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A. D. MELVIN, CHIEF OF BUREAU.

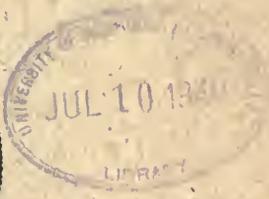
THE ACTION OF ANTHELMINTICS ON PARASITES
LOCATED OUTSIDE OF THE
ALIMENTARY CANAL.

BY

BRAYTON HOWARD RANSOM,
Chief of the Zoological Division,

AND

MAURICE C. HALL,
Assistant Zoologist, Zoological Division.



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LETTER OF TRANSMITTAL.

U. S. DEPARTMENT OF AGRICULTURE,
BUREAU OF ANIMAL INDUSTRY,
Washington, D. C., May 2, 1912.

SIR: I have the honor to transmit herewith, and to recommend for publication as a bulletin of this bureau, a manuscript entitled "The Action of Anthelmintics on Parasites Located Outside of the Alimentary Canal," by Dr. B. H. Ransom, Chief of the Zoological Division, and Mr. Maurice C. Hall, assistant zoologist in the Zoological Division of this bureau.

This paper details the results of some attempted medicinal treatment of sheep for tapeworm disease, and also summarizes our knowledge of the use of anthelmintics against parasites located outside of the intestinal lumen. While the experimental results were negative, the evidence brought together here indicates the need of further work, and this paper is intended to simplify additional work by furnishing a systematic summary of all previous work. It also has immediate practical utility as an aid in judging the claims made for proprietary medicines.

Very respectfully,

A. D. MELVIN,
Chief of Bureau.

Hon. JAMES WILSON,
Secretary of Agriculture.

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THE ACTION OF ANTHELMINTICS ON PARASITES LOCATED OUTSIDE OF THE ALIMENTARY CANAL.

INTRODUCTORY.

As commonly employed, the remedies known as anthelmintics are usually efficacious preparations. Their action is based on the premises that they are poisons which can be taken into the digestive tract of such animals as man, the horse, dog, or cat, in quantities not large enough to poison the host but sufficient to stupefy or kill verminous parasites with which they come in contact. The parasites are usually in the small intestine (intestinal helminthiasis) and occasionally in the stomach (gastric helminthiasis). In order to avoid dilution of the medicine, and also to give a more effective contact with the parasite, the patient is prepared in advance by fasting to empty the stomach and intestine. Finally a purgative is administered to carry out the dead or stupefied worms. All this is comparatively simple and in practice effective.

Though anthelmintics may be used very successfully in treatment for parasites in the stomach and small intestine of certain animals, they are, as a rule, less satisfactory when applied to ruminants. Medicines administered to ruminants must first pass the first, second, and third stomachs, some or all of which are usually well filled with food and difficult to empty in any reasonable period of fasting, before reaching the usual location of gastric parasites, the fourth stomach, through which in turn the medicines must pass before they reach the small intestine. In some cases, however, gastric and intestinal helminthiasis in ruminants may be treated successfully. Perroncito (1885)¹ and Stiles (1902), for example, have reported satisfactory results from the use of various remedies for stomach worms of sheep. Certain experiments have indicated that under the right conditions remedies may pass directly through the first stomach and thus arrive more or less promptly in the second and following stomachs and the intestine. Powers (1909), however, has questioned this, and considers medicinal treatment for stomach worms in ruminants unsatisfactory.

As to the treatment of parasites located in the large intestine, it has been found in actual practice, even in animals with simple

¹ References to literature will be found in bibliography at end of bulletin.

stomachs and short alimentary tracts, such as the dog, that the results from the administration of remedies per orem are generally very unsatisfactory. Stiles and Pfender (1902), for instance, found that thymol, a classic remedy for hookworms, was without effect on whipworms of the cecum of the dog. On the other hand, Miller (1904) claims to have succeeded in removing whipworms from the dog by the use of oleoresin of male fern. Parasites located in the large intestine are, however, difficult to reach with ordinary anthelmintics administered by mouth.

In view of the difficulty of reaching parasites located in the alimentary tract beyond the stomach or small intestine, or even in these organs in ruminants, by means of anthelmintics administered through the mouth, it would seem on first thought that treatment with such remedies for worms in the liver, pancreas, muscles, brain, blood, or in other locations outside the direct course of the digestive tract, would be certain to result unsuccessfully. Nevertheless several more or less commonly used anthelmintics have received favorable consideration in the treatment of verminous parasites located outside the lumen of the stomach and intestine, and the results of the tests made in some cases apparently afford a basis for a belief in their efficacy.

HISTORICAL REVIEW.

A consideration of the work done on this subject shows that writers, in general, have recognized two lines of work: First, the treatment of somatic and extraintestinal tæniasis where parasites are located in the brain, muscles, liver, or subcutaneous tissue; and second, the treatment of certain forms of distomatiasis, where the parasites are located in the liver or blood. Parasites in the liver are, of course, relatively nearer the usual site of operation of anthelmintics. To the first line of work we wish to add some notes on the treatment of tæniasis where the parasites are located in the liver and in the pancreatic and bile ducts. In this case the parasite, *Thysanosoma actinioides*, is also an intestinal parasite, and we use, therefore, the terms extraintestinal and intestinal thysanosomiasis to indicate the two forms of infestation with the adult worm.

Since writers along either of the two lines mentioned have usually confined their abstracts and criticism of related work to work along the one line, this review will summarize the two lines of work separately.

SOMATIC AND EXTRAINTESTINAL TÆNIASIS.

Zürn (1882a) states that after trying for 24 years to find some medication that would cure gid in sheep, he has concluded that successful treatment of the sort is impossible, and cautions against the administration of poisons, which, in his opinion, results in nothing

but a waste of time and money. It is unfortunate that he did not give his experiments in detail, or at least name the remedies he tried; but from the fact that he speaks of them as poisons it seems reasonable to suppose that he tested the various common anthelmintics, all of which are poisons.

Curtice (1889a and 1890c) records tests of various remedies in intestinal and extraintestinal thysanosomiasis of sheep, and says:

Various tœniáfuges were tried with little success. The powdered preparations of pumpkin seed, pomegranate-root bark, koosoo, kamala, male fern, and worm seed proved of no avail. * * * The presence of tœniæ in the biliary ducts is another reason why tœniáfuges can not be entirely successful in treatment of sheep with *T. fimbriata* [*Th. actinoides*]. Any medicine which would affect the tœniæ in these ducts would also affect the sheep seriously. It is doubtful whether they can be killed or driven from the ducts.

Feletti (1894c) administered ethereal extract of male fern in three cases of human cysticercosis, as follows:

1. Patient had had *Tœnia solium*. Present symptoms: Convulsions, cephalalgia, vertigo, vomiting. Small subcutaneous nodules appeared and grew to the size of olives; one of these was excised and found to be *Cysticercus cellulosæ*. No cestode proglottids or eggs were found on fecal examination. Feletti administered 1 to 3 grams of extract of male fern per diem to the patient until he had given 18 grams. The patient could not stand more. The cysticerci diminished to the size of a wheat grain, but the cerebral trouble did not improve, and the man died a month later. No autopsy was permitted.

2. Patient had 34 subcutaneous nodules. One of these was excised and found to be *Cysticercus cellulosæ*. No cestode proglottids or eggs found on fecal examination. Feletti at first administered 1 to 1.5 grams of extract of male fern per diem, but this was not supported and the dose was accordingly cut down to 40 centigrams. The total amount administered was 26.5 grams. The nodules diminished until they could not be felt.

3. Patient had had a tapeworm three years before and had not recovered the head in several attempts at removal. Present symptoms: Convulsions, vertigo, and vomiting. For this he was treated with sodium and potassium bromid. Seven nodules developed. One of these was excised and found to be a cysticercus. Feletti administered 60 centigrams of extract of male fern per diem, and in a month the nodules had disappeared. The nervous condition was improved, but the trouble subsequently recurred and was treated with bromids with good results. Feletti thinks the recurrence was due to brain alterations, but considers that the cysticerci were dead.

According to Feletti, these cases demonstrate that extract of male fern kills subcutaneous and muscular cysticerci and that it probably acts upon cerebral cysticerci also. He advises a dose of 30 to 40 centigrams per diem for 30 or 40 days.

De Renzi (1908) renewed the interest in this line of work by his report of the administration of extract of male fern in four cases of human somatic tœniasis. We quote the following abstract of De Renzi's cases from Hall (1909):

1. The patient had occasion to eat badly cooked pork and uncooked sausage; had an infection with *Tœnia solium* five years previous; had attacks of con-

vulsions and insensibility three years later, and on treatment with a vermifuge had passed a tapeworm with the head. Two months later the patient had stronger convulsions, dizziness, and shortness of breath on slight exertion. About this time growths appeared on the temples and the sternocleidomastoideus. Five months later the patient had three cramp-like attacks in one day, followed by great exhaustion. At this time the patient came to De Renzi, who found small swellings over the entire body and great nervous depression. On the history given here he diagnosed cysticercus of the brain and skin. After a year's ambulant treatment with male fern the nervous trouble had disappeared, so had the swellings, with the exception of one over the left temple, and this was removed by operation and showed the presence of a cysticercus. The eosinophilia present at the beginning of the treatment had disappeared.

2. The second patient, a woman, had an infection with *Tenia solium* three years before. For two years previous to treatment she had suffered from dizziness, headache, weak memory, polyuria, and weakness. A swelling over the manubrium sterni showed all the characteristics of a cysticercus. After a week's treatment the nervous symptoms had disappeared and the swelling was reduced to one-third its original volume. A microscopic examination of the swelling was made, but De Renzi states that in this examination nothing of special importance was noted.

3. In De Renzi's third case there was a history of increasing pain in the hypochondrium for 20 months, no fever or emaciation, increase in the area of liver dullness, eosinophilia present, urine normal. The case was diagnosed as hepatic echinococcosis, and all symptoms disappeared under treatment in 20 days. * * * Fecal examination did not show parasites or their eggs.

4. The fourth patient was a woman who had suffered for a year with a pain in the thorax and often coughed blood. In the absence of tubercular symptoms and because the patient coughed up membranes, "Häutchen," a diagnosis of lung echinococcosis was made by De Renzi and confirmed by two associates. In the brief period of six days she was cured by male fern.

Dianoux (1909) has recorded a case in which ocular and subcutaneous cysticercosis, possibly complicated by cerebral cysticercosis, was apparently cured by the administration of male fern.

Before coming under Dianoux's care, March 25, the patient had had several epileptiform attacks, and had nearly lost the sight of the left eye. Examination with the ophthalmoscope showed the presence of a cysticercus in the vitreous humor, and some weeks later a nodule, presumably a cysticercus, was found beneath the skin of the groin. After treatment with male fern and calomel the patient passed 4 or 5 meters of tapeworm (*Tenia solium*). May 2 the patient experienced an epileptiform convulsion. From May 3 to 20 the patient took 2 grams of extract of male fern per day; treatment was then suspended a few days. On May 24 a slight epileptiform attack occurred. Examination with the ophthalmoscope showed that the cysticercus had become shriveled and motionless. From May 25 to June 5, 2 grams of extract of male fern per day were administered. June 12 the cyst in the groin was discovered. June 16 an epileptiform attack occurred, lasting 15 minutes, and the following day there was another attack. Treatment was resumed. July 2 treatment was suspended; the cyst had disappeared from the groin; the general health of the patient was excellent. During 10 days in August the patient was given 1.5 grams of extract of male fern per day. November 15 the patient was discharged as cured. The cysticercus had entirely disappeared from the eye. The only evidence of its former presence was a cicatrice and vascular condition of the retina at the

point where the parasite had been located. Altogether 102 grams of extract of male fern had been administered during a period of 71 days, and presumably as a result of this treatment a cysticercus of the eye, one under the skin of the groin, and probably others in the motor centers of the brain, had degenerated and become absorbed. Dianoux concludes that male fern destroys cysticerci because of some selective action against these parasites.

Railliet in his abstract of De Renzi's article (De Renzi, 1909) has noted that it would be interesting to test male fern on domestic animals suffering from parasitic diseases of the muscles and viscera, and mentions gid as one disease in which this treatment should be attempted. Such treatment was attempted and reported by Hall (1909). The treatment was tried on three sheep as follows:

1. Sheep showed characteristic symptoms of gid. Fifty grams of male fern powder administered on two consecutive days. The third day the attendant accidentally got the dose in the windpipe of the sheep, killing the animal. Post-mortem examination showed a large living cœnurus in the cerebrum.

2. Sheep showed pronounced symptoms of gid. Ethereal extract of male fern administered in 5 c. c. doses on 27 days between April 22 and May 30, a total of 135 c. c. Sheep found dead May 30, following a gradual increase in unfavorable symptoms from May 1. Post-mortem examination showed a large living cœnurus in the cerebrum.

3. Sheep showed characteristic symptoms of gid. Ethereal extract of male fern administered in 5 c. c. doses on consecutive days, with the exception of one day, until a total of 45 c. c. had been given. No improvement in condition. Treatment discontinued and sheep found dead four days later. Post-mortem examination of the brain showed a small live cœnurus.

Hall has given a critical review of De Renzi's cases, and concludes that they are open to suspicion of error as regards diagnosis and the connection between the disease, the treatment, and the cure.

Moussu (1910) has also reported some tests of ethereal extract of male fern administered for two months to two giddy sheep. There was a marked amelioration of symptoms, but at the autopsy, two months after the cessation of treatment, there was a cœnurus in the brain of each, very large in one case and the size of a hazelnut in the other, and neither of them degenerated. Moussu also tested the treatment on a pig affected with cysticercosis which had been developing for more than six months, the vesicles being readily visible under the tongue and the conjunctiva. The condition of the pig, instead of improving, became worse from day to day.

In view of the conflict between his results and those obtained by De Renzi and Dianoux, Moussu concludes that the influence of male fern only makes itself felt on young lesions and those in course of development, but that where the cysts are entirely developed the medicament remains entirely without effect.

The most recent published work upon this subject available to us is that of Dévé (1911). His test of the treatment was as follows:

Three rabbits were given a subcutaneous injection of brood capsules from a hydatid cyst. No. 1 was kept as a check. No. 2 was given each day for 52

days 4.5 c. c. of ethereal extract of male fern. The weight of the rabbit was 2.9 grams. No. 3, weighing the same, was given 9 c. c., or 6 c. c. per kilogram, or double the corresponding dose for man. The treatment was begun the same day as the injection. Five months later normal live echinococcus cysts were found in all three rabbits. From this Dévé concludes that in doses as large or twice as large as De Renzi used and extending over a much greater length of time the male fern was without effect on the hydatid cysts. The treatment showed itself incapable of affecting the delicate metamorphosis of the scolex, an initial phase in which it seems that the parasite would be especially vulnerable. Male fern is therefore provisionally deemed inefficacious in hydatid disease.

Dévé notes that his results in echinococcosis are in agreement with the negative results obtained by Hall in cysticercosis (Dévé's error; Hall's cases dealt with *cœnurus*, as noted above), by Moussu in *cœnurosis*, and finally with the very unsatisfactory results obtained by Railliet, Moussu, and Henry in distomatiasis.

A summary of the foregoing indicates that results following the administration of male fern were claimed as follows:

Successful in 6 cases of human cysticercosis (4 subcutaneous, 1 subcutaneous and cerebral, and 1 subcutaneous and ocular), and in 2 cases of human echinococcosis (1 hepatic and 1 pulmonary); a total of 8 cases of human somatic *tænia*sis.

Unsuccessful in 5 cases of ovine cerebral *cœnurosis*, 2 cases of leporine general echinococcosis, and 1 case of porcine muscular and ocular cysticercosis; a total of 8 cases of somatic *tænia*sis in lower animals.

A critical discussion of these cases will be given later. It is sufficient at this point to note that all tests on man were claimed to be successful and that all experiments on animals were failures. The cases of Zürn and Curtice are too indefinite to include in this summary.

DISTOMATIASIS.

Under this heading hepatic distomatiasis will be considered first and venal distomatiasis second.

Grassi and Calandruccio (1884 and 1885) record the first cases of which we are aware where extract of male fern was used in distomatiasis. The article published in 1884 is not available to us, but from the article of the following year it appears that they administered to sheep a single dose consisting of 5 grams of ethereal extract of male fern in 50 grams of ethereal tincture of male fern. They note that one might use injections of male fern, but that it would not always be necessary. The injection should consist of 1 gram of the ethereal extract mixed with 1 gram of the tincture and injected directly into the liver by means of a Pravaz syringe. A postscript, based on later work, adds that this injection should not

be employed. They find that for 24 to 48 hours after the administration of the medicine the feces contained numerous flukes and nematodes. After three days the feces show no eggs, and on autopsy no flukes or strongyles are found. The number of tests and other details are not given.

They point out that this remedy should be tried in human distomatiasis, and that the injection method might be useful in echinococcus infections.

Perroncito (1886) has repeated the experiments of Grassi and Calandruccio and reports favorably on the use of male fern, noting, however, certain unfavorable results from its use. His experiments were as follows:

1. Sheep with symptoms of fluke disease. Fecal examination showed two to three eggs of *Strongylus*, probably *S. contortus*, and three to four fluke eggs per slide. Administered 10 grams of ethereal extract of male fern in 48 grams of ethereal tincture. The animal became tympanic, due to ethereal vapor developed in the stomach, and in a few minutes fell as if struck dead. After 40 minutes rose. At the end of 2 hours it had recovered from the symptoms of anesthesia and other phenomena of etherization. Some weeks later the feces showed one strongyle egg and one distome egg per slide.

2. Administered to sheep affected with liver fluke, 5 grams of ethereal extract of male fern in 50 grams of the tincture. Usual symptoms of flatulence and defecation. After 30 to 40 minutes sheep gradually returned to normal condition. Examination of the feces showed numerous distome and strongyle eggs. Two days later examination showed distome and hookworm eggs, but noticeably diminished in number. There had been 10 to 12 eggs per slide; there were now 4 to 5.

Two days later repeated the dose, substituting 6 grams of ethereal extract in place of 5 grams. The animal showed more severe symptoms than on the first occasion. There was considerable flatulence at the end of an hour.

Feces collected 40 hours after the second dose of male fern showed 2 to 3 distome eggs per slide. Animal seemed much improved. Seven days after the second dose the feces showed only one distome egg to three or four slides.

3. A sheep infested with a large number of liver flukes, about 800, was given a large dose of male fern and died in 10 or 12 hours. Autopsy showed that the flukes were apparently all dead.

This last case had been previously published by Perroncito (1885).

The next article dealing with experimental medication of hepatic distomatiasis which has come to our attention is that of Romagnoli (1903), who claims to have had good results in the treatment of distomatiasis in sheep from the daily administration of 1 grain of salol in a teaspoonful of water for 8 days. According to that author the salol kills the cercariæ which are still in the stomach and thus prevents further infestation, so that if the sheep are meanwhile given plenty of nourishment they rapidly recover their health and finally become completely cured. Romagnoli's treatment is of a different character from that reported by other writers in that it is supposed

to act upon parasites during their invasion of the body and not upon those which have already become established in the host.

Floris (1907, 1908) has used carbon bisulphid, a remedy which Perroncito and Bosso (1894) and Wessel (1901) had reported as efficacious against *Gastrophilus* in the horse, and which Taar (1907) had found efficacious against *Gastrophilus* and *Ascaris* in the horse. Floris administered the carbon bisulphid in gelatin capsules in doses of 10 to 15 grams three or four times a week. The treatment was not attended by unpleasant effects and served to free the animals of flukes, the feces containing 5 to 10 flukes at a time. Floris notes that this is a very inexpensive remedy.

Alessandrini (1908) reports that he had administered extract of male fern to two sheep which were severely infested. The sheep were dead two days later. Autopsy showed the flukes in the intestine and liver to be dead and degenerated.

Pericaud (1908) has a rather glowing account of the virtues of a so-called "distomasine," said to consist of a glucosid and some plant essence. He gives no experimental tests, and the paper apparently adds nothing to our knowledge.

Borini (1911) states that in 1905, at the suggestion of Perroncito, ethereal extract of male fern was used to arrest a plague of bovine distomatiasis occurring on the estate of a rich proprietor in Calabria. Experiments have been made on laboratory animals from that year on, the treatment being especially tested on sheep. These experiments, according to Borini, confirm the therapeutic value of male fern against distomatiasis. In light infections cures were always obtained; in the worst cases of advanced cachexia the treatment failed. The use of thymol in connection with male fern is recommended.

Railliet, Moussu, and Henry (1911) have recently published a series of articles on the treatment of distomatiasis. In their first papers (1911a and 1911b) they note the desirability of some medication in view of the considerable losses suffered in France in 1910. They first experimented with medicines which may be eliminated by the liver, especially aloes, calomel, sodium salicylate, and "boldo." Most of the animals treated with these remedies improved, but there was no cure, no destruction of the parasites. Autopsy showed the flukes to be still alive after treatment extending over 15 days to three weeks. It seemed as though the treatment reduced the activity of the flukes without really having a specific effect on them.

In another series of experiments they used compounds of phosphorus, arsenic, and mercury, as phosphorated oil, arsenic, atoxyl, arseno-benzol, trypanblau, benzoate of mercury, and fluid extract of broom. None of them gave certain, positive results.

In a third paper (Railliet, Moussu, and Henry, 1911c) these authors report better success in their tests of a new series of substances, including particularly tartar emetic, urotropin, atoxyl, and ethereal extract of male fern.

The sheep used were for the most part heavily infested and had an intense cirrhosis and often a perforation of the capsule of Glisson, the flukes which caused the perforation escaping to the peritoneal cavity. Many had a mixed infection with *Fasciola hepatica* and *Dicrocoelium lanceatum*.

Tartar emetic and urotropin proved to be inefficacious. Atoxyl produced the evacuation of degenerated *F. hepatica* in one heifer.

The tests with ethereal extract of male fern were more satisfactory. An abstract is given of Alessandrini's (1908) experiments with male fern, noting this as the only work of the sort of which they were aware. Their own tests were made on five sheep, three others being kept as checks. The sheep were given 5 grams of ethereal extract in 25 c. c. of oil. Autopsy was made immediately after death. The experiments are as follows:

1. Sheep received one dose and died 12 hours later. Three hundred and ninety *F. hepatica* and numerous *D. lanceatum* in liver; all alive.

2. Sheep received two doses at 16-hour intervals and was killed in extremis 24 hours after the second dose. The biliary canals contained numerous live *D. lanceatum* and 55 *F. hepatica*, 4 of them being alive and the rest degenerated and of a yellowish-green color. The gall bladder contained 142 *F. hepatica*, all dead, though only 3 showed the same alteration as the preceding. The small intestine contained 16 degenerated specimens and the large intestine contained 10 dead but not degenerated specimens.

3. Sheep received three doses at 16 and 24 hour intervals. Killed 3 days after the last dose. Biliary canals contained several live *D. lanceatum*. There were 9 *F. hepatica*, all degenerated, in the gall bladder, but none in the biliary canals or in the intestine.

4. Sheep received four doses at 24, 24, and 48 hour intervals. Died 7 hours after the last dose. Biliary canals contained numerous live *D. lanceatum*. There were 5 degenerated *F. hepatica* in the gall bladder, none in the biliary canal, 1 degenerated specimen in the large intestine, and about 50 live specimens in the peritoneal cavity, associated with peritonitis.

5. Sheep received four doses at 48, 24, and 24 hour intervals. Killed 3 days after the last dose. Biliary canals contained several *D. lanceatum*, all living. There were no *F. hepatica* in the bile ducts, the gall bladder, or the intestine.

The three check sheep were killed at the end of the experiment and showed 178, 85, and 497 *F. hepatica*, respectively, and numerous *D. lanceatum*, all living.

The degeneration undergone by *F. hepatica* under the influence of male fern, and to a lesser extent of atoxyl, begins at the posterior extremity and progresses anteriorly, some individuals being green and flabby at the posterior end, while the cephalic end was still capable of movement.

They conclude that male fern is a satisfactory treatment for infection with *F. hepatica* if taken before there are irremediable lesions and at least four doses of 5 grams each administered. This

will kill *F. hepatica* in the liver, but not in the peritoneal cavity. At the same time it is effective against gastrointestinal strongylosis. It has no effect on *D. lanceatum*.

In a later paper (Railliet, Moussu, and Henry, 1911d) these authors recapitulate the foregoing, noting the earlier work of Grassi and Calandruccio and of Perroncito. They add the following experiments:

Four sheep were given 5 grams of ethereal extract of male fern in 25 c. c. of oil for four successive days, a fifth animal being kept as check. All the sheep showed fluke eggs in the feces. Four days after the last dose they were all killed. Autopsy showed the following:

1. Liver contained 1 *F. hepatica* (presumably alive), but marked lesions of cirrhosis indicated the recent disappearance of other flukes.

2. Liver contained 2 live *F. hepatica* in the terminal ducts and 3 dead and degenerated forms. Hepatic lesions moderated.

3. Liver, abnormal in appearance, contained 26 live *F. hepatica* and 1 dead one.

4. Liver contained 1 live *F. hepatica*.

5. Check animal. Liver strongly cirrhotic, contained 296 live *F. hepatica*.

All animals contained a number of live *D. lanceatum*.

They conclude that male fern is effective, and, for sheep, suggest a dose of 1 gram of ethereal extract for every 5 kilos of live weight of animal; for cattle, about 30 grams for 350 to 400 kilos of live weight. They note that male fern is comparatively cheap and suggest that it be administered by means of a rubber tube.

The status of anthelmintics in bilharziasis is indicated in the following summary:

Stiles (1904) says: "Favorable results are claimed from repeated doses of male fern; some authors consider specific treatment futile."

Sandwith (1909) writes of bilharziasis:

No method has as yet been discovered of killing the worms in the human body; the ordinary vermifuges are useless. * * * The liquid extract of male fern, in doses of 15 minims 3 times a day, is the only drug of known value, for, though it does not expel the parasites [How could it?], it seems to weaken their power of doing harm; it diminishes hematuria, allays vesical irritation, and reduces the number of eggs passed in the urine and feces.

Joannidès (1911) has tried salvarsan in bilharziasis in 8 cases, and reports that a single injection of 0.5 to 0.6 gram (?) of salvarsan in the case of adults and 0.25 gram (?) in the case of a 12-year-old child resulted in cessation or great diminution of hematuria, relief from vesical and urethral irritation, and a disappearance of the eggs from the urine. He concludes that salvarsan is destructive of *Schistosomum hæmatobium* and its eggs and thus brings about a cure of the disease.

Looss (1912) takes exception to the conclusions of Joannidès and states that bilharziasis is a disease characterized by lesions due to the passage through or retention in the tissues of the bladder, rectum,

etc., of vast numbers of eggs, the parasite itself in the blood vessels having practically no direct pathological significance. By the time the patient goes to a physician for treatment for hematuria the worms producing the eggs which cause this are probably dead or near their end. Looss looks upon the cures reported by Joannidès as resulting from an artificial retention of the eggs in the tissues, causing thereby a suppression of the symptoms but not a cure of the disease. For the purpose of this article—a consideration of the question whether anthelmintics are effective against metazoan parasites located elsewhere than in the digestive tract—the question as to whether the killing of the fluke is desirable or not, or as to whether the bilharzia disease is, strictly speaking, one due to flukes or to fluke eggs, is not material. Looss does not attack Joannidès's conclusions that the embryos in the fluke eggs and possibly the adult flukes, also, are killed by salvarsan.

Conor (1911) has tried salvarsan in one case of bilharziasis and found it inefficacious. Eggs containing living miracidia were found in the patient's urine every day but one for a month after the treatment.

Fülleborn and Werner (1912) have also tried salvarsan in a case of bilharziasis, with the same negative result.

Day and Richards (1912) have criticized Joannidès's findings, and report three cases in which salvarsan was administered with no effect on the passage of living ova or, in two cases examined, on the eosinophilia.

A summary of the foregoing papers on the treatment of hepatic distomatiasis shows the following:

The administration of anthelmintics has been declared effective by Grassi and Calandruccio as a result of experiments (number not given) followed by fecal examination and post-mortem (male fern); by Perroncito after three experiment cases followed by fecal examination and post-mortem (male fern); by Floris after experiments (number not given) in which no autopsies or subsequent fecal examinations showing absence of eggs are noted (carbon bisulphid); by Alessandrini after two experiment cases followed by autopsy (male fern); by Borini after experiments (number not given) in which no autopsies or subsequent fecal examinations showing absence of eggs are noted (male fern and thymol); and by Railliet, Moussu, and Henry after nine experiment cases, four other animals being used as checks, followed by autopsy (male fern). This is a total of 14 detailed experiments and 2 other sets of tests with the number of animals not given. Romagnoli's treatment is omitted from consideration in this summary, as no claim has been made that it affects parasites already established in the host.

In the case of venal distomatiasis, male fern has been commended as being efficacious, with no data found by us on casual examination

of the literature as to autopsy showing that the death of the fluke actually follows the administration of the male fern. Salvarsan has been commended on the basis of a cessation of symptoms following its administration in eight cases of bilharziasis, and opposed on the findings in five cases in which its administration was without effect. Looss questions the benefits of salvarsan as regards the organic lesions due to the parasite, while the other writers take exception to Joannidès's findings as not conforming to other known facts.

AUTHORS' EXPERIMENTS.

Being engaged in a study of tapeworm disease of sheep, due to *Thysanosoma actinioides*, the authors have taken advantage of opportunities to test carbon bisulphid and male fern as remedies for this disease. At the request of a sheep owner we also tested a certain proprietary remedy. This remedy was found on analysis by the Biochemic Division of the Bureau of Animal Industry to consist of 49 per cent ferrous sulphate, 13 per cent arsenious oxid, 8 per cent oxids of calcium, potassium, silicon, and magnesium, and 29 per cent organic matter, nature not determined but not containing santonin or any other vegetable alkaloid.

Tests of carbon bisulphid were made by the junior author at the ranch of Mr. Wells, near Resolis, Colo., in July, 1911. A Mexican herder at one camp was instructed to cut out six sheep, picking the poorest and weakest as being the most likely victims of thysanosomiasis. Events proved that some of the sheep selected were really too sick for the experiment.

The experiments were as follows:

1. Administered 6 grams of carbon bisulphid in capsule to a sheep. Sheep crushed one or two capsules and seemed greatly distressed thereby. Repeated dose after 30-hour interval. Sheep found dead the next day. Post-mortem showed appearances similar to those of hemorrhagic septicemia. A number of live bile-stained *Thysanosoma* found in the enlarged bile ducts and a number of others in the duodenum. One specimen of *Thysanosoma* was found with the head in the fourth stomach and the rest of the worm in the third stomach; this might have been due to post-mortem wandering or to a reverse peristalsis. Two specimens of *Cysticercus tenuicollis* were found adhering to the liver and one to the duodenum. The fluid content of the cysticerci was stained with blood. Death was perhaps hastened by the administration of the carbon bisulphid. Two doses of 6 grams each had not killed the tapeworms in this case.

2. Administered 6 grams of carbon bisulphid in capsule. Repeated dose after 30-hour interval. Sheep found dead the next day. Post-mortem showed appearances similar to those of hemorrhagic septicemia; death perhaps hastened by the administration of the carbon bisulphid. There were no tapeworms anywhere, and no lesions, such as thickened and enlarged bile and pancreatic ducts, to show that there had been any tapeworms.

3. Administered 6 grams of carbon bisulphid in capsule. Repeated dose after 30-hour interval. Sheep found dead the next day. Post-mortem showed

appearances similar to those of hemorrhagic septicemia. Death was perhaps hastened by the administration of carbon bisulphid. No *Thysanosoma* or lesions attributable to this worm were found.

4. Administered 6 grams of carbon bisulphid in capsule. Fifty hours later administered 4.5 grams of carbon bisulphid and repeated this dose 24 hours later. Killed the sheep 20 hours afterwards. No tapeworms were found on autopsy, but the gall ducts were thickened and enlarged, as was also the pancreatic duct, probably the result of former infestation with *Thysanosoma*. No worms had been found, however, in the feces of this or any of the other sheep.

5. Administered 6 grams of carbon bisulphid in capsule. Fifty hours later administered 3.5 grams of carbon bisulphid and repeated this dose 24 hours later. Killed the sheep 20 hours afterwards. No tapeworms were found on autopsy.

6. Administered 6 grams of carbon bisulphid in capsule. Forty-eight hours later sheep was down, with a respiration rate of 210. Sheep found dead 24 hours later. No evidences of the efficacy of the drug—that is, dead specimens of *Thysanosoma*—were found. Other notes regarding this autopsy lost.

A summary of the above experiments shows that sheep No. 1 had live tapeworms in the liver and intestines after receiving two doses of 6 grams each of carbon bisulphid on two successive days; that Nos. 2 and 3 after the same treatment had no tapeworms or lesions indicating their presence; and that Nos. 4, 5, and 6 showed no dead tapeworms on autopsy. As stated before, no tapeworms were found in the feces of any of these sheep. These experiments were inconclusive, but they point to the inefficacy of carbon bisulphid in that where tapeworms were found, as they were in one case, after 12 grams of carbon bisulphid had been administered, the tapeworms were alive.

It should be noted in this connection, as a matter of passing interest, that no stomach worms were found in these sheep on post-mortem.

The next set of experiments was made by both of us at Mr. Wells's ranch later in July. This time four sheep, selected as probably suffering from *Thysanosoma* infection, were used to test the ethereal extract of male fern, and two sheep in good condition were used to test the proprietary medicine previously referred to. The experiments were as follows:

Sheep Nos. 1 and 2 were given two tablets each of the proprietary medicine, according to the directions furnished with the medicine. No. 1 was killed 24 hours later. A number of *Thysanosoma* were found in the gall bladder and intestine, and *Haemonchus contortus* and *Ostertagia bullosa* in the fourth stomach. All the worms were alive, although the advertisement of the remedy claimed that the dose given would kill any worm in the digestive tract. No. 2 was killed 48 hours after receiving the dose. Specimens of *Thysanosoma* were found in the gall ducts, two in the pancreatic duct, and a num-

ber in the intestine; *Hæmonchus* and *Ostertagia* in the stomach. All the worms were alive.

The analysis, already given, of this medicine, indicated that it is practically inert as a vermifuge and that any improvement following its use would be attributable to the tonics contained in it. The negative results with this medicine were precisely what might be expected. At a time when parasitologists in practical work are not aware of adequate remedies for all kinds of worms, and especially of any one remedy which is efficacious against all kinds of worms, it is unlikely that the manufacturers of proprietary medicines will have this information.

In the male-fern experiment, sheep Nos. 3, 4, 5, and 6 were given 9 c. c. of the ethereal extract thoroughly mixed with 25 c. c. of linseed oil—the dose recommended by Railliet, Moussu, and Henry—in the morning of four successive days. They were killed the afternoon of the fourth day. No. 3 had one dead and partly digested *Thysanosoma* in the gall bladder; No. 4 had one live *Thysanosoma* in the gall duct and one live one in the pancreatic duct; Nos. 5 and 6 had no tapeworms. No *Hæmonchus* was found in any. Live *Ostertagia* were found in Nos. 1, 2, and 3. All of the sheep had some signs of pneumonia, a marked retention of urine, with a slight cystitis, due apparently to the male fern. Considerable purging occurred during the last two days, which is attributable to the linseed oil. No tapeworms were found in the feces.

The finding of a dead *Thysanosoma* in the gall bladder of No. 1 is a fact pointing to a possible efficacy of the male fern; the presence of live *Thysanosoma* in No. 2 rather offsets this.

As the experiments were not conclusive, we repeated them later on the ranch of Mr. Kennedy, near Amo, Colo. Five sheep were selected, one of them being used as a check. Four sheep were each dosed with 6 c. c. of ethereal extract of male fern thoroughly mixed with 25 c. c. of linseed oil, on four successive days. The sheep were killed on the fifth day. Autopsy findings were as follows:

1. Twelve *Thysanosoma* in gall ducts and duodenum and 2 *Strongyloides papillosus* in intestine. No *Hæmonchus*.

2. Twelve *Thysanosoma* in duodenum, 1 in common bile duct, 4 in biliary ducts, 1 in gall bladder, and 1 in pancreatic duct, a total of 19; 4 *Hæmonchus* and 2 *Ostertagia* in fourth stomach.

3. Five *Thysanosoma* in duodenum, 1 in gall bladder, and 3 in bile ducts, a total of 9; 158 *Hæmonchus* in fourth stomach and 10 *Nematodirus filicollis* in intestine.

4. Seven *Thysanosoma* in duodenum and 5 in gall ducts, a total of 12; a few *Hæmonchus* and about 20 *Ostertagia* in fourth stomach.

5. Check animal. Two *Thysanosoma* in the gall ducts; a few *Hæmonchus* and *Ostertagia* in fourth stomach and 3 *Strongyloides* in intestine.

The *Thysanosoma* were all alive, as were the nematodes.

It appears from these experiments that male fern as administered is not efficacious against thysanosomiasis. While the negative findings of the former experience are inconclusive, the findings in this case are fairly conclusive. The failure of the medicine to exert any effect on four infected sheep indicates that male fern is not a remedy which could be recommended in thysanosomiasis.

GENERAL SUMMARY AND CRITICISM.

It appears from the foregoing that anthelmintics have been claimed to be efficacious in 8 cases of human somatic tæniasis (male fern); inefficacious in 8 cases of somatic tæniasis in the lower animals (male fern); inefficacious in at least 6 cases of intestinal and extraintestinal thysanosomiasis (carbon bisulphid and male fern); efficacious in over 14 cases of hepatic distomatiasis (carbon bisulphid and male fern); efficacious in 8 cases of venal distomatiasis (salvarsan); inefficacious in 5 cases of venal distomatiasis (salvarsan); and efficacious or inefficacious, according to various authors, in an indefinite number of cases of venal distomatiasis (male fern).

While the figures in the above paragraph are preponderantly in favor of the efficacy of anthelmintics against somatic helminthiasis, it should be borne in mind that there is much more likelihood of cases being published where the administration of a medicine is followed by apparent cure of disease than where it is followed by evident failure to cure. Further objections to the figures as they stand are based on a critical examination of the cases. This criticism may be summarized as follows:

Zürn's experiments are entirely indefinite and lacking in detailed statement. In Feletti's cases one patient died in spite of treatment and there was no autopsy, and in the other cases the possibility of spontaneous degeneration of the cysticerci, a not uncommon thing, is not excluded. De Renzi's cases, as we have already stated, have been criticized by Hall (1909) as open to suspicion of error as regards diagnosis and the connection between the disease, the treatment, and the cure. Dianoux's case is open to much the same criticism as those of De Renzi. Granting that the diagnosis was correct (as it apparently was in this case), the possibility of spontaneous degeneration of the parasites is not excluded, and it is not safe to conclude that their disappearance was due to the treatment. At least one of Hall's cases was not at all conclusive. None of the cases dealing with distomatiasis specifically eliminate the possibility of the natural death and spontaneous evacuation of the flukes, the usual ending of the yearly life cycle, although the use of check animals, where such checks were used, probably meets this objection. Peroncito's cases show that on the basis of fecal examination the flukes apparently were not killed in two cases out of three. Floris and

Borini cite no post-mortem findings or final negative fecal examinations in support of their statements. Among the cases reported by Railliet, Moussu, and Henry, autopsy showed that *Fasciola hepatica* in four cases and *Dicrocoelium lanceatum* in all cases had survived the full dose advocated by them. None of Joannidès's cases were followed by post-mortem examination; and, so far as case records are available, no cases of bilharziasis treated by male fern have been followed by post-mortem examination to ascertain whether the administration of the male fern had resulted in the death of the flukes.

In spite of these objections, the total evidence collected here indicates that further work along this line is necessary and desirable. It is possible that the common opinion that medicines administered per orem or subcutaneously can not be successfully used against metazoan parasites outside of the digestive tract, that the higher orders of parasites can not be killed by a selective action of drugs without injury to the host animal in whose tissues they are located, may be erroneous. Improved technic and better medicines have marked great advance in the treatment of protozoan and bacterial diseases. Similar improvements have led to greater success in the treatment of intestinal helminthiasis. May not careful experiment lead to the same results in the treatment of somatic and extra-intestinal helminthiasis? The subject is worth investigating. The location of metazoan parasites often makes surgical treatment impossible, dangerous, or unprofitable. Adequate methods of medicinal treatment would have great medical and economic value as well as scientific interest. The present state of our knowledge does not warrant any conclusion other than this, that a great amount of additional work is necessary and desirable.

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