INTESTINAL PARASITICIDES

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Various substances and compounds, chiefly of vegetal origin have been employed by man, some almost since the dawn of history, in efforts to free himself or his domestic animals of the parasitic organisms with which they were beset. Many of these were empirically used: in fact, it remained for a long time, and to no small extent still remains for their value to be demonstrated by modern critical methods. Some, of course, like the cinchona bark of the Peruvian Indians have stood the tests of time. There are those, as for example santonin, though their complete rejection is not indicated, which today are not regarded as highly as formerly. Still others, as recent tests have demonstrated, possess no parasiticidal virtues whatsoever.

In the main, parasiticides have been developed to combat helminths. This is not strange, for man must have been aware of tapeworms and ascarids from his earliest periods of existence. The presence of intestinal protozoa was not disclosed until the indefatigable Leeuwenhoek found the flagellate *Giardia* by means of his rudimentary microscope. That protozoa could be pathogenic required a much later period to prove. Considerable progress has been made in combating parasitic protozoa, to which brief consideration will be given.

As has already been intimated a consideration of anthelmintics will compromise the major part of this paper. Many of the chemicals used as such have survived through a long period of traditional empiricism. Then during the last quarter of the nineteenth century what might be designated as an era of traditional empiricism was ushered in, that is, an effort to appraise known anthelmintics, or substances used as such, to a great extent on a clinical basis. During this period thymol was established as the premier uncinariacide of the time. Actuated by good results reported from Brazil against hookworm with oil of chenopodium Baumler and Fribourg in 1881 tried the chemical in only one case. They judged the results to be unfavorable for further treatment. Because of this unscientific procedure recognition was delayed more than thirty years until Schüffner and Vervoort demonstrated its efficacy against hookworm

in Sumatra. Inability to procure a supply of thymol from Germany during the World War and ample confirmation of the superiority of chenopodium over thymol practically caused the displacement of the latter in this filed of medicine. Had the true worth of oil of chenopodium been known in the days of the construction of the St. Gothard tunnel, it would doubtless have served as the drug of choice in the anti-hookworm campaigns in Porto Rico and elsewhere from their inception almost to the present time.

While the second epoch, in so far as the appraisal of anthelminthics was concerned, yielded vastly superior results than did its predecessor, yet it left much to be desired, since it contributed practically no accurate data regarding the subject. The beginning of modern anthelmintic medication may be said to date from 1915, when critical testing of various substances to determine their anthelmintic value was inaugurated by the Bureau of Animal Industry of the United States Department of Agriculture. Since then notable progress along this line of investigation has been achieved.

The mere fact that worms are passed after medication constitutes no criterion that such treatment is effective, for the great majority of invading organisms, in no wise affected, may still remain in their accustomed site. Several means of evaluating anthelmintic efficiency have been devised. One of these is the worm count, which at the hands of Darling and his associates threw much light upon problems in this field. After treatment the excreta passed over a definite period is examined, and the worms it contains removed. Later accurate qualitative means to determine the presence of ova, such as the brine flotation method, follow. This procedure may be repeated one or more times until no evidence of the presence of eggs remains. Worm counts require absolute control over patients or subjects for at least three days during and after treatment. Even then we cannot be certain that all the worms have been removed. Through the employment of a test drug and then following with a standard anthelmintic to evict as many of the remaining worms as possible, provided there be any, we may also decide whether a substance shows any promise. One of the most useful of all means is the employment of experimental animals. After treatment the animal can be killed, and through a comparison of the parasites still present with those evacuated, an accurate gauge of the value of the compound tested may be obtained.

In many ways experimentation of this type shows definite superiority over other methods. With the exception of criminals about to be executed it is not applicable to man. Though in many in-

stances, the parasites of dogs for example, possess close kinship with those of man, yet the effects of an anthelmintic upon the two groups may not be identical. Nevertheless the divergence is not so great that the results found for one group may not obtain in part at least, for the other.

Since Stoll's outstanding experiments at Utuado, egg counts have provided us with another technique for attacking such problems. Through it we are enabled to establish the number of eggs per gram of feces. By means of estimates of the number of ova present made before and after treatment, such a *modus operandi,* while not absolutely accurate, provides an excellent means of ascertaining the worth of a compound. In vitro, tests may impart information of value if properly interpreted. By such tests a chemical may seem to be of no value, since it has not exerted a lethal effect upon worms within a reasonable period. Yet in the intestine the substance under consideration may actually function as a vermifuge, even though it not be fatal. The difference between a vermifuge and vermicide from the practical viewpoint, is, after all, merely an academic one since both types may give the desired end of ridding the host of its parasites. Carbon tetrachloride kills hookworms, while santoni on the other hand merely stuns ascarids. Subsequent purges and peristalsis must therefore play an instrumental part in expulsion.

A pitfall into which an inexperienced student might drop is that of placing implicit dependence upon the absence of ova in feces after treatment. According to a physician of my acquaintance oil of chenopodium serves as an excellent therapeutic agent for *Schistosoma mansoni* infestation. His post-treatment examinations must have extended over too short a period. I have followed the course of chenopodium treatment for hookworm infestation complicated by that of *S. mansoni.* About the third week ova of the latter can be recovered in the feces in as great abundance as formerly. Merurochrome and gentian violet on the other hand when injected intravenously into cats and dogs harboring *Clonorchis sinensis* cause a great initial increase in the number of eggs passed. All of these however are imperfect and immature.

Another fact to be considered is that practically all chemicals used against intestinal parasites exert a toxic effect, whether apparent or not, upon the host as well as the invader. Hall, discussing carbon tetrachloride made a statement to the following effect: "The chief organ of insult for many anthelmintics is the liver." It might further be stated that each compound has a characteristic effect upon the host. The ideal to be striven for is the administration of

a dose so graduated that while the parasites are eliminated the least possible damage is inflicted upon the host.

The inclusion in this paper of some therapeutic agents dealing with animals rather than man is considered because of the economic factor involved, their possible bearing upon similar parasites in the human host, and because some parasites occur in both man and animals.

Male fern, one of the oldest known anthelmintics dates from at least the days of Galen and Pliny, both of whom were familiar with its action and use. The active principle of male fern is said to be a non-nitrogenous acid, filicic acid, of which two forms, a crystalline $C_{36}H_{40}O_{12}$ and an amorphous form, $C_{36}H_{42}O_{13}$, are known. Its success has been most marked with cestodes, especially the rare tapeworms which only occasionally occur in man, and therefore are not so well adapted to the environment of the human intestine as the two common species of *Taenia*. Cestodes of the horse, dog and cat are often evacuated as well. Grassi, Calandrucci and Perroncito (1884–1886) demonstrated that this drug will kill the liver fluke, *Fasciola hepatica*, in sheep. This drug therefore provides one of the few available therapeutic means of combating this parasite.

Male fern is often considered an innocuous drug. This opinion, however, has not always been borne out. A number of deaths have resulted from its administration. Toxic symptoms may attend its use. Filicic acid excites a tremendous irritation of the gastro-intestinal tract and reflexly stimulates the uterus. Pregnancy may therefore be considered a contra-indication to its use. It also affects the central nervous system. Filix mas tends to deteriorate, the extract more so than the oleoresin. This probably accounts in part at least for the irregular results obtained against *Taenia saginata* and *T. solium*. Sometimes complete expulsion of the worm has not been effected even after five or six treatments.

Oil of chenopodium has been used for untold centuries by the American Indians as an anthelmintic. Though tested in Europe in 1881 it gained no place in medicine until Shüffner and Vervoort in 1913 demonstrated its superiority over all known drugs against hookworm. Since then its use has greatly spread. The oil itself is distilled from herbs of the goose foot family technically known as the Chenopodiaceae. Plants of this group grow abundantly in many parts of the globe, though not all are of value for anthelmintic purposes. In Haiti I encountered a plant which I was informed the natives used for worm infestations. From it emanated the identical odor so characteristic of oil of chenopodium.

Oil of chenopodium not only is efficacious for hookworm, but is also our main reliance for the eviction of ascaris. The substance responsible for its effectiveness is an organic peroxide known as ascaridol, the formula of which is $C_6H_2O_2$. Fortunately this forms the main fraction of the oil, varying from 45 to 70 per cent of the total. Ascaridol would be the ideal substance for therapeusis within its province, especially so since it possesses a definite chemical composition, and does not consist of a mixture of various substances. The obstacle to such a desired end lies in the great cost of isolating ascaridol from other constituents of oil of chenopodium.

As in the case of male fern the toxic effects of oil of chenopodium concern chiefly the gastro-intestinal tract and the central nervous system. Children are specially susceptible to its action. In instances of poisoning, autopsy discloses inflammation of the gastro-intestinal tract, liver and kidneys, adn hyperaemia of the brain. Toxic effects as a rule, are in large measure prevented by saline purges or castor oil shortly after treatment. Such measures tend to check absorption into the blood stream, and to promote elimination from the alimentary canal. Castor oil possesses the additional advantage of spreading the oil of chenopodium over a larger surface. Ordinary therapeutic doses usually give rise to no symptoms in well nourished individuals. Oil of chenopodium should be administered with caution, or not at all, to those suffering from renal or chronic disorders, or to poorly nourished persons of a neurotic type.

Mention has already been made regarding the effectiveness of oil of chenopodium against hookworms and roundworms. Chandler states that in adults doses of 30 minims remove 90 to 95 per cent of necators, 80 to 85 per cent of the ancylostomes, to completely cure 40 per cent of the necator cases, 30 per cent of the ancylostome cases: a performance decidedly superior to that shown by thymol and beta-naphthol, substances previously commonly used for hookworm infestations. Against these parasites it is almost on a par with carbon tetrachloride. Whipworms may also be expelled, though in the main only those in the intestine are liable to be affected, since the oil but seldom finds its way into the cecum. Frequently pinworms are expelled, but again only those situated in the lower part of the alimentary canal. Oil of chenopodium has been reported as useful against the human liver fluke, *Clonorchis sinensis*. Since this species occurs chiefly in the liver and the bile duct, probably only those few in the duodenum feel its action.

Chenopodium administered intramuscularly and intravenously according to Fernán Núñez, has a specific action against whipworms

and pinworms infesting man. The following charts are copied from an article published by Fernán Núñez:

RESULTS AFTER INTRAMUSCULAR INJECTION FOLLOWED BY ONE OUNCE OF CASTOR OIL GIVEN DAILY FOR SEVEN DAYS

Day	Hookworm	Ascaris	Enterobius	Trichuris
1	0	0	10	5
2	0	12	2	19
3	0	2	6	3
4	0	0	0	0
5	0	0	0	0
6	0	0	0	0
7	0	0	0	0

RESULTS AFTER INTRAVENOUS INJECTION OF 1.5 cc. FOLLOWED BY 30 cc. OF CASTOR OIL DAILY FOR 7 DAYS

1	0	1	273	3
2	0	2	364	5
3	0	0	2	14
4	0	0	0	1
5	0	0	0	0
6	0	0	0	0
7	0	0	0	0

These experiments, it seems to me, should have been controlled by oral treatments of castor oil, provided volunteers were available. Hall and Foster found that in a series of fifty dogs only 27 of 351 *Belascaris marginata* were expelled by castor oil. Hookworms and whipworms remained unaffected. From man only 2 of 1,256 hookworms were evicted, while ascarids were undisturbed. It would seem therefore, that castor oil was not directly responsible for the results obtained. The results obtained by Fernán Núñez have been neither confirmed nor refuted. While the method is of limited applicability, yet if found of value it may have its place under special conditions.

Against helminthic parasites of domestic animals oil of chenopodium treatment has likewise yielded successful results. Practically all roundworms, a goodly proportion of hookworms, and some whipworms are removed when this substance is given orally to dogs. Good results also attend its use for ascarids in hogs: many of the intestinal nematodes of horses are likewise expelled. With the last named host those nematodes inhabiting the cecum are reached, since that organ in equines is not a blind tube. Chenopodium successfully removes *Ascaridia* from poultry.

Oil of chenopodium may be employed as a parasiticide beyond the field of helminthology. *Balantidium coli*, as all authorities agree, is the one protozoan inhabiting the intestine of man that may pathogenically affect its host. Cort in Siam first gives the patient suffering from balantidial dysentery a large cleansing enema of

physiological saline, then 15 cc of oil of chenopodium in 150 cc. of olive oil are slowly given per anus. The enema is held for two hours if possible. Of twelve cases so treated, none showed ciliates in their stools over a period ranging from 9 to 29 months. That fatal sequelae may follow the administration of this drug is evidenced from its use in an attempt to treat a child suffering from balantidial dysentery. The case has been reported by Dr. Américo Serra in the June number (Vol. 6, No. 4) of this Journal.

Hall's discovery of the ability of carbon tetrachloride (CCl_4) to remove hookworms marks an epoch in the development of curative medicine. He, as well as other investigators, had noted the excellent results which attended the use of chloroform for hookworm infestations. Pronounced toxic action following chloroform administration, however, precluded its use against intestinal parasites. Hall reasoned its close chemical relative CCl_4 might serve as an acceptable therapeutic agent, and at the same time inflict much less injury upon the host. Excellent results against dog hookworms in tests unaccompanied by untoward pathogenic conditions moved him to advocate its trial for similar parasites of man. Twenty thousand successful treatments in Fiji left no doubt as to its worth. Since then millions of individuals have profited physically from the benefits conferred by this chemical. CCl_4 has become the drug of choice in hookworm infestations, especially where *Necator americanus* constitutes the etiological agent.

This drug readily lends itself to mass treatment because of ease of administration, the fact that a saline purge can be given simultaneously, low cost, and relative innocuousness. Furthermore, pregnancy need not be considered a contra-indication.

The sphere of usefulness of CCl_4 is not limited to hookworms. Oil of chenopodium is somewhat superior as regards *Ancylostoma*, but CCl_4 surpasses the oil where *Necator* is concerned. While CCl_4 acts fairly well for ascarids it is decidedly inferior to chenopodium in this respect. Owing to the superiority of the former in one field and the latter in another, their combination is often resorted to for this dual purpose.

Several years ago Dr. Hall, during the course of a conversation, informed me that CCl_4 serves excellently as a taeniafuge in human infestations, but not for those of the tapeworms of domestic animals. Just why such a condition should obtain is not clear. The dog for instance, serves as the host of several members of the genus *Taenia*, all fairly closely related to the human forms *T. saginata* and *T. solium*, while the cat harbors another. Why should not the same

material act equally well against all these closely related organisms? Slight differences in the life history or habits of these parasites, or various modifications in the environment, that is, the alimentary tract of the host, may be responsible.

Approximately two years ago the opportunity of testing CCl_4 as a taeniacide presented itself. A man well known in public life had on several previous occasions been unsuccessfully treated for tapeworm infestation (*T. saginata*) with male fern. I then recommended the usual hookworm prescription of CCl_4 suitable for an adult, namely 3 cc. followed an hour later by a saline purge. The patient failed to cooperate to the extent of preserving the feces evacuated 48 hours after treatment. However, he did inform me that tapeworm segments can no longer be demonstrated in his stools.

In another instance a local physician had received five unsuccessful treatments of male fern for a *T. saginata* infestation. He had lost considerable weight. Symtoms of a nervous nature were present, doubtless occasioned to some extent by the knowledge that he harbored the parasite. The evening before treatment the patient partook only of a very light meal. Early the following morning he was given a capsule containing 3 cc of CCl_4. Within two hours the head had been passed. Two other individuals received similar treatment for the same cause. Owing to circumstances they could not be controlled. They were directed to return should segments reappear in their feces. This they have not done. On another occasion CCl_4 failed to expel a beef tapeworm. Later application of male fern proved successful.

With a fairly extensive series of tapeworm cases Dr. Galbreath, of the Presbyterian Hospital, San Juan, Porto Rico, has experienced successful results on every occasion but one. His dosage is much greater than that recommended in standard texts, namely 5 to 7 grams instead of 2 grams. Magath and Brown recommend similar amounts. In none of Dr. Galbreath's cases have untoward symptoms been noted.

Fasciola hepatica the liver fluke, known locally as "cucaracha", probably levies greater toll upon our domestic ruminants than any other helminth. Situated in the bile ducts as it is, ordinary means useful for intestinal parasites would not seem capable of displacing it. Male fern has already been mentioned as a remedy. CCl_4 given orally to sheep so afflicted exerts a profound effect. Doses as great as 7 cc per 43-pound sheep give rise to no symptoms, such a quantity being well within the limit of tolerance. Even animals with advanced liver rot sustain a dosage of 50 cc without any difficulty.

Immature trematodes remain unaffected. Cattle, which are the principal livestock produced locally, stand the treatment but poorly: young animals seem more resistant to the toxic effects of the drug. Because it may be devoted to a variety of anthelmintic uses CCl_4 may be considered as one of the most valuable substances thus far put to such purposes.

For some time it seemed as though CCl_4 were entirely innocuous except for slight concurrent feelings of discomfort that were occasionally noted. Lambert in Fiji gave more than 50,000 treatments before a fatality occurred. Then two took place within a week. Since then some have been recorded from various parts of the hookworm belt. The amount prescribed could scarcely have been the responsible factor since 2.5 to 3 cc is considered the proper amount. Yet adults have succumbed from as little as 1.5 cc, and children from 3 to 5 minims. On the other hand an individual is known to have taken a 40 cc. dose which caused no symptom whatsoever. Alcoholism, chronic or otherwise, indicates a risk for CCl_4 medication. Another factor which complicates CCl_4 treatment is ascariasis. In cases of heavy infestation by *Ascaris lumbricoides* this drug should not be used. In some hospitals of the Orient I have been informed that chenopodium treatment for ascaris expulsion constitutes a routine procedure preceding operations, in order to prevent the wandering of the parasites, or their formation into masses so as to give rise to intestinal stasis. Chloroform stimulates such behavior on the part of the worms. Stating that CCl_4 may do the same, Lamson, who has made thorough studies of this drug, even goes so far as to advise against its joint use with oil of chenopodium for persons heavily infested with acaris.

In other instances deaths or severe symptoms not attributable to the causes enumerated above, nor to the presence of impurities, have occurred. For a long time the etiology of these lay in doubt. Lamson and his associates in extensive experiments with dogs, in spite of heavy doses, were unable to duplicate the symptoms occurring spontaneously in man. Then suddenly, regardless of the quantity ingested, a number of the experimental animals died. Some of the symptoms so closely resembled those of infantile tetany that calcium deficiency suggested itself as a factor. Investigation disclosed that the diet of the dogs had been changed from one of mixed scraps to one of lean meat without bones, a ration low in calcium. The resulting symptoms, even when pronounced, could be checked by intravenous injection of $CaCl_2$. We know that the daily food of many people, especially of those in a reduced economic state, often

contains an insufficient proportion of this essential element. A diet rich in calcium would go far to prevent sequelae such as those mentioned. However it would of necessity have to be given for some time before treatment, since oral dosage lacks the rapid curative effect of an intravenous injection. Ammonium chloride, hydrochloric acid, and parathyroid extract also improve the conditions brought about by CCl_4 administration to calcium-deficient individuals, probably through their action upon blood calcium.

Hall and Schillinger have since introduced another carbon derivative, carbon tetrachlorethylene (C_2Cl_4). This chemical the authors assert is, if anything, slightly more potent against hookworms and less injurious than CCl_4. Some who have tested C_2Cl_4 in cases of human infestation claim it possesses no superiority over CCl_4 as regards anthelmintic power, and that its administration is attended by similar symptoms. Furthermore it tends to form decomposition products. C_2Cl_4 is taken somewhat more readily by patients owing to its pleasanter taste.

In a personal statement Dr. Faust of Tulane University asserted that a recent preparation of C_2Cl_4 now placed upon the market in 1 cc. enteric capsules is fully as potent toward hookworms as CCl_4, and that it exerts practically no deleterious after effect upon the patient. It is being used on an increasingly greater scale in the Southern States. In addition this product does not seem susceptible to decomposition as was the case with a similar compound tested several years previously.

Fur production in the United States and Canada is a young but thriving industry. Helminthic parasites, especially nematodes, have been the cause of considerable mortality among foxes, the young being more susceptible. Hanson has found C_2Cl_4 to be fully as efficacious as CCl_4 in the removal of hookworms, and more so for ascarids. Even the young, susceptible as they are to the effects of most anthelmintics, tolerated C_2Cl_4 very well.

The anthelmintic power of the chlorine hydrocarbons seems to reside in the halogen member of the compound. Hall reasoned that if chloroform was effective, then CCl_4 might be more so, and possibly less toxic: all of which was amply proved. Then he went a step further with C_2Cl_4 which approximates CCl_4 in anthelmintic value. Hexachlorethane, C_2Cl_4 on the other hand, with a still greater chlorine content, showed no activity at all. These comparative studies demonstrated that another factor had to be considered, namely solubility. The halogen hydro-carbons considered have the fol-

lowing solubility in water: chloroform, 1–161 at 22°C.; CCl_4, 1–1250 at 25° C.; C_2Cl_4, 1–10,000; C_2Cl_6, insoluble. In the treatment for intestinal parasites the main objective to be kept in view is to employ a drug that is absorbed but little through the intestinal walls, or failing in this, to permit retention of the compound for the shortest period necessary in which to deleteriously affect the parasites. In this way minimum absorption takes place and the gastric and intestinal walls and the organs liable to damage escape prolonged exposure. It is for this reason that the simultaneous or subsequent purge finds employment. (For somatic or extra-intestinal parasites, on the other hand, the principal aim lies in using a substance quite easily absorbed.) When this phase is considered it is readily seen that chloroform is far too soluble, while at the other extreme C_2Cl_6 being insoluble is inert. Much of the CCl_4 is absorbed and finally excreted via the lungs. Hall considers the relatively insoluble C_2Cl_4 the drug nearest the ideal solubility from the viewpoint of treatment.

Correlation between chemical composition and anthelmintic effect has been noted elsewhere than among the halogen hydrocarbons. In the benzene series various substances have been shown to possess such properties, as for example thymol and beta-naphthol. Such powers seem to depend to no small extent upon a phenolic constituent, in which the hydroxyl plays an important part. If these phenols are esterified or otherwise modified, the vermicidal ability is either decreased or lost.

Since santonin has for centuries enjoyed high repute as an anthelmintic a few words regarding recent tests with the drug might not be amiss. The ease with which it may be taken and the fact that it causes no evacuation of ascarids have combined to make it a popular remedy. However, santonin may be toxic, and therefore in common with other vermicidal drugs should be used with caution. Furthermore its high cost militates against general adoption. That it will remove ascarids is readily admitted. However the efficiency of the compound seems far below that claimed for it by the contentions of commercial firms. Schillinger, Hall, and others conclude that the efficacy of santonin against the ascarids of swine and dogs shows a variation from 0 to 46 per cent. Hall and Augustine claim it was no more than 27 per cent efficacious in removing ascarids from man in Honduras when used in 3, 4, and 5 grain doses, the last mentioned amount representing the limit of tolerance for an adult. Symptoms occurred in 75 per cent of the individuals treated. Hall and Schillinger consider that the drug is grossly overrated, and

decidedly inferior to chenopodium in effectiveness against roundworms.

The last anthelmintic of vegetal origin is the sap of two fig trees *Ficus laurifodia* and *F. glabrata,* plants indigenous of Central America and the northern part of South America. Throughout the area of distribution the sap has for long been widely used by the natives to expel intestinal worms. Owing to rapidity of fermentation the substance could be used only locally. A commercial preparation called "Higuerolatex" has been marketed in Colombia. The claims for it are as follows: "A vegetal compound, absolutely harmless. A general anthelmintic and powerful specific for the expulsion of such parasites as *Necator americanus,* Ancylostoma duodenale and *Tricocephalus dispar.*"

Hall and Augustine state that while many of the anthelmintics in common use remove whipworms, yet the action of these, at best, is very uncertain. The difficulty apparently cannot be ascribed to resistance, but to the failure of these substances to pass the ileocecal valve. They further state that in their experience only "*Leche de Higuerón*" succeeds in regularly forcing out these parasites, though not necessarily all of them. Some success was noted with regard to ascarids, and an occasional hookworm was evacuated.

Since then Caldwell and Caldwell have conclusively shown that "Higuerolatex" is an effective agent against both trichuris and ascaris. On the basis of egg counts 85 to 90 per cent of the former and 80 to 90 per cent of the latter were expelled. "Higuerolatex", it would seem, as an ascaricide ranks second only to oil of chenopodium. The Caldwells also established the fact that "Higuerolatex" if kept cool and in a dark bottle, retained its efficiency for more than a year. The prevailing impression regarding this material was that it functioned in a mechanical manner, because a successful result against the worms required the use of large quantities of the sap. The recent researches of Robbins have given us a different conception. The active principle he has found to be a proteolytic enzyme which actually dissolves ascaris in vitro in a dilution of 0.1 per cent. A pH of from two to three adversely affects the enzyme. This would account for the large amounts needed for treatment, since much of the principle is destroyed or modified during passage through the stomach. Possibly in the future we may expect the preparation of the active principle filicin in enteric coated capsules.

Johnson and Hodge (1913) synthesized a number of alkyl resorcinols. Following some promising work of Rettger, Veader

Leonard studied the group. He discovered that with the addition of alkyl radicals the bactericidal powers increased and the toxicity fell. Ratcliffe applied these researches to the flora and fauna of rats. The protozoa commonly found in the intestine of the rat are the flagellates *Trichomonas muris, T. parva,* and the ameba *Endamoeba muris,* all of which occur in the cecum. *E. muris* in both morphology and habits approximates *E. coli* of man. *N*-butyl resorcinol, when added to the ration of experimental animals, eliminated *E. muris* and *T. muris,* and decreased the numbers of *T. parva.* *N*-butyl resorcinol caused such intense intestinal irritation that the rats lost weight rapidly due to refusal of food. The others, hexyl, heptyl and octyl resorcinol caused no disturbance of this type. With increased alkylation the effect upon protozoa became more pronounced. All caused the disappearance of aciduric (*B. acidophilus*) bacteria, but the lactic fermenters (*B. alkiligenes*) increased proportionately with the alkylation.

Ratcliffe's findings interested me, and at my request Dr. Leonard sent a large quantity of Di-hydranol, which is *n*-heptyl resorcinol (2–4 dihydroxy phenyl *n*-heptane). Three infections of *Trichomonas hominis* responded to Di-hydranol, and the feces of the cases concerned have remained negative over periods ranging from two months to a year. An *Endamoeba histolytica* infection likewise cleared up. No amebae could be found in stools a short time after the initiation of treatment. Then the patient departed from Porto Rico. Subsequent examination in New York demonstrated that she had continued to improve. Administration of Di-hydranol caused the disappearance of vegetative forms of the intestinal flagellate *Giardia lamblia.* Cysts were never encountered. Diarrhoeic symptoms also disappeared. Two days after the compound was first given a few dead organisms were found in the stool. Three days later none could be found, and during the following six months the feces continued to be negative.

Faust in a series of experiments concluded that Di-hydranol exerts a specific action upon *Endamoeba histolytica, Iodamoeba williamsi, Endolimax nana,* and *Trichomonas hominis* of the human intestinal tract. Protozoa with more resistant cyst capsules such as *Endamoeba coli* and *Giardia lamblia* seem less amenable to the action of the drug.

That the alkyl resorcinols show some catholic therapeutic tendencies is clearly demonstrated by Lamson and his co-workers. They have succeeded in removing 100 per cent of the ascarids from 16 to 17 dogs, and 90–100 per cent of the ascarids from 20 patients

with Hexylresorcinol. Subsequent studies by the same group amplify their earlier findings. Crystals in amounts of from 0.5 to 1.0 gm. placed in gelatin capsules seem to confer the best results. No food should be taken by the patient the morning of treatment, nor for at least two hours afterward. The ease with which Hexylresorcinol combines with proteins accounts for its lessened efficiency under such conditions. Solvents such as vegetable oil or glycerin likewise reduce its ascaricidal properties.

Gentian violet as a means of treating various bacterial infections has been known for some time; but not until a relatively recent date has it been tried with any success against animal parasites. Faust and Klaw in 1927 found it of value for ridding dogs and cats of *Clonorchis sinensis*. Faust and Yao had tested a number of chemicals on experimental animals. In the one human case mentioned they succeeded in effecting a reduction in the egg count with gentian violet though not entirely eliminating them. In his text on human helminthology Faust advocates the oral administration every other day of this dye in 30 mg. doses, the total dosage not to exceed 300 mg. per kilo of body weight, these to be given as enteric coated pills. Intravenous injection every other day in amounts of 40 cc., 0.5 of a per cent solution until a total quantity of 6 grams has been given, is also recommended. By these methods cases of relatively recent origin may be completely cured. In chronic conditions the gentian violet does not gain access to the worms nearly as readily, and their total elimination is therefore seldom accomplished. Olivier and Kandou in Java confirmed the experimental work of Faust and his colleagues in a series of 18 clonorchis infected patients, all of whom showed marked improvement.

Strongyloides (*Anguillula*) *stercoralis* has always successfully resisted all attempts to displace it from the intestine. De Langen after noting the favorable results obtained by Olivier and Kandou with clonorchis infestations decided to make a trial of gentian violet against strongyloides. In a group so affected oral dosage of 0.1 to 0.3 gm. three to five times a day caused the disappearance of morbid symptoms and eosinophilia in a most striking manner. An occasional larvae could still be detected in some of the stools. At New Orleans where strongyloides infestations can be frequently encountered Faust experienced equally successful results with the same remedy.

Giardia lamblia, a flagellate, is the one intestinal protozoan excluding *E. histolytica* and *B. coli*, to the presence of which many investigators are inclined to assign a pathogenic role. Zahorsky and McLoon emphasize its coincidence in children with diarrheic symp-

toms. They also point out that Wenyon and O'Connor in the Far East obtained fairly successful results in eliminating giardia through the use of bismuth salicylate. Until recently this therapeutic hint had apparently passed unnoticed. Zahorsky and McLoon also cleared up several infestations with the chemical.

About three years ago a man of middle age, engineer of an ocean-going vessel, was sent to this laboratory for a stool examination. The sample submitted seemed to consist almost entirely of giardia cysts, so severe was the infestation. These findings failed to satisfy the physician concerned; and the patient was again sent to the School, this time with the request that the patient be examined for sprue. The findings were negative. The patient was suffering from a constant diarrhea, and had lost considerable weight. Efforts in favor of treatment for the flagellate infestation finally prevailed, and bismuth salicylate at the rate of 0.5 gm. three times a day was advised. Two weeks later, upon a return journey, the seaman was much improved in appearance, and no longer suffering from diarrhea, submitted another fecal sample. On this occasion only a few cysts could be noted. The patient apparently had continued to improve since he failed to appear again as requested.

For a long time parasiticidal substances of vegetal nature have enjoyed greatest use. They also constitute the bases of many therapeutic agents employed for these purposes. However, a number of synthetic preparations have come into use, some of which have provided means of attack against intestinal parasites, upon which all opposing methods had been unsuccessful. As time goes on the latter will probably play an increasingly greater part in this field of medicine.

REFERENCES

Chopra, R. N. and Chandler, A. C.: (1928) Anthelmintics and their uses. Williams and Wilkins Co., Baltimore, Md.

Cort, E. C.: (1928) Infection with *Balantidium coli*. J. A. M. A., **90**: 1430.

Faust, E. C.: (1929) Parasiticidal potencies of the tri-to hepta-methyl derivatives of rosanilin. Proc. Soc. Exp. Biol. & Med., **26**: 748.

Faust, E. C.: (1930) Experiments on the effect of Di-hydranol on intestinal protozoa of man and laboratory animals. Proc. Soc. Exp. Biol. & Med., **27**: 905.

Faust, E. C. and Khaw, O-K.: (1927) Studies on *Clonorchis sinensis;* Amer. Jour. Hyg., Monogr. ser. No. **8**: 151.

Faust, E. C., Yao. K-F., Khaw, O-K., and Chao, Y-A.: (1926) Experimental therapy in clonorchis infections. Proc. Soc. Exp. Biol. & Med., **23**: 607.

Faust, E. C. and Yao, K-F.: (1926) Specific therapeusis in clonorchis infections; Arch. Schiffs. u. Trop. Hyg. **30**: 383.

Fernán-Núñez, M. A.: (1927) A contribution to helminthic therapy. J. A. M. A., **88**: 902.

Hall, M. C.: (1914) Unusual case of fatal poisoning from the administration of male-fern as a vermifuge. J. A. M. A., **63**: 242.

Hall, M. C.: (1921) Carbon tetrachloride for the removal of parasitic worms, especially hookworms. Jour. Agr. Res., **21**: 157.

Hall, M. C.: (1926) Developments in anthelmintic medication. Amer. Jour. Trop. Med., **6**: 247.

Hall, M. C.: (1926) Some practical principles of anthelmintic medication. Jour. Parasit., **13**: 16.

Hall, M. C.: (1928) Recent developments in the use of carbon tetrachloride. North Amer. Vet., 8(11).

Hall, M. C.: (1928) A theoretical and practical consideration of anthelmintics; De Lamar Lectures (Johns Hopkins University). 1927–28. Williams & Wilkins Co., Baltimore, Md.

Hall, M. C. and Augustine, D. L.: (1929) Some investigations of anthelmintics by an egg and worm count method. Amer. Jour. Hyg., **9**: 584.

Hall, M. C. and Cram, E. B.: (1925) Carbon trichloride as an anthelmintic, and the relation of its solubility to anthelmintic efficacy. Jour. Agr. Res., **30**: 949.

Hall, M. C. and Schillinger, J. B.: (1923) Miscellaneous tests of carbon tetrachloride as an anthelmintic. Jour. Agric. Res., **30**: 163.

Hall, M. C. and Schillinger, J. B.: (1925) Tetrachlorethylene, a new anthelmintic. Amer. Jour. Trop. Med., **5**: 229.

Hanson, K. B.: (1927) Critical tests of tetrachlorethylene as an anthelmintic for foxes. Jour. Agr. Res., **34**: 129.

Lambert, S. M.: (1925) Tests with tetrachlorethylene: A new anthelmintic. Med. Jour. Australia, **2**: 699.

Lamson, P. D., Caldwell, E. L., Brown, H. W., Ward, C. B.: (1931) Hexylresorcinol in the treatment of human ascariasis. Amer. Jour. Hyg., **13**: 568.

Lamson, P. D., Minot, A. S. and Robbins, B. H.: (1928) Prevention and Treatment of carbon tetrachloride intoxication. J. A. M. A., **90**: 345.

Lamson, P. D., Ward, C. B., Brown, H. W.: (1930) An effective ascaricide-Hexylresorcinol. Proc. Soc. Exp. Biol. and Med., **27**: 1017.

Lamson, P. D. and Wing, R.: (1926) Early cirrhosis of the liver produced in dogs with carbon tetrachloride. Jour. Pharm. and Exp. Therap., **29**: 191.

de Langen, C. D.: (1928) Anguillosis and the syndrome of the "idiopathic hypereosinophilia". Medel. Dienst. d. Volksgezon. in Nederl. Indie, **17**: 515. (Abstr. in Trop. Dis. Bull., **21**: 499).

Leonard, V.: (1924) Secretion of bactericidal urine and disinfection of urinary tract following oral administration of certain alkyl derivatives of resorcinol. J. A. M. A., **83**: 2005.

Magath, T. B. and Brown, P. W.: (1927) Standardized method of treating tapeworm infestations in man to recover the head. J. A. M. A., **88**: 1548.

Ratcliffe, H.: (1929) The oral administration of certain alkyl resorcinols and their effects upon the intestinal protozoa and bacteria of rats and upon intestinal protozoa in chicks. Amer. Jour. Hyg., **10**: 463.

Wells, H. S.: (1925) A quantitative study of the absorption and excretion of the anthelmintic dose of carbontetrachloride. Jour. Pharm. and Exp. therap., **25**: 235.