THE TOXICITY OF PHENOTHIAZINE

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SUMMARY

Phenothiazine, the parent compound of a multitude of present-day drugs, has been employed on an extensive scale for its insecticidal, fungicidal, antibacterial and anthelmintic properties. Almost a catholicon, its widespread use in animals and man has led to the uncovering of many adverse reactions encompassing effects on blood elements, neuromuscular problems and photosensitization. The high lipophilicity of phenothiazine and the formation of two redox systems amongst its many metabolites can facilitate the occurrence of generalised macromolecular disruption. Information from the literature has been garnered and appraised in this review to enable an insight into the possible mode(s) of interaction of phenothiazine with living systems.

KEY WORDS

phenothiazine, anthelmintic, insecticide, fungicide, adverse reactions

I. INTRODUCTION

Phenothiazine (Fig. 1) owes its origin to the aniline dye industry of the latter half of the nineteenth century /1/. The desire to replace expensive natural dyes with cheaper synthetic colouring agents derived from the products of coal tar led to the production of many colorants including Lauth's violet (thionine) and methylene blue (basic blue 9) /2,3/. These thionation products of substituted anilines contained a then unknown conjugated triple ring system as their nucleus which, together with the amino functions, permitted their chromogenic behaviour /4/. The structure of this nucleus was unravelled by the elegant researches of Heinrich August Bernthsen who named the compound thiodiphenylamine, reflecting its route of synthesis /5-7/.

II. USES AND APPLICATIONS

For some fifty years phenothiazine remained a chemical curiosity. It was an interesting result of systematic chemical research and provided the nucleus for the development of artificial dyes and biologically active compounds. Indeed, it was and still is the parent compound of a

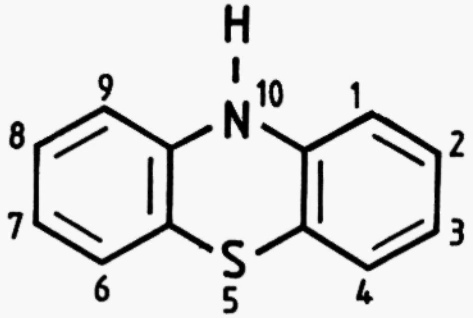

Fig. 1: The structure of phenothiazine.

multitude of drugs which have found varied and extensive use in clinical practice. Methylene blue was investigated as an analgesic in 1890 /8/ and was used as the first synthetic antimalarial agent /9/. In the 1950s the discovery of chlorpromazine and the subsequent renewed interest in N-substituted phenothiazines provided a host of new pharmacologically active compounds. By the early 1970s over 3,000 phenothiazine derivatives had been synthesized and at least one hundred of them have been in clinical use as tranquillisers, antihistamines, antiemetics, sedatives, analgesics and agents for the treatment of Parkinsonism /10/.

2.1 Insecticidal aspects

It was not until 1934 that phenothiazine itself was shown to possess any useful biological properties. During a routine screening of sulphur-compounds phenothiazine surprisingly surpassed nicotine and rotenone in its ability to destroy culicine mosquito larvae /11/. It was later shown to be highly effective in eradicating newly hatched codling moth larvae (apple maggot) /12/ and further studies demonstrated a variable potency to many insect species /13,14/. However, it was in the control of the apple maggot that phenothiaizine excelled and extensive orchard trials led to it replacing lead arsenate as a fruit spray to control this pest.

2.2 Fungicidal effects

As well as its advantage in not leaving toxic residues, sprayed fruits did not become infected or decay as rapidly as unsprayed produce. This slight fungicidal activity was attributed to phenothiazone, a carbon oxidation product of phenothiazine formed under suitable weathering conditions especially in the presence of inert carriers, such as bentonite and lime, which facilitated the spraying of the insoluble compound /15,16/.

2.3 Antibacterial properties

The contact of phenothiazine with foodcrops destined for human consumption prompted investigations into its interactions with mammaliam systems. During such studies it was noted that urine from rats receiving oral phenothiazine turned red on exposure to air but did not develop the usual offensive odour and that bacterial growth was not evident within the urine even after standing exposed for several weeks /17/.

Initial inquires revealed retardation of the normally expected growth of *Escherichia coli* when deliberately added to the urine of rats, rabbits and a human previously fed with phenothiazine, suggesting an antiseptic action of phenothiazine or its metabolites /18/. Further studies showed that the oral administration of phenothiazine brought about some improvement of experimentally induced cystitis (*E.coli*) in male rabbits and clinical investigations in patients with various urinary tract infections showed that 84% (41/49) secured relief from symptoms and 31% (15/49) were clinically cured following phenothiazine therapy /19/.

Exploration of the underlying mechanism of action revealed little except that the bacteriocide was not unchanged phenothiazine but its urinary oxidation product, thionol. Thionol had been shown to possess an additional bacteriocidal action *in vitro* against *Staphylococcus aureus* /18/ and had actually been put forward many years previously for use as an antiseptic and disinfectant /20/. Interestingly, phenothiazine itself inhibited the growth of tubercle bacilli *in vitro* in high dilution, the bacteriostatic effect being diminished in the presence of serum but still significant, whereas the oxidised forms of phenothiazine only gave a moderate degree of inhibition /21/.

2.4 Anthelmintic activity

In 1938 phenothiazine was reported to be effective in preventing the development of horn fly larvae in the faeces of cattle previously treated with this compound. Not an unexpected observation, in light of its known insecticidal properties, but ingenious as a way of reducing the numbers of these blood-sucking insects by rendering their ubiquitous breeding grounds inhospitable /22,23/.

Other studies being carried out at the same time showed a rather variable but nevertheless marked action of oral phenothiazine in removing ascarids (roundworms) and nodular worms from the gastrointestinal tract of pigs /24/. Following this initial lead, workers in several countries found the compound to be effective against strongyloid worms in sheep and during the next few years many more convincing demonstrations of the anthelmintic activity of phenothiazine were presented /25-27/.

For a time phenothiazine was viewed as a panacea for parasitic infections. The use of the compound to control livestock parasites with its powerful indirect effect on human health, overshadowed its other values. In the U.S.A. the production of phenothiazine rose from 408 kg in 1939 to 1,260,300 kg in 1943, largely for anthelmintic consumption /28,29/. During the early 1940s the use of phenothiazine against sheep parasites was estimated as preventing an annual loss of one million dollars in the State of Kentucky alone /30/.

The compound was extensively used in animals throughout the world for some twenty years after its introduction and, although still used on a small scale as a cheaper form of therapy and as a prophylactic in the control of manure-breeding flies, it effectively disappeared from the agricultural scene in the mid 1960s, being superseded by more efficient and safer broad spectrum anthelmintics. However, recent studies have shown phenothiazine to be effective against some strains of sheep nematodes which have become resistant to modern agents, suggesting that the compound may not be totally redundant /31/.

III. METABOLISM

Phenothiazine, like many other foreign compounds, undergoes chemical modification during its passage through the body before being discharged into the environment. Out of the many metabolic transformations which may occur to xenobiotics, phenothiazine only appears to be susceptible to oxidation and conjugation; the molecule itself remains intact and is not degraded (Fig. 2).

Carbon oxidation can occur on the ring atoms which are diametrically opposed to the heterocyclic nitrogen centre (para-position) to form leucophenothiazine (3-hydroxyphenothiazine) and leucothionol (3,7-dihydroxyphenothiazine). One of these hydroxyl groups may be further oxidised to yield the corresponding coloured quinoid structures, phenothiazone (phenothiaz-3-one) and thionol (7-hydroxyphenothiaz-3-one), respectively. Nitrogen oxides have been alleged to result from incubation of the drug with guinea-pig liver microsomes /32/ but they could not be detected during whole animal studies /33/; these putative metabolites may in fact have been the previously mentioned carbon-oxidation products /34,35/. Oxidation at the sulphur atom gives phenothiazine sulphoxide (phenothiazine-5-oxide) which does not appear to be oxidised further to the sulphone. However, administration of the sulphoxide to sheep, rabbits and guinea-pigs /33,36,37/ leads to the urinary excretion of both phenothiazine and phenothiazone, indicating both reduction and (reduction-oxidation) effective oxygen migration around the ring (via phenazothionium and 3-carbonium ions) /38-40/.

Conjugation with the ubiquitous glucuronic acid can occur directly with phenothiazine to form the oft described ‘water-soluble acid-labile conjugate of phenothiazine’ which has been given the tentative assignment of an N-glucuronide /33/. Thionol (or leucothionol) may also conjugate with glucuronic acid, existing as the colourless leucothionol glucuronide or the coloured quinoid form, thionol glucuronide, whilst leucophenothiazone may be condensed with sulphuric acid to form the colourless leucophenothiazine sulphate.

Two more unusual conjugates have been described: an unidentified phenothiazine-fat complex within the intestinal fluid of rats and chickens /41/ and a series of polypeptide conjugates from the urine of young calves which contained between two and six amino acids attached via the peptide carboxy-terminal to the nitrogen atom of phenothiazine or leucophenothiazone /42-44/.

The major routes by which phenothiazine and its metabolites leave the mammalian body are via the urine and faeces; even so it takes many days or weeks for a near-complete elimination to occur (Table 1) /33, 45-52/. The urine is the most important route of elimination for that part of the dose which has actually been absorbed into the body, as

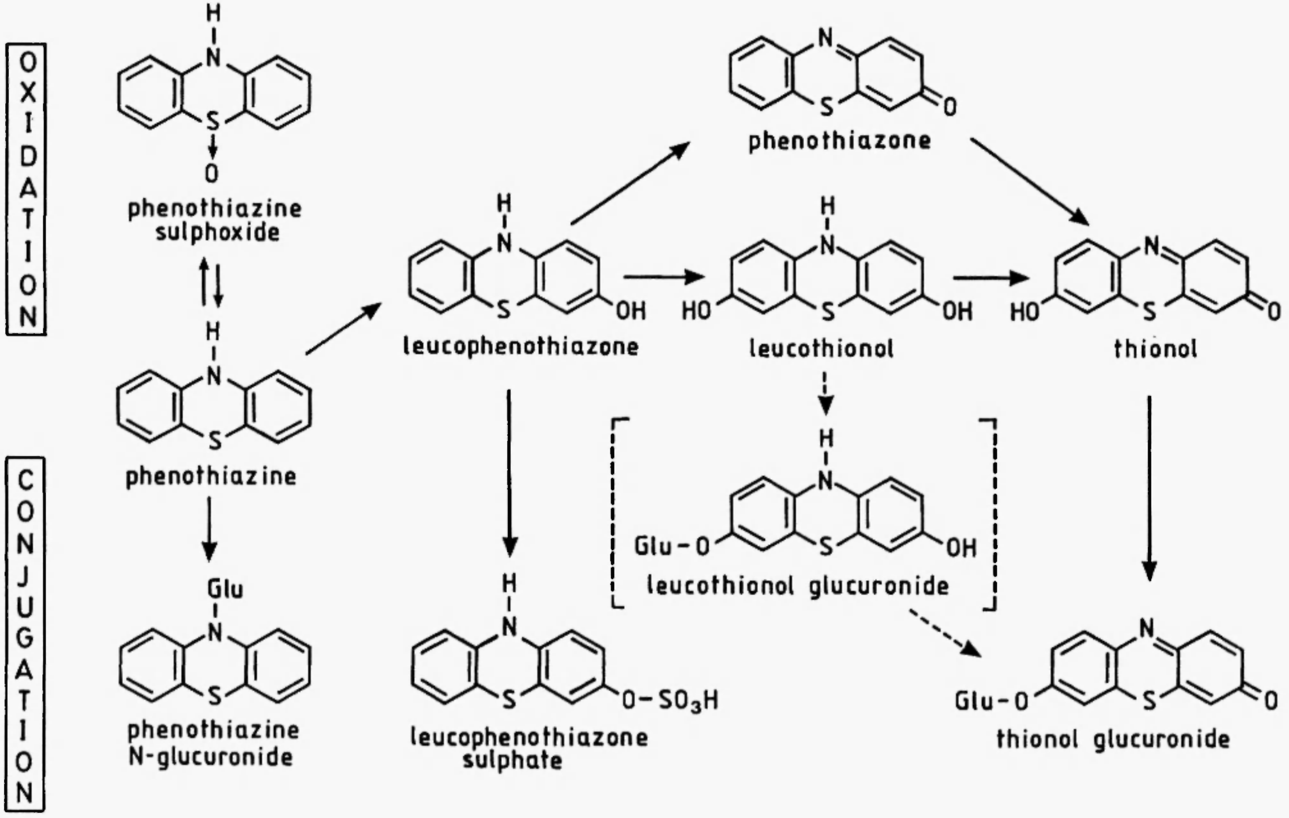

Fig. 2: Metabolism of phenothiazine.

TABLE 1

Urinary and faecal excretion of parent compound and metabolites by different species following oral administration of phenothiazine

Species	oral dose rate (mg/kg body wt.)	percentage dose excreted urine	faeces
man	6	25(1)	-
horse	40-60	12(1)	21(5)
sheep	220-840	15(1)	25(5)
cow	220	25(1)	23(1)
rabbit	1500	25(1)	-
guinea pig	150	37(1)	24(7)
gerbil	150	30(1)	-
hamster	150	44(1)	-
rat	150	18(1)	-
mouse	150	44(1)	-

Values calculated as percentage administered radioactivity or the sum of excreted metabolites. Numbers in brackets indicate duration of collection in days.

- indicates data not available.

Data taken from original references /33,45-52/. The table has been amended and reprinted with permission from reference /40/, page 327, by courtesy of Marcel Dekker, Inc., New York.

opposed to that which is carried through the enteric tract unabsorbed to be voided in the faeces. It is also the route which has been most extensively investigated and in which the greatest number of metabolites have been identified (Table 2) /26,33,36,37,42,43,45-49, 51,53,60/. Phenothiazine, phenothiazone, thionol and phenothiazine sulphoxide have been identified in the faeces of several animals /33,46, 51,52,57,58,60,61/. There is also evidence that following absorption compounds enter the gut via the biliary tract /33,36,41-43,53,58,61, 62/.

IV. INTERACTION WITH LIVING SYSTEMS

4.1 Mode of action

Both the fungicidal and antibacterial properties of phenothiazine have been attributed to the carbon oxidation products, phenothiazone and thionol, respectively, although no mechanisms of action have been cited except vague references to interference with redox systems. There is little understanding as to how the compound functions as an

TABLE 2

Urinary metabolites of orally administered phenothiazine

	unconjugated metabolites				conjugated metabolites		
					glucuronides		sulphate
	phenothiazine	phenothiazine sulphoxide	phenothiazone	thionol	phenothiazine	thionol	leucophenothiazone
Species							
Man	+	+	+	+	++		++
Dog			+	+			++
Horse			+	+			++
Pig			+	+	++	+	+
Sheep	+	+	+	+	+		++
Cow	+	+	+	+	+		++a
Rabbit	+		+	+	++	++	+
Guinea pig	+	+			++		++
Gerbil			+	+	++	+	++
Hamster				+	++		+
Rat			+	+	+	++	++
Mouse		+	+	+	+	+	++

++	indicates a major metabolite (20% and over)
+	indicates a minor metabolite (up to 20%)
blank space	indicates not detected or not reported
a	only present in animals over 4 weeks old; calves up to 6 weeks excrete a polypeptide conjugate

Table constructed from original data from references /26,33,36,42,43,45-49,53,60/ and reprinted with permission from /40/, p. 328, by courtesy of Marcel Dekker, Inc., New York.

insecticide and a satisfactory explanation of its vermifugal action is also lacking /63/.

However, in the latter case, investigations with phenothiazine and its derivatives have suggested that the compound is not converted into an active anthelmintic by metabolism /41/ and it is therefore assumed that large doses are required to ensure that the parasite absorbs toxic amounts of the unchanged drug. Although the compound has a very low aqueous solubility (1.25 ppm) it is generally accepted that it enters the parasitic nematode through the cuticle /64/ and must be in solution before this absorption can occur. It is known that the anthelmintic efficiency increases as the particle size of administered phenothiazine decreases (total surface area increases) /65-67/. No anthelmintic activity was observed when the carbon oxidation products, phenothiazone and thionol, were administered to goats heavily infected with parasitic worms /26/, and phenothiazone had no effect on removing nematodes from sheep which could be successfully treated with phenothiazine /36/. Metabolism of phenothiazine within nematodes does not appear to occur; the phenothiazine content of nematodes taken from treated animals did not decrease when the worms were kept in drug-free medium for up to 24 hours, suggesting that once phenothiazine has entered the parasite it has great difficulty in leaving /41,64,68,69/. Phenothiazine does not exert a lethal action on the parasite as worms eliminated from phenothiazine-treated animals are alive and can be maintained *in vitro* for just as long as parasites from untreated animals /63/. The only definite effect so far demonstrated both *in vivo* and *in vitro* is the inhibition of egg laying which is thought not to be related to any specific drug action on the nematode reproductive system but an overall change in the well being of the adult organism /63/.

Metabolic studies have shown that between 10 and 45% of orally administered phenothiazine is eliminated via the urine (hence absorbed) and that the compound undergoes extensive metabolism /40/. Amongst the many metabolites formed are two redox systems (phenothiazone/ leucophenothiazone; thionol/leucothionol) (Fig. 3) which have been purported to prevent the operation of an oxygen transfer mechanism essential to helminth metabolism. Circumstantial evidence for this view comes from structure-activity studies in which phenothiazine derivatives with substituents in both the 3- and 7-positions, which precluded the formation of such redox systems, were shown to be devoid of anthelmintic activity. In addition, only compounds with an unsubstituted nitrogen position were active, this presumably reflecting the ability to loose hydrogen and enabling charge redistribution during carbon oxidation and formation of semiquinone species. The inactivity of phenothiazine sulphoxide and sulphone also suggested the importance of free electron pairs in the sulphur atom, which itself could be replaced by oxygen (phenoxazine) with only a slight loss in anthelmintic activity. Overall, an apparent association was found between vermifugal activity and the ability to form, by a univalent oxidation step (E_i = 28 mV), a high proportion of a stable semiquinone

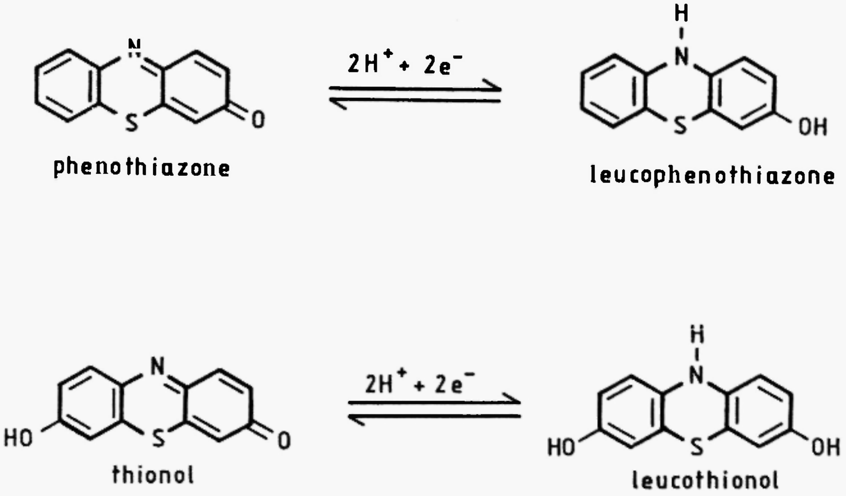

Fig. 3: Two redox systems which exist amongst the many metabolites of phenothiazine.

radical with an oxidation potential in the region of 0.55 to 0.85 volts /70/. However, despite much theoretical reasoning, the influence of the drug on any nematode redox system which could account for the anthelmintic activity remains to be demonstrated.

4.2 Enzyme interaction

A possible insight comes from reports that phenothiazine and its metabolites display inhibitory effects towards the *in vitro* activity of a variety of enzyme systems belonging to the functional categories of oxidoreductases, hydrolases and transferases /71-80/ (Table 3). Speculation as to the means of inhibition has been made but there appears to be no simple unifying characteristic or property possessed by these diverse enzyme systems to make a universal mechanism tenable. It is more probable that several mechanisms are in operation.

TABLE 3

Inhibitory effect of phenothiazine and derivatives on enzyme systems

Enzyme activity	Source of enzyme activity	Compounds showing inhibition (a)	Reference
1) <u>Oxidoreductases</u> <u>oxidases</u>			
cytochrome oxidase	beef heart	D,E,	71,72
	cockroach coxal muscle	A	73
<u>dehydrogenases</u>			
lactic dehydrogenase	yeast	D	72
succinic dehydrogenase	beef heart	C,E	72,75,76
	rat liver mitochondria	A,B,C,E	74
glucose-6-phosphate dehydrogenase	rabbit erythrocytes	C,E	77
<u>hydroperoxidases</u>			
catalase	guinea pig liver	B,D,E,F,	71,72,75
2) <u>Hydrolases</u> <u>esterases</u>			
cholinesterase	horse serum	C	75,78
<u>amidases</u>			
urease	jack beans (?)	C	72
<u>lyases</u>			
glyoxalase	human erythrocyte	A,C	79
	rabbit erythrocyte	A,B,C	79
3) <u>Transferases</u> <u>transphosphorylases</u>			
hexokinase	rat brain (b)	C	80

(a). Inhibitor substance; A = phenothiazine, B = phenothiazine sulphoxide, C = phenothiazone, D = leucophenothiazine, D = thionol, E = leucothionol.

(b). This tissue was homogenised in the presence of fluoride to depress apyrase activity.

a) Sulphydryl influences

It is known that the activity of rat liver succinic dehydrogenase, an enzyme of the tricarboxylic acid cycle which catalyses the oxidation of succinic acid to fumaric acid, is inhibited by quinones and related compounds and interaction with sulphydryl groups has been proposed /81/. A similar mechanism has been advocated for the observed inhibitory effects of the carbon oxidation products of phenothiazine which have quinone-like structures /72,74-76/. It was further assumed that these derivatives would act in an inhibitory fashion via the sulphydryl groups of glyoxylase (aldoketomutase), an enzyme system which catalyses the intramolecular oxidation-reduction of methylglyoxal (pyruvic aldehyde) to lactate. This was indeed the case, but inhibition still occurred even in the presence of a large excess of glutathione which is known to act as a protective agent for such sulphydryl groups. This was in direct contrast to p-chloromercuribenzoate, which inhibits enzyme activity by sulphydryl interaction and loses its inhibitory properties in the presence of excess glutathione /79/. Clearly, some additional explanation is required.

b) Redox systems

The existence of two oxidation-reduction systems amongst the metabolites of phenothiazine has prompted the suggestion that the inhibition of succinic dehydrogenase may be related to the high redox potentials possessed by these systems. Phenothiazone has an E'_0 value of 0.13 volts at pH 7.3 and the thionol system an E'_0 of 0.16 volts at pH 7.0, both of which are higher than that of the fumarate-succinate couple ($E'_0 = 0.03$ volts at pH 7.0) /72,82,83,53,55/. However, such reduction potentials were determined *in vitro* and apply only to 50% reduced systems, a situation which may not exist in living cells.

The inhibitory effects noticed with phenothiazine may well be due to its oxidation to phenothiazone within the incubate. Phenothiazine has been shown to completely inhibit cytochrome oxidase activity in cockroach muscle but only after one hour of pre-incubation, up to which time only partial inhibition occurred /29,73/. It is possible that the inhibition of cytochrome oxidase activity occurs because of the maintenance of cytochrome *c* in its reduced state. Leucophenothiazone can bring about such a reduction of cytochrome *c* /71/.

c) Molecular binding

The inhibition of catalase activity, a hydroperoxidase enzyme which breaks down hydrogen peroxide with the evolution of molecular oxygen, by hydroxyphenothiazines has been attributed to the phenolic hydroxyl group which possibly forms covalent complexes with the active iron atoms of these haemoprotein catalysts /71,72,75/. Phenothiazone and thionol have also been shown to bind to serum albumin and nucleic acids /84/ and disruption of tertiary structure may occur as a result of van de Waal intercalation of the aromatic phenothiazine with essential protein and porphyrin/corrin centres.

V. ADVERSE REACTIONS

The side-effects which accompany the use of phenothiazine are quite variable, not only between different species but sometimes between individuals belonging to the same species. Animals have died after receiving the customary therapeutic dose whereas others have survived many times this amount. It has been recommended that small gradual doses of the drug be given rather than larger quantities /85/, although continuous treatment may be more insidious in its harmful effects /86/ and it is almost certain that phenothiazine would be toxic to all animals if the acute or chronic dosage were too high /87,88/. The various species which have shown phenothiazine toxicity can be placed in order of increasing sensitivity, from dogs, through birds, rabbits, goats, sheep, cattle, pigs and horses to apparently the most sensitive animal, man. Phenothiazine has been used to treat many other animals including the bear (brown and polar) /89/, beaver /90/, bison /91/, camel /91/, deer /92,93/, elephant /94/, fox /95/, goose /96/, pidgeon /97/, sable /98/ and yak /99/, but few toxicological data are available.

Undoubtedly, a variety of factors play a role in determining the susceptibility of any animal, although idiosyncrasy alone does not appear to be a satisfactory explanation for all cases of poisoning. Toxic manifestations often tend to occur in groups, suggesting some localised environmental or genetic influence, and the literature provides several instances where such clustering has been seen. In particular are two examples where related children are reported to have developed haemolytic anaemia following the use of phenothiazine as an anthelmintic /100,101/. One thing that is apparent is that the young of a species are generally more prone to adverse reactions than adults.

5.1 Effects on blood elements

The most widely reported side-effect of phenothiazine therapy is acute haemolytic anaemia and its sequelae. The severity of this condition can vary between being slight and transient to fatal in its outcome and has been reported as occurring in many species, including mouse /102/, rat /103,104/, rabbit /103/, dog /105,106/, pig /107,108/, cattle /97/, horse /46,110-119/ and man /19,120,121/. Anaemia has also been demonstrated in chickens after phenothiazine administration, but this may have been due to trauma during the catching and confining of the birds /122,123/. An indicator of differing species susceptibility may be that no significant blood changes have been reported in the guinea-pig or golden hamster /106/.

It is difficult to obtain a reliable measure of the incidence of haemolytic anaemia within a species or population as most articles only cite affected individuals and do not contain controlled studies. Nevertheless, the literature contains several instances where horses have been efficiently dosed without the appearance of any clear signs of intoxication /26,124-128/ and it is certain that many thousands of horses throughout the world have been successfully treated without adverse reaction. A few reports exist where the efficiency of phenothiazine therapy in humans has been studied and the number of subjects developing changes within their blood profile have been cited /19,129-132/ (Table 4). The observed overall incidence of 18% is similar to the 13% quoted by other authors for their review of 58 patients /101,133/, although the latter included nine patients treated by one investigator who reported no side-effects /24/. However, a wide variation is seen to exist between the various studies and the quoted mean value may be an underestimate. Indeed, a slight but definite anaemia occurred in 50% of group of 73 children, aged between 4 and 12 years, treated with phenothiazine /134/, and other workers have also mentioned a transient but measurable anaemia in about half of their subjects /129,132/. The few cases of severe haemolytic anaemia cited /130,134/ and the report of a death due to phenothiazine poisoning /135,136/ led to the withdrawal of this compound for human use.

In addition to the general picture of a decreased haemoglobin content, decreased red blood cell count and an increase in the percentage of circulating reticulocytes (rat /103/, dog /106/, man /19/), anisocytosis (dog /137/, horse /119/) and poikilocytosis (horse /119/)

TABLE 4

Incidence of haemolytic anaemia in patients undergoing phenothiazine treatment

number of patients examined	patients developing haemolytic anaemia		reference
	number	percent incidence	
23	9	39.1	129
8	3	37.5	130
19	3	15.8	19
28	3	10.7	131
34	2	5.9	132
total 112	total 20	average 17.9	

have been observed as well as polycythaemia in frequently treated lambs /138/.

Effects on white blood elements include neutrophilia (dog /106, 137/), low polymorphonuclear cell counts (man /130/) and general predisposition to agranulocytosis (sheep /138/, man /139/). Other signs reported include haemoglobinuria (horse /112,113/), albuminuria (horse /112,113,119/; goat /140/), an increase in lactic acid and bilirubin in the blood stream (horse /141/), jaundice (dog /106/, man /142/), nephritis and hepatitis (man /130,143/).

Post-mortem examination has shown severe injury to the urinary system (horse /46/) together with pathological lesions in the kidney (sheep /138/), including changes in the tubules and Malphigian corpuscles (horse /144/), and coagulated masses in the bladder, kidney hilus and uterus (horse /145/). A mention of organ congestion, fatty degeneration and advance cloudy swellings of the liver, interstitial lesions of the heart (horse /144,146/) and enlargement of the spleen (horse /145/, weasel /98/), heart, liver and kidneys (horse /116/) has also been made. Most, if not all of these changes may well be secondary to the haemolytic anaemia present.

The observation of an increase in erythrocyte fragility preceding phenothiazine-induced anaemia in dogs was interpreted as being due to the direct action of the compound and its metabolites on erythrocytes, subsequently producing haemolysis /106/. These compounds are known to become bound to erythrocyte membranes but do not enter the cells /33,40,57,79,84,147/ and may induce conformational changes thereby increasing the permeability of the red cell membranes to water or macromolecules. Such effects have been demonstrated with substituted phenothiazines /148-150/. However, *in vitro* studies with human and horse erythrocytes (two susceptible species) have failed to reveal any haemolytic action of phenothiazine and its metabolites /79, 133/. It is possible that these compounds may damage the erythrocyte in such a way (change in surface characteristics, plasticity, shape) that it is selected for premature removal by the reticuloendothelial system. Overstimulation of the spleen and destruction of erythrocytes by hyperactivity has also been proposed /46/ and descriptions of splenomegaly lend some support to this hypothesis /98,112,145,151/.

Phenothiazine, phenothiazone and thionol, when incubated with buffered suspensions of human erythrocytes, led to the rapid formation of methaemoglobin. There was no appreciable haemolysis of the cells and haemoglobin within intact erythrocytes was oxidised more rapidly than that free within a lysate. It was presumed that the compounds acted upon the haemoglobin via a one-electron transfer directed across the intact and functional membrane to oxidise the haem iron (from ferrous to ferric). However, no indication of 'charge-carrier molecule' has been forthcoming (H.B. Collier, 1982, 1987; personal communication).

It has been suggested that the susceptibility of some mammalian species to phenothiazine-induced anaemia may be attributable to a low glucose 6-phosphate dehydrogenase activity within the erythrocytes, such low levels being further reduced by the inhibitory effects of phenothiazone. However, sheep have a naturally low activity of this enzyme within their erythrocytes but are nevertheless notably resistant to the haemolytic action of the vermifuge /77/.

Workers have shown that the *in vitro* haemolysis of horse erythrocytes by saponin and lysolecithin was rapidly accelerated in the presence of phenothiazone or the leucophenothiazine sulphate conjugate. Erythrocytes from sheep (a more resistant species) required three times the concentration of these metabolites to produce the same effect. A concentration of 300 μM of the conjugate has been detected in horse plasma following phenothiazine treatment which, *in vitro*, was sufficient to cause this rapid haemolysis /152/. The mechanism by which phenothiazine metabolites accelerate this haemolytic process is not known but it is believed that erythrocytes are being constantly subjected to lytic tendencies and the presence of the drug in some way (thiol depletion? /153,154/) hastens this process.

5.2 Neuromuscular problems

Loss of equipoise and power of coordination in movement with difficulty in walking, staggering gait, muscle weakness and general paralysis of the hind quarters has been observed in pigs /107,155-158/, horses /116,159,160/ and cattle /161/ undergoing phenothiazine treatment. These problems in cattle have been shown to be dose dependent; animals receiving around 50 g of the vermifuge showed no side-effects whereas those receiving 250 g developed anorexia and hind limb incoordination /162/. It has also been reported that of a thousand pigs treated with phenothiazine only one mild reaction was encountered, whereas in other herds the majority of animals have reacted, some fatally /156,163/. It is quite possible that local environmental factors played a role or perhaps there was a predisposing genetic susceptibility, exaggerated by herd inbreeding.

Nevertheless, the neurological phenomenon is most dramatic in pigs where some animals are so badly affected that they are unable to move, lying prostrate with opithotonus (a tetanic spasm in which the spine and extremities are bent with convexity forward) being observed /156/. This rigid tetanic spasm with increased muscular tone is usually associated with damage to upper motor neurons as opposed to the local flaccid paralysis seen with lower motor neuron lesions. The staggering gait with loss of balance and power of coordination /107, 116,155-161) is suggestive of cerebellar involvement and possible extrapyramidal lesions. Phenothiazine is known to be concentrated in the brain stem (cat, monkey, man) /164/ but lacks a side-chain on the ring nitrogen for interference with dopaminergic transmission, as displayed by the N-substituted antipsychotic phenothiazines /165/.

In addition to central actions, potential peripheral effects must not be overlooked. Phenothiazine has been shown to depress neuromuscular transmission and raise the excitation threshold potential in the shore crab (*Carcinus maenus*) at very low concentrations (*c.* 0.5 μM) /166/ and this may be the result of a direct effect on the neuronal membrane. However, it is known that curare, an alkaloid which produces a non-depolarising blockade at cholinergic (nicotinic) terminals, has no effect at the nerve-muscle junctions of the crab, which are therefore different from the neuromuscular junctions found in mammalian systems, where curare is a potent blocking agent /167/.

Phenothiazine itself has no effect *in vitro* on liver flukes (*Fasciola hepatica*) and failed to evoke any response in the exposed neuromuscular apparatus of the roundworm (*Ascaris* sp.) /168-170/. Both the liver fluke and roundworm musculature are stimulated by acetylcholine and possess cholinergic components but it is not certain that the acetylcholine-cholinergic system is important in nematode physiology /63,169,171/.

However, *in vitro* studies with phenothiazone have shown it to produce paralysing effects on both the liver fluke and large roundworm (*Ascaris lumbricoides*). Thionol and phenothiazine sulphoxide were less effective but still produced paralysis in both animals /172,173/. The inhibitory effect of phenothiazone on horse serum cholinesterase /75,78/ must also be borne in mind, especially if such inhibition could also occur with the enzyme present within nervous tissue.

5.3 Photosensitization

The phenomenon of photosensitization has been frequently described in man. The reaction consists mainly of an itchy rash and inflammatory dermatitis resembling sunburn, developing after several hours direct exposure of the skin to sunlight.

The reported cases have either followed direct contact of the skin with a spray containing phenothiazine or a dust of the chemical /174-177/ or after the ingestion of phenothiazine (or in one case thionol) /132,178/, suggesting that both a topical irritation and a systemic mechanism may be in operation. The topical application of phenothiazine mixed with alcohol or wool fat (lanolin) to the forearm of volunteers was shown to produce no irritation even when exposed to irradiation, implying a systemic mechanism /178/. However, a case has been cited where an individual suffered photosensitization on parts of the body contaminated with phenothiazine dust but no similar irritation on simultaneously exposed but uncontaminated parts of the body /162/. It has been stated that skin contact with freshly prepared phenothiazine will not induce a dermatitic reaction but once it has been allowed to oxidise then such adverse reactions are almost certain, suggesting that the oxidation products are the causative agents /179/.

It is generally appreciated that both the drug and direct sunlight must be present for the reaction to occur; ranchers in Texas avoided this irritation by dosing their herds at night /180/. The additional complication that fine particulate phenothiazine may enter the body by inhalation whilst spraying must also be borne in mind.

Other animal species also show photosensitization but do not react with the same frequency. White animals, or animals with white spots, may react whenever unpigmented parts are exposed to the sun. Infrared irradiation of horses, dogs and mice previously treated with phenothiazine resulted in rapid desquamation and the loss of hair over the whole body surface. Severe skin pigmentation was also seen in dogs. However, such effects were not produced by irradiation in the absence of ingested phenothiazine /181/. The role of phenothiazine or its metabolites in the trapping of quantal radiation is apparent but the mechanisms remain unknown.

Animals having a general pigmentation may only show inflammation of the cornea and associated signs such as lacrimation and oedema of the eyelids. The keratitis may develop into opacity of the cornea and eventual ulceration leading to temporary and in some cases permanent blindness. Such reactions, in varying degrees, have been reported as occurring in pigs /182/, sheep /183-186/, cattle /42, 187-191/, goats /192/ and pheasants /193/. The injection of phenothiazine, leucophenothiazone sulphate conjugate, thionol or phenothiazine sulphoxide into the anterior chamber of the calf eye followed by a deliberate exposure to bright sunlight (90 min) resulted in the development of an intense keratitis. Such reactions were absent following injections of saline. Post-mortem investigations of calves treated with phenothiazine showed that the only metabolite present in the lacrimal fluid and aqueous humour of the eye was the sulphoxide, no sulphoxide being detected in the analogous parts of sheep who are not normally susceptible to this ailment except when given massive doses. The effective wavelength of light which produced keratitis lay between 320 and 360 nm which corresponded to an absorption maximum in the sulphoxide spectrum; phenothiazine, phenothiazone and thionol lying outside of this range /40,42,146,194/. This strongly implicates phenothiazine sulphoxide as the reactive metabolic species.

5.4 Other reactions

A variety of other adverse reactions have been cited in the literature and have been linked with phenothiazine therapy. These include shock resembling anaphylaxis after oral administration to a horse /195/, increased thirst in pigs /155/ and horses /46/, enteritis diagnosed at post mortem in a horse /196/, and gastrointestinal irritation in man /197/. Colicky pains, diarrhoea and constipation have also been reported together with impaction of the colon in the horse /145/.

Subnormal temperatures have been recorded in cattle /161/ and pigs /198/ and fever in man /132/ together with a scarlet rash and slight oedema about the eyes and hands /132,197/. Sores and severe dermatitis resembling scabies have been described in pigs /156,198/ and acute dermatitis with exfoliation has been reported in man /199/. Abortion in sheep /200/ and an increased incidence of stillborn lambs have also been cited /201,202/.

VI. CONTRIBUTING FACTORS

Before any general conclusions may be drawn regarding the mechanisms of phenothiazine-induced toxicity a few contributing factors which may obscure the issue should be considered.

6.1 Chemical impurities

It is quite possible that poisoning attributed to phenothiazine has been due to impurities within the preparations. In eastern Siberia during March 1955, 1350 foals were each given phenothiazine (40 to 60 g) as a prophylactic measure. Thirty of the animals became ill within two to three days and 22 (1.6%) subsequently died. During post-mortem examination an alkaloid was detected in the organs and a compound, recovered from the stomach contents, was shown to be poisonous when administered to rabbits. It was proposed that this was derived from the phenothiazine and was responsible for the poisoning, but it was not stated whether or not the alkaloid was detectable in the phenothiazine before dosing /203,204/. The possibility that the fatal compound was a plant alkaloid taken in whilst feeding must also be considered.

In another study involving horses undergoing phenothiazine treatment it was concluded that the upset in the blood picture was caused to a large extent by impurities, mainly diphenylamine /205/. Diphenylamine is employed in the synthesis of phenothiazine and is itself used topically in the treatment of screwworm infestations. Large oral doses of diphenylamine (up to 30 g) given to sheep have been shown to produce similar but more severe lesions than those occasionally found with phenothiazine /206/.

Several workers have shown that commercial phenothiazine reduces the uptake of radioactive iodine by the thyroid gland /207-211/ but did not induce hypothyroidism /212/. Blood levels of iodine increased in sheep given phenothiazine /213/ and the thyroid glands of treated animals were shown to contain nearly twice as much iodine as the glands from control animals, although there was no significant increase in the mean wet weight /214/. Such effects were not seen when purified phenothiazine was administered and it was assumed that they were due to iodine or iodide present as an impurity in commercial phenothiazine /209,211,215/, iodine being used as a catalyst in its synthesis. Other workers have suggested that another factor, much less potent than iodine, was also responsible for a slight depression of thyroid uptake of radioactive iodine, but its identity has not been stated /216/.

Other compounds, such as methylamine, may be added in small amounts (0.3 to 1.0% w/w) to phenothiazine to prevent its oxidation in bright sunlight, especially when in the presence of a finely divided inert carrier, which leads it to acquire a greenish-brown tint. A non-toxic dark green oxidation product may be present in commercial preparations (to about 1% by weight) and is thought to be a dimer of phenothiazine together with longer polymers. This can be readily removed by virtue of its insolubility in diethyl ether /14-17,194/. It is possible that trace contaminants, either remaining from the manufacturing process or being deliberately added afterwards, may contribute to the toxic reactions observed, especially as such large doses of phenothiazine are routinely given. However, adverse reactions still occur following the use of purified phenothiazine.

6.2 Physical aspects

The post-mortem finding of an impacted colon together with the many reports of constipation after phenothiazine treatment suggests that a large proportion of the dose, which may be up to 1 kg in some horses /217/, remains within the gut lumen bringing about bowel dysfunction and leading to colicky pains and other diffuse symptoms of general ill health reported in the literature /116,119,145,161/. It is also possible that a large volume of virtually insoluble phenothiazine within the colon will interfere with water reabsorption (diarrhoea has also been reported) leading to an increased thirst, as observed in pigs and horses /46,155/, dehydration in ponies /218/ and impairing urinary excretion of the drug and its metabolites, perhaps encouraging the formation of insoluble precipitates within the kidney. When lambs were subjected to a process of slow dehydration they were far more susceptible to phenothiazine toxicity (kidney lesions) than those not dehydrated and this is strongly suspected as being a factor precipitating mortality in New Zealand sheep /206,219/. Phenothiazine itself has been shown to possess a mild diuretic action and the fraction absorbed would therefore accentuate the state of dehydration /206/

6.3 Nutritional considerations

Animals suffering from infection will be in a state of general ill health before phenothiazine administration, and dietary deficiencies, whether owing to inadequate feeding in ill health or to insufficient nutriment value of fodder, especially over the winter months, may give rise to a general predisposition to toxicity /116,220/. Experience with the mass treatment of horses in the U.S.S.R. indicated that toxic reactions only occurred in stable horses during the winter months and were thus attributed to nutritional deficiencies /221/. However, this point is controversial, with some workers reporting that horses in good or fair condition are more likely to show severe anaemic reactions than horses in thin condition /222/, whereas others suggest that emaciated or aged subjects are more at risk and that a high protein diet can protect, at least in part, against the haemolytic effects of phenothiazine /117/. Indeed, one dog on a diet deficient in vitamin B experienced a greatly intensified anaemia and jaundice than that normally induced by phenothiazine treatment, although addition of vitamin B complex to normal diets did not prevent the anaemia /106/. In chickens phenothiazine has been shown to increase the deposition of vitamin A in the livers as well as increase the growth rate when added to vitamin E deficient diets containing 10% cod liver oil /223/. The significance of these latter observations and complex interactions is not known.

VII. CONCLUSIONS

For a compound that has enjoyed extensive and widespread use for more than two decades surprisingly little is known with any certainty about its mode of action. The insecticidal, antifungal, antibacterial and anthelmintic actions of phenothiazine and the production of unwanted adverse reactions presumably arise from common underlying mechanisms. The adverse reactions perhaps manifest themselves in animals which may have an environmental or genetic predisposition.

Various ways in which the phenothiazine molecule may interact with the cellular components of living systems have emerged from evaluating the available literature. The high lipid solubility of phenothiazine permits macromolecular disruption of the lipid phase of membranes, whereas van de Waals interactions allow non-specific binding to the protein phase of membranes and to functional proteins, including enzymes. The generation of two redox systems amongst the metabolites of phenothiazine permits energy transfer which may lead to gross disruption of cellular components, inhibition of enzyme function and photosensitization (phototoxicity). The formation of allergens (via previous mechanisms and photoactivation) may explain photosensitization (photoallergy) and anaphylaxis-type reactions /224-226/. Nevertheless, the picture is far from complete.

"A completely satisfactory explanation of the mechanism by which phenothiazine eliminates parasitic nematodes has defied research workers for over twenty years."

This statement was delivered at a London symposium on parasitic infection in 1962 /63/, a time when phenothiazine had enjoyed two decades as the most efficient and widely used anthelmintic known. The subsequent decline in popularity of phenothiazine therapy during the mid 1960s and its gradual replacement with less troublesome anthelmintics has meant that many of the modern investigative techniques now available have not been applied to the problem of phenothiazine's interaction with living systems. The information which is available in the literature is usually incomplete or inconclusive, especially when viewed under the light of modern scientific assessment. As a consequence, little additional information has been gleaned over the past thirty years and the position of understanding today shows little advance over that achieved in the 1960s. With the reemergence of the use of phenothiazine for resistant infestations perhaps the time is now appropriate for investigations to continue.

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