The following graphs are plotted with the liters of oxygen absorbed by a gram-molecular amount of Carstanjen's compound, treated with a gram-molecular amount of potassium hydroxide, against the time, in minutes, required to absorb the oxygen.

Experiment V.—To avoid the obvious errors in time exposed, the oxygen was transferred to the reaction chamber and allowed to remain during the entire course of the experiment. The reaction chamber was placed in a shaking machine and shaken during the time the solutions were exposed to the action of the oxygen. In this manner the following results were obtained:

Wt. of Carstanjen's compound.	Wt. of KOH.	Cc. of O_2 abs.	Wt. of O_2 abs.	Time.
2.0 Gm.	0.5 Gm.	82.1	0.1163 Gm.	7 min.
1.0 Gm.	0.25 Gm.	44.0	0.0620 Gm.	2 min.
0.5 Gm.	0.14 Gm.	28.0	0.0395 Gm.	1 min. 35 sec.
0.25 Gm.	0.085 Gm.	14.8	0.0209 Gm.	1 min. 30 sec.
0.10 Gm.	0.045 Gm.	5.2	0.0073 Gm.	1 min. 5 sec.

These reactions are of special interest to the student of the biochemistry of the Monardas and other plants containing thymoquinone and its hydroxy derivatives.

FROM THE LABORATORY OF EDWARD KREMERS.

CHEMICAL CONSTITUTION AND ANTHELMINTIC ACTION.*

BY ANTOINE E. GREENE.

Having studied a large number of the commonly employed anthelmintics, the writer attempts to group them into definite classes, according to similarity in chemical structure and analogous pharmacological action.

Six groups are drawn off. There are the following groups which might conveniently fall into an orderly classification according to the modern system: 1, Paracymene or Thymol Group; 2, Phlorglucinol-Butyric Acid Group; 3, Lactone Group; 4, Alkaloid Group; 5, Halogen Group; 6, Heterogeneous Group.

The writer submits this chemical classification to provoke the study of these drugs and medicaments in the light of chemical structure and relationship and corresponding medicinal action. The question is raised whether synthetical organic chemistry may some day furnish medicine an "Anthelmintic Molecule" which will possess all of the desirable and none of the undersirable and dangerous properties of those drugs which are employed to-day in helminthic therapy.

The present trend in synthetic organic chemistry and pharmacology is to interpret and predict the physiological action of drugs and synthetics on the basis of chemical structure. It has been found that the position of substituents in aliphatic chains and aromatic nuclei may profoundly affect the color, odor, taste and toxicity of the molecule. The introduction of alkyl, hydroxyl, carboxyl and amino groups may modify the solubility, stability and pharmacology of many drugs of the cyclic series. Stereoisomerism plays a part in the pharmacodynamics of medicinals, for optical isomers may evidence great differences in characteristic physiological reactions when tested on animal or vegetable organisms. It is only necessary to consider phenol and salicylic acid, aniline and acetanilide and phenol, resorcinol and hexyl-resorcinol to note how the presence of substituents may alter

* Scientific Section, A. PH. A., Baltimore meeting, 1930.

the physical, chemical and pharmacologic properties of organic drugs. It is well known that the official lævogyrate epinephrine is fifteen times more powerful as a vasoconstrictor than the dextrorotatory isomer. Accumulated evidence from the study of chemical structure and medicinal action has formulated the hypothesis that like chemical structure indicates, in a large number of cases, analogous pharmacological action, and the natural and synthetic drugs may be classified into groups which show a similarity in molecular configuration and physiological activity. A study of the structures of cocaine, procaine, benzocaine, stovaine and other local anesthetics will show striking relationship between the chemical constitution and specific pharmacological action. Since it is well established that on a basis of the possession of like structure, there is a classification of drugs into antiseptics, local anesthetics, hypnotics and antipyretics, the writer, who is at present engaged in the study of the bio-evaluation of anthelmintics, sought to investigate the chemical structures of drugs commonly used in helminthic therapy, and determine if it was possible to classify these medicaments of proven therapeutic value according to the modern idea of chemical constitution and specific physiological action.

Excluding chloroform, carbon tetrachloride, tetrachlorethylene and those vegetable drugs, the constituents of which do not fall into any definite class, the following anthelmintics offer possibilities for the modern classification: Thymol, carvacrol, menthol, cineol, ascaridol, oil of turpentine, camphor, aspidium constituents and derivatives of phlorglucinol, santonin, coumarin and synthetic lactones, naphthalene, betanapthol, and the alkaloids of *Areca Catechu* and *Punica Granatum*. In the study of these groups the writer arranges them in the following manner:

Thymol Group (Thymol, menthol, ascaridol, etc.)
Phlorglucinol Group (Aspidium constituents, etc.)
Lactone Group (Santonin, etc.)
Alkaloids (Arecoline, pelletierine, etc.)
Heterogeneous Group (Naphthalene, betanaphthol, methyl salicylate, turpentine, halogen compounds would form a fifth group of unrelated anthelmintics)

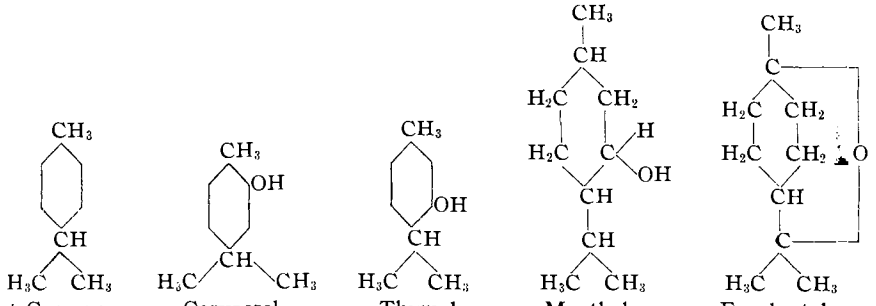
All of the above named drugs have been employed in the treatment of human and animal helminthiasis. Some are specific in their action. Santonin shows a selective toxicity against *Ascaris lumbricoides* and *Tricocephalus dispar;* chenopodium, thymol and betanapthol manifest marked uncinaricidal properties; the phlorglucinol derivatives of *Aspidium* and *Brayera* possess considerable toxicity for tænia.

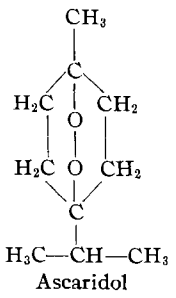
These drugs are sparingly soluble in the body fluids, but, even in small doses, the exhibition of oleaginous fluids and by prolonged contact with the intestinal juices, cause disagreeable symptoms and often intoxication. The ideal anthelmintic therefore, should possess the following properties:

1. Insolubility in the gastro-intestinal fluids.
2. Maximum parasitropic power.
3. Absence of taste.
4. Low toxicity for patient.
5. Availability (from natural or synthetic products).
6. Rapid elimination.
7. General specificity for intestinal parasites.

None of the much used drugs known as anthelmintics can satisfy the requirements, but it is hoped that chemical synthesis may some day produce a compound which, fulfilling the desired requisites, might be called the "Anthelmintic Molecule." Infestation by intestinal protozoa and metazoa is still a problem which confronts the physician, whether he practices in the temperate zone or in the tropics.

The following formulas may show the close structural relationship of the members of the Thymol Group.

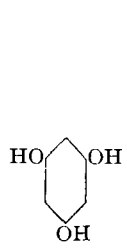




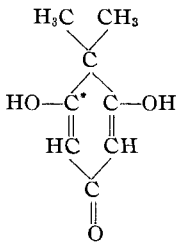
A cursory examination of these molecular constitutions will show that whether, cyclic or isocyclic, there exists three important groups. These are the Methyl, Hydroxyl and Isopropyl Groups. The ascaridol molecule with its internal oxygen bridge might well be compared with menthol and eucalyptol. Ascaridol, one of the chief constituents of oil of chenopodium, is a proven anthelmintic, while eucalyptol and menthol possess feeble anthelmintic properties when tested against the ascarides. Using Schneider's modification of the Trendelenburg method, the writer compared paracymene, thymol and carvacrol. All of these drugs possessed lumbricidal properties, but thymol killed the test animals most rapidly. Menthol may be considered a hydrogenated thymol, but it is interesting to compare the source, physical and chemical characteristics, and medicinal action of the two compounds. Thymol is a powerful agent in the treatment of infestation by the hookworm, *Ankylostoma duodenale* or *Necator Americanus*, while menthol is an indifferent vermifuge against *Oxyuris vermicularis*, the thread worm.

For a long time male fern and its ethereal extract have been used in the treatment of tape worm infestation, and this remedy enjoys considerable use to-day in the treatment of this form of helminthiasis. The official oleoresin possesses the virtues of the crude drug in a concentrated form and is the preparation most

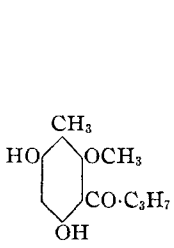
frequently exhibited. This extract contains at least four interesting compounds. Analysis indicates that these substances are derivatives of phlorglucinol. On acid or alkaline hydrolysis of aspidium extracts, phlorglucinol and butyric acid are found among the products of decomposition. The following formulas will show the structural relationship of phlorglucinol and aspidium constituents.



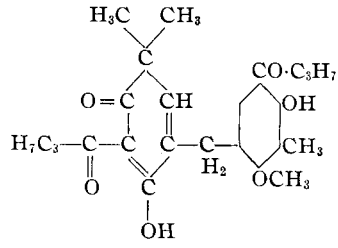
Phlorglucinol



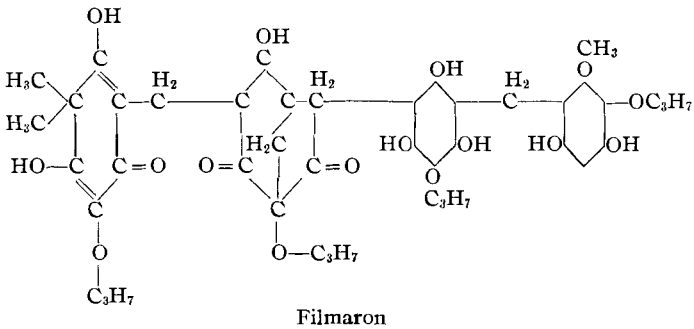
Filicic Acid



Aspidinol

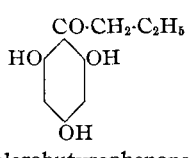


Aspidin

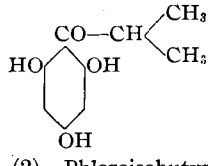


Filmaron

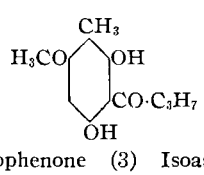
From an examination of these structures it appears that aspidinol and filicic acid may be cleavage products from aspidin. The formula of filmaron with its carbon bridge points to chemical instability, and some of the constituents of the ethereal extract may be the products from the decomposition or breaking up of this molecule due to drastic methods of extraction. Karrer and Widmer succeeded in synthesizing a number of compounds, which according to them, possess anthemintic properties comparable to the preparations of aspidium. The formulas of these synthetics may be compared with the structures of the above aspidium constituents.



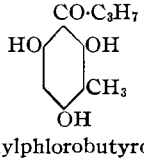
(1) Phlorobutyrophenone



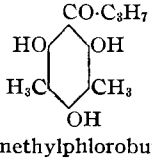
(2) Phloroisobutyrophenone



(3) Isoaspidinol



(4) Methylphlorobutyrophenone



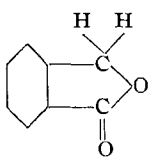
(5) Dimethylphlorobutyrophenone

By the action of butyric acid nitrile and hydrochloric acid on methylphlorglucinol-beta monomethyl ether, these workers prepared aspidinol, a constituent of oleoresin of aspidium, considered by some authorities to be devoid of anthelmintic activity. While iso-aspidinol possesses vermicidal properties, aspidinol, an isomer, is inactive. This is an interesting example of how the position of substituents and radicals in a compound may condition pharmacological action.

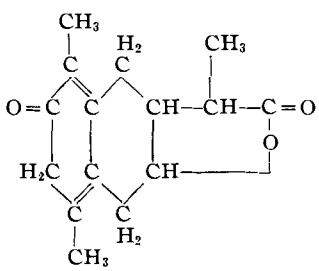
Turning now to the santonin or lactone group, we may consider the molecular structure of the compound and its derivatives. One of the drawbacks to the use of this drug is its toxicity for the patient. While specific against the ascaris, the literature bears abundant evidence of many cases of intoxication caused by the use of the drug in helminthic treatment.

Von Oettingen attempted to reduce the toxicity of santonin by saturating the double linkages in the compound. These tetra-hydrosantonins proved to be less toxic and more efficient than santonin, testifying to the influence of modification of structure and detoxification.

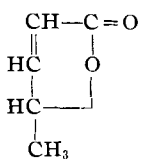
Lautenschlager, investigating the specific anthelmintic power of the lactone group, prepared a number of aromatic lactones which possess anthelmintic action. A single example may bear out the result of his researches. He found that a phthalid, prepared from phthalic anhydride, exhibited ascaricidal properties comparable with santonin. The formula for this synthetic anthelmintic is



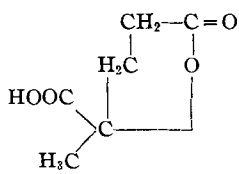
Some investigators contest the value of the lactone structure in conferring specific action upon this class of drugs. Caius and Mharask aver that the ketone structure confers definite helminthicidal action upon the compound. Oshika



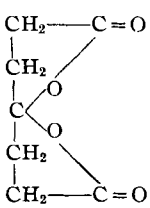
Santonin



Beta Angelica Lactone



Valero Lactone Carboxylic Acid



Dilactone of Acetone Diacetic Acid

claims that the conversion of the lactone into free carboxyl caused a loss of activity, but the esterification of the acid would restore the vermicidal power. It is interesting to observe that, while salicylic acid is not a good vermifuge, the methyl ester manifests considerable toxicity for the ascaris.

Von Oettingen prepared lactones from the aliphatic series and tested these synthetics for anthelmintic power. The foregoing formulas are submitted for a comparison between chemical constitution and pharmacological action.

On comparing the toxicity of these compounds with santonin, using the Lumbricus terrestris as a test animal, Von Oettingen obtained the following results:

Lactone.	Time, hours.	Per cent killed.	Time hours.	Per cent killed.
Concentration	0.04 molar		0.004 molar	
Beta-angelica-lactone	2–3	100	24	20
Valerolactone-COOH	4	100	24	0
Dilactone	3	100	24	0
Santonin	3	100	24	100

The above evidence points to the specificity of the Lactone Group in anthelmintic activity.

Chloroform, tetrachlorethylene, carbon tetrachloride and paradichlorbenzol are representatives of the Halogen Group of vermifuges. Carbon tetrachloride has earned sufficient reputation to justify its employment in the treatment of uncinariasis. Chloroform has been used to expel ascarides.

Petroleum ether, petroleum, kerosene, napthalene and alpha pinene from turpentine have been exhibited in various forms in the treatment of intestinal infestation, but these agents are not very powerful anthelmintics. Betanaphthol has been used, but its taste and toxicity bar its exhibition as a valuable remedy. According to Caius and Mhaskar, esterification of betanapthol converts it into an inactive compound. Alphanaphthol is too poisonous for use in internal medication, although *in vitro*, it is actively lumbricidal.

The alkaloids of *Pomegranate* show interesting similarities to coniine, the chief alkaloid of *Conium maculatum*, or hemlock. Arecoline, the anthelmintic alkaloid of *Areca catechu*, or the betel nut, is sometimes used to kill and expel intestinal parasites. The other constituents of Areca, namely arecaine and guvacine need investigation to discover their anthelmintic possibilities.

The subject of anthelmintics needs a serious and extended investigation. Synthesis may furnish an anthelmintic molecule, endowed with all of the advantages of an ideal remedy and free from the dangers and disadvantages. More study should be placed upon the natural products and their characterization. The writer is investigating the employment of microscopic plants and animals as test objects in the bio-evaluation of that important class of remedial agents known as anthelmintics.

In the opinion of the writer, it is possible to classify anthelmintics according to chemical constitution, and chemical pharmacology may well make use of this modern classification of medicinal agents.

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FAILURE OF A DIABETIC TO UTILIZE INULIN.

BY E. C. WISE AND F. W. HEYL.

In a previous paper (1) the failure of a diabetic to utilize the carbohydrate in dried artichoke powder was discussed. The sugar tolerance of the subject was carefully determined on a weighed analyzed diet both before and after supplemental feedings of dried artichoke powder. These data were obtained during an experimental period covering thirty days. While the subject was available and his diet in balance with his apparent sugar tolerance, an additional short experimental period was instituted during which time a supplemental feeding of inulin prepared from artichokes was made. These data were not published at that time but in view of the considerable interest in the results of the feeding of dried artichokes it was thought that the results of the inulin feeding would also prove of interest.

A number of papers have appeared in the literature in the past which indicate that levulose, as well as some of its condensation complexes such as inulin, may serve as a source of a more utilizable carbohydrate in diabetes. A number of references are reviewed by Shohl (2).

Jerusalem artichokes contain approximately 80 per cent moisture and 15 per cent of carbohydrates. The carbohydrates consist largely of inulin and other condensation products of levulose which make up about 85 per cent of the total carbohydrate. The remaining 15 per cent of the carbohydrate consists of sucrose, levulose and dextrose. The quantities of the various sugars vary rather widely with the season of the year. In the preparation of artichokes for food the proportions of the various sugars may also be altered, that is, a portion of the inulin may be hydrolyzed to levulose.

There is evidence to show that inulin is not absorbed. Lewis (3) doubted the value of inulin feeding. Lewis and Frankel (4), working with phlorhizinized dogs, state that there seems to be little probability that an appreciable amount of inulin is converted into any substance that can give rise to glucose in the diabetic. Root and Baker (5) state that inulin produced no significant increase in the blood sugar in either normal or diabetic subjects. It did, however, have a slight effect upon the respiratory quotient of two patients, but the evidence is difficult to consider favorably.

In the case of the diabetic under our observation it is doubtful if any inulin at all was absorbed. The subject was fed on a level very close to his sugar tolerance and in addition to this ate rather large quantites of inulin. Accepting 12 per cent as the amount of inulin in Jerusalem artichokes, the daily ration of inulin, 30 Gm., represents a feeding of about 250 Gm. of whole artichokes. If any appreciable hydrolysis and absorption of the products of hydrolysis had taken place the subject must necessarily have shown some glycosuria. Such, however, was not the case and we feel convinced that inulin is not utilized. However, no inulin was