SOME RECENT WORK ON ANTHELMINTICS

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IN a recent report Dr. F. A. Miller states that in the course of the anti-hookworm campaign, of which he is director, in Colombia, out of 53,390 persons examined in 1921, 49,940 (93 per cent.) proved to be infested and that of 47,822 treated, 37,488 (78 per cent.) were cured. This report relates to the work of one of the many similar campaigns against hookworm now in progress in tropical countries under the auspices of the Rockefeller Foundation. Work on the same lines is also being carried on by Governmental and other agency, so that the number of people now being treated for hookworm disease (ancylostomiasis) probably runs into millions, and they still represent only a fraction of the victims needing treatment, 75 per cent. or more of the native population in many tropical countries being frequently infested with hookworm. Everyone engaged in this work recognises that the best method of dealing with the disease is prevention, but this implies the education of natives into cleanly habits and the immediate provision of sanitary appliances on a gigantic scale, and though neither is being neglected, both can only be accomplished slowly.

It is clear that if mass remedial treatment is to be successful, the drugs used must be safe, efficient and cheap, and it is to the credit of the Hookworm Commissions that they spare no pains to secure these three desiderata in the order given.

Two species of hookworm are concerned, *Ancylostomum duodenale* and *Necator americanus*. These parasites infest the duodenum, where they lie firmly attached to the intestinal wall and protected by a copious exudation of mucus.

The worms (*Taenia*, *Ascaris*, *Ancylostomum*, etc.), which are parasitic in man and other animals, are comparatively highly developed organisms, and as such should be susceptible to attack by drugs in various ways: but it seems to be true that, with the exception of the mixture of alkaloids known commercially as "pelletierine," and possibly santonin, all the anthelmintics in use act by paralysing, more or less completely, the external musculature of the parasites. Several of the text-books on pharmacology and materia medica state that there is, "pelletierine" again being an exception, nothing specific about the action of anthelmintics on worms, that the substances so used are toxic to both parasite and host, and that the host escapes damage from the drugs only because the latter are not readily absorbed. The case does not seem to be quite so simple as this, since there are numerous substances which fulfil these conditions and yet the number of effective anthelmintics is small. In hookworm disease the drugs have to be given in comparatively large doses to secure a local concen-

tration sufficient to render the parasites harmless and the amount of drug absorbed is often considerable, although the technique of administration is constantly being improved to avoid this secondary action. It is also difficult to explain on this view why santonin should be active against round worm (*Ascaris*) and inactive against tapeworm (*Taenia*), the reverse being true as regards filicic acid and its allies (extract of male fern), though both are believed to be effective in virtue of their action on the external musculature.

Perusal of the voluminous medical literature on the treatment of hookworm disease shows that a great variety of drugs has been used in practice, including extract of male fern, quassia decoction, a mixture of chloroform with eucalyptus oil, and in certain parts of South America the latex of two species of figs, called higuero or higuero. All these drugs still have their advocates, but in the organised campaigns against hookworm, the drugs used are β -naphthol, thymol and chenopodium oil, which are named in ascending order of importance. Many efforts have been made to extend this range of drugs, but the only addition that need be referred to is carbon tetrachloride, with which promising results have been obtained recently in Fiji by Hall, and have been confirmed by Nicholls and Hampton in Ceylon and by McVail in India. Carbon tetrachloride is said by Joachimoglu to be 50 per cent. more powerful as a general anaesthetic than chloroform and it is probably this greater activity which makes it more effective than chloroform since Caius and Mhaskar have shown that the latter merely acts on the worms as an anaesthetic and in their view is not a true anthelmintic. The soporific action of carbon tetrachloride on hookworm patients has been noted by McVail in India.

β -Naphthol and thymol are both phenols, and most of the recent work on possible new anthelmintics has been devoted to the study of phenols and especially derivatives of phloroglucinol and resorcinol, following a suggestion made by Fränkel that the active constituents of a number of well-known anthelmintics contain butyric or isobutyric acid residues, with or without phloroglucinol, e.g., filicic acid derived from *Filix mas* and other ferns, rottlerin from kamala, kosotoxin from couso flowers, and ascaridole from chenopodium oil. The examples are not very impressive since filicic acid and its allies are at best uncertain in their action, kamala and couso flowers are now but little used, and ascaridole, though like other terpene derivatives it yields isobutyric acid on oxidation does not contain, strictly speaking, an isobutyric acid residue.

Following Fränkel's suggestion, Karrer and his co-workers have prepared an extensive series of condensation products of aliphatic acids with phloroglucinol and resorcinol analogous to filicic acid (Formula I) and aspidinol (Formula

II) which may be regarded as the nuclear units on which the complex and more active constituents of *Filix mas* and other ferns are built up.

Of these synthetic compounds Karrer has stated recently that the *isohexoyl* derivatives of either resorcinol (resorcinohexophenone: Formula III) or phloroglucinol (phloroisohexophenone: Formula IV) are the most promising, and that the *isoacyl* residue appears to confer greater activity than the normal acyl residue, phloroisobutyrophenone being twice as active as phlorobutyrophenone. The naturally-occurring fern compounds become more active with increasing complexity, albaspidin (Formula V) being more active than filixic acid (Formula I) and less active than filixic acid, which is represented by Boehm as containing three rings. The synthetic compounds on the contrary become less active with increasing complexity: thus methylphlorobutyrophenone condenses with formaldehyde in presence of alkali to form 2 : 4 : 6 : 2' : 4' : 6'-hexahydroxy-5 : 5'-dibutyro-3 : 3'-dimethyldiphenylmethane (Formula VI) which should have an activity similar to that of albaspidin, but is in fact less active than the starting material.

It is probable that the simple mono-, di-, and tri-hydric phenols are all capable of yielding anthelmintics of practical value in proportion as their solubility and toxicity are modified by the nuclear substitution of either alkyl or acyl groups. Phenol itself is used as a remedy for thread worms, but is too irritant for general use and that also applies to its methyl, ethyl, propyl, and butyl homologues, but thymol (methylisopropyl phenol), which is solid at ordinary temperatures and sparingly soluble in water, is a valuable anthelmintic, which is

not toxic to the host even in large doses, provided that it is given in the absence of oils or other substances in which it is soluble and which would increase its rate of absorption by the intestinal walls. Its isomeride, carvacrol, as Darling has shown, is also a valuable anthelmintic for hookworm, but being liquid it spreads and penetrates better than thymol, and is therefore too irritant for use.

Attempts have also been made to lower the toxicity of alkylphenols by converting them into non-irritant esters, such as carbonates, carbamates and *N*-dimethylcarbamates. One of these, thymol carbonate, is stated to have given good results in the outbreak of hookworm disease which occurred during the boring of the St. Gothard Tunnel, but recent trials by Dr. Wilson G. Smillie in Brazil (*private communication*) and by Caius and Mhaskar in India show that the drug is of little value. Another of these preparations, *p*-benzylphenylcarbamate, has been reported on favourably by Koslowsky as a remedy for oxyurids (thread worms). Alkyl ethers of the phenols have been shown to be inactive.

The other known effective remedy against hookworm, chenopodium oil, has been re-examined recently in these laboratories and its constituents isolated and tried in field operations in Brazil by Dr. Smillie as part of a general investigation of possible new remedies for hookworm disease. The clinical results, which are not yet published, show that the sole constituent of the oil which is active against hookworms, is the organic peroxide, ascaridole (Formula VII), and that the variation found by different observers in the action of chenopodium oil is due largely to the varying quantities of this somewhat unstable component in the commercial oil. On heating, ascaridole passes into the isomeride, ascaridole glycol anhydride (Formula VIII), and this on hydration yields a mixture of α - and β -ascaridole glycols (Formula IX) which in turn can be converted into thymol and carvacrol. The

three intermediate products, which may and do occur in carelessly distilled oil, are all inactive against hookworm so that this series of changes begins with an active substance (ascaridole),

passes through three that are inactive and ends with an active compound (thymol). It is interesting in this connexion to mention that cineole (Formula X), which has had some vogue in the treatment of hookworm but has been found by Smillie and by Caius and Mhaskar to have but little action, is fairly near to ascaridole glycol in constitution, but the latter differs from cineole in containing two secondary alcohol groups and, so far as they have been tried, secondary and tertiary aromatic alcohols have proved useless against hookworm in man.

Aneylostomiasis is in the main a tropical disease, and though it is not unknown in temperate regions, the parasitic worms usually prevalent in Northern Europe, viz., *Ascaris*, *Taenia* and *Oxyuris*, are much less dangerous and receive less attention. Against *Taenia* (tape worm) the drugs most commonly used are male-fern extract, the constituents of which have been discussed already, and "pelletierine" tannate; the latter is not the simple substance its name implies, but is the precipitate formed by the addition of tannin to an extract of pomegranate bark and so contains all the alkaloids known to occur in the bark of which two—pelletierine and isopelletierine—probably form the most active constituents. "Pelletierine," according to von Schröder, is a specific poison for *Taenia* spp.; thus *Taenia serrata*, which infests the intestinal canal of the cat, will live for several days in a warm (37° C.) faintly alkaline solution of sodium chloride, but is killed in 5 to 10 minutes if 1 part in 10,000 of "pelletierine" is added, whilst the round worm (*Ascaris mystax*) is only killed in much stronger concentration of the alkaloid.

Of the drugs used against round worm (*Ascaris* spp.), the most important is santonin. Chenopodium oil is as good or better, and its use for this purpose is common in the United States, and may extend to other countries if the present scarcity of santonin continues. Santonin, as every reader of this *Journal* is no doubt now aware, is at present only obtained from one source—Soviet Russia—being made in a factory in Tashkent from santonica flowers (wormseed) collected locally. Greenish, Simonsen and Goodson have shown independently that it is also present in *Artemisia brevifolia*, found in India. According to Lautenschläger, and in confirmation of observations by Trendelenburg, the activity of santonin is associated with the lactone ring (Formula XI), the sodium salt of the corresponding acid being inactive, an observation which is difficult to reconcile with the existing use of sodium and other salts of santoninic acid as anthelmintics, though it is true that the sodium salt is no longer largely employed owing to its toxicity. These observations appear to be based solely on the results of experiments in the application of the drugs to worm muscle, and they need confirmation by clinical trials. If confirmed they will be of

considerable practical importance since Lautenschläger found that whilst open-chain lactones have no action on worm muscle, such action is not confined to lactone-groups in association with dimethylnaphthalene, as in santonin, but is also shown by phthalide (Formula XII), and its dimethoxy derivative (meconin) and can be increased by the replacement of one of the methylene hydrogen atoms by an alkyl group or diminished by similar substitution of an aromatic group, e.g. phloroglucinol.

It is interesting to note that the introduction of a second lactone-group into the santonin molecule, as in Wedekind's α -tetrahydro-santonilide (Formula XIII), reduces the anthelmintic action.

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THE PRESENT POSITION OF FAT-HARDENING

IN a recent issue of the *Zeitschrift für Angewandte Chemie* (1922, pp. 437-440), Dr. W. Normann, one of the earliest authorities on the subject, discusses in detail certain technical, scientific and economic aspects of the fat-hardening industry. In the summary of the article which follows only brief references are made to those topics which have been treated recently in these columns (cf. J., 1922, 384 R, 392 R, 415 R).

The pivot upon which the whole art of fat-hardening turns is the catalyst, which nowadays is almost always the metal nickel. The noble metals that were used to a limited extent in the past have been abandoned owing to their prohibitive cost. Neither cobalt nor copper is employed alone; the use of mixtures of them with nickel has been proposed, but whether they have been utilised on a manufacturing scale is unknown to the author.

The method of preparing the catalyst has become practically a standard procedure, viz., the precipitation or decomposition of an easily decomposed nickel compound upon some inert material as carrier. Generally the carbonate is precipitated upon kieselguhr but sometimes gaseous nickel