Council on Physical Therapy

THE COUNCIL ON PHYSICAL THERAPY OF THE AMERICAN MEDICAL ASSOCIATION HAS AUTHORIZED PUBLICATION OF THE FOLLOWING REPORT.
H. A. CARTER, Secretary.

GOMCO SYRINGE STERL-CASE NOT ACCEPTABLE

The Gomco Syringe Sterl-Case, manufactured and submitted by the Gomco Surgical Manufacturing Company, Buffalo, N. Y., may be described as a hypodermic needle enclosed in a compact vest pocket carrying case resembling a fountain pen. By means of an alcoholic preparation the needle is said to be sterilized and ready to carry. The length is about 5¼ inches over all and ¾ inch in diameter. It weighs about 40 Gm.

In the advertising matter accompanying the hypodermic needle it is claimed that the needle itself is "rustless" and the syringe case offers a means of complete syringe sterilization.

Tests were made as follows: Without previously boiling or sterilizing the syringe, except as described in the advertising material, sterile broth culture medium was aspirated and reinjected into the culture tube. No growth was obtained, indicating that sterilization was adequate. Several repetitions of this gave the same results.

While the needle may be made of the so-called rustless steel, it nevertheless rusts and becomes unfit for use after being carried in the pocket case syringe for about a week. Renewals of the needles at such short intervals would be objectionable.

It is probable that most physicians would prefer to boil the syringe and to make sure of the patency of the needle by use of a wire obturator.

Because the needle rusts very readily and therefore becomes unfit for use, the Council on Physical Therapy declines to include the Gomco Syringe Sterl-Case in its list of accepted devices.

Council on Pharmacy and Chemistry

THE COUNCIL HAS AUTHORIZED PUBLICATION OF THE FOLLOWING PRELIMINARY REPORT.
P. N. LEECH, Secretary.

THOROTRAST

Thorotrast was presented by the Heyden Chemical Corporation for consideration by the Council as a colloidal thorium dioxide preparation suitable for use in retrograde pyelography and for roentgen visualization of the liver and spleen by intravenous administration. This was first introduced by Radt.[1]

COMPOSITION

Thorotrast is claimed to be a stabilized thorium dioxide solution, containing 25 per cent by volume of thorium dioxide, ThO_2 (from 19 to 20 per cent by weight) and about the same amount of protective colloid (from 16 to 19 per cent by weight) said to be of a carbohydrate nature and further defined as a dextrin preparation. It contains as a preservative 0.15 per cent of methyl *p*-hydroxy benzoate. The addition of alcohol to Thorotrast results in flocculation with the liberation of hydrochloric acid.[2] The A. M. A. Chemical Laboratory has not so far reported on the product.

Despite the fact that the immediate toxicity of Thorotrast appears to be low, the Council believes that the manufacturer should be required to be more explicit with regard to the composition of the protective colloid under the terms of rule 1, especially as it is used intravenously. The intravenous dosage of the preservative, methyl parahydroxy benzoate, would be about 0.1 Gm., which, on the assumption that this compound partakes of the same toxicity as sodium benzoate, would probably prove innocuous; but the Council has no definite information on this point.

1. Radt, P.: Med. Klin. **26**: 1889 (Dec.) 1930; Deutsche med. Wchnschr. **56**: 2025, 1930; Verhandl. d. Deutsch. Ges. inn. Med. **43**: 443, 1931 (cited from Irwin).
2. Irwin, W. A.: Canad. M. A. J. **27**: 130 (Aug.) 1932.

NAME

The only claim that might entitle the Heyden Chemical Corporation to a proprietary name for colloidal thorium dioxide is the one that this firm was the first to produce such a product suitable for intravenous administration. The firm admits that colloidal thorium dioxide was available in Germany at about the time it introduced its first product, Umbrathor. So far as immediate toxicity is concerned, Thorotrast is suitable for intravenous administration, but as a considerably longer period must elapse before the remote toxicity may be ascertained with certainty, it appears that this claim cannot definitely be substantiated at the present time, and hence under the terms of rule 8 the Council believes a proprietary name cannot now be allowed, unless evidence is furnished that Thorotrast involves a fundamental improvement over other thorium preparations for use in pyelography and the like.

PROPERTIES

The firm claims that Thorotrast is miscible with body fluids in all proportions without flocculation. Irwin has observed definite flocculation in blood removed from an experimental animal from five to ten minutes after injection. This was still observable in blood removed up to forty-eight hours, after which visible particles were no longer discernible. The maximum size of these particles is not stated, but presumably they are small enough to pass through the finer vessels, as no reports have been found of embolic phenomena with Thorotrast, although these have been noted with other colloidal thorium dioxide preparations.[1]

ADMINISTRATION

1. *Hepatosplenography.*—Thorotrast is usually injected intravenously in 25 cc. portions, over a period of from three to five minutes, either undiluted or diluted to various degrees with physiologic solution of sodium chloride or isotonic dextrose. Generally three such injections are required and are usually given every other day, but these may be administered daily, depending on the patient's tolerance. If it is desired merely to outline the liver and/or spleen, one half, one third and sometimes less of the total dose may be sufficient. Roentgenograms are taken not sooner than twenty-four hours after the last injection.

Reactions are infrequent and when they occur their manifestations are of the variable sort referable to alteration of the colloidal equilibrium of the blood. Occasionally, symptoms already present are exaggerated. Generally these reactions subside rapidly. The reactions include: slight to moderate febrile reactions of up to twenty-four hours or so in duration; vomiting in hepatic cirrhosis, sometimes lasting several days; other reactions of an anaphylactoid variety (relieved by epinephrine in one case); hematemesis in patients with gastric ulcer or a malignant growth; severe asthmatic attacks in individuals so predisposed, and moderate and transient anemia of a few days' duration coincident with a transient, moderate, mononuclear leukocytosis. It is generally agreed that such reactions as occur are not ordinarily of a serious nature and do not provide serious contraindication to the use of the solution if care is taken to give fractional dosage to sensitive patients.[3]

No untoward reactions over a period of four months have been noted after total doses of up to 5 cc. per Kg. in rabbits.[4]

Moniz, Pinto and Lima[5] have obtained good roentgenograms of the vascular tree of the head by injecting a common carotid artery. Erhardt[6] has been able to diagnose the position and number of placentas in pregnant animals by large intravenous doses; Menville and Ané[7] have confirmed this in rats. Liepmann[8] has injected the human placenta in situ post partum, from the umbilical cord. The effects of various pharmacologic

3. (*a*) Radt.[1] (*b*) Kadrnka, S.: Schweiz. med. Wchnschr. **61**: 425 (May 2) 1931; Fortschr. a. d. Geb. d. Röntgenstrahlen **44**, number 1, 1931 (cited from Irwin); Radiology **18**: 371 (Feb.) 1932. (*c*) Stewart, Einhorn and Illick: Am. J. Roentgenol. **27**: 53 (Jan.) 1932. (*d*) Dickson, W. H.: Canad. M. A. J. **27**: 125 (Aug.) 1932. (*e*) McDonald, I. G.: Ibid. **27**: 136 (Aug.) 1932. (*f*) Tripoli, Haam and Lehman: Am. J. Roentgenol. **27**: 265 (Feb.) 1932. (*g*) Bauke: Deutsche med. Wchnschr. **57**: 1148 (July 3) 1931.
4. Irwin.[2] Muramatsu: Grenzgebiet., number 9, 1931 (cited from Irwin).
5. Moniz, Pinto and Lima: Roentgenpraxis **4**: 90 (Jan. 15) 1932.
6. Erhardt, K.: Zentralbl. f. Gynäk. **56**: 847 (April 2) 1932.
7. Menville, L. J., and Ané, J. N.: Proc. Soc. Exper. Biol. & Med. **29**: 1045 (June) 1932.
8. Liepmann, W.: Med. Klin. **27**: 1813 (Dec. 11) 1931.

agents on the size of liver and spleen have been studied after administration of Thorotrast.[9]

The preponderant consensus among clinicians who have used Thorotrast is that it is a valuable adjunct in differential diagnosis and furnishes information not obtainable by other means short of exploratory surgery. The questionable point remains that of ultimate toxicity.

2. *Retrograde Pyelography.*—Thorotrast is diluted with two parts of physiologic solution of sodium chloride or water for pyelography and with five parts for cystography. The solution so prepared is said to be somewhat viscid. Observers have not found this objectionable, although the excess pressure required for such solutions might be disadvantageous. The dilutions are said to be nonirritant, to give excellent pictures, and to be completely eliminated within twenty minutes so far as the x-ray opacity is concerned. Thorotrast has been used in Europe for visualization of various body cavities, particularly for pyelography, but, while comments are favorable, no case reports are available to the Council at this time. Experience with Thorotrast pyelography in this country has been very limited and no case reports have come to the Council's attention. Dickson [3d] believes that the solution possesses considerable advantage over the iodine solutions but this opinion is not held by Lewisohn,[3c] who considers the latter superior. The Council believes that a more extensive application of Thorotrast in this field would be necessary before definite conclusions may be drawn as to its place in urography. Thorotrast has also been recommended in various dilutions for outlining fistulas, sinuses, cysts and empyema cavities.[10] While excellent roentgenograms are obtained, completely convincing data are lacking as to their usefulness here, particularly in view of the possible retention of large quantities (discussed under Radioactivity).

DISTRIBUTION

Thorium dioxide is taken up over a period of several days following intravenous injection, by the cells of the reticuloendothelial system, in the liver, spleen, lymphoid tissue and bone marrow and to a lesser extent by the ovary and suprarenal. Rarely are particles visible in the kidneys.[11] Leipert [12] has performed chemical determinations on the liver, spleen, kidneys and other organs of three patients who died following Thorotrast injections and of three rabbits experimentally injected with doses as indicated. His data are given in the accompanying tables.

TABLE 1.—*Thorium Dioxide Recovered from Tissues Following Intravenous Injection of Thorotrast (from Leipert [12])*

Number and Diagnosis	Organ	Weight, Gm.	Thorium Dioxide in Grams: Found	Thorium Dioxide in Grams: Injected	Per Cent Recovered	Time after Injection
Man						
1. Gastric carcinoma	Liver	850	3.22			
	Spleen	50	0.193	6.0	56.9	4 days
	Gallbladder	15	0.0			
2. Carcinoma of rectum	Liver	2,310	8.9			
	Spleen	209	0.7			
	Kidneys	170	0.004	15.0	64.3	2 days
	Gallbladder	33	0.0			
	Skin	43	0.0			
	Bone marrow	28	0.0			
	Tumor	1,600	0.0			
3. Tumor of bile duct	Liver	1,400	12.95	16.5	97.0	60 days
	Spleen	200	3.04			
Rabbit 1	Liver	88.0	0.97			
	Spleen	4.5	1.94	6.0	48.5	28 days
	Kidneys	13.0	0.0			
Rabbit 2	Liver	97.0	1.72			
	Spleen	2.2	0.38	2.125	98.8	67 days
	Kidneys	16.0	0.002			
Rabbit 3	Liver	76.0	0.54			
	Spleen	1.5	0.08	0.875	70.9	91 days
	Kidneys	9.5	....			

Leipert's data on human beings are of course of limited significance, not only in view of the few cases examined but also because all these patients had tumors which could conceivably have greatly modified the distribution of the material. It is particularly to be noted that 97 per cent of the injected dose was recovered from the liver and spleen in one clinical case two months after injection. The ratio of clinical to experimental doses can be estimated here only roughly from the organ weights, as the body weights are not given. It is of interest that in the rabbits a larger quantity of thorium dioxide was recovered from the kidneys than from the spleen, which data are not in accordance with the histologic observations. Following subcutaneous injection, thorium dioxide has been found in regional lymph nodes.[13]

TABLE 2.—*Ratio of Thorium Dioxide Recovered from Liver and Spleen (from Leipert [12])*

	Number	Gm. Thorium Dioxide in 1 Gm. Liver	Gm. Thorium Dioxide in 1 Gm. Spleen	Ratio
Man	1	0.00379	0.00386	1:1
	2	0.00386	0.00343	1:0.9
	3	0.00926	0.0152	1:1.64
Rabbit	1	0.0111	0.4320	1:38.9
	2	0.0177	0.1740	1: 9.85
	3	0.0071	0.0544	1: 7.66

TOXICITY

Stewart, Einhorn and Illick [3c] reported four clinical cases of acute splenitis demonstrated at necropsy following the administration of approximately half the usual dose of Thorotrast. Lewisohn reports nuclear damage in the reticulo-endothelial system following what were apparently massive doses in rabbits. Huguenin, Nemours and Albot [14] were able to produce hepatitis, cirrhotic changes and splenitis by the injection of moderate to large doses in rabbits. Harris and Friedrichs [15] have also noted pathologic changes in the liver and spleen. Other reports indicate no apparent cellular damage in doses up to 5 cc. per kilogram, which is about six times the dose necessary for hepatosplenography in man.[2] Following subcutaneous injections, fibrotic changes have been noted in regional lymph nodes.[16]

ELIMINATION

Data as to the elimination of thorium dioxide are at the present time very sketchy and incomplete. In general it may be said that the liver gets rid of a certain portion of its quota partly at least by cellular transport to the lungs and elimination in the bronchial mucus.[2] Claims vary from a 50 per cent diminution in three months to no hepatic elimination in eight months.[17] The spleen, bone marrow, lymph nodes and ovary have as yet given no evidence of elimination.[18] The only chemical estimates of quantities remaining in the organs that are at present available to the Council are those of Leipert, already quoted.

RADIOACTIVITY

It is important to recognize that a determination of the radioactivity of a specimen of thorium is not necessarily a permanent measure of its emanative properties, since the radioactivity of freshly prepared and relatively pure thorium and its preparations may increase with age with the formation of mesothorium and radiothorium (two of the main constituents of the radioactive paint that produced fatal poisonings in factory workers), thorium X, thorium emanation, and so on.[19] A specimen of "chemically pure" thorium may continue to increase in activity for several years as its disintegration products accumulate and until they all reach equilibrium one with with another.[20] Furthermore, as pointed out by Martland [21]

9. Paffenholz, W., and Schuermeyer, A.: Klin. Wchnschr. **10:** 2076 (Nov. 7) 1931. Baumann, H., and Schilling, C.: Klin. Wchnschr. **10:** 1249, 1931. Haam, E.; Tripoli, C. J., and Lehman, E. B.: Proc. Soc. Exper. Biol. & Med. **29:** 1056 (June) 1932.
10. Gros: Schweiz. med. Wchnschr. **61:** 549 (June 6) 1931. Kremser, C.: Roentgenpraxis **4:** 189 (Feb. 15) 1932.
11. Kadrnka.[3b] Randerath: Inst. d. Med. Akad. Düsseldorf, 1931 (cited from Irwin). Kadrnka and Rossier: Acta Radiol. **12:** 369, 1931.
12. Leipert, T.: Wien. klin. Wchnschr. **44:** 1135 (Sept. 4) 1931.
13. Menville, L. J., and Ané, J. N.: Roentgen Visualization of Lymph Nodes in Animals, J. A. M. A. **98:** 1797 (May 21) 1932.
14. Huguenin, Nemours and Albot: Compt. rend. Soc. de biol. **108:** 879 (Dec. 4) 1931.
15. Harris, W. H., and Friedrichs, A. V.: Proc. Soc. Exper. Biol. & Med. **29:** 1047 (June) 1932.
16. Harris, W. H.: Proc. Soc. Exper. Biol. & Med. **29:** 1049 (June) 1932.
17. Kadrnka.[3b] Stewart. Einhorn and Illick.[3c] Dickson.[3d] Popper, H. L., and Klein, E.: München. med. Wchnschr. **78:** 1829 (Oct. 29) 1931. Naegeli and Lauchi: Med. Klin. **27:** 1878 (Dec. 18) 1931.
18. Irwin.[2] Dickson.[3d]
19. Hevesy, G., and Paneth, F.: A Manual of Radioactivity, London, 1926.
20. Hevesy and Paneth.[19] Starling, S. G.: Electricity and Magnetism, London, 1926.
21. Martland, H. S.: Occupational Poisoning in Manufacture of Luminous Watch Dials, J. A. M. A. **92:** 466 (Feb. 9), 552 (Feb. 16) 1929.

and by Flinn,[22] the alpha ray activity is by far the most important emanation with regard to direct effects on tissues, despite the low penetrating power through tissue (approximately 1 mm.). These rays are screened out in the therapeutic use of radioactive substances and it is only in intoxications that alpha ray effects are seen. The more widely distributed the radioactive substance, the greater will be this alpha ray reaction, as the numerous small foci more than compensate for the low penetration. The ratio of toxicity for tissue of alpha, beta and gamma rays is as 10,000 to 100 to 1 in the order given,[21] which is in inverse proportion to the penetrating power.[23]

The radioactivity of Thorotrast has been determined as follows:

Alpha ray: Twenty-five cubic centimeters of Thorotrast is equivalent to a maximum of 1 microgram and a minimum of 0.5 microgram of radium (Schlundt).

Beta ray: "Too feeble to be of physiological significance" (Schlundt).

Gamma ray: Twenty-five cubic centimeters of Thorotrast is equivalent to 0.4 microgram of radium (Radium Institut Bergakademie, Freiburg); equivalent to approximately 0.3 microgram of radium (Flinn). "Too feeble to be of physiological significance" (Schlundt).

As a total of 75 cc. is ordinarily used for intravenous administration, a quantity of thorium dioxide equivalent in alpha ray activity to from 1.5 to 3.0 micrograms of radium and in gamma ray activity to from 0.9 to 1.2 micrograms of radium would be widely distributed throughout the body, particularly in the reticulo-endothelial system. Such portions of the thorium salt as are not excreted, on the assumption that the preparation was fresh when injected, would increase in activity with the formation of disintegration products until these all had attained equilibrium.

On the assumption that an original maximum is the equivalent of 3 micrograms of radium: Definite destruction of bone and change in tooth structure have been noted with the presence in the body of quantities of radioactive substance estimated as the equivalent of 2 and of 4 micrograms of radium.[24] The limit of tolerance for the average normal person was formerly thought to be about 10 micrograms; as time has brought to light a greater number of radioactive intoxications it has become apparent that as little as 1 or 2 micrograms may be toxic.[22] Thorotrast would be used, not in normal persons, but in those in which a disease process is already in evidence (often a borderline malignant condition); the more so then the equivalent of 3 micrograms of radium must be considered a highly dangerous dose (even on the assumption that elimination may counterbalance the increase in activity of the remaining thorium). Martland, whose experience with radioactive poisonings has been extensive, is of the opinion that the normal radioactivity of the body should not be increased for any reason because of the danger of malignancy.

Stewart, Einhorn and Illick[3c] were able to obtain a photographic image on a plate after twenty-four hours' exposure to a section of spleen removed at necropsy. In this individual approximately one-half the usual dose of Thorotrast had been injected. Dickson[3d] was not able to obtain an image after "several days' exposure" of "heavily impregnated" sections of liver and spleen to photographic plates. Neither of these workers states whether the tissue was exposed directly to the plate by contact or with an intervening air space, or whether a sheet of paper was interposed. With the contact method Martland was able to obtain images only after an average of from seven to ten days' exposure with sections of bone that contained quantities of radioactive material which had proved fatal. By the interposition of a piece of paper that screened out the alpha rays, up to three weeks or more was required for the production of an image with fatal quantities. Therefore, the image obtained by Stewart and his co-workers represents either a very high concentration of radioactive material, a much more sensitive plate than used by Martland, or faulty technic. That Dickson was unable to obtain an image after several days' exposure does not constitute evidence one way or the other. Dickson further states that "concentrated liver pulp of rabbits receiving large doses of thorium dioxide gave no reaction of any importance with the electroscope." This can be attributed to absorption of alpha radiation by the liver pulp or possibly to temporary de-emanation of the thorium as the result of the process of "concentration," which might tend to occur if the latter was performed in vacuo.

Martland[21] remarks, "As the charge of the alpha particle is positive and the colloid systems of the erythrocytes are strongly electronegative and are permeable only by anions, the red blood corpuscles are particularly liable to injury." This may well account for the early anemia seen in some of the experimental animals and in a few patients, as the occurrence of this anemia coincides approximately with the presence of floccules in the blood stream (Irwin) and clears up in a few days when these floccules have disappeared.

To date, no evidence has been brought forward, to the Council's knowledge, that the thorium dioxide is removed from certain areas such as the bone marrow, spleen, lymph nodes and ovary; as far as the longest period of observation in the American literature is concerned (nine months) the material appears to be permanently fixed in these areas. In the liver a 50 per cent reduction in opacity in three months is claimed,[3d] although Stewart and his co-workers found no decrease in opacity in their one surviving patient at eight months.

Martland says: "It is important to note that the known cases of radium poisoning all affected the girls who had worked steadily in this plant from one to two or more years. . . . The symptoms [develop late], occurring from *one to seven years* [italics ours] after the patients leave the employment. . . ."

It is certain that the period of observation on patients and on animals since the introduction of Thorotrast has been insufficient to rule out the possibility of ensuing necrotic and/or malignant changes, although it is conceivable that a shorter period might suffice in the case under consideration, when massive doses are given at one time, than was required for the production of pathologic changes in the cases of occupational poisoning, in which very small doses were daily ingested and inhaled over periods of several years.

There exists further the possibility of sensitization of tissues locally by the presence of thorium to the subsequent action of roentgen rays. This was demonstrated by Ellenger and Gans[25] and by Siedamgrotsky and Picard[26] for the local injection of thorium nitrate, this effect not being shared in common with other protein precipitants and hence probably being a thorium effect. This possibility has been recognized by the Toronto group of workers: "Thorium . . . possesses a very short wavelength and the wavelength of its secondary radiation when bombarded by x-rays is also very short. With long-continued storage of the thorium dioxide in the liver and bone marrow, the question of exposure to radiation from the x-ray tube in cases suffering from metastases in these areas is an interesting one. At the present time Dr. Richards is carrying on research along these lines."[3d] While this property of secondary radiation may be of distinct value in the treatment of malignant conditions, it may well impose a definite risk on those patients who have had the injection as a diagnostic measure and subsequently are exposed to roentgen radiation.

In view, therefore, of the very imperfect elimination of thorium dioxide, its fairly high alpha ray activity, the possibility of further increase in radioactivity by partial conversion to mesothorium and radiothorium, and the possibility of sensitization of tissues to roentgen rays; considering the short period during which patients have been kept under observation, the Council voted that Thorotrast be not accepted for *intravenous administration.* The Council also voted that acceptance of Thorotrast for use in retrograde pyelography and for outlining various body cavities be deferred until more satisfactory evidence becomes available as to its therapeutic usefulness in these fields. The Council further decided that acceptance of the proprietary name "Thorotrast" be deferred until satisfactory evidence becomes available that this preparation involves a fundamental improvement over other thorium preparations for use in roentgenography.

22. Flinn, F. B.: Am. J. Physiotherapy, June, 1932.
23. Russ, Clark and Waters: Physics in Medical Radiology, London, 1928.
24. Flinn,[22] Leake, J. P.: Radium Poisoning, J. A. M. A. **98**: 1077 (March 26) 1932.
25. Ellenger and Gans, cited from Solis-Cohen and Githens: Pharmaco-Therapeutics, New York, 1928.
26. Siedamgrotsky and Picard, cited from Arzt and Fuhs: Roentgen Rays in Dermatology, New York, 1927.