# Veterinary Arsenicals*

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Feed medication and other forms of chemotherapy in our meat-producing animals have caused heated controversies. Some of this confusion is due to both a distortion of and a lack of information. Arsenicals are some of the oldest compounds whose use in agriculture has been questioned. An attempt will be made to trace the historical use of arsenicals and to discuss their metabolism and side effects from a veterinarian's viewpoint.

Man's experiences with arsenic has, at times, been dramatic. Inorganic arsenic was notorious as a criminal poison during the Middle Ages.[9] It was easy to obtain, odorless and almost tasteless. The appetite of the victim remained good and the syndrome was not particularly diagnostic; a chronic gasteroenteritis followed by a mild nephritis and progressive neuritis. Because the old-time embalming fluids contained arsenic, once the casualty was embalmed assays for tissue residues were meaningless. Advances in the diagnosis of chronic arsenic poisoning about 1900 A.D. discouraged its use for nefarious purposes.

The classic reference to the arsenic-eating mountaineers of the Austrian Alps has been quoted and requoted until separation of fact from fiction is difficult. By taking arsenic regularly to build up strength and endurance, doses ordinarily fatal were tolerated.[9, 28] One can theorize that the tolerance was due to the oral consumption of a relatively coarse insoluble form of arsenic trioxide or the development of a more efficient excretion of any absorbed arsenic. The arsenic-eaters died just like the rest of mankind; maybe some of them died from arsenic poisoning.[22]

A famous incident of mass poisoning involved 6000 people in England in 1900.[15] Physicians in two countries observed a marked neuritis and a less prominent skin rash common to those consuming alcoholic beverages. The neuritis was at first thought to be a symptom of chronic alcoholism. The accompanying rash cast doubt on this diagnosis. Arsenic has an affinity for keratin tissue found in hair, nails, skin and in nerves where it is known as neurokeratin. The arsenic in the hair and nails was harmless because it wasn't reabsorbed; that in nerves interfered with nerve conduction causing a neuritis. The source of an arsenic-containing beer was traced to breweries who used malt high in arsenic. This contaminated beer was sold for about three years during which time 6000 topers were affected, seventy of whom died from arsenic intoxication. Subsequent legislation prevented a recurrence. Note that the arsenic-containing beer incident occurred at about the same time as the previously mentioned advances that eliminated arsenic as a criminal poison. Improved methods of diagnosing arsenic toxicity were instrumental in solving both problems.

Arsenic had a prominent place in the veterinarian's dispensary during the 1920's. The list of indicated uses was impressive: alterative, tonic, vermifuge and caustic agent for topical application. Arsenic was recommended in the treatment of dyspnea, enteritis, rickets, osteomalacia, surra, dourine, infectious anemia, trypanosomes, spirochetes and pinworms.[30] Taken internally arsenic was thought to act on mucous membranes by relaxing capillaries and increasing circulation. In this way digestion, gaseous exchange in the lung, general health and vitality were improved. Externally arsenic trioxide was a corrosive

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agent applied to remove warts and small tumors. Today caustic agents are seldom applied to tumors because viable tumor cells may be released into the blood stream causing metastasis, and normal tissue may be destroyed leaving a painful wound.

By the 1940's veterinarians were becoming more discrete in their use of arsenic.[20] With the advances in pharmacodynamics many of its former uses seemed empirical. Also the rather unpredictable toxicity of inorganic arsenic was known; for example, enteritis increased absorption and the hazard of overdosage. Organic arsenicals such as neoarsphenamine were routinely administered. The greatest value of arsenicals during this period was as insecticides and parasiticides. By 1950 antibiotics and other faster-acting and more effective drugs were replacing the arsenicals in the veterinarian's armamentarium. When used as insecticides or parasiticides arsenic compounds are converted to oxides which inactiviate sulfhydryl enzymes necessary for tissue respiration. Thus as an antiparasitic treatment arsenic (1) is ineffective in the absence of oxygen, (2) has a latent period before being active and (3) is ineffective if exogenous sulfhydryl-containing enzymes are administered.[10] The precise action of arsenic on cells is still being explored.[18]

Man cannot escape contact with arsenic. Because this element has always existed in nature, it has been ingested by past generations just as it is by today's civilized society. Arsenic is used in manufacturing glass, paints, dyes and as a wood preservative and hardener for metals. Lead shot, containing arsenic can be made harder and more spherical. The arsenic content of some common substances are recorded in Table I. Published values vary[26] because of (1) sampling errors such as failure to differentiate between urban and rural communities, (2) arsenic impurities in laboratory reagents used during the assay procedure, (3) failure to capture volatile arsenic during the assay process and (4) lack of precision in the assay methods. A literature review is inconclusive on quantitative results but not on the qualitative findings.

As the earth's crust was disturbed by mining operations the arsenic content of man's environment increased. Arsenic is present in ores mostiy in combination with sulphur and iron. Coal, oil, gas and other petroleum products contain arsenic some of which contaminates the atmosphere during combustion. Sea water is higher in arsenic at the mouth of large rivers used as shipping lanes than elsewhere. Forms of life in this water concentrate the arsenic.

TABLE I: Arsenic in Man's Environment.

| Substance Assayed | PPM Found | References |
|---|---|---|
| *Sea Food* | | |
| Oysters | Up to 1.1 | 5 |
| Clams | Up to 2.6 | 5 |
| Crabs | Up to 3.0 | 5 |
| Fishmeal | 1.4 to 7.2 | 17 |
| Lobsters | Up to 5.0 | 5 |
| Shrimp | Up to 32.0 | 4 |
| Shellfish, crustaceans | Up to 170.0 | 3, 21 |
| *Other Food* | | |
| Plants | Traces | 36 |
| Vegetables, fruits, wine | Traces | 32 |
| Milk | Up to .06 | 13 |
| *Human Body* | | |
| Blood | .02 to .14 | 14, 29 |
| Urine | .03 to .08 | 14 |
| Hair | .30 to .70 | 31 |
| Nails | 1.5 to 4.0 | 31 |
| *Miscellaneous* | | |
| Sea water | .006 to 1.0 | 33 |
| Earth's crust | 5 | 16, 27 |
| Soil | 0 to 40 | 36 |
| Tobacco | 5 to 50 | 12, 25 |
| Coal dust | 50 to 400 | 6 |

TABLE II: Present Classification of Arsenical Compounds

However, the human assimilation of arsenic from sea food is thought limited[32] because of the peculiar chemical binding. The arsenic from this source is not liberated when eaten but is excreted via the urine in a short time compared to the excretion rate of inorganic arsenic.[4] Any arsenic residues in the meat of swine receiving organic arsenicals behave similarly when consumed.[23, 24] Cereals, fruits, vegetables and even milk may have traces of arsenic both from naturally-occurring origins and from arsenical sprays used as insecticides. The soil build-up from arsenic-containing sprays is insufficient to interfere with plant life unless the application exceeds several hundred pounds per acre annually. Leaching and volatilization keep the arsenic content at less than 2 ppm, *i.e.* below levels that interfere with the growth of vegetation. The arsenic content of American tobacco increased 300% from the 1930's to the 1950's. This led to many studies on the relationship between the arsenic in tobacco and lung cancer in smokers; to date no evidence has been found that conclusively links the two. The many arsenic-containing materials around us explain why the human body also contains variable quantities.

Arsenical usage today has progressed from individual treatment to feed medication for mass therapy in integrated operations. The inorganic compounds have been gradually replaced by organic. Commonest usages are the treatment and prevention of dysentery in swine and as a poultry histomonastat and cecal coccidiostat. Arsenicals are also used to improve growth, feed efficiency and pigmentation in chickens and to prevent bluecomb in turkeys. The annual amount, in dollars, of medication used for these purposes has been estimated at: 2.5 million for hogs, actually sufficient to medicate only a small percentage of all hog feed; 2 million for broilers, about 90% of all broiler feed has arsenical medication; and 3 million for turkeys, about 20% of all turkey feed contains an arsenical. In the field of agronomy, large quantities of arsenicals are still used as weed killers and defoliants. Over 1 million acres of cotton crop are desiccated each year with arsenic acid.[1] Veterinary practitioners realize that these applications are potential hazards to livestock grazing in the area.

Table II gives a classification of some arsenical compounds in use today along with examples of each class. Inorganic arsenicals are more toxic than organic, and trivalent more than pentavalent. The most toxic compounds are both trivalent and inorganic, the least toxic are pentavalent organic. Presently, inorganic arsenicals are limited to industrial uses, herbicides and defoliants. The organic arsenicals tabulated are used as feed additives with the exception of arsenamide, a filaricide. These additives all have a structural formula containing the aromatic nucleus; only the side chains are slightly different. There is no indication that the pentavalent organic arsenic compounds are converted to trivalent prior to excretion. In fact pentavalent arsenicals are generally excreted faster and are less toxic than the trivalent ones.[2] The compounds in Table III are arranged with respect to the magnitude of their use level. The middle column contains the level of arsenic given and the column on the right contains the per cent arsenic in the compounds. If the quantity of arsenic in a drug governed the "use" level then all the values making up the middle column would

TABLE II: Present Ciassification of Arsenical Compounds

| | Inorganic | Organic |
|---|---|---|
| Trivalent | Arsenic Trioxide<br>Sodium Arsenite | Arsenosobenzene<br>Arsenamide |
| Pentavalent | Arsenic Acid<br>Lead Arsenate | Arsanilic acid, Sodium arsanilate<br>3-Nitro-4-hydroxyphenylarsonic acid<br>4-Nitrophenylarsonic acid<br>p-Ureidobenzearsonic acid |

TABLE III. Use Level Relative to Arsenic Content.

| Arsenical | Use Level (%) | % Arsenic Given | % Arsenic Drug |
|---|---|---|---|
| Arsenosobenzene | .002 | .0009 | 45 |
| 3-Nitro-4-hydroxyphenylarsonic acid | .0025 - .005 | .0007 | 28 |
| Arsanilic acid | .005 - .01 | .0017 | 35 |
| 4-Nitrophenylarsonic acid | .01875 | .0056 | 30 |
| p-Ureidobenzenarsonic acid | .0375 | .011 | 29 |

case nor are the values in the right-hand column arranged in order of magnitude. Therefore, one may conclude that the arsenic content of an organic arsenical is not an accurate estimate of its use level. Rate of excretion is important in establishing the safe use level.[2]

Large animal veterinary practitioners giving counsel on feed medication should have some knowledge of two publications available from the Miller Publishing Company, Minneapolis, the *Feed Additive Compendium* and *Feedstuffs*. The former gives government approved feed additives, their legal use levels and recognized claims or indications for use. Also given are withdrawal periods and the names of companies that market the approved additives. Many arsenical combinations with antibiotics may be legally used according to this compendium. *Feedstuffs*, published weekly, carries current news on nutritional and disease research, FDA (U.S. Food and Drug Administration) regulations, changes in employment or rank of important professional people, and changes in ownership or management of agriculturally-oriented drug and chemical firms. Both of the above-mentioned publications are semi-technical.

Because arsenic is ubiquitous in man's environment, criteria are necessary to indicate when the intake is high or low. These act as guidelines in detecting accidental arsenic toxicosis. Table IV lists some of the approved levels. The U.S. Public Health Service has set drinking water tolerances. The FDA has set tolerances for various food products. It is not known whether arsenic is necessary for life. Under certain circumstances the addition of arsenicals to the diet is beneficial, especially in poultry production. Arsenicals reduce selenium toxicity in seleniferous areas.[8, 31, 34, 35] As indicated in Table IV, arsenic-free purified diets are not available. Low arsenic diets contain 0.02 to 0.1 ppm of arsenic.[7] Aquatic plant and animal life, necessary to consume decomposition products in water keeping it clean and fresh, thrive well at 2 to 4 ppm.[32] Eight ppm definitely interfere with this "self-purification" of water. In Argentina there is at least one area with natural water containing enough arsenic to cause poisoning if continually consumed by man;[31] no adverse effect on aquatic life is recorded.

Organic arsenicals were fed to farm animals for two weeks or longer after which they were slaughtered and their livers assayed for arsenic using a slight modification of Winkler's method,[37] see

TABLE IV: Tolerated Arsenic Levels in PPM

| | PPM |
|---|---|
| Drinking water for man | .01 - .05 |
| Fruits and vegetables (3.5 ppm $As_2O_3$) | 2.66 |
| Meat | .5 - 1. |
| Poultry: muscle | .5 |
| eggs | .5 |
| edible by products (liver, kidney) | 1.0 |
| Cottonseed meal | 3.0 |
| Purified lab diets | .02 - .1 |
| Self-purification of water | 2.0 - 4. |

TABLE V: Liver Arsenic Levels (PPM)

| Drug | Level | Species | Residue |
|---|---|---|---|
| 3-Nitro | 0 | Swine | 0.34 |
| 3-Nitro | 10 | Swine | 0.53 |
| 3-Nitro | 100 | Swine | 2.45 |
| 3-Nitro | 200 | Swine | 2.38 |
| 3-Nitro | 450 | Swine | 2.80 |
| 4-Nitro | 0 | Turkeys | 0.35 |
| 4-Nitro | 1875 | Turkeys | 2.94 |
| 3-Nitro | 0 | Chickens | 0.29 |
| 3-Nitro | 50 | Chickens | 1.50 |
| Arsanilic acid | 0 | Laying hens | 0.07 |
| Arsanilic acid | 100 | Laying hens | 0.86 |
| Arsanilic acid | 200 | Laying hens | 0.07 |

Table V. Recommended use levels in ppm are 25 to 50 for 3-Nitro, 187 for 4-Nitro and 50 to 100 for arsanilic acid; in each instance experimental levels equal to or above the "use" levels were fed. The swine fed 200 and 450 ppm and the turkeys receiving 1875 ppm were incoordinated (overmedicated) at the time of slaughter yet their liver levels of arsenic were less than 3 ppm. Thus one cannot base a definite diagnosis of arsenic poisoning on a tissue analysis for arsenic. In 1964 a news release[19] stated that all pork liver marketed in the USA has up to 7 to 8 ppm of arsenic. Certainly the liver would contain more than any other edible body tissue but the quoted levels seem high. A USDA inspector reported in 1965 that the results from 1000 liver tissue samples assayed for arsenic indicate good compliance with legislation including the withdrawal of medication prior to marketing.[11] According to the data in Table V, arsenic does not build up beyond a certain level before morbidity occurs. Antemortem inspection would prevent the slaughter of such individuals for human consumption.

The organic arsenic overmedication encountered today differs from the inorganic arsenic poisoning once seen by practitioners. There is no severe enteritis and accompanying paralysis with the former as with the latter. The symptoms of chronic organic arsenical toxicity are a characteristic stiffness progressing to incoordination (of the hind limb in hogs). The condition is more often seen in cold weather when the water intake is at a minimum; however, it can occur whenever the arsenic content of the feed is too high as in the feeding of two arsenicals simultaneously or in mixing errors. The appetite remains good unless the incoordination prevents access to feed and water. Urine analyses are reliable only if repeated at intervals because the elimination of arsenic may be spasmodic. At necropsy a mild nephrosis may be noted.

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# Book Review

Dr. William G. Magrane, well-known lecturer and canine eye specialist, brings forth a new text for the veterinarian interested in problems of the eye.

The first chapter provides a good review of the normal eye including its general anatomy. This is followed by an excellent chapter on examination procedures of the eye and its related structures. Succeeding chapters discuss eye therapy, problems of the lids and lacrimal apparatus and the diagnosis, therapy and surgery of the lens, and the relation of the eye to systemic diseases. Each chapter is systematically organized, well referenced, and abundantly illustrated. The author includes over one hundred fifty figures, many of which are published in color; in general their quality is excellent although a few pictures are lacking either in observable detail or clarity of description. Two valuable indices are also included—one on breed predisposition of eye conditions and another on the use of adrenal steroids in eye therapy.

Although many veterinarians are not trained in intraocular surgery, this book describes several simple extraocular procedures that could prove useful to any canine clinician. The occurence of common, minor problems in practice makes the section on therapy very useful.

*—Robert E. Froehlich, '66*

(Canine Opthalmology, 1st. edition August 1965, by William G. Magrane. 240 pages; illustrated—75 in color. Lea and Feabiger, 600 S. Washington Square, Philadelphia, Pa. Price: $18.00.)