PRINCIPLES AND THEORIES OF ANTHELMINTIC MEDICATION *

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Anthelmintic medication, although in principle and theory analogous to medication in general, deserves more consideration and attention than it has heretofore received. Even now, too little is known concerning long-used remedies and that little is apt to be somewhat vague and empirical.

The observations which follow are founded on the author's own experience and outline the uses of anthelmintics as far as they may be outlined at present.

What is the essential factor in successful and safe anthelmintic medication in practice? Good judgment and experience in the physician, who, realizing the more or less poisonous nature of the necessary drugs, will administer them in just and reasonable proportions and under suitable conditions.

What should the physician know about parasites in order to treat parasitism successfully? He should know the habits and life histories of the parasites involved. The location of the parasite is a determining factor in the success or failure of certain treatments. The fact that whipworms occur in the cecum or vermiform appendix is, apparently, the principal reason why they are so difficult to remove. Our experiments indicate that whipworms are relatively susceptible to almost any anthelmintics which come in contact with them, and can be removed by almost any of the drugs effective against any other nematodes, as well as by drugs, such as mercurochrome, which have little or no efficacy against other worms. Apparently much of the contents of the small intestine passes through the ileocecal valve to the colon without entering the cecum, or at least without penetrating to its terminal portions where the whipworms usually occur. By repeated doses of

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such non-irritant drugs as santonin, which can be given safely in repeated small doses, one takes advantage of the mathematical probability that in the course of time some one dose or several doses will come in contact with the worms; or by giving drugs such as *leche de higuerón,* which by virtue of their composition and relatively low toxicity can be administered in large amounts, one takes advantage of the fact that some part of the dose will probably enter the cecum and reach the worms.

Another illustration of the necessity for knowing something about the habits of worms is one in connection with ascarids. These worms have the habit of wandering into the bile ducts and the pancreatic duct and it probably happens from time to time that when repeated treatments with suitable anthelmintics fail to remove all of the ascarids present, as evidenced by the persistence of ascarid eggs in the feces, the explanation is that gravid female worms are present in the bile ducts or the pancreatic duct, and hence inaccessible to attack by the drug.

A knowledge of the life history of a parasite is particularly important in successful anthelmintic medication. Illustrations of this fact may be found in such cases as those of the ascarid and the pinworm. The ascarid life history involves a wandering of the worm larvae into the tissues or through the body of the host outside of the lumen of the host's digestive tract. In the cases of all such wanderers, these including not only ascarids, but also hookworms, strongyloides, nodular worms and various strongyles other than those named, the successful removal of all the worms present in the lumen of the digestive tract may be followed by the appearance of worm eggs in the feces of the patient within a comparatively short time and in the absence of any exposure of the patient to reinfection after treatment. This is the result of the return to the intestinal lumen of worms which were wandering larvae in the tissues, out of reach of drugs at the time of treatment, and the maturing of these worms to the stage of egg production. Knowing this, we realize that it is advisable to hold a patient before treatment in surroundings where he is safe from reinfection, for sufficient time to permit any wandering larvae to return to the lumen of the digestive tract.

The pinworm presents the unusual case of a female nematode which is parasitic in the digestive tract but which does not lay eggs there; hence the eggs do not pass out in the feces. The nematode behaves very much like a gravid segment of the tapeworm *Dipylidium caninum*. When the female is gravid, completely filled with eggs, she migrates through the anus, usually within the first hour after the patient goes to bed, travels forward on the perineum, and deposits her eggs, the worm shriveling as her egg content flows out. The gravid females occur in the large intestine, and the young females and the males occur in the small intestine. It follows from this life history that we may attack the worm as young adults, by anthelmintic medication by mouth; as gravid females, by enemas; and as eggs, by cleanliness, bathing, and various sanitary measures.

What should the physician know about anthelmintics in order to use them effectively and safely? He should know against which worms an anthelmintic is effective, and in what dosage; he should know the effect of the anthelmintic on the patient; he should know which purgatives to use with each, when to administer them, and in what amounts.

Anthelmintics are not entirely specific in their action, but they are more or less specific. When we know more about how anthelmintics affect worms, we may know why this should be; but at present we know almost nothing. Trendelenburg's work [1] has indicated that santonin produces muscular incoördination in ascarids, the worm being able to move but not able to steer its course, so that peristalsis produced by a purgative will move the ascarid out of the host. In effect, the explanation means that the worm is ejected while "drunk and disorderly", and we must assume that muscular incoördination implies an effect of santonin on the nervous system of the worm.

To demonstrate the effect of a drug on the nervous system of the worm, or any effect on any system of a worm, calls for *in vitro* experiments which have not been made, and for a knowledge of invertebrate pathology that we do not possess. Here is a rich and almost untouched field for research. In passing, it may be said that *in vitro* experiments have sharply limited fields of usefulness in the study of anthelmintics. Any number of drugs, such as corrosive sublimate, will kill

worms *in vitro,* and will also kill any host animal. Any number of drugs, such as alcohol, will kill worms *in vitro* but will not kill worms in a host animal; if alcohol were an anthelmintic *in vivo* as well as *in vitro,* man should have been rid of his worm parasites ages ago. Many drugs, such as iodine, will kill worms *in vitro* and also *in vivo* if not fixed by organic matter and rendered inert, but it is a difficult undertaking to clear the digestive tract of organic matter that does render iodine inert.

Precision in dosage is highly essential in securing effective and safe anthelmintic treatment. The dosage of drugs for children should be based on the apparent age, the physical age of the child, rather than on its chronological age.

The most important factors in securing safety in anthelmintic medication are dosage, consideration of contraindications, and purgation, and the factor which needs and deserves the most emphasis is purgation. Why purgation is so important and so valuable in protecting patients is not known. The old textbooks defined an anthelmintic as a relatively insoluble drug which was allowed time to act on the worms present, and was then swept out of the digestive tract by a purgative. This concept seems to be none too accurate. Regardless of purgation, most anthelmintics are relatively soluble, at least to the point where most of the drug administered is absorbed. Probably two-thirds of the therapeutic dose of thymol, a relatively insoluble drug, is absorbed and conjugated with glycuronic acid in the liver. According to the workers at Vanderbilt University, practically all the carbon tetrachloride, a more insoluble drug, which is administered, is absorbed and can be recovered from the expired air. My own theory, which is merely a theory to serve the temporary purpose of a plausible explanation in default of precise knowledge, is that a purgative produces a favorable time and space distribution of the anthelmintic absorption. The purgative moves the anthelmintic along the digestive tract, slows its absorption, and distributes and thus lessens the insult of absorption over a larger area of mucosa, producing a less marked degree of insult over any given area, such as the production of irritation, degeneration or whatever form it may take.

The rôle of purgation in safety is one that appears to be quite well established. In treating a large series of human

patients with any anthelmintic, a rather large proportion of the patients will report one or more of three symptoms, *i. e.*, headache, dizziness, or nausea, and these conditions need occasion no apprehension, for as a rule they disappear as soon as the bowels move. In all probability, one of these symptoms, nausea, is associated with purgation, especially with salts, as much as with the anthelmintic.

An inspection of case reports of deaths following anthelmintics shows that at times the drug selected had definite contraindications; at times the dose was excessive or injudicious; and at times that there was a failure to take adequate steps to ensure purgation. The following rules should be observed in connection with purgation:

Always use adequate doses of purgatives, never trivial doses. Give the purgative with the anthelmintic or very soon afterwards.

Use Glauber's salt in preference to Epsom salt, since the latter is more toxic, and use a solution not over one-third of saturated strength rather than saturated, since it is more effective and less nauseating. A solution consisting of 30 cc. of saturated Glauber's salt plus 60 cc. of water is a good purgative to use.

Have the patient report to a physician or a nurse four hours after treatment, and if the bowels have not moved administer a dose of salts, regardless of whether the purgative first administered was salts, oil or some other thing. Have the patient report again in another four hours, and if the bowels have not moved, take all steps necessary to obtain prompt purgation. For this purpose use salts, enemas, abdominal massage, etc. If a patient dies without a bowel movement in 24 to 48 hours after treatment, with evidence showing that little or no effort was made to insure purgation, the death should not be charged to the anthelmintic but to the physician.

In general, preliminary purgation the night before an anthelmintic treatment to be administered the following morning, is omitted as of no value except in certain special cases. These cases, are: 1. *Cases of constipation.* Since purgation is important in protecting the patient, it is inadvisable to start anthelmintic treatment with a constipated patient and risk an uncomfortable experience in securing evacuation of clogged bowels after an anthelmintic has

produced unfavorable effects. Moreover, badly constipated patients are more susceptible to poisonous effects of drugs than persons not constipated. 2. *Treatments for tapeworm infestation.* Experience indicates that anthelmintics for the removal of tapeworms are usually less dependable than anthelmintics for the removal of nematodes, and that the reason for this is the difficulty in removing the tapeworm head. This is due to the fact that the head is usually buried in the intestinal mucosa, where it functions as an anchoring device, and in that location it is probably not readily accessible to drugs, especially since a normal amount of mucus and of intestinal content may be an effective barrier in keeping a drug from contact with the head. There is little to be done about changing the position of the head, but the use of a preliminary saline purgative might make the difference between success and failure of treatment by removing the mucus and other intestinal contents from the region about the tapeworm head and thus exposing it to the drug action. 3. *Treatment for very small worms.* In general, such small worms as trichinae and *Strongyloides* have proved very refractory to anthelmintics. It is not known just why small worms are hard to remove, but it is plausible and reasonable to assume that whereas a large worm will project above the mucus which covers the villi, a small worm may be embedded in mucus or lie between the villi and under the mucus and thus escape an anthelmintic. It has not been demonstrated that a saline given with or previous to an anthelmintic will increase the efficacy of the latter, but on theoretical grounds this procedure is worth trying.

There are certain general considerations in regard to procedures in anthelmintic treatment which may be noted at this point. These considerations involve such matters as diet, fasting, the time at which food may be permitted after treatment, and the symptoms which may be expected to occur in many cases as a result of the effects of the anthelmintic on the patient.

The day previous to treatment and on the day of treatment, the patient should abstain from alcohol, fats, oils and cream, and from such fatty foods as avocados (alligator pears). Olive oil in particular is contraindicated, as it has a tendency to remain for a long time in the stomach and if used with such irritant drugs as oil of chenopodium there

may be a resultant gastritis, with severe effects upon the patient. Castor oil is, of course, a special case and is the one oil which is permissible in human medicine as a purgative. In veterinary practice, linseed oil also may be used, and possibly certain other oils. Some writers have found no bad effects in connection with the use of wine at the time when patients are being treated with such drugs as thymol, but since alcohol is very definitely contraindicated with such drugs as carbon tetrachloride, it is a safer practice to regard alcohol as contraindicated with anthelmintics. In general alcohol and fatty substances favor absorption and the production of systemic effects. Apparently absorption in fats by the lymphatics may cause increased effects of drugs on the central nervous system.

In dealing with human patients it is advisable to give a liquid meal the evening before treatment and to treat early the next morning. A longer period of fasting appears to serve no good purpose and is likely to leave the patient in an abnormal condition, with such result as headache due to prolonged fasting, and since anthelmintics commonly cause certain unpleasant symptoms, even in patients not in an abnormal condition, it is unwise to prolong the fasting period and thereby increase the intensity of the disagreeable effects of the drug. It has been found to be a good practice in this connection to permit the patients to drink all the coffee they wish at the time of treatment as it appears to be of value in preventing or diminishing the intensity of unpleasant reactions. The patient should not be permitted to eat anything until after the bowels move. The precise procedures to be followed in connection with purgation have already been given.

Our knowledge of anthelmintics is derived from various sources. In part our judgment as to the efficacy of an anthelmintic is based on clinical observations, and clinical observations give sound but not necessarily complete information. In our experiments at Washington we have had excellent clinical results with drugs which are only approximately 50 per cent effective in removing the worms responsible for the clinical condition. The explanation for this is obviously that the removal of half of the worms present was sufficient to lower the degree of infestation from an intolerable infestation, capable of producing severe clinical symptoms and death,

to a tolerable infestation which, while more or less injurious to the animals, was no longer capable of causing visible clinical symptoms or death. Clinical observations of this sort warrant the use of anthelmintics with such a relatively low efficacy as 50 per cent in default of a knowledge of better anthelmintics. In other words, observations of this sort constitute a fairly sound form of empiricism, but it should not be assumed that the removal of some worms establishes the value of an anthelmintic.

As a result of an increasing knowledge of the importance of human hookworm disease, anthelmintics have been receiving an increasing amount of attention in the past 50 years and especially in the past 15 years. Various methods, other than the clinical approach, have been used to ascertain the efficacy of these anthelmintics. Historically this was first attempt in connection with human medicine on the basis of comparative egg counts before and after treatment. This method has given us much valuable information, but the information so obtained is not ordinarily examined in a critical way with sufficient allowance for the inherent limitations of the procedure. It is obvious that immature worms, males and senescent females, will not be represented by eggs in the feces. Furthermore, since much of this work was published it has been learned that certain drugs, such as chenopodium, will inhibit egg production for as much as 12 days after the administration of the anthelmintic, and that the decreased egg count will indicate a much more effective removal of the worms than is actually the case. Furthermore, there are data in the literature indicating that following a treatment with anthelmintics for the removal of ascarids and with the removal of female ascarids accomplished, there may be an actual increase in the egg count. Finally, studies on immunity in connection with certain parasites of the gastrointestinal tract indicate that some worms apparently produce a partial immunity, which in a subsequent infection leads to a pronounced slowing of development on the part of the worms and a considerable inhibition of egg production, with the result that an animal may have a negative egg count and still have numerous mature worms of which the females will not be producing eggs. All of these things inevitably lead to the conclusion that one must not take too

seriously the findings in regard to the efficacy of anthelmintics on the basis of the egg counts reported in the old literature.

The work which was carried out in the Zoölogical Division of the Bureau of Animal Industry for the testing of anthelmintics during the past 15 years has been done for the most part on the basis of worm counts. Animals are treated with an anthelmintic, the feces are collected and all worms removed, identified and counted, and the animal is then killed and all worms present *post-mortem* are removed, identified and counted. This method of testing gives rather definite information and is distinctly superior to the old egg-count method. Nevertheless it has its limitations. It is not readily applicable to worms in the stomach, for the reason that if an anthelmintic kills a worm in the stomach and the worm is not rather promptly removed by peristalsis, the worm is then so much dead proteid, and is likely to be completely digested or digested to a point where subsequent digestion and disintegration in its passage through the intestine will leave nothing to be recovered on fecal examination.

Since it is impossible to apply this method of critical testing, which involves *post-mortem* examination, in the treatment of human beings, except in the rare cases where criminals have agreed to take anthelmintics before execution, the efficacy of anthelmintics has been tested to a slight extent in human medicine by egg counts, preliminary to and subsequent to, anthelmintic treatment, and the worms passed have been recovered and identified and counted. While this method is somewhat tedious it is an improvement on the method of egg counts alone, since it brings to light some of the inaccuracies in the egg counts and also affords an opportunity to check up on males, immature worms and senescent females which may be removed.

There is much more that might be said in regard to the limitations of our methods for ascertaining the efficacy of anthelmintics, but only a few of these things need be mentioned. For one thing it may be noted that in examining feces for eggs, such methods as the smear method are crude, and that while they have real value under certain conditions, there is a distinct limitation to their usefulness. The Stoll egg count has the limitation that while it takes advantage of mathematical probabilities and does so on a very sound basis, this same element of mathematical probability will go

against the method when there are very few eggs and large amounts of feces, as a negative egg count under those conditions will not be truly indicative of the absence of egg-producing females. Under such conditions resort must be had to such elaborate methods as the Lane technic, an excellent technic, with the only disadvantage of being somewhat intricate.

We have many special cases where our methods are not readily applicable, and one of these is the case of the pinworm, since the gravid female does not deposit eggs in the intestine but migrates from the bowel to the exterior, with its egg content intact. Because of this it is not possible to investigate the efficacy of anthelmintics against pinworms by egg-counting methods. While it is fairly simple to outline a technic for the investigation of the efficacy of anthelmintics against pinworms, it does not appear that anyone has ever taken the trouble to do so. The technic would involve treatment of the patient, the counting of pinworms removed by treatment, and a careful consideration of the females which migrate from the patient, as the worms usually do during the first hour or so after the patient goes to bed.

Finally we have the cases of anthelmintics for the destruction of worms outside of the lumen of the digestive tract and here the case is complicated in many ways. It has been found that where the eggs of these worms arrive at the exterior of the body, as in the case of schistosomes, a cessation of egg-production over a considerable period of time is fairly good evidence that the worms have been killed, although even here there is the likelihood that in some cases egg-production has been inhibited or the worms sterilized. On the other hand, with such worms as the filarids, the disappearance of microfilariae from the peripheral blood has not been found to be a good index as to the deaths of the adult worms and in general the microfilariae reappear after varying intervals.

A line of investigation in anthelmintics which has been opened up of late years, and one which gives great promise as something which may lay the foundation for more basic research, is one which is being undertaken to ascertain the correlation between the anthelmintic efficacy of a drug and its chemical composition and physical properties. A preliminary study of this sort was made more than a decade ago by Hall and Wigdor [2], but owing to its interruption by

the World War their work was not published until some time later. They were unfortunate in their selection of a group of drugs to be tested as they selected the terpenes, and the complexity and variability of these products would not permit of any conclusions. Caius and Mhaskar [3] undertook a much more thorough investigation of the common anthelmintics, but ran into much the same difficulties in that the common anthelmintics represented such diverse products that there was little in the way of a common denominator as a basis for comparative results. They concluded that the efficacy of carbon tetrachloride was due to its halogen content, that of chenopodium to its dioxide structure, and that of thymol and beta-naphthol to their phenolic radicals. In subsequent work by Hall [4, 5, 6] and his collaborators, where the drugs tested were restricted to chlorinated hydrocarbons, it appeared that there might be a correlation between the amount of chlorine and the efficacy, and also a correlation between the water solubility and the efficacy. They concluded that there was probably an optimum solubility, and this conclusion has had additional confirmation from the work of Wright and his collaborators. Wright and Schaffer [7] find some evidence indicating that the position of the chlorine in the hydrocarbon chain has a bearing on the efficacy and safety of the drug. This line of investigation promises to produce results which will enable us to predict the anthelmintic efficacy of certain chemicals from their structural formula and water solubility, and perhaps to synthesize drugs better than those we have at the present time.

What should the physician know about purgatives? Experience indicates that there are certain things of importance in connection with purgation with which the physician should be familiar. For one thing saline purgatives are especially valuable in connection with most anthelmintics for several reasons. One reason is that these purgatives act rapidly, thereby affording the prompt purgation which has already been discussed. For another thing, saline purgatives are probably of value in retarding and diminishing the absorption of anthelmintics. Macht and Finesilver [8] have pointed out that various drugs when administered with saline purgatives fail to exhibit their usual therapeutic action and have advanced as an explanation of this the theory that the well-known salt action, producing an osmotic flow from the walls

of the intestine to the lumen, prevents the establishment of an absorption flow in the opposite direction. Since anthelmintics are drugs intended to exert their effect on parasites in the intestine, and since the systemic effect of the anthelmintic on the patient is usually undesirable, the use of saline purgatives with anthelmintics is ordinarily very sound practice, if the theoretical consideration just mentioned is sound. In actual practice, involving the treatment of millions of patients, the use of salines with anthelmintics has proved very satisfactory. Salines have the additional advantage in mass treatment that they are inexpensive.

Castor oil is a special case among the purgatives in that it appears to be highly satisfactory for use with such anthelmintics as oil of chenopodium. Whenever castor oil is used with an anthelmintic it should be administered simultaneously with the anthelmintic. It appears to diminish the irritant action of oil of chenopodium on the mucosa of the digestive tract and it offsets the constipating action of chenopodium. The mixture of chenopodium and castor oil is highly effective for the removal of ascarids from man and most other animals on which it has been tested.

Santonin is one of the drugs about which there has been much dispute as regards its efficacy. A recent work by Morris and Martin[9] has resulted in findings to the effect that the classical method of administering santonin with an equal amount of calomel is not a satisfactory method and that saline purgatives should be used. The experiments which have been carried out in the Bureau of Animal Industry on santonin and calomel have indicated that the combination is not very effective and it may be that the findings of Morris and Martin are sound. Trendelenburg indicates that santonin causes muscular incoördination in ascarids, and it is possible that calomel does not produce sufficient peristalsis to remove worms temporarily unable to maintain their position in the digestive tract against a forceful peristalsis, and that salines will remove them by producing a more powerful form of peristalsis and at the same time providing a large amount of fluid by virtue of salt action, in which fluid the ascarids are more readily washed out of the intestine.

What should the physician know about the patient? The physician should take as much care in ascertaining the anamnesis and *status praesens* of the patient in connection

with anthelmintics as he would in connection with any other proposed therapeutic procedure, and should give special attention to certain things of known importance.

In connection with the anamnesis, special attention should be paid to a previous history of recent acute alcoholism or chronic alcoholism. Cases of chronic alcoholism, or persons who have been drunk recently, or are drunk at the time of the examination, are poor subjects for anthelmintic medication, especially with such drugs as carbon tetrachloride. A history of malaria is a contraindication for treatment with such a drug as beta-naphthol, which is said to cause destruction of red blood cells and hence is contraindicated in patients in which there is already an anemia or a marked tendency towards anemia. The food habits of the patients should be investigated, as the use of large amounts of fats, oils, cream and similar things is a contraindication for the use of certain anthelmintics which are readily soluble in fatty and oily substances. It appears probable that such fat-soluble drugs are not only more readily absorbed in the presence of fat solvents, but are taken up by the lymphatics and carried through them to the circulatory system in such a way as to produce more than the usual amount of effect on the central nervous system, thereby giving rise to nervous symptoms which may be profoundly disturbing.

In connection with the *status praesens* of the patient, there is the usual necessity for considering the age, sex and presence or absence of pregnancy. As already noted, in dealing with children, especially in the Tropics, one should establish the apparent age, as indicated by physical development, as well as the chronological age, and dosages should be based on apparent age and not on chronological age. In general, extreme youth and extreme old age are contraindications for anthelmintic treatment, at least to the extent that the therapeutic dose should be diminished and that, if necessary, one should elect repeated treatment with small doses of drugs rather than a single treatment, on the theory that it is better to remove part of the worms by each of several treatments and gradually restore the health of the patient, than to risk the patient's life by attempting to remove all of the worms with one treatment.

Pregnancy is regarded as a contraindication for the use of oil of chenopodium, since this drug has been regarded as

an abortifacient. There does not appear to be very much evidence indicating that chenopodium will produce abortion and there are a number of cases in the literature where pregnant women have been treated with chenopodium and abortion has not occurred. Furthermore, chenopodium has been extensively used in veterinary medicine and I recall no case in which an abortion has been recorded as a result of its use. Nevertheless it is advisable to play safe, and for the time being pregnancy should be regarded as a contraindication for the use of chenopodium.

Specific contraindications for the use of various drugs will be considered later. These contraindications, of course, depend on the specific action of the drugs on the host animal, their relation to the diet of the patient, and their fate in the body of the host.

What should the physician know about prophylaxis? Prophylaxis is the final business of the physician, and his professional obligations have not been discharged until the treatment of the patient for worm infestation has been followed by advice as to measures for preventing reinfection. The precise measures to be recommended will depend upon the kind of infestation present, and here again it is essential that the physician know the life histories of the parasites involved in order that he may make rational recommendations as to how to prevent reinfection. In a general way, infection is a result of swallowing infective material in contaminated food or water, or a result of eating meat, fish or other foods containing the larvae of parasitic worms, or a result of exposing the skin to penetration by such larvae as those of hookworms, or a result of the attack by arthropod vectors conveying parasitic larvae, such as those of the filarids, or a result of swallowing such intermediate hosts of parasitic worms as the insects and other arthropods which carry *Hymenolepis diminuta.*

SUMMARY

In conclusion the outstanding points which have been made may be summarized as follows:

The physician is the most important factor in successful and safe anthelmintic medication and should be well trained, well informed and experienced.

The physician should be well informed in regard to the habits and life histories of parasites, as these things have an important bearing on anthelmintic medication. Anthelmintic medication may fail because certain worms are permanently or temporarily in locations which cannot be reached by anthelmintics, or can be reached only with difficulty and by certain special drugs or methods.

Anthelmintics are more or less specific and should be carefully selected. Their precise effect on worms has had too little investigation and the subject requires much more research.

In vitro testing will answer certain questions in regard to the effects of anthelmintics on worms, but cannot be trusted to determine whether a drug which will kill a worm *in vitro* will constitute an anthelmintic when used *in vivo*.

The most important safety factor in connection with supposedly therapeutic doses of anthelmintics is purgation. Adequate doses of purgatives should always be given, and should be given with the anthelmintic or very soon afterwards. Saturated saline solutions are less effective, less safe and more unpleasant than larger doses of salines administered in more dilute solutions.

Routine treatment of patients is given, concerning suitable diets, preceding and subsequent to administration of anthelmintics, purgation and its importance, and the resumption of ordinary food.

The world's literature on anthelmintics must be interpreted against the background of present-day knowledge, as many of the conclusions which have been drawn from the early work in testing anthelmintics are now known to be inaccurate because of limitations which were not known at the time the work was done. Ten years from now some of the propositions set forth here will need modification for the same reason.

REFERENCES

1. TRENDELENBURG, P. Ueber die Wirkung des Santonins und seiner Derivate auf die Wurmmuskulatur, und Bemerkungen zur Wirkung des *Oleum Chenopodii*. Arch. f. exper. Path. u. Pharmakol., Leipz., **79**: 190. Figs. 1–17. 1915.

2. HALL, M. C. and WIGDOR, M. Miscellaneous anthelmintic investigations. J. Am. Vet. Med. Ass., **22**: 195. 1926.

3. CAIUS, J. F. and MHASKAR, K. S. The correlation between the chemical composition of anthelmintics and their therapeutic values in connection with the hookworm inquiry in the Madras Presidency. 22. Summary and conclusions. Indian J. Med. Research, **11**: 371. 1923.
4. HALL, M. C. A theoretical and practical consideration of anthelmintics. In De Lamar Lectures, 1927–28. The Johns Hopkins University School of Hygiene and Public Health. Baltimore, 1. 1928.
5. HALL, M. C. and CRAM, E. B. Carbon trichloride as an anthelmintic, and the relation of its solubility to anthelmintic efficacy. J. Agric. Research, **30**: 949. 1925.
6. HALL, M. C. and SHILLINGER, J. E. Critical tests of miscellaneous anthelmintics. J. Agric. Research, **29**: 313. 1924.
7. WRIGHT, W. H. and SCHAFFER, J. M. Critical anthelmintic tests of chlorinated alkyl hydrocarbons and a correlation between the anthelmintic efficacy, chemical structure and physical properties. Am. J. Hyg. **16**: 325. 1932.
8. MACHT, D. I. and FINESILVER, E. M. The effect of saline purgatives on the absorption of other drugs. The Johns Hopkins Hospital Bull. **33**: 330. 1922.
9. MORRIS, H. and MARTIN, J. A. Santonin as an anthelmintic for swine. J. Am. Med. Ass., **31**: 531. 1931.