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## X-RAY CONTRAST COMPOSITION

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This invention relates to contrast materials adapted to be used in X-ray photography.

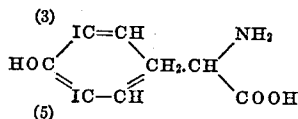
The principal object of the present invention has been to provide a fluid substance which is opaque to X-rays and non-toxic to the human system. The material is adapted to be used by injecting it into body cavities wherein the openings which it fills are delineated as shadow areas upon an X-ray photographic negative by virtue of its radio opacity.

Compositions of this type, used by injection, as distinguished from materials intended to be ingested orally for examinations of the stomach, have been proposed and used to a limited extent in the past but their use has been unsatisfactory for one or more of several reasons; either they are toxic and cause reactions in the patient, the severity of which varies according to the quantity administered or the cavity in which they are disposed, or, on the other hand, the substances are not absorbed by the system but remain for prolonged periods, sometimes collecting in pockets where their presence causes irritation.

The present invention is directed to a material, which is non-toxic to the system, of such a nature that it is readily absorbed by the body and of sufficient X-ray opacity that injections of it provide the contrast which is requisite for good X-ray diagnosis.

Briefly, the contrast compositions of the present invention are comprised essentially of diiodo tyrosine. This substance is indigenous to the human system being found in relatively small quantities in excretions from the thyroid gland. We have found that this substance may be injected into the system in appreciable quantities without subjecting the patient to toxic reaction or to irritation.

Diiodo tyrosine has the general formula—



and, upon the molecular basis contains approximately 58% iodine. By reason of the substantial quantity of iodine which it contains only a small quantity of diiodo tyrosine is required to endow a substantial volume of any X-ray transparent fluid with the opacity that is requisite in X-ray photography.

The limited solubility of diiodo tyrosine in water makes administrations of aqueous solutions of it relatively difficult since some of the material sep-

arates upon standing. However, we have determined that completely stable mixtures can be made, which are entirely suitable for injection, by suspending diiodo tyrosine in an aqueous colloidal vehicle, for example, a solution of gelatin. The colloid selected for the purpose should be non-toxic to the system and for this reason gelatin is preferred.

The amount of diiodo tyrosine employed in the vehicle is governed by the opacity desired; quantities less than approximately 10% by weight usually being insufficient to provide the desired contrast. Good definition is obtained by the use of compositions containing approximately 25% of diiodo tyrosine.

A quantity of colloid is employed in the vehicle in amount sufficient to suspend the quantity of diiodo tyrosine which is used. Thus, generally speaking, the amount of diiodo tyrosine is governed by the opacity desired and a sufficient quantity of colloid is employed to maintain that amount of diiodo tyrosine in suspension in the vehicle.

Gelatin is the preferred colloid used in the vehicles of the present invention because it is non-toxic to the average human system, being converted by the body and consumed. Upon injection the diiodo tyrosine component is excreted through the kidneys. Absorption takes place rapidly and it is, therefore, to be observed that the X-ray photography should be completed within a few hours at the most after injection.

From the clinical point of view, the present contrast compositions may be used in a variety of ways; for example, by injection with a syringe into the subarachnoid system of the spinal cord and brain, the lungs, kidneys, anal fistulae, pilonidal cysts, persistent draining sinuses, joint cavities and glands, that is, parotid and submaxillary. Injections may be made, as by catheterization, into the bladder and uterus. The compositions, by virtue of their non-toxicity, are adapted particularly to be used in neuro diagnoses by injection into the ventricles of the brain, the patient usually suffering no reactions except slight headaches in some cases or a slight temporary rise in temperature. In this latter technique the details of the ventricular system are sufficiently clear as to make fewer views necessary than the twelve to twenty-four X-ray plates heretofore required in the conventional air injection technique.

The material also has been found useful for injection into the knee joint in arthritic cases for visualization of the changes in the inner surface

of the joint. In genitourinary examinations mechanical injection can be made in the usual way.

For the preparation of a typical composition of the present invention, it has been found satisfactory to prepare a gelatinous vehicle and then suspend the diiodo tyrosine in it by agitation. A suitable method for preparing a sterile gelatin vehicle is as follows:

#### Example

To a solution containing approximately 130 c. c. of distilled water is added 1.8 grams of sodium chloride, 1.0 gram chloro butanol, .2 gram of sodium bisulfite, and 40 grams of gelatin (Eastman photographic is suitable). The gelatin is added last and the preparation is mixed vigorously by rotation. This quantity of gelatin is conveniently made in a one liter flask since the mixture tends to boil over if it is sterilized in too small a container. Sterilization is effected by autoclaving the gelatin preparation for thirty minutes at twenty pounds pressure. Aerobic and anaerobic cultures are then made and kept at 37° C. before the sterility of the mixture is decided upon.

Diiodo tyrosine is added to this gelatin mixture in amount sufficient to make up a solution of the desired strength, for example, a 25% solution; the greater the percentage of the diiodo tyrosine the greater the opacity of the composition to X-rays. Upon addition of the diiodo tyrosine the preparation is mixed vigorously and aerobic and anaerobic cultures are made and kept to ascertain that the material is bacteriologically sterile. The composition remains stable for prolonged periods of time if kept in a refrigerator or placed in suitable ampoules. Sterility cultures are made after bottling the preparation to make sure that it is suitable for use.

The typical contrast composition made with gelatin is a gel at room temperature or at the temperature of the refrigerator in which it should be stored. At body temperature, it is a liquid and, for administration, it can be liquefied most easily, when withdrawn from the refrigerator, by placing the vial in which it is contained in a vessel and covering it for a few moments with hot water. It is also desirable that the syringe be kept warm while the gel is liquefied to avoid clogging of the needle passage. Needles of 18 gauge or larger are suitable for administration of the composition by injection.

For use in the subarachnoid the pH of the composition should be between the range of 7.2 to 7.6 and preferably 7.4. For use in other body cavities it is desirable that the pH of the composition be neutral or substantially so.

It has been found preferable to use iodine for halogenation of tyrosine, the amino acid. However, bromine also is opaque to X-rays and dibromo tyrosine may be used in place of the iodo compound.

While gelatin is disclosed herein as the pre-

ferred colloidal substance in which the diiodo tyrosine may be suspended because it is readily absorbed by the body and sufficiently stable to withstand sterilizing by autoclaving, acacia, arabic, and tragacanth and other colloidal substances which the body can absorb may be used instead, though it should be noted that special sterility precautions are required with those colloids that break down at elevated temperature.

The chemical diiodo tyrosine is commercially available in pure form, however, the supply is limited at present. The product can be made by iodination of the amino acid by one of several different methods, as for example, the method of E. Abderhalden, reported in Pfeuger's Archives, volume 201, 1923, pages 432 to 444.

A typical procedure is to mix 1.8 grams of tyrosine and 4.2 grams of sodium bicarbonate in 200 c. c. of water. This composition is treated in ice, with stirring, with 20 c. c. of N. I. and after two hours, with another 20 c. c. of I., whereupon the product is stirred for approximately three hours. It is believed that mono-iodo tyrosine occurs in the formation of diiodo tyrosine but the mono iodide breaks down free hydrogen which combines with another mono-iodo tyrosine molecule forming diiodo tyrosine.

Having described our invention, we claim:

1. An X-ray contrast composition which is adapted to be used by injecting it into body cavities, said composition comprising a material selected from the class consisting of diiodo tyrosine and dibromo tyrosine suspended in an aqueous colloidal vehicle.

2. An X-ray contrast composition which is adapted to be used by injecting it into body cavities, said composition comprising a suspension of diiodo tyrosine in an aqueous vehicle containing gelatin, the said composition being substantially neutral and having a pH value not substantially greater than 7.4.

3. An X-ray contrast composition which is adapted to be used by injecting it into body cavities, said composition comprising approximately 10 to 25% by weight of diiodo tyrosine suspended in an aqueous vehicle containing gelatin, the amount of gelatin present in the vehicle being sufficient to maintain the diiodo tyrosine in stable suspension.

4. An X-ray contrast composition which is adapted to be used by injecting it into body cavities, said composition comprising an aqueous colloidal medium having diiodo tyrosine dispersed in it as the principal contrast producing agent.

5. An X-ray contrast composition which is adapted to be used by injecting it into body cavities, said composition comprising a suspension of a material selected from the class consisting of diiodo tyrosine and dibromo tyrosine in an aqueous vehicle containing gelatin.

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