THE HEMATOLOGY OF PHENOTHIAZINE POISONING IN HORSES

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When phenothiazine is given orally as an anthelmintic it can, under certain circumstances, be toxic to man and other species (6, 8, 14, 29). Of the domestic animals likely to be affected, sheep are the most resistant and horses the least (14). It is not known exactly how phenothiazine causes toxicity but evidence suggests that its metabolites are probably responsible (6, 19, 25, 40). Britton (4) believed that absorption of the oxidation products of phenothiazine accounted for the toxic symptoms. Garner (19) stated that "relatively insoluble phenothiazine is converted within the intestine into soluble derivatives, mainly phenothiazine sulphone, which are then absorbed into the portal venous system and there converted into leuco-phenothionol". Jones et al. (25) produced indirect evidence to show that the oxidation products of phenothiazine were toxic to horses.

While the site of oxidation and absorption of phenothiazine is not definitely known, it is believed to take place in the cecum (7). A number of normally occurring substances in the plasma and tissues are known to be at least potential lysins, and it is thought that phenothiazine, while not lytic itself, may act as an accelerator for several of these (33). Collier et al. (6) demonstrated that when phenothiazine plus lysolecithin (a naturally occurring lysin) was added to horse cells in vitro, hemolysis was greatly enhanced. They postulated that this acceleration might explain the hemolytic anemia seen in horses poisoned with phenothiazine. In 1953, Collier et al. (9) demonstrated that phenothiazine would inhibit the activity of the enzyme glyoxalase in both human and rabbit red cells. They speculated as to whether this was a factor in the hemolytic anemia produced by phenothiazine.

Evidence has been presented which suggests that phenothiazine or its derivatives can be retained in the body for some time. Collier et al. (7) noted that in horses, less than half of the administered dose of phenothiazine could be recovered from the excreta. They believed that this was due to fixation in the tissues. Evidence obtained by necropsy examination suggested that the phenothiazine derivatives might combine with the tissue proteins of the liver, kidney, and spleen. Swales et al. (40) were of the opinion that not all of the drug was excreted immediately and that this retention might account for the continuing hemolysis. Davey et al. (14) reported that leucohophenothiazine reached a maximum concentration in sheep's blood six hours after dosing and was measurable for a further 66 hours.

It is generally agreed that 30 gm. of phenothiazine per 1,000 pounds of body weight is a safe dose for a horse and that toxicity is unlikely to occur at this level (4, 14, 15, 16). Davey et al. (14) were of the opinion that the chance of an accident following a 30 gm. dose was one in several hundreds, if not thousands. No significant hematological changes were reported when horses were fed 0.5–4.0 gm. daily for 14 months (21), nor when four healthy horses were each given 25–30 gm. of phenothiazine (20). Many reports, however, indicate that excessive dosing will produce poisoning (3, 4, 15, 16, 23, 27, 30, 38, 41, 42, 46) and instances are recorded where a dose of 30 gm. or less have been attended by toxicity (17, 34, 39, 41). Purchase et al. (34) described poisoning in six out of nine horses treated with 25 gm. of phenothiazine. Swales (40) produced anemia in a horse by giving 80 gm. of the drug, but 97 days later when 30 gm. were administered to the same horse no toxic symptoms developed. Davey et al. (14) believed that horses were more prone to show toxic effects following a second dose. Martin (28) produced hemolytic anemia in a mare by giving it 20 gm.
of phenothiazine on each of three consecutive days.

Clinical experience has led some workers to believe that individual sensitivity or idiosyncrasy to phenothiazine may play an important role in the poisoning. Conversely, the fact that poisoning with the drug has frequently affected groups of animals rather than individuals, and that under certain circumstances toxicity is more likely to occur, has suggested to other workers that environmental factors may be concerned (4, 14, 17, 41). Many reports indicate that weak, debilitated or anemic animals, those receiving an inadequate diet, or those with digestive disturbances (in particular, constipation) are more liable to phenothiazine poisoning (4, 14, 17, 19, 26, 30, 35, 41, 43, 45, 48).

It is possible that the condition of the animal at the time of treatment will, to a large extent, decide whether or not the drug will be toxic. Woolf et al. (48) demonstrated that horses fed a good diet would not, under the conditions of their experiment, develop phenothiazine toxicity, while horses fed a poor diet would.

It appears that a change in the normally low level of absorption, such as might be associated with digestive disturbances, as well as a change in the excretion rate occurring with debility can, by allowing more oxidation products to be formed and retained, play an important part in phenothiazine poisoning.

The form in which phenothiazine is used may have an influence on the degree of toxicity (4, 7, 26, 38). Collier et al. (7) compared micronized phenothiazine, in which 80% of the particles are less than 4 microns in diameter, with the coarse commercial product. They found that 90% of the former was oxidized and absorbed compared to about 50% of the latter.

The clinical signs generally attributed to phenothiazine toxicity are: anorexia, dullness, weakness, colic, constipation, anemia with pale mucous membranes, icterus and hemoglobinuria (3, 4, 14, 15, 17, 28, 30, 39, 40, 41). Less frequently mentioned are: diarrhea (41), fever (4, 17, 24, 34), albuminuria (15, 39), pain on urination (40), stocking of the hind legs (15), conjunctivitis (30), bronzed appearance of mucous membranes (27, 40), accelerated respirations (34), and red or purple urine (23, 25, 27, 34). In some cases clinical signs may appear and death may occur within hours of treatment (25, 41) but it is more usual for signs to become apparent 24 hours to 72 hours after dosing (3, 17, 23, 24, 25, 34, 39, 41).

Phenothiazine, when given to normal horses, in a therapeutic dose will not produce hematological changes (15, 16, 20, 21). Anemia is, however, a dominant feature in phenothiazine poisoning (3, 4, 6, 15, 16, 17, 18, 26, 27, 28, 30, 34, 37, 39, 40, 42, 45, 46, 48). The anemia is hemolytic in nature (6, 8, 9, 19, 38, 40) and has been reported to develop over a period of 6 to 13 days following dosing. It takes 30 to 55 days for the hemoglobin to return to pretreatment levels (3, 16, 17, 18, 34, 37, 48). Swales (40) concluded that there was hemolysis of the circulating red cells, the fragility of which was moderately increased. He believed there was evidence to suggest that the smaller red cells (microcytes) were more susceptible to the hemolytic agent. Although he was unable to find reticulocytes or normoblasts in the blood of these anemic horses, he was of the opinion that the marrow was functional.

The presence of Heinz bodies in phenothiazine toxicity in the horse was described by Swales (40) and Schalm (37, 38). These bodies have also been described in phenothiazine poisoning in the dog (8). Heinz bodies are newly formed particles derived from red cells in the course of an irreversible reaction with a toxic agent. The presence in the blood stream of significant numbers of these is evidence of some injury to the erythrocytes. Initially, they were considered to be pathognomonic of poisoning by phenylhydrazine but it is now known that many inorganic and organic substances, including sulphonamides and some feeds can produce these bodies (31, 32, 43, 47). The subject of Heinz bodies is excellently reviewed by Webster (44).

Swales (40) measured direct and indirect serum bilirubin in horses experimentally poisoned with phenothiazine. He found no elevation in the direct reading and concluded there was no suggestion of hepatic dysfunction. Elevated indirect levels (up to 8 mg.) led him to conclude that the icterus was cytohemolytic. As
there was an increase in fecal urobilinogen in poisoned animals he concluded that the jaundice was not obstructive. Leukocytosis has been reported in phenothiazine toxicity in horses (38, 40, 46) and was a constant finding in dogs experimentally poisoned (8). Treatment of phenothiazine poisoning has been directed mainly towards relieving the anemia. In the dog, a diet deficient in B vitamins greatly intensified the anemia produced by phenothiazine. Addition of B vitamins did not entirely prevent it although it did suppress Heinz body formation (8). The treatment of poisoned horses with vitamin B$_12$, copper, or iron, had little beneficial effect (34, 40). Blood transfusions have been the most effective treatment reported (18, 28, 34, 38, 41).

**Methods**

Disodium versenate was used as an anticoagulant for blood samples. Hemoglobin was determined by an alkali hematin method, the colour intensity being measured in a photometer. The packed cell volume (PCV) was measured using a microhematocrit centrifuge. Total white counts were estimated using a model 75 Sanborn-Frommer cell counter.\(^1\) As Heinz bodies were present, the white counts were at times checked by routine counting methods. Plasma bilirubin was determined by the modified method of Malloy and Evelyn (1). Blood smears were routinely stained with Wright's stain and Brilliant Cresyl Blue was used to demonstrate reticulocytes. Heinz bodies were vitally stained with the New Methylene Blue technique suggested by Schalm (37). Bone marrow was obtained by sternal puncture. Smears were made directly from the aspirate and in addition, some of the aspirated material was allowed to clot. After formalin fixation it was cut and stained by the usual pathological techniques.

**Clinical Observations**

Fifteen parasitized horses weighing 800 to 1,000 pounds were fed 20 gm. of micronized phenothiazine on day 1. The drug given consisted of a mixture of phenothiazine (10%) and piperazine adipate (38%) in a soybean oil base. Three of the horses (Cases 1, 2 and 3) became ill following the treatment. These three were thin and unthrifty, while the remaining twelve were in good condition.

**Case 1.** This mare was thin and for this reason had been wormed four months earlier with a drug other than phenothiazine. As the mare was again losing weight she was treated on day 1. On day 3, partial anorexia was noted. This became complete by day 4, at which time the animal was very depressed, had pale icteric mucous membranes, rapid heart rate and respirations. On day 4, one gallon of whole blood plus one gallon of an electrolyte solution was given intravenously. The blood was not cross-matched. Vitamin B$_12$ plus iron dextrose were given intramuscularly on day 5. The urine was reported to be red in color on day 3 but was not observed after this.

**Cases 2 and 3.** Both of these mares were unthrifty. One of them (Case 2) had a puncture wound of the knee while the other had just weaned a foal. They both exhibited anorexia and depression on days 5 and 6. Their return to normal followed a slow but uneventful course.

**Results**

Blood from five horses was presented for laboratory study. Case 1 was the most severely affected and was sampled frequently enough to follow the hematological trend. Cases 2 and 3 were clinically ill but less so than Case 1. Cases 4 and 5 were treated animals that did not appear clinically ill and their blood was submitted for comparative purposes. Samples from Cases 2, 3, 4 and 5 were taken irregularly and do not present a complete study. Pre-treatment data was not available and it is presumed that the values obtained on day 44 represent these.

**Case No. 1**

Table I condenses the data obtained and demonstrates that anemia, leukocytosis and elevated serum bilirubin levels were prominent. Four days after treatment the
### TABLE I

**Data Obtained from a Mare with Phenothiazine Poisoning (Case No. 1)**

<table>
<thead>
<tr>
<th>Days after dosing</th>
<th>Hemoglobin (gm. per 100 ml.)</th>
<th>Packed cell volume</th>
<th>WBC (per cmm.)</th>
<th>Free Bilirubin (mg. per 100 ml. plasma)</th>
<th>Conjugated Bilirubin</th>
<th>Total Bilirubin</th>
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**Figure 1.** Section of normal bone marrow from horse showing numerous fat spaces.

**Figure 2.** Section of bone marrow from mare suffering from phenothiazine poisoning (Case 1). This illustrates the marked hypercellularity due entirely to red cell precursors.
hemoglobin was 6.8 gms. per 100 ml. and this declined to a low of 2.7 gms. on day 13. A gradual increase was then evident until, on day 44, the value was 13.5 gms. The packed cell volume paralleled the hemoglobin levels. A leucocytosis (18,500 wbc per cmm.) was present on day 4 and persisted until day 12. The differential count was not remarkable; the normal lymphocyte-neutrophil ratio was maintained. Eosinophils were few and basophils were present (up to 4%) during the recovery phase. Platelets were present in all smears.

Anisocytosis was prominent, large red cells being present from day 5 to day 33. The greatest number were present on day 17. The macrocytes were normochromic and did not exhibit polychromasia. Reticulocytes were never found but the occasional normoblast could be found in all smears made between days nine and 22. Howell-Jolly bodies were present in moderate numbers.

Heinz bodies were prominent in the stained smears and in the blood when it was supravitally stained (Figures 1, 3A and 3B). In the former they appeared as small spherical bodies about one micron in diameter, staining the same colour and having the same density as the red cell. In some instances they were entirely within the parent cell. When this occurred they were located most frequently at the periphery of the cell and caused a bulging of the cell membrane. A slight thinning of the red cell cytoplasm around the body helped to outline them. From a location entirely within the cell the body progressed to a point entirely outside of, and having no connection with, the cell. In many instances the body lay partially

Figures 3A and 3B. Smears (Wright's stain) made from the peripheral blood of mare suffering from phenothiazine poisoning (Case 1). The arrows point to Heinz bodies.
within the cell but separated from it by a vacuole-like space. A half-moon shaped piece was missing from the cell membrane in many red cells, indicating where the body was expelled. They did not, at any time, appear to be attached to the parent cell by a stalk. It was apparent that the Heinz bodies were only associated with the smaller cells. Usually one, and seldom more than two, bodies were associated with one red cell. Using vital staining these bodies appeared as refractile spheres both inside and outside the cells. When the red cells were lysed with distilled water the Heinz bodies resisted lysing and could be centrifuged out of the supernatant fluid.

By studying either the Wright’s or supravitally-stained preparations, it was possible to estimate roughly the number of Heinz bodies present. They were very numerous from day 4 to day 10. On days 11 and 13 their numbers had decreased, while on day 15 they could be found occasionally and after this, not at all.

Marked marrow hypercellularity was obvious from the examination of the smears and the sections of the aspirated material taken on day 8. The smears indicated that the increase was due exclusively to proliferation of erythrocyte precursors. Using the terminology suggested by Dacie and White (13) the red cell precursors consisted of: hemocytoblasts 4%, pronormoblasts 8%, basophilic normoblasts 22% and later normoblasts 66%. The myeloid-erythroid ratio was 0.4. Numerous red cell precursors were observed in mitosis. Early neutrophils and eosinophils were few. Histological sections confirmed that active marrow predominated and that the proportion of fat spaces was small (Figures 1 and 2). Clumps of the aspirate stained for iron indicated that iron stores were plentiful.

The total plasma bilirubin was 21.9 mg. per 100 ml. on day 4. It declined abruptly to 7.15 mg. per 100 ml. by day 7, and then more gradually to 3.48 mg. per 100 ml. on day 15. The elevation was due to free bilirubin.

The data from Cases 2, 3, 4, and 5 is presented in Table II. Elevation of serum bilirubin was present in all cases. Anemia was observed on day 26 in Cases 2 and 3 and leukocytosis was present in Case 2 on days 4 and 8. Heinz bodies were seen in moderate numbers in Cases 2 and 3 on days 4 and 8 but were not observed at any time in Cases 4 and 5.

### TABLE II

Data obtained from Mares with Phenothiazine Poisoning
(Cases No. 2, 3, 4 and 5)

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<tr>
<th>Case number</th>
<th>Days after dosing</th>
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PHENOThIAZINE POISONING

DISCUSSION

Fifteen horses were treated on the same day with 20 gm. of micronized phenothia-
zine and three of these (Cases 1, 2, and 3) became clinically ill within 36 hours. These three had been recognized previously as being in less than optimum health. Twelve horses did not demonstrate any obvious illness and blood from two of these (Cases 4 and 5) was examined for comparison. These findings were in accord with the observations of other workers, that physical and environmental conditions play an important role in pheno-
thiazine poisoning. The fact that the drug was micronized probably accounted in part for the appearance of poisoning after what would otherwise be considered a safe dose. The clinical symptoms of anorexia, lethargy and weakness were similar to those described by others. It was noted that, in Case 1, clinical improvement preceded hematological improve-
ment by several days. The horse was clini-
cally improved before day 13 even though on this day its hemoglobin level was at its lowest. This would suggest that all the clinical signs in phenothiazine poisoning may not be referable to the anemia. This has been suggested by others (12, 45).

Case 1 demonstrated extreme anemia and it is surprising that the clinical signs associated with this anemia were not more profound. Edema was at no time present. It is likely that the transfer of the animal to the Ontario Veterinary College clinic on day 8 and its maintenance in warm, comfortable, quiet quarters allowed it to withstand such a severe anemia.

According to Harris (22) hemolytic anemia exists in any situation in which the red cell life span is shorter than normal. If this occurs, and the red cell production in the marrow cannot expand sufficiently to counteract the short life span, anemia results. The red cell life span in the horse is reported to be 150 days (11). It is presumed here that the marrow of the horse can, like that of man, expand its production 6 or 8 times and that anemia is not likely to develop until the red cell life span is shortened to about one-sixth of normal. The marrow in Case 1 exhibited extreme normoblastic hyperplasia by day 8 but was unable to compensate for the very rapid destruction of the red cells. It is presumed that the life span of the red cells in this case was very short.

In hemolytic anemia, the red cell de-
struction is usually accompanied by a reti-
culocyte response in the peripheral blood and, if the anemia is extreme, normoblasts will also be seen. Reticulocytes and normo-
blasts were conspicuously absent in this instance. Swales (40) also mentioned this fact. Schalm (36) stated that “in the horse the erythrocytes are released from the bone marrow in the mature state and that reticulocytosis is not characteristic of hemolytic anemia in the horse”. His opinion is supported by the findings of the authors. In general, a young red cell is larger and lighter than the more mature cells and the presence of macrocytosis, plus a diphasic sedimentation rate seen in this case, can be taken as further evidence of increased red cell production.

Consequent to red cell breakdown, the excess bilirubin released from the conver-
sion of hemoglobin may accumulate in the plasma and tissues. The general statement that free bilirubin is increased in hemolytic anemia while conjugated bilirubin is in-
creased in hepatic icterus is not entirely valid in any species and definitely not so in the horse. In the horse the normal values for total and conjugated serum bili-
rubin are 0.2–6.2 mg., and 0–0.4 mg. per 100 ml., respectively (10). Cornelius et al. (10) have pointed out that in the horse free bilirubin predominates in either hepatic or hemolytic icterus and that marked elevations in serum bilirubin may be ob-
served secondarily to many environmental conditions. In the present case the total bilirubin was elevated, this being due to an increase in free bilirubin. In Case 1 the greatest increase occurred on days 4 and 5, and this suggests that the maximum hemolysis was at this time. These findings are in accord with those of Swales (40) who reported values of 4.7 and 8.0 mg. of indirect (free) bilirubin in horses experimentally poisoned with phenothiazine. He noted a rise by the second day after dosing, with a return to normal by the 34th day. It is concluded that in this pre-
sent case the elevation of free bilirubin was due to red cell breakdown. The blood transfusion that was given to Case 1 on day 4 was administered after the sample
for bilirubin estimation had been taken and thus did not influence the high values seen on this day. In Case 1 marked clinical improvement was followed shortly by the return of serum bilirubin to normal.

Hemolytic anemia occurs in association with many chemicals and in certain of these the anemia is accompanied by Heinz body formation (22, 44, 47). Heinz bodies were an important feature in these cases and the degree of hemolysis appeared to be related to their frequency. Whether the toxin damaged all the susceptible red cells on the day it was given, or rather became fixed in the tissues and from there exerted continuing damage, is speculative. If, as has been postulated, the spleen effectively removes Heinz bodies as they are formed, then their continuing presence for 15 days after dosing would suggest that the toxin was still in the body during most of this time. Webster (44) has pointed out that after experimental animals had been exposed to pyrodine, it took 8 to 18 days for the Heinz bodies to disappear. He found it difficult to reconcile this with the theory of splenic filtering. The present data suggest that neither the red cell precursors in the marrow nor young red cells (macrocyes) in the circulation are involved in Heinz body formation. This is in agreement with Swales (4) who felt that the macrocytes seen in phenothiazine poisoning are more susceptible to hemolysis, and with Schalm (38) who noted that as new red cells appeared the Heinz bodies decreased in number. Likewise in primaquine sensitive anemia in humans, it is the older red cells that are hemolized, the younger ones being resistant. The marked clinical improvement of Case 1 coinciding with the disappearance of Heinz bodies might suggest that the toxin was completely eliminated at this time.

While Case 1 gives the most information regarding the sequence of hematological events in phenothiazine poisoning, the other four cases are also of interest. Data from Cases 2 and 3 suggest that Heinz body formation can be present in the absence of marked anemia. The leukocytosis seen in Case 2, which had more Heinz bodies than Case 3, suggests that the leukocytosis might be directly related to the degree of hemolysis (47). The elevation of serum bilirubin in Cases 3 and 4 suggests that while these animals were clinically and hematologically normal they might have compensated for a hemolytic anemia.

The blood transfusion administered to Case 1 on day 4 did not prevent the subsequent development of extreme anemia but it is possible that it did help the animal to survive.

**Summary**

Fifteen horses were treated with 20 gm. of micronized phenothiazine. Three of these horses developed varying degrees of hemolytic anemia which was characterized by hyperbilirubinemia and Heinz body formation. The affected animals were unthrifty prior to treatment and it is believed that this was an important factor in producing the signs of toxicity. Two animals that did not become clinically ill nor had other evidence of anemia, did have hyperbilirubinemia which was probably related to hemolysis.

**Résumé**

Quinze chevaux ont été traités avec 20 gm de phénothiazine. Trois d’entre-eux ont développé, à différents degrés, une anémié hémolytique caractérisée par une hyperbilirubinémie et par la formation de corpuscles de Heinz. Les animaux ainsi affectés étaient en mauvais état avant d’être soumis au traitement et l’on croit que c’est là un facteur important dans la production des signes de toxicité. Deux chevaux qui n’ont montré aucun symptôme de maladie ou d’anémié ont développé une hyperbilirubinémie due vraisemblablement à l’hémolyse.

**References**

PHENOTHIAZINE POISONING


BOOK REVIEW


The first six editions of this book were entitled Animal Pathology, but for almost thirty years, were more familiarly known to veterinary students, simply as "Runnells". Now in retirement, Dr. Runnells has retained his identification with this book in an advisory capacity but active authorship has been taken over by Drs. W. S. and A. W. Monlux. Pathologists will recognize these men as amply qualified to carry on the worthy task.

The authors have presented the study in four parts. Part I contains an introductory chapter and a chapter devoted to the history of pathology. The latter is a fascinating summary of the development of veterinary medicine during the past 4,000 years.

Part II consists of three chapters devoted to the causes of disease. Particular stress is placed on extrinsic causes, especially those of a nutritional nature. The authors state that "no other factor is as important a cause of disease as food" and have devoted a large chapter to discussion of the effects of incorrect diets and of diseases produced by deficiencies or excesses of proteins, carbohydrates, fats, minerals and vitamins in the various species of domestic animals and poultry. A further chapter deals with diseases which are caused by physical, chemical and viable agents.

Parts III and IV cover general and special pathology respectively. Chapters are presented in the classical sequence used in books intended for veterinary students. A very wide range of diseases affecting domestic animals and poultry is described and stress is placed upon the relationships among causes, clinical signs and pathological changes.

Pathologists and graduate students will be disappointed that no bibliography is provided. Selected references, particularly those having good bibliographies, would have increased the value of the text.

The publishers are to be commended for the high quality of the book in general and particularly for the excellent reproduction of the illustrations. Typographical errors are rare.

Veterinary students will find this a very useful book which presents the study in an interesting and lucid manner. Practitioners will not find it a dry "ivory tower" textbook but rather a stimulating review of pathology and a means of updating their understanding of more recently recognized disease conditions. In this book pathologists and graduate students will find the views and interpretations of three leading animal pathologists.

A. Robertson.