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Experiments on the Chemotherapy of Blackhead in Turkeys *

By NEAL F. MOREHOUSE AND WILLIS C. MCGUIRE

Infectious enterohepatitis, or blackhead, is often regarded as the most important disease of turkeys since all ages and breeds are susceptible and mortality is high. The yearly financial losses resulting from blackhead have stimulated increasing interest and experimentation on chemotherapy of this disease. Many compounds have been tested, but at the present time no other group of compounds seems to offer as much promise as the organic arsenicals. Several members of this class of compounds as well as a few non-arsenicals have been found to have a limited effect against the blackhead organism; but none, whether arsenical or non-arsenical, has thus far found widespread practical use among turkey raisers.

Tyzzler (1923) reported that nearsphenamine, injected intravenously in toxic doses, had a somewhat favorable effect on the course of the spontaneous disease and tended to lower mortality. Less favorable results were obtained with atoxyl. Using tryparsamide intravenously in turkeys at dosages as high as 1.0 gram per kilogram of body weight, he found that the birds which had acquired the disease spontaneously showed clinical improvement and that mortality was greatly lowered. However, he found that in cases of inoculated blackhead, recovery was more difficult to obtain.

Delaplane and Stuart (1935), reporting work done by Hadley, May and others of the Rhode Island Experiment Station, stated that nearsphenamine, among other compounds, was of little or no value for preventing blackhead infection in turkeys. Hinshaw (1937) stated that atoxyl, nearsphenamine and tryparsamide had been tried with but little success. He observed that the only promising one was tryparsamide, commenting on Tyzzler's statement that this drug was too expensive except for a few very valuable flocks. Blount (1938), Bolin and Vardiman (1941) and McCulloch and Nicholson (1941) have reported the successful use of mapharsen, a trivalent arsenic compound, intramuscularly for the treatment of blackhead. All of these reports on the use of mapharsen were based on comparatively small numbers of turkeys. When Bolin and Vardiman used 0.006 grams of mapharsen intramuscularly, they reported a recovery of six out of eight cases (75%) of blackhead while McCulloch and Nicholson, administer-

* The chemotherapeutic activity of the substances disclosed in this paper are subject matter of a patent application.

ing 0.005 grams of the compound intramuscularly, reported a 63% recovery in 27 turkeys. Bolin, Goldsby and Eveleth (1947) reported the recovery of seven out of ten poults (70%) which had received 0.006 grams of mapharsen intramuscularly. Conversely, Jaquette and Marsden (1947), after injecting 0.006 grams of mapharsen into the pectoral muscles of 72 turkeys, reported the death of 19 of these birds from blackhead during a 41-day period. The loss among 72 controls was also 19 turkeys. Furthermore, Glover (1948) reported that 0.006 grams of mapharsen, injected intramuscularly into a large number of turkeys exposed to blackhead while on range, gave no protection.

Sautter, Pomeroy and Roepke (1950) used tryparsamide intravenously and orally, under varying schedules of treatment, for the control of blackhead. They found that late therapy was of little value and that multiple dosages intravenously were more effective than single doses. When medication was started later than the second day after infection, tryparsamide had little or no effect on the course of the disease. When neoarsphenamine and Eagle's Compound were used at intravenous dosages of 0.050 grams and 0.005 grams respectively, they were found to be of little or no value against blackhead. Tryparsamide and stovarsol, when used at several different concentrations in feed and in drinking water under varying schedules of treatment, were found to have some effect against blackhead, stovarsol having shown a more favorable effect than tryparsamide.

Thus, it becomes apparent from the above review that arsenicals such as stovarsol and tryparsamide have some merit for the control of blackhead while others have been of little or no value when subjected to duplicate and/or modified testing procedures. The conflicting results of various investigators working with a given compound also serve to indicate the need for critical evaluation of any preparation by extensive testing under varied conditions in order to determine its true worth.

The purpose of this investigation was to determine whether certain selected organic arsenic compounds exert prophylactic action against *Histomonas meleagridis*, the causative agent of blackhead in turkeys.

MATERIALS AND METHODS

All experimental birds were obtained from commercial hatcheries as day-old poults and were raised in battery brooders until they were four to eight weeks of age. They were then moved to individual wire-bottomed metal cages in clean, disinfected rooms

where they were placed on experiment. Precautions were taken to protect the birds from extraneous infection before and after the tests were started. No case of "spontaneous" blackhead has been observed when following our management methods. These poults were started on a nutritionally adequate mash ration which they continued to receive throughout the experiment.

When placed on test, the poults were allowed three days to become accustomed to their individual cages, feeders and waterers before medication was attempted. All birds were weighed prior to starting the tests, and the birds were divided in a manner to equalize the mean weights of all groups. Feed and water consumption records were kept daily and weight changes recorded weekly. Infection was accomplished by the method of McKay and Morehouse (1947), who utilized embryonated ova of *Heterakis gallinae* as the vector for disease transmission. This method was found to produce typical blackhead within the normal parasitologic period as it occurs under natural conditions.

When screening tests were carried out, only medicated-infected, unmedicated-infected, and unmedicated-uninfected groups of experimental birds were housed in the same isolated tests rooms. When more critical evaluation of a drug was indicated, a medicated-uninfected group was added in order to evaluate toxicity.

All the compounds used were prepared by members of the Organic Chemistry Department of Dr. Salsbury's Laboratories. These purified compounds were dissolved by adding solutions of sodium carbonate or sodium hydroxide, keeping the solutions as near neutrality as possible. New stock solutions were prepared for each test although the same stock solution was often used for preparing different dosage levels.

In our experiments we have medicated our turkeys for a period of twenty-one days, starting the medication three days before infection. Surviving turkeys were observed for a ten-day period while the turkeys remained in their individual cages. The turkeys were then removed from their cages and kept for an additional twenty days in growing batteries, brooder houses, or were confined in range shelters, during which time they were observed daily for symptoms of, or mortality from blackhead. In no case were the poults allowed access to contaminated soil during post-medication periods.

Observations were made daily on the appearance of the droppings of all experimental poults during the medication period and

the subsequent ten-day period, recording any deviation from normal.

Post-mortem examination was made of all turkeys which died during the experiments in order to determine whether death was due to blackhead. Wet smears from cecal contents as well as the macroscopic appearance of livers and ceca were used as diagnostic criteria for the determination of blackhead.

EXPERIMENTAL

Experimental data has been obtained on the prophylactic effect of four compounds against blackhead disease, namely, 3-iodo benzene arsonic acid, 4-amino 3, 5-diiodobenzearsonic acid, 2-nitrobenzearsonic acid and 4-nitrobenzearsonic acid.

Table 1 illustrates the results of a screening test involving medication with 3-iodobenzearsonic acid. The drinking water concentrations used in this experiment, ranging from 0.003 to 0.03%, all showed prophylactic effect against histomonas infection during the medication period. A severe relapse condition was seen in the last group (0.003%) as three of the five birds died of typical black-

Table 1
Summary of Experiments on the Effect of 3-Iodobenzearsonic Acid Against Blackhead Infection in Turkeys

| Per cent Conc. in Drinking Water | Blackhead Mortality of Medicated-Infected Poults | | Poults Showing Blackhead Lesions at Postmortem* | Survival of Poults on the Experiments | | |
|----------------------------------|--|------------------------|---|---------------------------------------|-------------|---------------|
| | 21 Days on Medication | 7 Days Post-Medication | | Med. Inf. | Unmed. Inf. | Unmed. Uninf. |
| 0.03 | 0 | 1 | 0/3 | 2/3 | 0/4 | 4/4 |
| 0.015 | 0 | 0 | 3/4 | 4/4 | 0/4 | 4/4 |
| 0.007 | 0 | 1 | 2/3 | 3/4 | 0/4 | 4/4 |
| 0.003 | 0 | 3 | 1/2 | 2/5 | 0/4 | 4/4 |

* All surviving poults were sacrificed for post-mortem examination on the seventh day after medication was discontinued.

head by the seventh day post-medication. When the two remaining survivors, receiving the latter dosage, were sacrificed for post-mortem examination, active cecal and liver lesions were seen in one of them. All of the unmedicated-infected birds died of typical blackhead within the normal parasitologic period, while none of the unmedicated-uninfected poults showed any mortality or symptoms of this disease.

Table 2 presents data on the effect of 4-amino-3, 5-diiodobenzearsonic acid on blackhead infection. Under our experimental conditions, this compound was 100% effective as a prophylactic against histomoniasis while the drug was being administered below

Table 2

Summary of Experiments on the Effect of 4-Amino 3-5 diiodobenzenearsonic Acid Against Blackhead Infection in Turkeys

| Per cent Conc. in Drinking Water | Blackhead Mortality of Medicated-Infected Poults | | Survival of Poults on the Experiments | | |
|---|---|-----------------------------|--|----------------|------------------|
| | 21 Days on Medication | 30 Days Post- Medication | Med. Inf. | Unmed. Inf. | Unmed. Uninf. |
| 0.079 | 2* | 1 | 1/4 | 0/4 | 4/4 |
| 0.066 | 1* | 3 | 3/4 | 0/4 | 4/4 |
| 0.053 | 0 | 2 | 2/4 | 0/4 | 4/4 |
| 0.05 | 0 | 1 | 3/3 | 1/4 | 4/4 |
| 0.04 | 0 | 1 | 3/4 | 0/4 | 4/4 |
| 0.03** | 0 | 1 | 2/3 | 0/4 | 4/4 |
| 0.02 | 0 | 2 | 2/4 | 0/4 | 4/4 |

* Death or deaths due to toxicity.

** This test was held only 10 days post-medication when the birds were sacrificed for post-mortem examination. No lesions of blackhead were found.

the toxic level (0.066%). The lack of mortality in the medicated-infected groups and the high incidence of mortality in the unmedicated-infected groups establish this compound as possessing distinct suppressive or inhibitive effects. However, approximately one out of three poults showed relapse during the post-medication periods. The death rate among the medicated-infected poults indicates ineffective sterilization of the body from histomonads.

Table 3 shows data from experiments where 2-nitrobenzenearsonic acid was tested at drinking water concentrations ranging from 0.0053 to 0.0264%. This range exceeds the toxic level and

Table 3

Summary of Experiments on the Effect of 2-Nitrobenzenearsonic Acid Against Blackhead Infection in Turkeys

| Per cent Conc. in Drinking Water | Blackhead Mortality of Medicated-Infected Poults | | Survival of Poults on the Experiments | | |
|---|---|-----------------------------|--|----------------|------------------|
| | 21 Days on Medication | 30 Days Post- Medication | Med. Inf. | Unmed. Inf. | Unmed. Uninf. |
| 0.0264 | 4* | — | 0/4 | 2/4 | 4/4 |
| 0.0211 | 3* | 1 | 0/4 | 2/4 | 4/4 |
| 0.0159 | 0 | 0 | 5/5 | 2/4 | 4/4 |
| 0.0132 | 1** | 0 | 3/4 | 1/4 | 4/4 |
| 0.0132 | 0*** | 0 | 4/4 | 1/4 | 4/4 |
| 0.0106 | 0 | 0 | 5/5 | 2/4 | 4/4 |
| 0.0053 | 2 | 1 | 1/4 | 2/4 | 4/4 |

* Died of toxicity.

** On medication twenty-nine instead of the usual twenty-one days.

*** Infection was given on the same date that medication was begun instead of the usual procedure, i.e. 3 days after medication was started.

includes the apparent minimal effective dosage against histomonas infection in turkeys. In preliminary testing of this compound it was noted that the relapse rate was not as high as we had previously noted in other drugs. It was for this reason that the medication period was extended a week longer and the infection given three days earlier than was our usual experimental procedure. No relapse occurred under these conditions. Further testing will be necessary before these results can be confirmed.

Table 4 contains data from ten separate tests wherein drinking water concentrations of 4-nitrobenzenearsonic acid varying from 0.0013 to 0.0528% were used. None of the turkeys receiving a

Table 4

Summary of Experiments on the Effect of 4-Nitrobenzenearsonic Acid Against Blackhead Infection in Turkeys

| Per cent Conc. in Drinking Water | No. of Medicated Groups | Blackhead Mortality of Medicated-Infected Poults | | Survival of Poults on the Experiments | | | |
|----------------------------------|-------------------------|--|-------------------------|---------------------------------------|-------------|-------------|---------------|
| | | 21 Days on Medication | 30 Days Post-Medication | Med. Inf. | Med. Uninf. | Unmed. Inf. | Unmed. Uninf. |
| 0.0528 | 1 (1)* | 2** | 2*** | 0/4** | 1/4 | 1/4 | 4/4 |
| 0.0396 | 1 (1) | 0 | 1 | 3/4** | 4/4 | 1/4 | 4/4 |
| 0.0317 | 1 (1) | 0 | 2 | 4/4 | 2/4 | 1/4 | 4/4 |
| 0.0264 | 7 (3) | 2 | 9 | 19/30 | 15/15 | 4/31 | 31/31 |
| 0.023 | 1 (1) | 0 | 1 | 7/8 | 8/8 | 4/8 | 8/8 |
| 0.0198 | 4 (1) | 0 | 6 | 16/22 | 4/4 | 2/17 | 17/17 |
| 0.0159 | 3 (1) | 1 | 2 | 9/12 | 4/4 | 2/12 | 12/12 |
| 0.0132 | 2 | 0 | 4 | 5/9 | — | 2/8 | 8/8 |
| 0.0066 | 1 | 0 | 3 | 1/4 | — | 1/4 | 4/4 |
| 0.0026 | 1 | 1 | 3 | 0/4 | — | 1/4 | 4/4 |
| 0.0013 | 1 | 3 | 1 | 0/4 | — | 1/4 | 4/4 |

* Numbers in parenthesis indicate the number of medicated-uninfected groups used at the specified dosages.

** Deaths due to toxicity.

*** One poult died of blackhead; the other died of toxicity.

concentration of this compound lower than 0.0066% survived blackhead infection while dosages higher than 0.04% were acutely toxic. Mortality from blackhead among poults receiving relatively non-toxic dosages within the effective range of medication (approximately 0.0066 to 0.04%), was only 4.1% compared to a blackhead mortality of 77.8% in the unmedicated-infected poults. Since 35.5% of all medicated-infected poults died of typical blackhead during the thirty-day post-medication interval, it was obvious that this medication did not sterilize the bodies of all poults of their histomonas infection. The survival of the unmedicated-infected groups varied among the ten tests from 0 to 50% with a mean of

22.2%. Many of these survivors, however, showed definite clinical symptoms indicative of severe infection.

DISCUSSION

Because of differences in method of infection, method of drug administration, length of observation periods and other experimental procedures, our data on the use of four arsonic acids for the prevention of blackhead in turkeys is not directly comparable with that of other investigators who have reported the use of various arsenicals for this purpose. Many investigators have not observed their turkeys for more than a few days, if at all, following the termination of medication and were apparently unaware of the tendency for birds to relapse after medication was withdrawn. In our investigation it has not been uncommon to find an arsenical which, in some degree, suppresses blackhead infection while medication continues; but most arsenic compounds which we have tested apparently did not sterilize the birds of their blackhead parasites, since relapse occurred even though the birds were kept under conditions where the acquisition of adventitious infection was highly improbable. It appears that some of our compounds, especially 2-nitrobenzenearsonic acid and 4-nitrobenzenearsonic acid, may possess at least one advantage not previously shown for other arsenicals. There seems to be less tendency for poults receiving these compounds to suffer relapse after medication has been withdrawn.

3-Iodobenzenearsonic acid and 4-amino 3, 5-diiodobenzenearsonic acid, in these limited observations, showed 100% efficacy against blackhead infection as long as medication was being administered. The relapse rate, however, was excessive when medication was discontinued.

Conversely, 2-nitrobenzenearsonic acid showed efficacy for the prevention of relapse after discontinuance of medication but did not give total protection during the medication period. 4-Nitrobenzenearsonic acid showed a 95.9% efficacy for blackhead prophylaxis while medication was being administered within the effective dosage range. Although there was some tendency toward relapse during the post-medication period, survival among the treated birds was 55.4% compared to 22.2% among the infected controls.

The tendency for turkeys to relapse following withdrawal of effective suppressive medication emphasizes the desirability of an extended period of observation following discontinuance of medication. It is for this reason that we have adopted a thirty-day post-medication period of observation.

SUMMARY

1. Data has been presented which indicates chemoprophylactic value for 3-iodobenzene arsonic acid, 4-amino-3, 5-diiodobenzene arsonic acid, 2-nitrobenzenearsonic acid and 4-nitrobenzenearsonic acid against the causative agent of blackhead in turkeys, *Histomonas meleagridis*.

2. Turkeys receiving 2-nitrobenzenearsonic acid and 4-nitrobenzenearsonic acid had a less tendency to suffer relapse after the termination of medication than poults receiving the other compounds.

3. An experimental procedure involving a prolonged period of observation following the termination of medication was suggested for determining the real value of preparations which are found to suppress blackhead.

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