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## Editorial Views

# *On the Fate of Chloroform*

It is well-known that the volatile anesthetics are metabolized by several mammalian species, including man.[1] Typical experiments in this area have been designed to find that percentage of a given dose converted to $CO_2$ and/or urinary metabolites within a given time. However, studies have not been designed to answer the question of how much of the anesthetic, if any, remains in the animal, and in what form, and changes in the distribution of anesthetic and metabolite that occur with time. Dr. Ellis Cohen and Miss Nancy Hood have attempted to answer these and other questions. Some of their results are reported in this issue of the Journal. They have applied the relatively new technique of low-temperature autoradiography to a study of the distribution of chloroform and its metabolites. This has produced some interesting results and, hopefully, will be the start of a very rewarding series of reports.

The results indicate that chloroform is converted to a metabolite, which in itself is not surprising, but that this metabolite accumulates in the liver is of extreme interest.

Anesthetics as a rule are lipophilic, and tend to accumulate in lipophilic sites such as cell membranes; this is the case with chloroform, as the authors point out. Following the initial accumulation in the fat depots, the anesthetic is redistributed. In this process some moves to the liver, where it is biotransformed to a product which is more water-soluble and, therefore, more easily disposed of by the excretory system. One of the factors controlling the rate of movement from the storage sites is the rate of biotransformation. Therefore, the product of the metabolism under usual conditions does not accumulate in the liver but is readily excreted. Chloroform follows the pattern, in that it is converted to the readily-disposable $CO_2$ and certain urinary products. However, the compound deviates from this pattern as a source of an additional product which apparently is not easily removed from the liver. Perhaps a review of the ways in which chloroform behaves chemically and biochemically will yield some clue as to why this product accumulates as the authors have found.

It must be kept in mind that chloroform is different from other volatile anesthetics in terms of chemical stability. Chloroform is base-unstable and, since the biological system is slightly basic, there is an opportunity for this instability to manifest itself. Thus chloroform can be decomposed oxidatively or reductively as a result of interaction with base

Chloroform also reacts readily with amines and sulfhydryl groups (and other nucleophylic sites) in proteins and other biological constituents, resulting in the release of inorganic chloride and either the binding of the remaining dichloromethane to these groups or the further chemical degradation of the dichloromethane molecule. Chloroform also has been shown to react with the cobalt in vitamin $B_{12}$.[2] This is a reaction similar to that which occurs with the amines in which the chloroform releases a chloride and the resulting dichloromethane radical binds to the cobalt. Another type of transformation of chloroform is one which could be termed oxidative breakdown. In addition to inorganic chloride, this yields such products as $CO_2$ (a direct conversion), formaldehyde or formic acid.[3] The latter two can go directly to $CO_2$ or may be incorporated into certain normal biological constituents, then oxidized, eventually, to $CO_2$.

From this description it is apparent that there are several ways that chloroform may be chemically altered:

1. Oxidative dechlorination:
   a. $CHCl_3 \rightarrow HCHO$ or $HCOOH + Cl^-$
   b. $CHCl_3 \rightarrow CO_2 + Cl^-$
2. Reductive dechlorination:
   $CHCl_3 \rightarrow CH_2Cl_2 + Cl^-$
   or $CH_3Cl$
3. Reaction with nucleophils:
   $CHCl_3 + R \rightarrow R - CHCl_2 + Cl^-$
   $(R = -NH_2, -SH,$ etc.)

It is not clear at present what contribution enzymes make in facilitating the above reactions. Each reaction could proceed in the absence of enzymes. However, the presence of living tissue does facilitate the reactions. Since reaction 3 is that which would result in the accumulation of isotope in the liver, most of the emphasis should be placed on this with respect to the authors' findings. The mechanism of this reaction is not clear, but several hypotheses have been proposed, most of which involve an intermediate radical such as $\cdot CCl_3$ or $: CCl_2$. While these radicals have not been isolated, it is known that the free radical concentration in the liver rises following dosage with chloroform. It is this radical intermediate which would bind to the cell constituents, thus showing an unusual accumulation of isotope. Furthermore, there are indications that this binding is produced enzymatically, but it is not clear if the enzyme is producing the radical, which is then free to bind, or transfers it to a receptor site such a described above.

As the authors pointed out, this metabolite is probably an important factor in the toxicity of chloroform and, therefore, it is essential to discover its identity. This article by Dr. Ellis Cohen and Nancy Hood contains some very fine and interesting results, and I believe that much will be gained by continuing this work and expanding it to include other anesthetics.

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