the reactions. In no case did the control Fractions A, B and C, give a positive reaction with 1-500 dilution. The results present at the most only slight and probably insignificant differences in reactivity between the 3 preparations, whether phenol was used in the preparations (Fractions A and C) or was completely absent (Fraction B).

The skin test results are in contrast to the comparative complement-fixing activities of Fractions A and B with a titer of only 1-200, and Fraction C, with a titer of 1-3200, constituting a 16-fold enhancement.

Summary. 1. Saline suspensions prepared from yolk sacs heavily infected with the virus of *Lymphogranuloma venereum* and inactivated with 2% urea or 0.5% phenol constituted satisfactory diagnostic skin test antigens in high dilutions.

2. Yolk sac suspensions treated with phenol so as to enhance their complement-fixing activity 16-fold were not appreciably more active as skin test antigens than urea-treated suspensions.

15813 P

Trypanocidal and Spirochetocidal Compounds Derived from BAL and Organic Arsenicals.

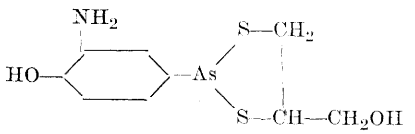
ERNST A. H. FRIEDHEIM AND HENRY J. VOGEL. (Introduced by M. B. Sulzberger.)

From the Laboratory of E. A. H. Friedheim, New York City.

This study is part of an investigation of the chemotherapeutic activity of organometallic compounds as affected by chemical combination with dithiols.

War research has brought out the fact that BAL (British Anti Lewisite, 2,3-dimercaptopropanol) protects man and experimental animals against the toxic effect of organic arsenicals, including 4-arsenoso-2-aminophenol (I), *i.e.*, oxophenarsine U.S.P., and counteracts *in vitro* the trypanocidal effect of this drug.[1-3]

The limited information published to date (February 18, 1947) suggests that the compound resulting from the condensation of I with BAL, *i.e.*, 2-amino-4-[methylol-(ethylenedimercaptoarsino)]-phenol (II)



(II)

would be significantly less toxic than its parent substance (I), but devoid of chemotherapeutic activity.

With a view to evaluating this proposition, we have synthesized (II) and tested *in vivo* its trypanocidal and spirochetocidal activity.

(II) crystallizes from methanol as white needles, soluble in propylene glycol and dilute hydrochloric acid, insoluble in water and anhydrous acetone. It gives a negative nitroprusside reaction at pH 8, positive at 10.

Analysis:

Calcd. for $C_9H_{12}O_2NS_2As$:	N 4.59,	As 24.6
Found:	N 4.52,	As 24.0
	4.49	24.8

(II) forms a crystalline hydrochloride (III), soluble in water, ethanol and propylene glycol, insoluble in anhydrous acetone.

Analysis:

Calcd. for $C_9H_{13}O_2NClS_2As$:	N 4.11;	As 22.0
Found:	N 4.10;	As 21.2

The free base (II), and more so its hydrochloride (III), are quite stable. Propylene glycol solutions of the hydrochloride may be sterilized by heating for one hour at 100°.

(III) cures the experimental *T. equiperdum*

[1] Peters, R. A., *Nature*, November 24, 1945.

[2] Waters, L. A., and Stock, C., *Science*, 1945, **102**, 601.

[3] Sulzberger, M. B., and Baer, R. L., *J. Am. Med. Assn.*, 1947, **133**, 293.

infection of the mouse with a single intraperitoneal dose of 0.02 g/kg, while the maximum tolerated dose, intraperitoneally, was found to be 0.12 g/kg, corresponding to a therapeutic index of 6. The immediate spirochetocidal effect of (II) was screened in rabbit syphilis: 16 animals with fully developed, dark-field positive chancres were treated with a single subcutaneous injection of (II) dissolved in propylene glycol in doses ranging from 2.5-40 mg (.0008-.013 g/kg). In all animals treated with doses equal to or greater than .006/kg the spirochetes were not demonstrable 5 days after the treatment. As to toxicity, a single intramuscular dose of .05 g/kg is well tolerated while .08 g/kg is lethal.

It follows from these experiments that the condensation product of a chemotherapeutically active arsenical with BAL may result in a new compound combining relatively low toxicity with a significant trypanocidal and spirochetocidal activity.

Similar results, to be reported in a forthcoming publication, have been obtained with analogous BAL derivatives of other aromatic arsenicals as well as with aromatic antimony compounds, including arsanilic acid, tryparsamide, carbarsone, stibanilic and acyl stibanilic acids.

Hence, in a general manner, inclusion of a phenyl substituted arsenic or antimony residue in a 5-membered sulfur-containing ring as in (II) is not incompatible with a significant chemotherapeutic activity.

The new BAL compounds seem of more than theoretical interest in view of their stability and solubility properties. As a group they are more soluble in nonaqueous solvents than the parent organometallics, a fact which may well have repercussions on their chemotherapeutic spectrum. The solubility, and consequently, the distribution within the organism, may readily be modified by replacing the BAL radical in the above-mentioned compounds by other dithiols, such as 2,3-dimercaptopropionic acid, BAL ethers, BAL glucoside, 1,2-dimercaptobenzene, etc.

The mechanism of the therapeutic effect of the BAL derivatives remains to be elucidated. There are at least 2 possibilities: (1) the molecule may act as a whole, which would imply a mechanism not foreseen by the "Ehrlich-Voegtlin SH-arsenoreceptor theory," (2) the BAL compounds are dissociated in the organism and act essentially like the parent compounds.

15814

Epithelial Keratinization as Evidence of Fetal Vitamin A Deficiency.*

JAMES G. WILSON AND JOSEF WARKANY.

From the Department of Anatomy, School of Medicine and Dentistry, University of Rochester and from the Children's Hospital Research Foundation, Department of Pediatrics, College of Medicine, University of Cincinnati.

The appearance of stratified keratinized epithelium in places where such epithelium is not ordinarily found is the cardinal sign of vitamin A deficiency. It has been stated that this histologic change, referred to as keratinizing metaplasia, occurs in all vertebrates regardless of age.[1] However, it has not been described in fetal or newborn animals whose mothers were in a state of vitamin A deficiency during pregnancy. This is noteworthy, since Hale,[2] using the pig, and Warkany and Schraffenberger,[3] using the rat, obtained fetuses that bore severe morphologic

* This work was aided in part by a grant from the Nutrition Foundation, Inc., N. Y.

1 Wolbach, S. B., and Bessey, O. A., *Physiol. Rev.*, 1942, **22**, 233.

2 Hale, F., *Am. J. Ophth.*, 1935, **18**, 1087.

3 Warkany, J., and Schraffenberger, E., *Arch. Ophth.*, 1946, **35**, 150.