream	
or	
Vanishing cream *q. s.*	100.0 Gm.

Cold cream should be used as the base when the soothing effect of an oily substance is desired or when the addition of salicylic acid is desired.

U. S. P. iodine ointment may be used as the base if the bacteristatic action of iodine is desired in addition to the fungistatic action of the thymol and oil of cinnamon.

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"To know things well, one must know them in detail, and as this is infinite, our knowledge is necessarily superficial."—La Rochefoucauld.

Ointments Prepared by Emulsification

Improvements and Advantages Gained; Choice of Emulsion Systems; Selection of Vehicles

*By A. J. Gibson, Ph.C., H. E. Parker, B.S.Pharm., and Anne Almus, A.B.**

For the purpose of this paper there are two basic methods of preparation of ointments regardless of the vehicles chosen in formulating the finished product. (1) They are those ointments made without water (non-emulsified) and (2) those made with water (emulsified). As will be shown, the second seems to offer the most practical approach to improvement in ointment compounding whether it be from the medical or pharmaceutical viewpoint. Recognition of the advantages of the emulsified type of ointment are becoming apparent in medical circles. Recently Fantus (1) pointed out that ointments are contraindicated in acute inflammatory conditions of the skin because of their "heating quality." He elaborates further and shows that the exception to this is in the use of cream ointments or emulsions. In fact, this clinician states that the success or failure of the treatment used may depend on the proper choice of the ointment base. Mumford (2), in discussing the role of emulsifying bases in dermatology, observes that the application of ordinary bases as petrolatum, lanolin or mixtures of these offers an objectionable barrier for the serous discharge of the skin. Contrasting this with the advantages of emulsions in overcoming this objection, he shows the superiority of emulsified ointments as carriers for both oil-soluble and water-soluble ingredients. Emphasis is placed on the lack of progress in prescribing ointments; in fact, Mumford goes so far as to state "progress in prescribing ointments has not proceeded far beyond the lanolin and vaseline of fifty years ago." Traub (3) calls attention to one of the prime reasons why patients do not follow instructions and quickly tire of the ointments prescribed—because

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the active ingredients are incorporated in simple greasy bases unsuited for convenient application and removal.

Bamber (4) is in agreement with Fantus and Mumford in stating that ointments applied to the skin must not interfere with its normal function of radiation of heat and secretion. His own observations show that antiseptics usually give better results in emulsions than when combined in simply greasy bases. It becomes clear, therefore, that interest in improvement of ointment bases is by no means confined to the pharmaceutical profession. It is becoming increasingly evident that medical circles are demanding it, partly due, no doubt, to pres-

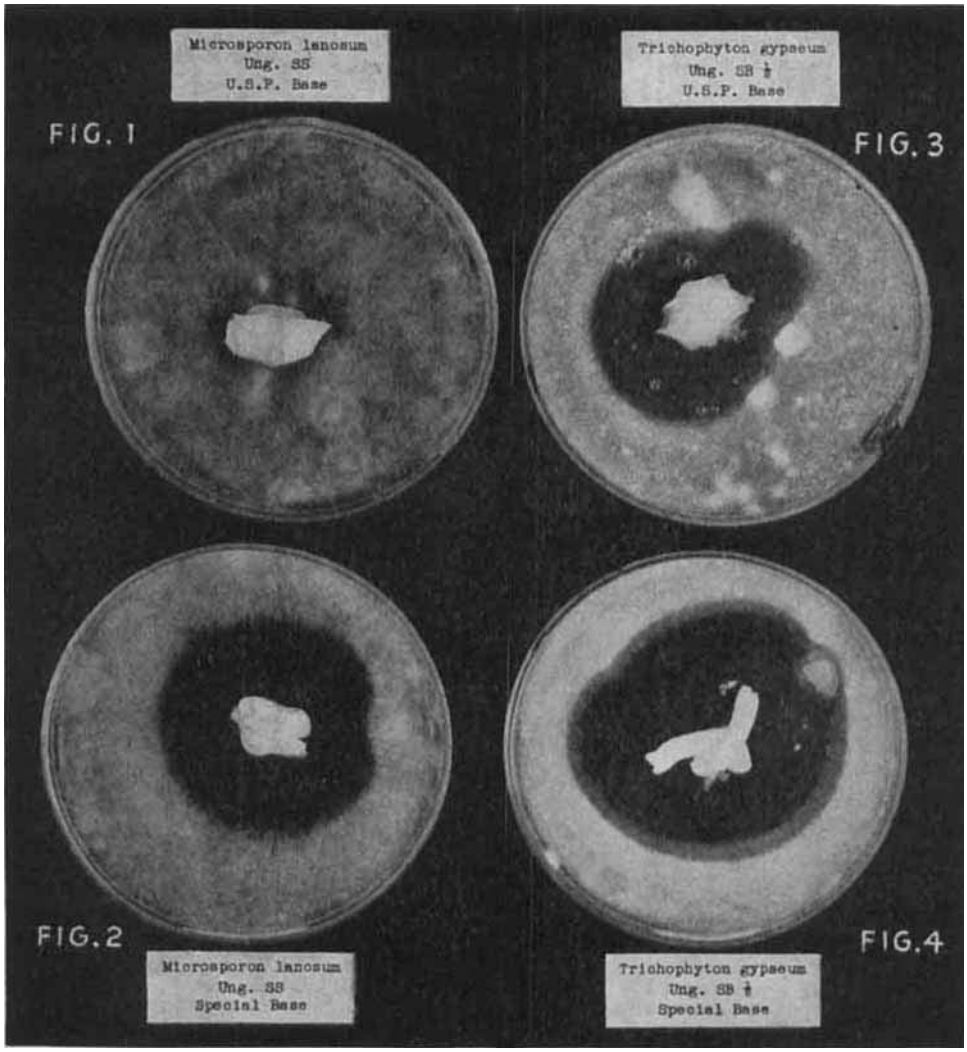

Fig. 1.—Test Organism: *Microsporon lanosum*. Period of Incubation: Seven Days at 20° C.

Sabourraud medium
Plate method
Width of zone: none

Fig. 2.—Test Organism: *Microsporon lanosum*. Period of Incubation: Seven Days at 20° C.

Sabourraud medium
Plate method
Width of zone: 19 mm.

Fig. 3.—Test Organism: *Trichophyton gypseum*. Period of Incubation: Seven Days at 20° C.

Sabourraud medium
Plate method
Width of zone: 14 mm.

Fig. 4.—Test Organism: *Trichophyton gypseum*. Period of Incubation: Seven Days at 20° C.

Sabourraud medium
Plate method
Width of zone: 25 mm.

sure from the public in logically expecting their local medication in a less obnoxious form. This fact is borne out by the experience of the authors in this laboratory in filling a large number of dermatological prescriptions over a ten-year period. It has been the experience of our staff physicians and the specialists in dermatology that better coöperation is obtained from the patients if the ointments are prepared in an emulsified manner. It has been found that they do not stain as readily, are less conspicuous when applied, and are easier to remove in washing from the skin or where the clothing comes in contact with the material.

Aside from the point that emulsified ointments do not seem to interfere in the same degree with the physiological processes of the skin secretions as previously indicated, and they are cosmetically more acceptable to the patient, there is another factor that can be illustrated to advantage. Better results are secured with the bacteriostatic or bacteriocidal agents when incorporated in this newer manner as measured with the agar plate or agar cup method. Kuever and Burnside (5) prepared a W/O ointment emulsion of mercuric nitrate of the same percentage as the N. F. VI. They found that their preparation was three times more effective as measured by the agar cup method, using *Staphylococcus aureus* as the test organism. Gershenfeld and Brillhart (6) recently studied some of the synthetic wax and oxycholesterin bases as emulsifiers for ammoniated mercury, phenol and mercuric chloride. They conclude that these bacteriocidal agents produce better results when emulsified in the newer bases as compared to the same agents in benzoinated lard, petrolatum, lanolin and the U. S. P. XI base. In evaluating the results, the F. D. A. agar plate and cup method with *Staphylococcus aureus* was used. Additional work here in this laboratory extending back some five years, bears out the investigation of Kuever and Burnside, Gershenfeld and Brillhart.

EXPERIMENTAL

In an attempt to appraise the effect of emulsified ointments and non-emulsified ointments on other than *Staphylococcus aureus*, the authors selected two mold cultures, *Microsporon lanosum* and *Trichophyton gypseum*. These were obtained from clinical cases from the department of dermatology of the University of Michigan Hospital. Our reasons for selecting these mold cultures were twofold. First, *Microsporon lanosum* is very commonly present in seborrhoea of the scalp. *Trichophyton gypseum* is one of the fungi responsible for tinea of the feet and hands. Secondly, both are very resistant to ordinary chemical agents commonly used in the treatment of the lesions caused by these fungi in man. Both groups of formulas listed below have been used in treating these infections, by the physicians on the staff for five years or longer. Those treated were student patients presenting themselves at the Health Service with the typical clinical picture of seborrhoea of the scalp or tinea of the feet or hands. It is hardly within our province to discuss any clinical results obtained with these emulsified ointments as contrasted with the same formulas of such commonly known ingredients incorporated in the U. S. P. XI base. However, we can demonstrate the distinctly superior results of the growth-inhibiting properties of the emulsion ointments on the two cultures named and illustrated in the photographs herein.

Formulas

No. 1		Per Cent
	Sulfur Praec.	5.0
	Acid Salicyl.	2.0
	Base U. S. P. XI	93.0
		100.0

No. 2		Per Cent
	°Tegacid[1]	8.0
	Cetac.	7.0
	Ol. Theobrom.	5.0
	Petrolat. Liq.	8.0
	Acid Salicyl.	2.0
	Sulfur Praec.	5.0
	Aq. Dest.	65.0
		100.0

No. 3		Per Cent
	Acid Salicyl.	3.0
	Acid Benz.	6.0
	Base U. S. P. XI	91.0
		100.0

No. 4		Per Cent
	°Tegacid	15.0
	Ol. Theobrom.	10.0
	Petrolat. Liq.	3.0
	Acid Salicyl.	3.0
	Acid Benz.	6.0
	Aq. Dest.	63.0
		100.0

Observing sterile technique, two poured plates were made with Sabourraud's medium and each of the molds (*Microsporon lanosum* and *Trichophyton*

[1] A type of Glyceryl Monstearate supplied by Goldschmidt Corp., New York, N. Y.

gypseum). On hardening, 1-Gm. samples of ointment No. 1 in U. S. P. base and No. 2 emulsified base were placed on the Microsporon plates. One-gram samples of ointment No. 3 in U. S. P. base and No. 4 emulsified were placed on the Trichophyton cultures. The plates were incubated at 20° C. for seven days and then photographed.

DISCUSSION

To recapitulate then the advantages of emulsified ointments compared to those not emulsified: (1) It has been shown that they do not interfere in the same degree with the normal function of the skin secretions. (2) There is reason to believe that they are more effective when applied. (3) They are certainly more acceptable cosmetically from the patient's viewpoint. (4) They are more effective as bacteriostatic or bacteriocidal agents when tested by the agar plate, agar cup or other acceptable procedures. If, then, ointment emulsions have decided advantages, what is the most desirable emulsion system to use and what type of emulsifiers should be selected? According to Clayton (7), who quotes Selmi and Hatschek, an emulsion is a system containing two liquid phases one of which is dispersed as globules in the other. Two types of systems are possible, water in oil or oil in water (8). The official cold cream is an example of the W/O type. Excellent as a cosmetic cream it is not suitable, or for that matter intended, as a base for ointments wherein the prescriber may wish to use a variety of therapeutic agents as benzoic and salicylic acids in Whitfield's ointment. It is obvious that the sodium soaps resulting from the reaction of sodium borate and the fatty acids of the waxes in the U. S. P. cold cream are incompatible with many of the every-day medicaments.

At this point attention is called to the premise that the type of emulsifier used will determine the type of emulsion formed (9). Therefore, for a W/O emulsion a hydrophobic colloid is indicated (10). In an emulsion of O/W the converse is true, namely, the hydrophilic colloid is the one of logical choice. Adherence to this cardinal principle will save time and trouble for the investigator in avoiding pitfalls in attempting to formulate emulsions using antagonistic emulsifiers (11). Powers, Leask and Warner (12) in a recent paper have added valuable information on hydrophobic colloids as emulsifiers for emulsions of W/O. They demonstrated that mixtures of cholesterols and cholesterol esters increase markedly the emulsion-forming properties of cholesterol. Fiero (13) calls attention to the use of hydrogenated oils in emulsions for formulating ointment bases. Much interest has been shown in late years by the pharmaceutical and medical professions in oxycholesterin so-called "absorption bases." Johnston and Lee (14) investigated these bases as vehicles in W/O emulsions for ointment use. They conclude that aside from extemporaneous use, they are sensitive to temperature changes and crack readily. The experience of the writers confirms this, in that absorption bases, as such, are not practical for ointment emulsions. We have found that attractive-appearing cosmetic creams can be formulated with twenty to thirty per cent of the material with as high as sixty-five per cent water. Even this emulsion, devoid of medicaments, did not shelf test well. If water contents of sixty to sixty-five per cent were used, the cream developed a granular appearance with slight "sweating" of water on long standing. The spreading quality was poor. Drag was noticeable. If the water content of the cream was reduced to a level of forty to fifty per cent, the emulsion developed "bleeding" of the oil fraction. Our experience covered the use of such proprietary bases as Protegin, Protegin X and Aquaphor.

Apparently the most logical approach to formulating stable ointment emulsions is with the O/W type. They are easy to formulate and from a cosmetic standpoint they approach the ideal in consistency, color and spreading qualities. Inherently, this emulsion system possesses a stability that has much to recommend it. It is possible to incorporate large amounts of water without upsetting the equilibrium of the two phases; a total of seventy per cent as the dispersing phase is not at all unusual. The importance of the water content has been set forth by Prout, Eddleman and Harris (15) in a study of silica gel as a vehicle for different germicides. They believe that high percentages of water allow greater diffusion of the antiseptic from the ointment base and enhance its efficiency when applied. From a medical viewpoint, Wise and Wolf (16) in discussing the parasiticidal action of sulfur on the skin conclude that this action is in all probability due to the formation of H_2S. It seems natural that this would be favorably influenced by a high water content in an ointment emulsion. Wood (17) confirms the greater efficiency of O/W emulsions. He studied emulsions of acriflavine in W/O and O/W using a resistant strain of *Staphylococcus aureus* to determine the value of the emulsion. His results show that "emulsions of the O/W type have far greater bacteriostatic and germicidal properties than those of the W/O."

As in the case of W/O alkaline emulsions it would likewise appear advisable to avoid alkaline O/W emulsifiers. As examples, soaps resulting from the reaction of sodium, potassium or ammonium hydroxides with fatty acids are a basis for satisfactory O/W cosmetic creams. However, the ease with which these emulsions hydrolyze will obviously act as a limting factor for their use in ointment creams. The same seems obvious for emulsions of O/W prepared with the hydroxyethylamines and fatty acids. Though the emulsions formulated may be neutral or nearly so, the ease with which they also hydrolyze is a serious objection. The use of finely divided solids as emulsifying agents has been suggested by Tainter, Kulchar and Stockton (18) as well as by Cox and Goedrich (19). Attention is also being drawn to the use of synthetic waxes, high molecular weight fatty alcohols and mixtures of these. Mumford (20)

Soulsby (21), Gershenfeld and Brillhart (22), Clark (23) and Burnside and Kuever (24) have investigated and suggested formulas. Typical examples of proprietary synthetic waxes are diglycol stearate and oleate derived by the esterification of glycols with different fatty acids. Certain esters of polyhydric alcohols with high molecular weight fatty acids have come into wide use as O/W emulsifiers. Representative of these esters are glyceryl monostearate and glyceryl monostearate stabilized toward acids with acylated alkylene diamines. Though the second, known under the trade name Tegacid (25) is useful as a stabilizing emulsifier of acid ointment creams of O/W, the very nature of all of these esters mentioned are such as to have distinct limitations in use. Their action in the presence of alkalies, acids, salts, metals and strong electrolytes is too often unpredictable. In an effort to overcome these objections, we have tried out a large series of emulsifiers with the following objectives:

1. One that would promote O/W emulsions.
2. One that would promote emulsions stable to nearly all medicaments the pharmacist might be called on to incorporate.
3. The emulsifier must be economical to use. The finished emulsion should compare favorably in price with petrolatum.
4. The emulsifier should permit the use of at least fifty per cent water concentration, otherwise the ointment cream approaches petrolatum in greasy characteristics.
5. The material used must lend itself to both extemporaneous and stock preparation of ointment emulsions.
6. The emulsifier to be readily available and its composition known.

The results of our work indicate that a mixture of one-half per cent sodium lauryl sulfate and eight per cent cetyl alcohol appears to fulfil the conditions named. From a practical standpoint cetyl alcohol in itself is not a strong enough emulsifying agent for general use; it requires the use of a booster or auxiliary agent Sodium lauryl sulfate is not only compatible, but in itself is an outstanding emulsifier. The following serves to illustrate the composition of the emulsion minus any medication.

	Per Cent
Sodium lauryl sulfate	0.5
Cetyl alcohol	8.0
Roba[2]	6.5
Petrolatum Alba	20.0
Water	65.0

Procedure.—In preparing extemporaneous ointment emulsions, it has been a time-saving element to have the base prepared beforehand. This consists of the cetyl alcohol, petrolatum and roba previously melted in a suitable container over a water bath, the sodium lauryl sulfate then added and the whole stirred until cool. As calls are received, the water is determined arbitrarily at a fifty per cent ratio of the weight of the preparation to be made. The percentages of medicaments are then weighed out. The combined weight of water and medication subtracted from the total gives the desired amount of base to use. The base and medication are worked together on an ointment plate, the water previously warmed is added by degrees until a smooth cream results. For extemporaneous work it is obvious that the per cent of base will vary with the per cent of medication called for. Dependent on this factor, the amount of sodium lauryl sulfate and cetyl alcohol will vary slightly from the fixed ratio of one-half and eight per cent. Water content has been retained at a fifty per cent ratio in ointment emulsions in which medication is added. There is no reason other than that this water ratio is a convenient amount to work with and gives satisfactory results The following chemicals have been incorporated in this emulsion system, either separately, or combined in varying percentages:

Salicylic acid 3%/c Benzoic acid 6%.
Juniper tar (Oil of cade) 10%/c Salicylic acid 3%.
Coal tar 5%.
Kaolin 10%/c Sulfur precipitated 10%.
Ammoniated mercury 5% and 10%.
Sulfur precipitated 10%.
Phenol 2%.
Sulfathiazole 1%.
Balsam Peru 10%/c Sulfur precipitated 10%.
Salicylic acid 2%/c Sulfur precipitated 5%.
Calamine 8%.

CONCLUSIONS

1. The objections and shortcomings of the simple greasy vehicles for ointment bases have been reviewed from a medical and pharmaceutical standpoint. The need for improvement seems clear.
2. It has been demonstrated that emulsified ointments offer distinct advantages over the older non-emulsified types, both from a medical and pharmaceutical viewpoint. These points have been set forth.
3. Two emulsion systems have been discussed in relation to ointment bases, water in oil and oil in water.
4. It would seem the O/W type of emulsion system is the better choice of the two. The advantages have been explained.
5. A mixture of sodium lauryl sulfate one-half per cent with cetyl alcohol eight per cent has been suggested as a suitable emulsi-

[2] This may be left out. Experience shows that the emulsions are equally good without it. Our purpose in this laboratory was to incorporate it as an inexpensive substitute for cocoa butter. Supplied by Proctor and Gamble.

fier for stable O/W emulsified ointments.

6. A representative group of common medicaments has been incorporated with good results. The water content in all cases was in the ratio of fifty per cent.

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"To read textbooks is easy, but to do research is to grapple, inch by inch, with the obscure, and battle step by step, with the unknown."—Victor Robinson

Book Reviews

Biological Stains, by H. J. CONN and others. 4th Edition. 308 pages. $5^1/_4$ x $8^1/_8$. 1940. Geneva, N. Y.: Biotech Publications. $3.40.

The Commission on Standardization of Biological Stains was organized in 1920 and its function is to certify the quality of stains which are used in the United States by bacteriologists, pathologists, clinicians, etc. At present, this Commission is working in coöperation with pharmacy and much of its work is to be included in the next edition of the National Formulary.

The book contains valuable information concerning many important stains, as follows: characteristics and uses of important stains, dye synonyms, formulas for the preparation of solutions used for staining, color index number, Schultz number, relation of stains to their color index number, special techniques and their authors' names, methods of testing the more important stains, etc. The book also contains a large bibliography for staining techniques.—A. G. D.

Biology in the Making, by EMILY EVELETH SNYDER. xii + 539 pages. $5^1/_2$ x 8. 1940. New York: McGraw-Hill. $2.80.

This book is written in a style which will attract the scientist as well as the layman; and the more important phases of the biological sciences and the biographies of leading scientists are presented.

In each chapter the latest advances in biology and the scientists responsible for these achievements are given. Various illustrations are included. Some of the subjects discussed are: physiology, nutrition, blood anesthesia, chlorophyll, the cell theory, fossils, the germ theory, evolution and heredity, contagious diseases, serums, antitoxins, etc.—A. G. D.

Chemists Dictionary of Synonyms, 136 pages. 5 x $7^1/_4$. 1940. London: THE CHEMISTS AND DRUGGISTS. 5s. plus $.75 for handling charges.

This book is prepared and published by *The Chemist and Druggist* and includes many synonyms which are of aid to the average pharmacist in the practice of his profession.

Although this book is based upon Rouse's Synonyms, it should prove itself of value to the pharmacists in the United States.—A. G. D.

Manual of Clinical Chemistry, by MIRIAM REINER. xv + 296 pages. $4^3/_4$ x 7. 1941. New York: Interscience Publishers, Inc. $3.00.

This small laboratory manual which is a useful and a practical laboratory outline of clinical chemistry should be of interest to any pharmacist who is contemplating carrying out this type of work in his pharmacy.

Under the heading of blood analysis, gases and enzymes, inorganic constituents, carbohydrates,