acted to adrenalin with a strong contraction. On the rabbit uterus the active substance acts in the same way as adrenalin. No graphs are included.

3. Eye (Cat, Rabbit, Dog).—The solution of active substance was instilled into the conjunctival sac of the cat, rabbit and dog. Time of exposure to the solution was varied as well as the lighting conditions. Absolutely no effects on the pupil were noted and no impairment of accommodation resulted as far as could be determined.

DISCUSSION

The effect of the active principle in producing a fall in blood pressure, dilatation of the heart and constriction of the smooth muscle of the intestine would seem to indicate that the active principle was parasympathotropic. However, this is not universally true. For example, there was no action on the pupil and at no time was any increased salivation observed although no special experiments were done to check this point. Furthermore, the undiminished activity after vagotomy, nicotine and atropine argue against a parasympathetic mediation. The action of the drug in causing contractions of virgin uteri regardless of the previous action of adrenalin on those uteri suggested a musculotropic action.

The assumption of musculotropic action means that the substance must act on smooth muscle in different locations in opposite fashion, that is, to relax the muscle of the vessel walls and constrict that of the uterus and intestine. This seems unusual but it can be pointed out that synephrine and one or two other closely related sympathomimetic compounds have similar paradoxical actions and these drugs have been shown almost surely to be musculotropic (5).

SUMMARY

1. A pharmacological study of a physiologically active compound from *Passiflora incarnata* has been made.

2. Neither the active substance itself nor the fluidextract of the crude drug had any action which could be construed as sedative.

3. The active substance caused lowering of the blood pressure and contraction of smooth muscle of the gut and uterus.

4. The activity of the substance has been shown to be unaffected by vagotomy, atropine, nicotine or pituitrin.

5. The drug probably exerts its characteristic activity by direct action on smooth muscle.

REFERENCES

(1) Ott, *Medical Bulletin*, 29 (1898), 457.

(2) DeNito, *Rassegna di Terapia e Patologia Clinica*, 3 (1931), 193.

(3) Fellows and Smith, JOUR. A. PH. A., 28 (1938), 565.

(4) Sollmann and Hanzlik, "Experimental Pharmacology," Saunders (1938), page 145.

(5) Tainter and Seidenfeld, *J. Pharmacol.*, 40 (1930), 23.

Toxicity of Selenium-Cystine and Some Other Organic Selenium Compounds*

By Alvin L. Moxon†

Earlier studies on the selenium problem (1, 2, 3) have demonstrated that the toxicity as well as the selenium is carried in the protein fraction of seleniferous grains. The selenium is thought to occur in organic combination (4, 5) and it has been postulated that selenium could be replacing sulfur in the amino acids: cystine and methionine (6). Jones, Horn and Gersdorf (5), by a special enzymatic hydrolysis of gluten from seleniferous wheat, have isolated two fractions which contained practically all of the selenium and most of the cystine. The remaining fractions were practically free from selenium and contained only traces of cystine.

The toxicity of a number of organic selenium compounds has been investigated (7) and it was found that the toxicity of the selenium in the particular compounds studied did not approach the toxicity of sele-

* The author wishes to thank Dr. Arne Fredga of Uppsala University, Uppsala, Sweden, for the generous supply of selenium-cystine and other organic selenium compounds, and Dr. C. A. Elvehjem, Dept. of Agricultural Biochemistry, University of Wisconsin, for courtesies and helpful suggestions during the course of the work. The work reported herein was done in the laboratories of the Department of Agricultural Biochemistry, University of Wisconsin, during a leave of absence from the South Dakota State College.

† Chemist, S. Dak. Agr. Expt. Station, South Dakota State College, Brookings, South Dakota.

nium in inorganic selenites or selenates or in seleniferous grains. It has been shown (8) that inorganic selenium (selenites and selenates) and naturally occurring selenium in the toxic grains are about equal in toxicity when orally ingested. Furthermore, it has been observed that, by intraperitoneal injection, inorganic selenium is several times more toxic than selenium in organic combination in such compounds as β,β'-diselenodipropionic acid (7).

Gordon (9) attempted to synthesize the selenium analog of cystine but failed to isolate the pure compound. Fredga (10), however, has been successful in synthesizing selenium-cystine and has been very generous in furnishing the author with a supply of this selenium-substituted amino acid and several other organic selenium compounds.

EXPERIMENTAL

A solution containing 0.5 mg. of selenium per cc. was prepared by dissolving the required amount of selenium-cystine in 50 cc. of distilled water to which had been added 3 cc. of $N/10$ HCl.

The required amount of solution was injected intraperitoneally into albino rats weighing 100 to 150 Gm. The intraperitoneal route of injection was chosen because it simulates oral ingestion of the toxic agent more closely than does intravenous or subcutaneous injection.

A solution containing 3 cc. of $N/10$ HCl per 50 cc. was injected into control animals and no toxic effects were noted when amounts equal to twice the volume of selenium-cystine solution were injected.

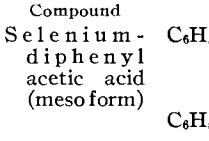
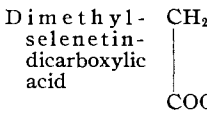
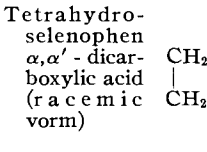
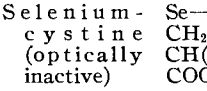
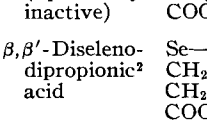
Table I.—Toxicity of Selenium-Cystine

Dosage Data	Mg. Se per Kg. Body Weight
Range of dosage used	3.0–30.0
Lowest dosage to cause death	3.50
Highest dosage which failed to cause death in 48 hours	4.25
Dosage killing 100% in 48 hrs.	4.5
Dosage killing 75% in 48 hrs. (M. F. D.)	4.0
Total number of rats injected	65

The minimum fatal dose (M. F. D.) was taken as the minimum amount of selenium (mg. per Kg. of body weight) to cause death in 75 per cent of the rats within two days (11). According to the results obtained (Table I) the minimum fatal dose of selenium in the form of selenium-cystine is 4.0 mg. per Kg. body weight which compares very favorably with the toxicity of selenium in the form of Na_2SeO_3 or Na_2SeO_4 (11). Since selenium-cystine contains 47.37 per cent of selenium the minimum fatal dose of selenium-cystine would be 2.11×4.0 or 8.44 mg. per Kg.

The toxicities of three other organic selenium compounds, generously supplied by Dr. Fredga, were also investigated and the results are given in Table II. These compounds[1] are much less toxic than selenium-cystine. It is of interest to compare the toxicities and structures of selenium-cystine and the other organic selenium compounds, especially the β,β'-diselenodipropionic acid (7).

Table II.—Comparison of Toxicity and Structure

Compound	Structure	Toxicity (M. F. D.), mg./Kg.
Selenium-diphenyl acetic acid (meso form)		Over 30
Dimethyl-selenetin-dicarboxylic acid		Over 30
Tetrahydro-selenophen α,α'-dicarboxylic acid (racemic vorm)		Over 30
Selenium-cystine (optically inactive)		4.0
β,β'-Diseleno-dipropionic[2] acid		25–30 (7)

Work under way at the present time indicates that selenium-cystine when administered orally is almost equal in toxicity to inorganic selenium (Na_2SeO_3 and Na_2SeO_4) and to naturally occurring selenium in toxic grains. This work will be reported later.

DISCUSSION

The results indicate that selenium-cystine is much more toxic than any other organic selenium compound which has been investigated to date (7, 12, 13). The toxicity of the selenium in selenium-cystine as shown in Table III is approximately seven times that of selenium in the form of β,β'-diseleno-dipropionic acid.

---

[1] For details on preparation and properties of these compounds, other than selenium-cystine, see "Studien uber Selen-Di-Karbon sauren und Diselen-Di Karbonsauren," Arne Fredga, Uppsala Universitets Arsskrift (1935) 5, 230 pages.

[2] Prepared by E. Page Painter, Division of Agricultural Biochemistry, University of Minnesota, St. Paul, Minnesota.

When injected intraperitoneally the toxicity of selenium in the form of selenium-cystine is approximately equal to the toxicity of selenium in sodium selenate or sodium selenite. The toxicities of the selenium in the two, above mentioned, inorganic compounds are in the same range as the toxicity of selenium in seleniferous grains. This has been indicated by oral administration of selenium-cystine.

SUMMARY

The minimum fatal dose of selenium in the form of selenium-cystine when injected intraperitoneally into albino rats was found to be 4.0 mg. per Kg. of body weight. This is equivalent to 8.44 mg. of selenium-cystine per Kg. of body weight.

REFERENCES

(1) Franke, K. W., *J. Nutrition*, 8 (1934), 609–613.

(2) Franke, K. W., and Painter, E. P., *Cereal Chem.*, 13 (1936), 67–70.

(3) Horn, M. J., Nelson, E. M., and Jones, D. B., *Ibid.*, 13 (1936), 126–139.

(4) Painter, E. P., and Franke, K. W., *J. Biol. Chem.*, 111 (1935), 643–651.

(5) Jones, D. B., Horn, M. J., and Gersdorf, C. E. F., *Cereal Chem.*, 14 (1937), 130–134.

(6) Painter, E. P., and Franke, K. W., *Ibid.*, 13 (1936), 172–179.

(7) Moxon, A. L., Anderson, H. D., and Painter, E. P., *J. Pharmacol.*, 63 (1938), 357–368.

(8) Franke, K. W., and Painter, E. P., *Cereal Chem.*, 15 (1938), 1–24.

(9) Gordon, J. C., Dissertation, Catholic Univ. of Am. (1935), 43 pages.

(10) Fredga, A., *Svensk Kemisk Tidskrift*, 48 (1936), 160.

(11) Franke, K. W., and Moxon, A. L., *J. Pharmacol.*, 58 (1936), 454–459.

(12) Kondo, S., *Japan J. Med. Sci.*, IV Pharm. (1933), No. 1, 213–232.

(13) Kondo, S., *Japan J. Med. Sci.*, IV Pharm. 9 (1935), No. 1, 29.

NOTICE

Please use graph paper for illustrations as specified under "Notice to Authors."

The Pharmacology of Soaps

II. The Irritant Action of Soaps on Human Skin

*By Byron E. Emery and Leroy D. Edwards**

In a previous paper (1) the actions of soaps on human red cells and earthworm segments were reported. During the past year, this work has been extended by the study of the irritant action of sodium and potassium soaps made from chemically pure fatty acids on human skin.

The literature gives many conflicting reports as to the component of a soap solution responsible for its irritant action on skin, *i. e.*, free alkali (2), hydrolytic alkalinity (2), free fatty acid (3, 4), acid soap (3), unsaturated acids (5), neutral soaps (3), added ingredients—perfumes (6, 7), antiseptic substances (8, 9), etc. The oils most commonly mentioned as being capable of producing irritant soaps are cottonseed (2, 8), cocoanut (5, 8, 10) and palm (5). Many writers (2, 11, 12) discuss the probability of differences in skin as being a contributing factor to soap irritation. Practically all of these workers used some form of a patch or swab test to determine the results reported.

EXPERIMENTAL

Method Employed.—The patch test, cited above, usually consists of the application to the skin of solid soap or bits of paper or gauze impregnated with a soap solution (alcoholic or aqueous) for some definite period of time. This method is held to be deficient for the following reaons: (1) insoluble soap cannot produce a reaction, (2) a definite volume or a definite concentration of a soap solution cannot remain in contact with the skin, (3) the volume of soap solution is not large enough, (4) paper and gauze have electrical charges which affect the state of a colloidal soap solution, (5) the area of skin covered by a soap solution on paper or gauze is not constant. In order to avoid these difficulties the device as shown in Fig. 1 was developed for use in this study of the irritant action of soaps on human skin. The diaphragm rim was lubricated with a jelly of tragacanth, Irish moss, glycerin, boroglycerin and benzoic acid. Approximately 25 cc. of a soap solution were added to the diaphragm and strapped to the inner surface of the arm or leg.

* From the Department of Pharmacology, School of Medicine, and the School of Pharmacy, Western Reserve University.