

A method for determining cinchophen in mixtures with some other organic acids has been worked out. The results obtained with it in a limited number of trials are approximately correct.

The writer wishes to acknowledge his appreciation to the several pharmaceutical manufacturers and to others who have aided in this study, either by contributing material or by collaborative work.

NUTRITIONAL VALUE AND STANDARDIZATION OF COD LIVER OIL
AND OF ITS NON-SAPONIFIABLE FAT-SOLUBLE VITAMINE
CONCENTRATE (OSCODAL).*

BY HARRY E. DUBIN.

The empirical use of cod liver oil for the treatment of such diseases as rheumatism, gout, osteomalacia, tuberculosis, scrofula and rickets is age old. To-day, based upon indisputable experimental evidence demonstrating that the therapeutic value of cod liver oil is due to its fat-soluble antirachitic and antiophthalmic vitamine content, cod liver oil, in one form or another, is employed throughout the world as a specific in the prevention and cure of rickets and as a valuable aid in the management of other diseases and disturbances in nutrition.

Necessarily, the older theories which attributed the medicinal value of cod liver oil to its iodine or phosphorus content or to its peculiar virtues as a fat have been thrown into the discard.

While numerous references have been made to the unpalatability of even the best grades of cod liver oil, there has been no evidence to show that cod liver oil might be detrimental to health. Recently, however, there has been a report from Sweden that cod liver oil, in doses of 0.1 cc. per day, has exhibited a deleterious effect upon young white mice fed on an ordinary basal diet. Such reports as this, if broadcast and left unchallenged, would undoubtedly cause uneasiness in the mind of the layman. The report in question gives no details as to the nature of the diet used nor does it describe exact experimental conditions; consequently, it is not entitled to serious consideration, particularly so in view of the great mass of exact evidence which has accumulated to show the astonishing therapeutic effect of cod liver oil.

Although the publications in this field of research are too numerous to mention in detail, the author cannot resist the temptation to quote the work of Sherman and Campbell (1) who pointed out that a certain proportion of the antiophthalmic vitamine A in the diet would suffice to support normal growth but would not permit of successful reproduction. Eventually, the animals showed a susceptibility to lung disease at an age corresponding to that at which young adults develop pulmonary tuberculosis. Increasing the vitamine content enabled the animals to grow to full size and to reproduce successfully.

Similarly, such representative investigators as Mendel, Park, McCollum, Hess, Steenbock, Drummond, Mellanby and a host of others have conclusively demonstrated the value of cod liver oil in the diet of infants.

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This brings up the problem of how to supply the necessary fat-soluble vitamins in many cases in which cod liver oil either cannot be tolerated because of its disagreeable odor and taste or cannot be administered because of the necessity of keeping down to a minimum the amount of fat to be metabolized.

It is believed that the problem has been solved satisfactorily by preparing, from cod liver oil, a concentrate—to which the name "Oscodal"¹ has been given—possessing the therapeutic properties of cod liver oil, without the latter's objectionable qualities (2). The degree of concentration is sufficiently high to permit of mixing the concentrate with sugar and preparing a small tablet equivalent in vitaminic potency to one-half of one teaspoonful of cod liver oil.

The therapeutic value of this cod liver oil concentrate has been established beyond doubt (2) (3) (4) (5). An additional point of superiority of cod liver oil concentrate over fresh cod liver oil is indicated in the work² of Dr. Hattie L. Heft of Teachers College, Columbia University. This investigator has found it possible to raise four generations of white rats on a basal diet in which the only source of fat-soluble vitamins was this cod liver oil concentrate, administered in amounts corresponding to 28 milligrams of cod liver oil per day.

In similar experiments in which the source of fat-soluble vitamins was a daily dose of 28 milligrams of fresh cod liver oil, the animals failed to reproduce. This is in agreement with the work of Evans and Bishop (6) who found that it was impossible to secure reproduction successfully upon a ration containing as much as 9 per cent of cod liver oil, corresponding to about 500 milligrams of cod liver oil daily. Further work is necessary in order to establish the reason for this difference in action.

Another advantage of cod liver oil concentrate is that it is tolerated by the most sensitive stomachs and may be used in warm weather as well as in cold, since it furnishes the essential fat-soluble vitamins free from oil. It is thus possible to regulate the fat-soluble vitamin content of milk or other food-stuff without increasing the percentage of fat in the diet.

Regarding the question of dosage, this has been largely a matter of guess-work in the past. As a result, relatively large doses have been prescribed. In many instances, this large dosage has been the direct cause of digestive disturbances which, undoubtedly, served to limit the use of cod liver oil.

On this subject, McCollum (7) states, "There is no unanimity of opinion covering the proper dosage of cod liver oil for infants. We find that young rats cannot tolerate very liberal amounts (*e. g.*, above 6 to 7 per cent of the diet), without injury. Anyone who has taken the oil knows the tendency to disturbances of digestion which it causes. Experiments on animals show that relatively small amounts exert a profound influence in bringing about the healing of the rickets lesion. It seems logical to believe that many people are now giving children considerably more cod liver oil than is necessary."

It is only within the last year or two that evidence has been adduced to show that a smaller dosage could be used to bring about the desired result. However,

¹ This concentrate has recently been accepted by the Council on Pharmacy and Chemistry of the American Medical Association for admission to "New and Nonofficial Remedies." (*J. Am. Med. Assoc.*, 87, 671 (1926).)

² Unpublished data.

this is true only if a highly potent cod liver oil is used. For example, Holmes (8) showed that there was a wide variation in the potency of a number of samples of cod liver oil purchased in the open market. Working with ten different samples of oil, he found that the minimal dose for white rats varied from 0.715 mg. to 18.15 mg. per day. This variation indicates the necessity for knowing the vitamine potency of a given sample of cod liver oil before it is prescribed.

It is evident that the dosage will depend entirely upon the potency which, in turn, must be determined experimentally upon white rats.

Considerable work has been done in an effort to evolve some colorimetric method of determining the potency of cod liver oil. Drummond and Watson (9) and Rosenheim and Drummond (10) have proposed colorimetric methods which were used by the author as the basis for an investigation along these lines.

Nine samples of cod liver oil¹ were tested colorimetrically and a certain order of potency established. On comparing with the order of potency obtained in animal experiments by Dr. Holmes, it was found that in only five samples was there any agreement in potency.

Further work gave additional evidence of the limitations of the colorimetric standardization of the potency of cod liver oil. Different samples of cod liver oil give different shades of color, while some samples of cod liver oil which give an indifferent color reaction manifest a high potency when tested biologically.

Absolute reliance cannot be placed upon the colorimetric method of standardizing the vitamine potency of cod liver oil. As a rough method of approximating the relative potencies of a number of samples of oil of similar origin, the colorimetric method has its uses. It is also of value in testing the activity of a series of fractions prepared from cod liver oil. However, for an exact knowledge of the potency of medicinal oil, the biological method of testing is indispensable. The colorimetric method may ultimately supplant the biologic method, but for the present, the latter is the method of choice.

In standardizing cod liver oil or cod liver oil concentrate, a number of different diets were used from time to time, each of which gave satisfactory results. However, inasmuch as the requirements for fat-soluble vitamins vary with the type of diet used, it is best to select one type of diet and use it exclusively in order that the results obtained may be comparable. Similarly, it is desirable that different manufacturers and investigators should agree upon a given diet to be used by all. Only in this way would it be possible to compare the respective findings.

Some progress has been made in this direction, for at present, the preferred biologic method for determining the antiophthalmic vitamine A potency of cod liver oil (or of any other source of this vitamine) is that described in the U. S. Pharmacopœia (11). Briefly, the assay requires that the vitamine A potency of cod liver oil shall be expressed in units per gram of oil, the unit to be the minimum daily amount of cod liver oil required to cure induced symptoms of vitamine A starvation in young albino rats, and to cause a gain in weight of from 10 to 20 Gm. within a period of 35 days, starting after not less than 7 days of stationary or declining weight on the specified basal diet. No oil may be labeled as assayed by the U. S. P. method unless it contains at least 50 units per Gm. of oil.

¹ Cod liver oil samples supplied through the courtesy of Dr. Arthur D. Holmes.

As regards the antirachitic vitamine potency of cod liver oil, it is my opinion that it is of greater importance than the antiophthalmic vitamine potency. While cod liver oil is the richest source of both antirachitic and antiophthalmic vitamine, the latter is more widely distributed in foodstuffs and is, therefore, more likely to be present in the ordinary mixed diet. Consequently, the antirachitic vitamine potency of cod liver oil should be known before it is used.

While no specified antirachitic vitamine assay is described in the U. S. Pharmacopœia, it is generally considered that the method of McCollum, Simmonds, Shipley and Park (12) (or Steenbock and Black's (13) modification of this method) is acceptable for the purpose, the antirachitic unit being the minimum amount of oil per day which will suffice to initiate recalcification in the leg bones of young albino rats, maintained on a rickets-producing diet.

A good grade of medicinal oil ordinarily contains at least 50 antirachitic vitamine units and 250 antiophthalmic vitamine units per Gm. of oil.

Based upon animal experiments with oils of this quality, the commonly accepted dosage is from 1 to 4 cc. (15-60 minims) 3 times daily for children and from 4 to 6 cc. (60-90 minims) 3 times daily for adults. In this connection, Howland and Kramer (14) found that the administration of 2 cc. cod liver oil per day for a period of 2 months healed rickets in a 35 months old baby, while a dose of 2 to 4 cc. daily for 3 to 10 weeks was sufficient to cause active healing.

It is at once apparent that using a potent standardized oil, smaller dosages than have heretofore been used will produce the desired effect. Nevertheless, there are still instances in which even this small dosage is not tolerated. In such cases, the therapeutically active, non-saponifiable, fat-soluble, antirachitic and antiophthalmic vitamine concentrate of cod liver oil is available.

A triple control is maintained on the potency of this concentrate, in that first, the cod liver oil from which it is made is standardized; second, the concentrate itself is standardized; and third, the tablets are standardized, so that each tablet contains an amount of concentrate equivalent in vitamine potency to approximately 2 Gm. (one-half of one teaspoonful) of the cod liver oil from which it is prepared.

Discussing the relationship between vitamine A and disease, a recent editorial (15) states, "In a critical examination of the problem, Bloch (16) has emphasized the contributory role of impaired digestion in the genesis of xerophthalmia. Obviously, if the protective foods cannot be adequately digested and absorbed from the alimentary tract, it is futile to expect them to exert their normal functions. It now appears that when butter fat and cod liver oil, for example, are furnished after the symptoms have developed, the coincident digestive disturbances may militate against the effectiveness of the dietotherapy. . . . The situation thus outlined presents the problem of administering the protective or curative vitamin A in some other manner than by the oral route. . . . The parenteral administration of fats, for example, by subcutaneous-injection, although it has been lauded by a few clinicians, still presents too many objections and uncertainties to encourage its adoption except as an emergency measure. Perhaps progress in the isolation of active concentrates of vitamine A will lead to a more satisfactory possibility of meeting the difficult situations."

Cod liver oil concentrate, the non-saponifiable portion of cod liver oil, is well suited for the above purpose, containing as it does, the antirachitic as well as the

antiophthalmic vitamine in a form that is easily tolerated and readily assimilated. There is no need for the digestive apparatus to be burdened with the duty of splitting up a comparatively large amount of oil in order to get at the "minute essentials."

While the exact chemical nature of these fat-soluble vitamins is as yet undetermined, we know by the profound physiological effects which they bring about that without them, life cannot exist. Consequently, every effort should be made to provide for the presence of these factors in the diet at all times as a prophylactic measure.

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ABSTRACT OF DISCUSSION.

A brief discussion followed, relating chiefly to preparations of gaduol, etc., that had been and are on the market, entered into by Messrs. Nitardy, Githens, Warren, Holmes, Munch, Berg, Dubin and others. In reply to Dr. Munch, the author states that each tablet of cod liver oil concentrate contains approximately, 100 antirachitic and 500 antiophthalmic units. Dr. Holmes commented upon the impossibility of making a therapeutically active alcohol extract of cod liver oil. The author said that it behooves the physician to scrutinize closely the source and the composition of any preparation purporting to be a substitute for cod liver oil and to demand scientific proof relative to the therapeutic value of such preparations.

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STANDARDIZING CLINICAL THERMOMETERS.

The Federal specifications for clinical thermometers appeared as provided for the needs of the Government in Federal specifications No. 309, and the Bureau of Standards has as one of its functions the testing and certification of clinical thermometers submitted for that purpose by the Government or manufacturers.

In a report of Assistant Physicist Johanna Busse a defect of some clinical thermometers is pointed out. A thermometer having this de-

fect is known as a "retreater" and it is dangerous because it may give the physician misinformation. Such thermometers drop very quickly after being removed from the mouth to nearly normal and in that way the physician may be misled. Even thermometers which have passed every other test have been found with this defect and it is for that reason attention is called here.

At least two States supervise the sale of clinical thermometers; they are Massachusetts and Connecticut; also New York City.