dose to rabbits. Such a control is maintained over mercurosal and is practically as necessary as the present government supervision of the manufactured lots of the arsenical compounds, arsphenamine and neo-arsphenamine.

Data relative to elimination, tolerance, and effect upon the kidney will probably be presented in another article.

In order to show that mercurosal is not affected by contact with alcohol (pure or denatured), ether or aldehydes, an experiment was conducted in which small portions of the same lot were treated for several hours with warm 95% alcohol, warm denatured alcohol, ether, and alcohol containing a large amount of aldehydes, respectively. The control and treated portions were tested for immediate toxic action upon rabbits and the average of several tests of 2% solutions of each was as follows:

Sample.	Immediate lethal dose.
Control	0.0271 Gm. per Kg.
Treated with denatured alcohol	0.0323 Gm. per Kg.
Treated with pure 95% alcohol	0.0348 Gm. per Kg.
Treated with aldehyde	0.0324 Gm. per Kg.
Treated with ether	0.0360 Gm. per Kg.

The results of this experiment are not as consistent as might be desired but considering the limit of error of a physiological test agree well enough to indicate that there was very little difference in toxic action in the samples and particularly that the treated portions were not more toxic than a portion of the same lot which was not treated experimentally.

CONCLUSIONS.

1. The toxicity of mercurosal is not affected by contact with alcohol, ether or aldehydes.

2. The wall of the vein is not injured by repeated intravenous injections of 2% solutions of mercurosal.

3. Mercurosal is approximately one-fifth as toxic as some other salts of mercury such as the bichloride, iodide, salicylate or succinimide even when equivalent mercury content is considered.

FROM THE
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A NEW ASPECT OF THE TOXICOLOGY OF ARSENIC.*

BY E. W. SCHWARTZE.†

This report deals with the toxicology of white arsenic (arsenic trioxide U. S. P. or arsenious oxide), and places a newly recognized responsibility upon the prescriber, the manufacturer and the dispenser of this substance in the undissolved form. Although it is customary to administer arsenic trioxide dissolved, it is at times prescribed undissolved, in which state the potency varies to a marked degree,

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depending upon the fineness of the preparation. It is easy to find preparations $^1/_5$ to $^1/_8$ as toxic (lethal dose method) as dissolved arsenic.[1]

The variation in toxicity correlates well with the observation in the chemical laboratory, that the rate of solution in water is very slow and the amount of this substance which dissolves is to a great extent dependent upon the fineness (surface of the arsenic particles exposed to the solvent). Moreover, particles of intermediate sizes adhere to mucous membranes and produce ulcers. Larger ones, however, presumably because of their bulk, are easily pushed down the intestine. Very small particles probably entirely dissolve before any or much damage is done to the intestine or stomach mucosa. These facts agree with the experience of pathologists who frequently, in case of delayed death from undissolved arsenic, find particles adhering to an inflamed intestine and stomach, sometimes long after burial.

Although in many cases preparations of arsenious oxide containing medium-sized particles (approximately 0.3 mm. in diameter) may be administered to animals in doses ordinarily just sufficient to produce vomiting without causing death, this is not always true. Death has resulted because of the retention of particles of arsenic on the mucous membrane, with the production of local ulcers. In this case the poisoning from a single dose was continuous over the course of days. The arsenic was probably absorbed chiefly through the ulcerated areas adjacent to adhering particles.

The obvious ideal remedy for these dangers is to discontinue the internal administration of undissolved arsenious oxide, inserting a suitable notice to this effect in the new U. S. Pharmacopœia. Probably the most effective remedy at present, since the deletion of this drug would not necessarily stop its internal use, would be to include in the new Pharmacopœia a requirement defining a certain degree of fineness. The large manufacturing houses could readily conform to this. The pulverizing, however, had better not be attempted without the use of adequate industrial equipment.

Dissolved arsenic is now administered in increasing doses until the therapeutic effect is obtained. Coarse preparations of the undissolved material require somewhat larger amounts, the administration of which is dangerous because the retention of particles in the stomach and intestine cannot be controlled. If arsenic trioxide of extreme fineness (0.0125 to 0.0025 mm.) is required by the U. S. Pharmacopœia, the difference in potency between this and the dissolved arsenic could be neglected.[1] Under these circumstances the ability of the patient to use relatively large doses would not be confused with the question of acquired tolerance. Moreover, it does not appear to be common knowledge that the potency of undissolved "arsenic trioxide U. S. P." is not uniform.

To make sure that this matter at present is absolutely uncontrolled, it is necessary only to examine numerous preparations of arsenic trioxide on the drug market labeled "powdered." The sizes of the particles vary; some have never been ground. Dental preparations which contain arsenic and which are used for killing nerves also vary. Some show the most perfect crystals, which apparently have never been in the mortar or the ball mill. Pills have not been examined,

[1] Preliminary communication in *J. Pharmacol. and Exper. Therap.*, 19, 258, 1922. The detailed report appeared in the same journal, 20, 181, 1922.

but, judging from experience in grinding arsenic trioxide, the particles contained in a single preparation probably vary greatly in size, because of the relatively short grinding to which the materials may have been subjected.

The recommendation herein made is consistent with the policy of raising the standard for drugs. It is important in the medicinal use of undissolved arsenic trioxide and will only slightly increase the work of the manufacturing pharmacist.

This subject is not without some importance to legal medicine and casts an interesting reflection on some medical logic. It has long been believed that the "Arsenic Eaters" of Styria (Austria) become immune to the effects of arsenic. It does not appear, however, that the toxicity of the arsenic which is eaten has ever been tested. Instead of an immunity of the individual to the arsenic, the arsenic is relatively impotent, according to the extent to which it remains undissolved. Since an absolute amount of one preparation representing a fatal dose is not a criterion of the lethal dose of another preparation, as has heretofore been assumed, habituation to arsenic may be said to have never been proved.

DISCUSSION.

Drs. Fantus and Viehoever emphasized the importance of these findings.

Dr. Fantus suggested that the discrepancies in the administration of calomel might also be explained by differences in the fineness of different preparations.

ISOLATED UTERUS ASSAY FOR PITUITARY EXTRACT.*

NOTES ON METHODS OF ELIMINATING SOME DIFFICULTIES ENCOUNTERED WITH THE ABOVE METHOD. (SECOND PAPER.)

BY PAUL S. PITTENGER AND ARNOLD QUICI.

The various laboratories interested in the assay of pituitary extract have used the Isolated Uterus Method with varying degrees of success.

Some workers report this method to be by far the best proposed, while others report that they have found it entirely unsatisfactory.

One of the authors has used this method continuously for the past ten years, and the other for the past six years, and both are of the opinion that it is by far the best which has been proposed for the standardization of pituitary extract as differences of activity which are only just appreciable by other methods are at once obvious in the test on the isolated uterus.

Our experience, however, has proved that satisfactory results cannot be obtained with this method unless all conditions are ideal.

The presence of minute amounts of impurities in the distilled water or chemicals used in preparing the Locke solution will destroy the sensitiveness of the uterus. Bacterial contamination of the Locke solution will poison the uterus and make it impossible to obtain concordant results.

Variations in the temperature of the solution and the amount of muscular tissue present in the uterus are also factors of prime importance.

The many criticisms of the isolated uterus method to the effect that it gave unsatisfactory results, without stating in what way the method was unsatisfactory, or suggesting means of improving it, led us to the opinion that in many cases these

* Read before Scientific Section, A. Ph. A., Cleveland meeting, 1922.