Lead Poisoning from Retained Missiles
An Experimental Study

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The problem of lead poisoning from bullets has been investigated by surgically implanting discs of lead, each enriched in a different natural isotope, into the tissue of two mongrel dogs and monitoring by mass spectrometry the release of the lead into each animal's blood over the course of 3 years. Lead placed in the knee underwent vigorous attack by the synovial fluid, far in excess of what would be expected from corrosion theory, and reached a maximum concentration in blood 4–6 months after operation. Thereafter, lead concentration exponentially declined as the remaining fragments became encapsulated. The disc placed in muscle was sparingly soluble immediately following implantation. It is concluded that the greatest danger of lead poisoning from an injury involving many fragments having collectively a large surface area will occur within a month, and that the cases of lead poisoning resulting from bullets in joints that occur 5 or more years after injury are caused by continual wear of metal on a joint surface, storage of lead so released in the skeleton, and its subsequent resorption during a change in osteocyte activity.

By virtue of its insidious and nonspecific clinical symptoms, lead poisoning can be difficult to diagnose. Lead poisoning from retained bullets is not only rare but it is also unpredictable—the interval between injury and manifestation of toxic effects vary between 2 days and 40 years.1,2 Understanding the pathogenesis of this particular form of plumbism obviously lies in uncovering the basic mechanisms, but only two attempts at experiment have been carried out, one in 19173 and the other in 1969.4 Both were hampered by the unavailability of accurate means of measuring lead in tissue.

With the advent of improved methods in the analytical chemistry of trace metals, the following study was designed to investigate the temporal relationship between the placement of a known lead source and its release into the circulatory system. The study was also designed to compare the absorption of lead from a joint space with that from soft tissue.

Materials and Methods

Two 20-kg conditioned mongrel dogs were obtained from a commercial kennel and were kept in the animal care facilities of the University of Texas Health Science Center for 3 months for baseline measurements of blood lead concentration and isotope ratio.

Lead carbonate, 99% enriched in 206Pb, was purchased from Oak Ridge National Laboratory and was reduced to the metal by heating in an atmosphere of hydrogen. 206Pb, 92% enriched, was obtained in wire form from the National Bureau of Standards as Standard Reference Material 983. One hundred mg of each was melted between slabs of graphite and pressed into subcircular discs about 6 mm in diameter, each having a surface area of about 0.5 cm². The right knee of each dog was surgically opened and the disc of 206Pb was pierced and attached to the synovium by a suture. The disc of 208Pb was placed in the vastus medialis muscle.

Up to 30 ml of blood was periodically drawn from each dog and was analyzed for lead concentration and lead isotope ratios. Details of the experimental techniques have been published elsewhere.5 A series of roentgenograms of the joints was also made.

From the measurements made of concentration and isotope ratio, it is possible to calculate the concentration of lead in blood attributable to each implant, provided that the endogenous component of lead in blood has remained constant in isotope ratio. By endogenous, we

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mean dietary lead plus lead resorbed from soft tissue and skeletal stores that are normally present in blood. This assumption is justified below.

Mass spectrometry has a distinct advantage over conventional techniques that detect only changes in blood lead concentration, because the relative contribution of each labeled source can be measured irrespective of overall changes in blood lead concentration.

**Results**

The blood lead concentration data for each dog are given in Table 1. Blood lead concentrations produced by the endogenous lead and by the implant in the knee are plotted in Figure 1. The concentration of endogenous lead in the blood of each dog fell steadily during the course of the experiment as previously acquired stores of lead in soft tissue and bone were excreted, presumably the result of the animals being housed in relatively clean conditions and being fed only dry food. This decrease is of prime importance as it demonstrates that most of what we have called endogenous lead is truly endogenous and may be assumed to have isotopic ratios identical to those obtained in the baseline measurements, thus validating our calculations.

The release of lead from the implant in the knee was immediate, and its contribution to the blood increased rapidly in each animal until 120–180 days after operation when the curves peaked and began an exponential decay, reaching a steady state 2 years after operation. By contrast, the contribution of lead from the implant in the thigh was very small except in the first measurements made 30 days after operation (Table 1). In both dogs, however, there was an exponential decline in concentration suggesting that quantity of lead in blood had its greatest value shortly after operation. The first roentgenograms were made 6 months after operation and showed that the implants in the knees had completely disintegrated into a number of particles with corroded outlines. Subsequent roentgenograms showed little change in the appearance in the joint, and most of the same particles visible in the first roentgenogram had changed neither shape nor position over the course of 2 years. No change was apparent in the implants placed in muscle, and they still retain the characteristic shapes they had when first implanted (Fig. 2).

**Discussion**

No true animal model of lead poisoning exists because all mammals possess in the sulfydryl bonds of the protein of their fur a large lead sequestering pool that is lacking in humans. As a result, an animal clears lead from its blood far more rapidly than do humans, or, put another way, an increase in lead intake will effect a far larger change in blood lead concentration in humans than will the same increase in an animal. In interpreting the results of our experiments, it is not the absolute concentrations that are important but rather the shape of the lead release curves.

From the shape of the curve for the disc placed in the knee, it is clear that the release of lead is controlled by two antagonistic processes, an initial one of rapid translocation to blood followed by an inhibitory process that, after 3 months, reverses the first process and almost completely shuts it down over the next 12 months. From the roentgenograms, the first process is one of vigorous attack
The dissolution of metals in the neutral, saline environment of the body has been compared to corrosion in oxygenated seawater. Whereas this generalization may be true for the ferrous metals, it does not hold for lead, which has high resistance to corrosive attack by seawater, losing less than 10 μm from its surface per year in tropical waters. Lead, however, is dissolved by organic acids. Thus, we suspect that hyaluronic acid with a concentration of about 3 g/L is the agent responsible for its dissolution in synovial fluid. Another fact that sets the process of dissolution in the body apart from electrolytic corrosion is the production of lead dioxide, which cannot occur in neutral solutions in the absence of an external voltage.

Machle reviewed the literature on lead poisoning from bullets up to 1940 and of 35 first-hand accounts believed that only 10 indicated intoxication, whereas another 13 indicated increased lead absorption. Our criteria for lead intoxication have changed over the years and today any abnormal absorption is a matter for concern. Unfortunately, Machle does not list which cases comprised the 13 indicating absorption. Bearing in mind that lead poisoning was a far more common clinical entity before 1940 than it is today and that the chances of a clinical diagnosis being correct were probably higher then than now, we have taken 32 accounts as valid diagnoses and excluded only those where the criteria were specious, such as lead in cerebrospinal fluid, or unlikely, such as systemic lead poisoning arising from a bullet in the brain.

In compiling Figure 3, which shows the time elapsing by the synovial fluid, which was sufficient to reduce the solid metal disc to a number of disaggregated particles within 6 months. The agent responsible has not been identified. We did not investigate the nature of the inhibiting agent by opening the joint at the end of the experiment, but there is good reason to believe that it is encapsulation, a process that was noted by Leonard who, like us, placed lead slugs in the joints of dogs.

We believe that the presence of lead from the disc placed in muscle in the blood of both dogs at 1 month signifies that lead placed in other tissue is also soluble until such time as it is encapsulated.
between injury and appearance of toxic effects, we have used Machle,1 the review of Dillman et al.,2 and the cases recently described by Cagin et al.,10 Switz et al.,11 and Linden et al.9 Shotgun wounds dominate the cases that occur within 1 year of injury, as already noted by Dillman et al.2 the 100-mg discs that we implanted are virtually the same weight (105 mg) as pellets of No. 7 shot (No. 6 British), the favored size for use against game birds. The normal 12-gauge load of 11/2 oz of this shot contains 287 pellets, having collectively a surface area of 61 cm²; thus, a shotgun wound could bring about 100 times the increase in blood lead concentration that we observed from the disc implanted in muscle. It must be remembered that this observation was made after 1 month, and we are ignorant of the shape of the lead release curve before that time. If it passed through a maximum, the release of lead could well be great enough to cause intoxication, and we would expect most cases of plumbism of this type to occur within 1 month of injury. There are three such cases in the literature. Van Rossem and Vlaardingerbroek12 observed colic and elevated blood lead in a man 2 days after a shotgun wound to the thigh. Nimier and Laval13 reported colic and a lead line 4 weeks after injury with 1.5 g of No. 9 shot (approximately 30 pellets). Roentgenograms showed clearly the infiltration of lead into the palmar aponeurosis. Curtillet and Lombard14 reported a man who died 12 days after a shotgun wound to the forearm. Diagnosis was based on colic, basophilic stippling, anemia, and possible encephalopathy. Clear evidence of lead poisoning is lacking in these cases, however. Other cases, even though comprising injury by 100 or more pellets, are reported manifesting themselves after several months.15,16

Our experiment predicts that the greatest danger from a projectile in a joint occurs 4–6 months after injury, yet there are only three cases described in which lead poisoning occurred within 12 months—Londres17 reported a man with a bullet in the knee, who developed the full range of symptoms after 2 months; Ranelletti18 reported a man shot in the knee, who also developed the full range of symptoms after 9 months; and Linden et al.9 reported a woman with a bullet in the knee, who died 5 months after injury. It is curious also that the military surgeon of the First World War, although familiar with the cloudy synovial fluid and the gray-stained synovium resulting from bullets in joints, did not record cases of plumbism or even comment on its possibility.19 The explanation may be that the joint space is a relatively small volume and, although dissolution of lead proceeds rapidly, the size of the projectile that can be lodged in a joint is seldom large enough to yield toxic concentrations before the process of encapsulation takes over.

After 12 months, little lead is released from the joint space, a fact commensurate with the paucity of cases reported between 1 and 5 years. The majority of cases occur after 5 years, and, remarkably, many are associated with a projectile in a joint space. We note that in our experiment the dogs were confined in cages, and we purposely investigated only the effects of chemical attack on the lead. If we had exercised the animals, it is possible that metal particles could have become caught between the opposing surfaces of the joint and the protective encaps-

![Figure 3](image-url)
sulating tissue worn away as quickly as it tried to grow. Many workers have remarked on the worn, polished appearance of bullets found in joints.\(^1,11,20,21\) Such continuous wear may also give rise to the fine radiopaque particles of lead dioxide, absent in our work, that are dispersed through the synovium and highlight the joint space on roentgenograms.

Continuous dissolution of a bullet fragment by the synovial fluid will cause a constant flow of lead out of the joint into blood, which, combined with the logarithmic clearance of lead from blood,\(^22\) will cause the blood lead concentration to rise to some steady-state value. If this value is below the threshold at which clinical symptoms of plumbism appear, the patient could live without ill effect indefinitely. To explain the sudden onset of plumbism, some authors\(^2,10\) have invoked the release of lead from bone as a result of a change in osteocyte activity. The hypothesis is an attractive one, as it has been shown that lead derived from bone may dominate blood lead,\(^23\) and, in plumbism, bone lead may be 50 times greater than values encountered in individuals without excessive exposure.\(^9,10\) Three different states may be recognized:

1. Osteoclast activity remains constant but osteoblast activity diminishes. This condition is not a diseased state but occurs naturally with advancing age or bed rest.\(^24\) More lead is resorbed from bone than can be redeposited in new bone, and the blood lead concentration increases. Cases involving elderly patients\(^25\) or patients who had been incapacitated shortly before the onset of plumbism\(^11\) may fall into this category.

2. Osteoblast activity remains normal but osteoclast activity increases, as in hyperparathyroidism. Although it is a very obvious condition, in which blood lead levels should rise, no cases are reported.

3. In certain physiologic states, the activity of the osteocytes may be greatly increased. Whereas this condition gives rise to increased turnover of bone, the plasma calcium is in no way affected, because as much calcium as is being resorbed is being used again to make new bone. About 40% of the lead so released, however, is bound by the red cells and enters the blood pool from which it is cleared with a half-life of about 24 days.\(^22\) The result is an increase in blood lead concentration. Pregnancy is a natural state in which bone turnover increases, and we note that one of the patients described by Lindem et al.\(^9\) gave birth to a stillborn child 15 months after sustaining a wound to her right shoulder and thereafter progressively deteriorated. Diseased states include thyrotoxicosis, Paget's disease, sarcoidosis, and neoplasias. Of these, only the first has been implicated.\(^10\)

Certain cases of plumbism are not explained by the mechanisms outlined above. We recognize two: a slow infiltration of lead into the surrounding soft tissue and the formation of a fluid-filled cyst. There is one very well documented example of the first case, where lead from a bullet adjacent to the greater trochanter of the femur diffused for a distance of 8–10 cm into the surrounding tissue over the course of 4 years.\(^26,27\) Here, for some reason, the encapsulation process had failed to take place. Two very similar examples of cyst formation are described.\(^9,27,28\) In each, bullets were lodged in the L3–L4 region and seemed to connect with the joint space. Over the period of 12 years in one example and 24 years in the other, the bullet became surrounded by a cyst-like process filled with a viscous fluid containing many finely divided particles of lead dioxide. The underlying cause of the dissolution is not known, but alcoholism may have been an intercurrent factor in one case.\(^9\)

There can be little doubt that the danger of plumbism is not widely recognized in English speaking countries. In the British literature, no report exists, and, in the American literature, there was no report between 1879 and 1940, whereas, from 1900 to 1939, five reports appeared per decade in French and German literature. Macle's review did create some interest in the problem and resulted in the appearance of a number of papers in American journals (Fig. 4), but his contribution has to some extent been forgotten in recent years. Although the majority of the cases in the literature date from more than 50 years ago, the problem cannot be considered irrelevant at the present time. In 1976, 31,000 deaths from gunshot wounds occurred in the United States, and nonfatal injuries may have amounted to three times that number.\(^29\)
As there is no reason to believe that these figures would be any less today, the probability for cases of this particular form of lead poisoning to occur exists and may occasionally be overlooked.

Conclusions

From the results of this study we conclude: (1) The solubility of lead in body fluids cannot be accounted for by corrosion theory and is brought about by other as yet unidentified processes. (2) A shotgun wound involving many pellets having a large surface area has the greatest danger of lead poisoning within a month of injury. Blood lead concentrations should be frequently monitored and chelation therapy used, if necessary, to keep blood lead concentration from rising to toxic levels. (3) A missile lodged in a joint space will be subjected to immediate attack by the synovial fluid, and blood lead concentration may rise to a peak 4–6 months after injury, provided that the encapsulation process is not interrupted by wear. In view of the well-documented risk of foreign body arthritis, missiles known to be in the joint space should be removed. If there is any question of a lead fragment being in a joint, it can be answered by making serial measurements of blood lead concentration. If the concentration continues to rise after 1 month, the bullet may be presumed to be in the joint space and undergoing solution. (4) Between 1 and 5 years, there is little chance of lead poisoning. It would seem prudent, however, to have a roentgenogram or a blood lead concentration measured 1 year after injury. (5) Accurate measurements of blood lead levels are difficult to make and reliability of a laboratory has been impossible to assess. Recently, however, the National Bureau of Standards has made available certified blood standards that can be used to check a laboratory’s performance.

References

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