TABLE 1

THE GROWTH-INHIBITING ACTION OF BLOOD PLASMA FROM DIFFERENT ANIMALS AGAINST *Br. abortus*

Source	Plasma sample: Agglutination titer	Hours of incubation	Dilution—growth inhibition: 1:10	1:20	1:40	1:80	1:160	1:320	1:640	Control
Normal calf age, 2 weeks	–	24	–	–	–	–	–	–	–	2+
		48	–	–	–	–	–	4+	4+	4+
Normal heifer age, 15 months	–	24	–	–	1+	2+	2+	2+	2+	2+
		48	1+	4+	4+	4+	4+	4+	4+	4+
Heifer, recovered from infection	1:25	24	–	–	–	–	–	1+	2+	2+
		48	–	–	–	–	–	4+	4+	4+
Heifer, 1 month after vaccine treatment	1:1,280	24(a)	–	–	–	–	–	1+	2+	2+
		48(a)	–	–	–	–	–	4+	4+	4+
Infected cow	1:1,280	24(a)	2+	2+	2+	2+	2+	2+	2+	2+
		48(a)	4+	4+	4+	4+	4+	4+	4+	4+

– = Tubes remain clear, no growth.
+ = Degree of growth.
(a) = Growth in aggregates.
Number of organisms added to each tube per ml = 1.5×10^6.

in the plasma dilutions of infected animals up to the corresponding agglutination titer of the sample. This also occurs beyond the zone of inhibition in samples from animals that have been injected with vaccine. When the aggregates of organisms, in the latter, are transferred to agar plates, most of the colonies grow up as dissociants. Transfers of growth in all dilutions of plasma from infected cows remain smooth.

Plasma samples from most young calves inhibit growth in all dilutions up to 1:160. Occasionally calves are encountered whose plasma shows little inhibition of growth in any dilution. The presence of bactericidal substances and degree of action of plasma in the new-born calf has been correlated with the ingestion of colostrum. Before the ingestion of colostrum the blood possesses no growth-inhibiting property for *Brucella*.

Plasma samples from heifers and adult cows after exposure to and recovery from natural infection inhibit the growth of *Br. abortus* in a higher dilution than those from normal ones. This also occurs in plasma from cows injected with a new type of killed *Brucella* vaccine. It is possible that these observed differences in the growth-inhibiting power of plasma can be made use of in determining the resistance of an animal to *Brucella* infection as well as in detecting those that are infected, as the studies conducted by Irwin, Beach and Bell,[2] and Irwin and Ferguson[3] have suggested.

Thus far, the growth inhibition test has proved to be a highly accurate means of identifying both young and adult cows that are infected with *Br. abortus*, and whose agglutination titers range from 1:25 to 1:5,000.

The test can easily be developed into a routine laboratory procedure and by its application bring about the retention of many cattle that might otherwise be disposed of because of the possibility of infecting other cattle.

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DETOXICATION OF ARSENIC TRIOXIDE BY ORAL ADMINISTRATION OF FLUORIDES

PHYSIOLOGICAL antagonism between arsenic and various chemical compounds has been demonstrated by a number of investigators. The work of Rosenthal and Voegtlin[1] indicates that reduced glutathione is an effective antidote against arsenoxide and arsenious acid. Moxon and his associates[2] have markedly reduced the toxicity of selenium by treatment with sodium arsenite. Sandground[3] has found p-aminobenzoic acid to be highly effective as a detoxicant for high lethal doses of carbarsone and certain other phenyl arsonates in rats. Ascorbic and other organic acids are known to exert a protective action against neoarsphenamine.[4] Arsenic has been suggested as a causative factor in goiter and has been shown to be antagonistic to iodine.[5,6]

The experiments to be described in this paper are an attempt to demonstrate *in vivo* antagonism between two elements, arsenic and fluorine, using arsenic in one of its most virulent forms, the inorganic trivalent arsenious acid.

The arsenic trioxide (As_2O_3) was administered

[2] M. R. Irwin, B. A. Beach and F. N. Bell, *Jour. Inf. Dis.*, 58: 15–22, 1936.
[3] M. R. Irwin and L. C. Ferguson, *Proc. Soc. Exp. Biol. and Med.*, 38: 451–452, 1938.
[1] S. M. Rosenthal and C. Voegtlin, *Jour. Pharmacol. and Exp. Therap.*, 39: 347, 1930.
[2] A. L. Moxon and M. Rhian, *Physiol. Rev.*, 23: 305, 1943.
[3] J. H. Sandground, SCIENCE, 97: 73, 1943.
[4] E. W. McChesney, O. W. Barlow and G. H. Klinck, Jr., *Jour. Pharmacol. and Exp. Therap.*, 80: 81, 1944.
[5] M. Scott, Third Int. Goiter Conf., *Trans.*, 34, 1938.
[6] G. R. Sharpless and M. Metzger, *Jour. Nutrition*, 21: 341, 1941.

orally by mixing with powdered sugar and allowing the rats to eat it voluntarily. In almost all cases the complete amount was consumed within two days. The rats which received fluoride were supplied with potassium fluoride (KF) in the drinking water. A 24-hour pretreatment was given to all rats during which they were starved, and the experimental group supplied with the fluoride-containing drinking water. The arsenic-sugar mixture was then placed in individual cages and the rats were observed for the succeeding 10 days. No supplementary food was given until all rats had consumed their sugar supply. At the end of the fifth day the experimental rats were returned to ordinary tap water.

Nineteen rats were fed 30 mg As_2O_3, and of these only 3, or 16 per cent., were alive on the fifth day of the experiment. These same 3 rats lived through the remainder of the 10-day period.

Sixteen rats were fed 30 mg As_2O_3 and were supplied with drinking water containing 15 mg KF per 30 cc of water. All these animals were alive on the fifth day, and 14, or 88 per cent., were alive at the termination of the experiment.

Twelve rats were fed 30 mg As_2O_3 and were supplied with drinking water containing 30 mg KF per 30 cc of water. Of this group 2 rats died during the first 5 days, while the remaining 10, or 83 per cent., survived the experiment.

These results have been analyzed statistically, using the appropriate chi-square test at the .01 level of significance. The results of the two fluoride-treated groups do not differ significantly, but each of them is significantly different from the control group.

The mechanism of action of arsenic on protoplasm as suggested by Voegtlin[7] consists of an interference with normal functioning of glutathione in the oxidation-reduction processes in living tissues. The injection of a toxic dose of arsenic leads to cellular asphyxia, possibly due to a chemical reaction between reduced glutathione and arsenic to form a compound incapable of normal respiratory activity. Rosenthal and Voegtlin[1] showed that glutathione administration can protect rats against a lethal dose of arsenic, probably substituting for the amount tied up by arsenic. They found that feeding of fairly large amounts of glutamic acid and cystin, precursors of glutathione, will give considerable protection against a subsequent minimal lethal dose of arsenic.

It is suggested by Hogan and Eagle[8] that the systemic toxicity of arsenicals is primarily determined by the varying degree to which they are bound by, and thus block, essential functional groups in vital organs. These assertions are in accord with Ehrlich's thesis that chemotherapeutic agents in general can exert their therapeutic effect only if bound by the parasite, and that their toxic action is due to a similar combination with vital tissues of the host.

The chemical compounds which have been described as detoxicants for arsenicals presumably perform their function by a variety of methods. Organic acids, such as ascorbic and lactic acid, appear to exert their effect as detoxicants of neoarsphenamine by preventing its *in vivo* oxidation to highly toxic inorganic oxides.[4] It has been suggested that because p-aminobenzoic acid bears a similar structural relationship to arsanilic acid as it does to sulfanilamide an explanation of the mechanism of detoxication may be found which parallels the enzyme blockade theory.

The presence of fluoride in the tissues of an arsenic-fed animal must in some way prevent the binding of an essential substrate, such as the physiologically essential sulfhydryl groups. There may be formation of a compound of arsenic and fluorine which has less affinity for body tissues, or is less readily absorbed, so that the arsenic is bound and excreted before it can attack a vital system. The concept of reduced absorption is strengthened by the conclusions of Smith and Shaner,[9] who prevented death of guinea pigs fed a double lethal dose of fluoride by buffering with calcium carbonate.

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DEPRESSION OF LYMPHOCYTE CONTENT OF THORACIC DUCT LYMPH BY ADRENOCORTICOTROPHIC HORMONE

EXPERIMENTAL evidence available at the present time has demonstrated a reciprocal relationship between the adrenal cortical functional state and the weight of lymph and thymic tissue present in the body. Thus adrenalectomy has been shown to result in increase in weight of thymus and lymph nodes as compared with the normal control rat.[2] On the other hand, stimulation of the adrenal cortex by administration of adrenocorticotrophic hormone (ACTH) or the administration of adrenal cortical extracts has produced a rapid decrease in the weight of thymus and lymph nodes in the mouse and rat.[3, 4]

[7] C. Voegtlin, *Physiol. Rev.*, 5: 63, 1925.
[8] R. B. Hogan and H. Eagle, *Jour. Pharmacol. and Exp. Therap.*, 80: 93, 1944.
[9] R. R. Smith and E. O. Shaner, *Jour. Am. Dent. Asn.*, 31: 1483, 1944.

[1] Aided by grants from the Board of Research of the University of California and the Rockefeller Foundation of New York City.
[2] W. O. Reinhardt and R. O. Holmes, *Proc. Soc. Exp. Biol. and Med.*, 45: 267, 1940.
[3] T. F. Dougherty and A. White, *Proc. Soc. Exp. Biol. and Med.*, 53: 132, 1943.
[4] M. E. Simpson, Choh Hao Li, W. O. Reinhardt and Herbert M. Evans, *Proc. Soc. Exp. Biol. and Med.*, 54: 135, 1943.