dal migration even though the color of the pigment is pink or purple, indicating no great acidity. However, often without further treatment than exposure to the air in *Ricinus* (also in *Rhoeo* when initially cathodal), and in the others with ammonia, anodal migration is easily induced. The iso-electric point of the substance concerned in migration may thus vary considerably in different species, from about neutrality up to a very acid region. Consequently the migration could easily be reversed during an experiment either by natural changes of pH in the cells (*e. g.*, by loss of CO_2) or by the diffusion of acid and alkaline products from electrodes. These may account for certain conflicting polarities given in the literature.

Begonia, oleander, *Solidago,* nasturtium stem, *Lantana, Salicornia* and *Sesuvium* constitute a third group in which the colored cells show no very definite migration of pigment in either direction. Possibly there is a different type of pigment cells, and much of the current may flow elsewhere, particularly in the latter 2, which are salt marsh plants.

None of these findings, of course, argues against a change of acidity due to current flow in other experiments, or even in these, though masked by the more conspicuous migration. The writer hopes shortly to present indirect evidence that such a change of acidity occurs in another case. Meanwhile a classic and apparently beautifully direct demonstration must be called into some question, as must the relevance of arguments based upon it.

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Notes on Toxicity and Pharmacology of Indium.

W. F. VON OETTINGEN

From the Department of Pharmacology, School of Medicine, Western Reserve University

Indium was discovered spectroscopically by Reich and Richter in Freiburg zincblende. Although widely distributed in minerals, it usually occurs only in very small quantities, and only recently Westbrook[1] worked out a process to isolate this element in larger quantities from crude zinc liquors which are residues from the manufacturing of sulphuric acid.

[1] Westbrook, L. R., Am. Electrochem. Soc., 57th General Meeting, St. Louis, May 29-31, 1930.

Indium is a white, lustrous metal, very soft and ductile and slightly heavier than zinc. It melts at 155° and boils at 1450°. It does not tarnish at ordinary temperature, but oxidizes rapidly above the melting point, burning with brilliant violet flame at higher temperature.

Chemically it resembles zinc in some respects and aluminum and iron in others. It is trivalent in stable compounds, and its sulphate forms alums with monovalent metal sulphates. Most indium salts are colorless, very soluble in water and hence do not crystallize easily. Alkalies precipitate the white indium hydroxide from the aqueous solutions of the salts, which precipitate may be redissolved by sodium and potassium hydroxide at room temperature, but it is reprecipitated at boiling temperature.

Preparation of Indium Solution. The material, for which we are indebted to the Grasselli Chemical Co., was stated to contain 268 gm. of indium chloride per liter. From this a tenth molar solution was prepared, containing 25.1 gm. of indium chloride per liter. This solution was found to have a pH of 1.8, using thymol blue as indicator. Attempts to neutralize this solution by means of alkali were not successful, because near the neutral point the hydroxide was precipitated. The mixture of indium chloride and sodium citrate, using 5 cc. M/10 indium chloride and 10 cc. M/10 sodium citrate can, however, be adjusted by means of alkali to pH 7.2 to 7.4.

Precipitation of Proteins. Two cc. of a 10% solution of fresh egg white in water were mixed with 1, 2, 3, 4, and 5 cc. of a 4% indium chloride solution, but gave no precipitate neither immediately after mixing nor after 24 hours. Similar experiments performed with 25% solutions of indium chloride showed precipitation only after some hours. Since these solutions were distinctly acid, they had to be compared with solutions of hydrochloric acid of the same pH. It was found that hydrochloric acid forms less precipitate after 24 hours than the 25% solution of indium chloride, from which it appears that the latter has some precipitant action on egg albumen.

Astringent Action on Mucous Membrane. This was studied by determining the filtration velocity through frog skin, according to Sollmann.[2] The following solutions were compared: 4% solution of indium chloride, diluted hydrochloric acid of the same pH, 4% indium chloride buffered with sodium citrate and alkali (pH 7.4), and sodium citrate of the same concentration.

After 4 hours, 4 cc. of the indium chloride solution, 7.9 cc. of the

[2] Sollmann. T., *J. Pharm. Exp. Ther.*, 1922, **21**, 200.

citrated indium chloride, 12 cc. of the diluted hydrochloric acid, and 18.2 cc. of the sodium citrate solution had passed the membrane. This shows that indium chloride, and less so, the citrated compound, have some astringent action.

Effect on the Fermentation by Yeast. This was studied by the method described by Sollmann and Pilcher,[3] using a 4% emulsion of yeast in 10% sugar solution. Five cc. of this emulsion were mixed with equal volumes of 0.5, 1, and 2% indium chloride solution buffered with sodium citrate and alkali, using for comparison equal concentrations of sodium citrate. These experiments showed no inhibition of the fermentation, and also series, in which unbuffered indium chloride and diluted hydrochloric acid of the same pH were used, showed only a very moderate inhibition, so that it appears that indium chloride has no marked antiseptic action.

Toxicity. The toxicity was first studied with earthworms, using the method described by Sollmann.[4] It was found that 4, 2, and 1% solutions of indium chloride buffered with sodium citrate and alkali, and also the corresponding concentrations of sodium citrate alone were fatal within from 5 to 15 minutes. Concentrations of 0.5 and 0.25% and corresponding concentrations of sodium citrate were distinctly toxic, whereas concentrations of 0.1 and 0.05% had no visible effect. Since practically identical results were obtained with sodium citrate solutions, with and without indium chloride, it appears that indium in form of its double salt is probably not more toxic for earthworms than sodium citrate.

The toxicity for the frog seems also to be very moderate, because after the subcutaneous injection of 2 cc. of 4% buffered indium chloride-sodium citrate mixture, the animals showed no other symptoms than those caused by sodium citrate alone. Injections of 2 cc. of a 4% indium chloride solution into the lymph sac had no effect for 24 hours, perhaps on account of precipitation of the material at the site of the injection.

The toxicity for mice is rather great (Table I).

From this table it appears that with subcutaneous administration the minimal fatal dose for mice is about 0.06 gm. indium citrate per kg. and that death may occur with a considerable delay. Oral administration appears to be less toxic. Mice stood daily feeding of a total of 24 gm. of indium hydroxide per kg. for 2 weeks, without apparent toxic effect.

The toxicity for rabbits is apparently higher, as indicated by the

[3] Pilcher, J. D., and Sollmann, T., *J. Lab. and Clin. Med.*, 1924, **10**, 103.

[4] Sollmann, T., *J. Pharm. Exp. Therap.*, 1918, **12**, 129.

TABLE I.

Toxicity of Citrated Indium Chloride for Mice after Subcutaneous Injection.

No.	Weight Gm.	cc. inj.	Gm. per Kg.	Days after Injection 1	2	3	4	5	6	7
		1 cc. = 0.215 Gm. citrated Indium chloride.								
I	29	0.1	0.74		+					
II	27	0.2	1.6	+						
III	32	0.4	2.69	+						
IV	28	0.6	4.6	+						
V	25	0.8	6.88	+						
		1 cc. = 0.0215 Gm. citrated Indium chloride.								
VI	26	0.1	0.083						+	
VII	24	0.2	0.179				+			
VIII	19	0.4	0.452				+			
IX	20	0.6	0.645			+				
X	21	0.8	0.818			+				
		1 cc. = 0.01075 Gm. citrated Indium chloride.								
XI	20	0.1	0.054				survived			
XII	20	0.2	0.107							
XIII	22	0.4	0.195							
XIV	23	0.1	0.047							+
XV	23	0.2	0.094							+
XVI	21	0.4	0.205							+
XVII	20	0.1	0.054				+ 11th day			
XVIII	27	0.2	0.08				+			
XIX	22	0.4	0.196					+		
		1 cc. = 0.0043 Gm. citrated Indium chloride.								
XX	19	0.2	0.045				survived			
XXI	18	0.25	0.055			8th day killed moribund				
XXII	28	0.5	0.077				survived			

results of E. E. Ecker, with subcutaneous injections of indium citrate in syphilitic rabbits.

Systemic Action. On account of the low pH of pure solutions of indium chloride and of the presence of sodium citrate in the buffered solutions, the effect of indium salts on isolated organs could not be studied. Some information could only be obtained by the subcutaneous injection of the citrated material into rabbits. The animals were prepared under local anesthesia for the registration of blood-pressure and respiration, and 0.54 gm. per kg. of indium citrate were injected subcutaneously. There was no visible effect during the first 7 hours. After this time, there was a slow but steady fall of the blood pressure. The amplitude of the heart beat was increased, showing a distinct diastolic tendency; as the fall of the blood pressure became more marked, the respiration was stimulated until the heart stopped suddenly in diastole. These animals showed no gross pathological changes.

Pathological Picture. Mice treated with subcutaneous injections of buffered indium citrate solutions showed a more or less marked depression shortly before death, the hind legs were paretic, the respiration rapid and spasmodic, later convulsions occurred and the

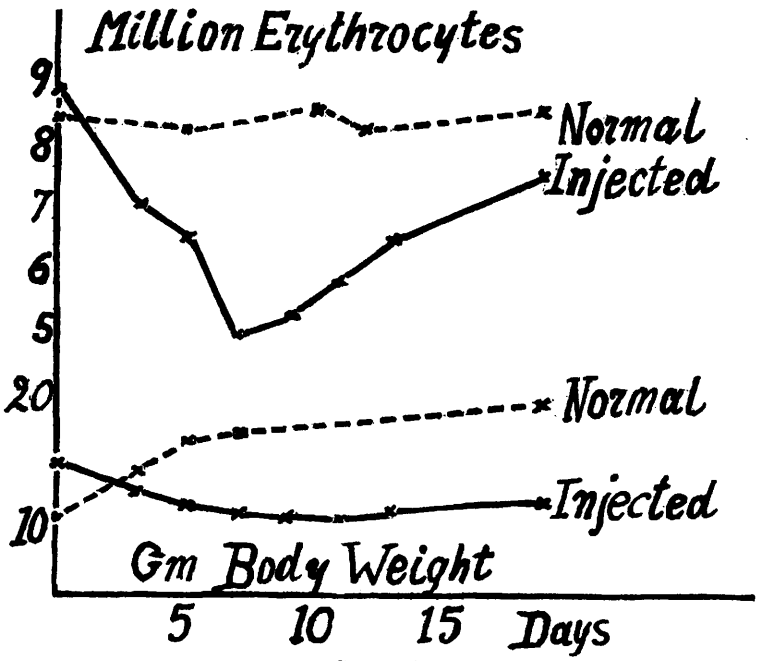

CHART 1.

Changes of the blood-count (upper diagram) and variations of body weight (lower diagram) in young mice after a single subcutaneous injection of indium citrate (0.06 gm. per kg.).

animals died from asphyxia. Animals treated with subfatal doses developed some anemia (Chart 1); and lost in weight, but recovered. With the same and even larger doses of zinc chloride prepared in the same way as the indium chloride solutions, several mice remained normal for several weeks.

Dr. H. Goldblatt examined microscopically the organs of some of the poisoned animals. The animals studied showed marked nephrosis and parenchymatic degeneration of the liver, but no pathological changes of the other organs, especially no edema or exudates. The site of the injection of all treated animals showed more or less marked induration which occasionally passed into necrosis.

Clinical Application. On account of the comparatively high atomic weight of indium (114.8), it was thought that indium iodide might be useful as contrast agent for fluoroscopy, but examination of the absorption of roentgen rays in the ionization chamber, performed by Dr. O. Glasser, showed that the absorption was in the same range as that of sodium iodide solutions of corresponding concentrations.

The resemblance of certain chemical properties of indium to those of bismuth suggested its trial as antisyphilitic agent. The citrated solution of the chloride, an oily suspension of the hydroxide, and an aqueous suspension of the metal are being tested in this respect by Dr. E. E. Ecker. Although these studies are not yet completed, they appear to indicate that indium in these forms has no curative effect on luetic lesions in rabbits.

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Biological Characteristics of Ovary-Stimulating Extracts Made from Blood of Pregnant Women*.

C. F. FLUHMANN

From the Department of Obstetrics and Gynecology, Stanford University School of Medicine

The demonstration that ovary-stimulating extracts prepared from human placenta (Collip *et al.*[1]), or from urine of pregnant women (Evans, Meyer, and Simpson[2]) differ from anterior pituitary gland implants in their influence on the weights of immature rat ovaries, is of considerable biological interest. It seemed of importance, therefore, to determine if extracts made from the blood of pregnant women were similar in this characteristic.

A crude estrin-free extract was prepared from blood by a method developed with the assistance of Dr. M. L. Tainter of the Department of Pharmacology, based on that of Wallen-Lawrence and Van Dyke[3] for the extraction of "hebin" from anterior pituitary glands. Forty to 50 cc., obtained by venapuncture, from each patient was placed in a receptacle containing a few crystals of sodium citrate, centrifuged, the red blood cells discarded, and the resultant clear blood plasma shaken up 5 times with ether. Ten volumes of 95% alcohol were then added to the blood plasma, the solution centrifuged, and the resultant precipitate washed twice with ether, dried, powdered, and extracted over night with 20 to 30 cc. of an isotonic sodium acetate-acetic acid buffer solution having a

*Supported by a grant from the Rockefeller Fluid Research Fund of Stanford University School of Medicine.

[1] Collip, J. B., Thomson, D. L., McPhail, M. K., and Williamson, J. E., *Can. M. A. J.*, 1931, **24**, 201.

[2] Evans, H. M., Meyer, K., and Simpson, M. E., *Am. J. Physiol.*, 1932, **100**, 141.

[3] Wallen-Lawrence, Z., and Van Dyke, H. B., *J. Pharm. and Exp. Therap.*, 1931, **43**, 93.