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X-RAY METHOD OF DIGESTIVE ENZYME DIAGNOSIS  
USING PROTECTED CORE OF CONTRAST AGENT  
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*Fig. 1.*

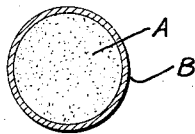


*Fig. 2.*

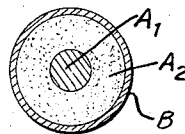


*Fig. 3.*

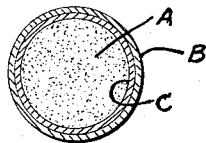


*Fig. 4.*

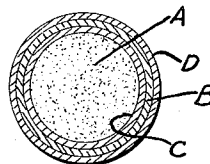


*Fig. 5.*

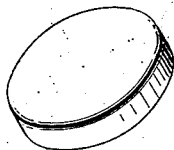


*Fig. 6.*



*Fig. 7.*

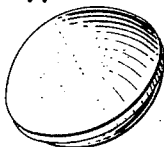
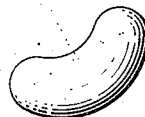


*Fig. 8.*



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## X-RAY METHOD OF DIGESTIVE ENZYME DIAGNOSIS USING PROTECTED CORE OF CONTRAST AGENT

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4 Claims. (Cl. 167-95)

Many different contrast agents and preparations for diagnostic X-ray examination, which mostly differ less in their manner of use than in their chemical constitution, have already been proposed. Especially for examinations of the stomach and intestines insoluble contrast agents in the form of powders, above all barium sulphate, sometimes also thorium oxide and/or mixtures in powder form containing these substances, have however been used nearly exclusively for some time. For practical application these powdery substances are stirred with the addition of water to a thin paste which must be swallowed by the patient. With the aid of this method it is possible to show stomach and intestines radiographically, to recognize ulcers, narrowings or dilations, and to observe the movement of these organs. It is however, impossible to observe in this manner the process of digestion itself or to draw any conclusions concerning the presence or absence of certain digestive enzymes.

It has however already been proposed to dispense X-ray contrast agents in the form of capsules and such-like, especially in order to avoid complaints or irritations of the stomach by such substances which easily cause irritations, or by such substances which are changed by the acid of the stomach.

It has also already been proposed to prepare small quantities of barium sulphate for inclusion in tablets or pills containing pharmaceutically active substances. Their use was however only for the purpose of determining whether tablets or pills of a certain composition guaranteed a good decomposition in the stomach. They thus served as a guide for the pharmaceutical preparation of pills or tablets similarly prepared, which are however free of barium, as to whether good decomposition and thus the desired action is achieved in their therapeutic application.

On the other hand it is possible with the aid of the formed X-ray contrast preparations, according to the present invention, to draw conclusions based on the time of the beginning decomposition of their cores, as to the quantity of enzymes present, respectively absent or insufficiently present, which attack the basic foodstuffs, such as fats, proteins and carbohydrates, and furthermore, to draw conclusions in respect of disturbances of the glands which produce the enzymes.

According to the present invention new compositions of matter are prepared, i. e. formed substances which contain a powdery inorganic contrast agent which is insoluble in water and incapable of resorption and contains in the molecule at least one atom of high molecular weight, e. g. difficultly soluble salts of bismuth (siliceous bismuth), barium silicate and silver iodide, especially barium sulphate or thorium oxide, in a core together with at least one suitable binding agent. This core is coated with one basic foodstuff, i. e. a fat or a protein or a carbohydrate. It is the purpose of this coating to protect the core extensively from decomposition in liquids which do not contain the specific enzyme, so that the

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core does not decompose or only decomposes after great delay after the immersion of the formed contrast agent in such liquids, whereas decomposition in the presence of corresponding enzymes occurs very much faster or may only then become possible. This means that an enzyme splitting fats will attack the new product, when coated with fat, an enzyme splitting proteins will attack the new product when coated with a protein and the same applies to the carbohydrates. This new composition of matter may be dyed by therapeutically harmless dye-stuffs. Only such basic foodstuffs are suitable which are insoluble in water or difficultly soluble without digestion enzymes or which are rendered insoluble or difficultly soluble without such enzymes by suitable means.

These conditions are met by many insoluble fats. Protein bodies are used which are soluble per se, but are made insoluble by suitable treatments. The carbohydrates must be insoluble in water, or difficultly soluble, and difficultly hydrolysable but they must be split up by digestion enzymes.

The invention will now be described in detail, reference being made to the accompanying drawings, wherein

Figures 1 to 4 represent cross-sections through pills or tablets; and

Figures 5 to 8 represent perspective views of different forms of preparations according to the invention.

The formed X-ray contrast preparations used, according to the present invention, have a suitable form, e. g. the form of pills, tablets as in Figure 5, lentils, as in Figure 7, beans, as in Figure 8, or peas, pearls as in Figure 6 and the like. The core A of Figures 1, 2 and 3 which contains the actual contrast agent can be prepared according to the usual processes with the application of suitable known binding agents which guarantee decomposition in aqueous media, as for example, starch, sugar, pectin, dextrin, gum arabic, starch-syrup and such-like. The process of the preparation corresponds to the methods already known. For example, a granulated substance can be prepared with the addition of starch, talcum powder and such-like, from the X-ray contrast agent, which is then pressed into tablets, preferably in the form of lozenges, on tablet presses.

Likewise a pill-mass can be prepared, from which pills of suitable sizes are formed with the aid of pilling machines, from X-ray contrast agents with the aid of sugar, sugar syrup and other suitable binding agents. Furthermore small cores A, of Figure 2, for example granulated material, crystallised sugar and such-like can be coated by a mixture of barium sulphate and sugar in a coating drum until these formed bodies A2 possess the desired size.

A layer B of one of the basic foodstuffs in suitable thickness is added to this formed body which is easily decomposed by means of the binding agent in water and which represents the core, and which contains the actual X-ray contrast agent insoluble in water. For examination for fat splitting enzymes this coating B consists of a solid fat which melts above 37° C. and which can be of vegetable, animal or synthetic origin. Fats which have been prepared by catalytic hydrogenation (hardening) of liquid vegetable or animal oils or such solid fats which are obtained from liquid fats by cooling and separation of the parts which have not solidified, can of course be used. Fats of a melting point of 43-48° C. have proved to be especially suitable. By way of example the following fats may be mentioned: beef-tallow, mutton-tallow, hardened peanut-oil, hardened cotton-seed oil, hardened palm-oil, hardened whale-oil, hardened rape-oil, distearate of propyleneglycol and glycerine esters of fatty acids with a carbon chain between 16 and 20 carbon atoms, as obtained when oxidizing paraffin.

For examination for protein splitting enzymes this coating layer consists of a soluble protein which is made insoluble in water and which then at the uttermost is only capable of swelling to a small degree (or not at all). For this purpose the core e. g. in the form of lentil is either coated with a protein which becomes insoluble by drying or heating or by treatment with aldehydes e. g. with formaldehyde, glyoxal or with tanning agents e. g. tannin or by treatment with thrombin, if fibrinogen was used. As protein may be used e. g. egg-albumin, serum-albumin and serum-globulin. Especially suitable for coating formed X-ray contrast preparations is muscle protein (actomyocin) which does not necessarily require after-treatment but for which, however, heat after-treatment is favourable, or fibrinogen, which has been after-treated with thrombin.

For examination for carbohydrate-splitting enzymes, such carbohydrates or mixtures thereof which swell in water very slowly and become water soluble in the presence of carbohydrate-splitting enzymes are of special advantage as a coating layer. A coating which contains agar-agar especially together with high molecular dextrin has proved itself to be especially suitable. Furthermore, by way of example, the following starches may be mentioned: potato-, wheat-, rice-, rye-, buckwheat-, arrow-rootstarch, tragacanth. Most suitable are mixtures with dextrin or with a sort of starch with a slimy viz. sticky, carbohydrate as tragacanth, agar-agar, gum arabic. It is especially advantageous to heat the starch, after it has been applied, to more than 100° C. e. g. 110°, especially 140–150° C. for about half an hour. Thereby the layer becomes very insoluble.

The thickness of the layer consisting of the basic foodstuffs can be of varying size according to the desired time of beginning decomposition of the core. Thus the thickness of the layer when using fats of a melting point of 43° C. is best 0.5 mm., when using a fat of a melting point of 48° C. is best 0.2 mm. Generally the thickness of the layer can be between 0.1 and 1 mm.

As these coating agents often diffuse into the core to a certain extent during the coating, it has proved advisable to use such X-ray contrast preparations which have the core isolated from the coating by an intermediate layer C of Figure 3. This intermediate layer C of Figure 3 must be at least easily decomposed in aqueous liquids, or even better must be easily soluble. Intermediate thin coating layers of sugar and/or pectin have proved best suited. Further suitable materials are milk-sugar, dextrose, fruit-sugar, mannite, water-soluble methyl-cellulose, gum arabic, polyvinylpyrrolidone.

In order to protect the coating layer consisting of the basic foodstuffs against the action of bacteria or the atmosphere it is convenient to use such X-ray contrast agents which possess above this foodstuff-layer a further suitable, protective indifferent and easily soluble layer D as in Figure 4 as for example, a layer of sugar. This layer of sugar can be aromatized and can also be dyed by means of a harmless dyestuff in order to characterize the kind of X-ray contrast agent concerned. Instead of sugar e. g. milk-sugar, dextrose, fruit-sugar, pectin, starch-sugar may be used. The whole preparation or at least the final outside layer may be dyed.

The layer of the basic foodstuff, such as fat, protein or carbohydrate, can also contain conserving agents (e. g. esters of p-hydroxy-benzoic acid, benzoic and salicylic acid) for better stability, and in case there is no final coating layer, can also contain harmless dyestuffs for characterization. Furthermore they can also contain admixtures which are not detrimental to the desired action of the layer. Thus for example a layer of fat can contain lecithin and such-like.

The coating layer of basic foodstuff is applied to the formed bodies whose preparation has already previously been described and which may be coated with an easily

soluble layer such as a layer of sugar, in a manner known already in that the basic foodstuffs in a liquid form, i. e., usually in dissolved form or liquified, is coated on according to any suitable process as evenly as possible. Liquid form means in a liquid state, in solution or suspension.

This process can be carried out by dipping the formed bodies into a suitable solution of the required basic foodstuff and evaporation of the solvent hereafter. In case an insufficient thickness is obtained after dipping once, the process can be repeated. The coating of the required layer in a coating drum has proved especially suitable whereby it is especially advantageous to remove the solvent by means of a current of air which can be cold or hot and which is blown into the drum, if solutions are used in the coating process. Furthermore it has proved advantageous to add the coating agent by means of a spray gun as used in the lacquer technique, as then the applied layer is freed almost instantaneously from the solvent and adhesion of the single forming bodies is avoided. A layer of fat is advantageously applied by means of a solution of fat in an organic solvent, but carbohydrates and proteins are advantageously applied in aqueous solution. Furthermore the application of fats can also be carried out by spraying a liquid, that means a molten fat upon the formed bodies. In this case air need not be blown into the coating drum. On the other hand it is advantageous to cool the coating drum in this case. Also pulverized (powdered) fat may be used advantageously. It is to be recommended when using fibrinogen solution as coating agent to spray alternately the said solution and a solution of thrombin. The after-treatment of the coated formed bodies, for example, by heat or with formalin, can be carried out in the coating drum itself, or also otherwise. It is mostly expedient, especially when using aqueous solutions, to blow an air current warmed to 40–50° C. into the coating drum, whereby the water is removed faster and also a certain after-treatment is then already achieved. A further especially advantageous kind of applying consists therein that two components (identical or different ones) of the same group (two fats, two proteins or two carbohydrates) are applied simultaneously one in the liquid form (liquified, in solution or in suspension) the other in powdered form. This process is carried out in a coating drum and the two components may be supplied either separately or together or the powdered component suspended in the liquid component. When coating with protein on the one hand e. g. finely powdered protein is used which may be already insoluble and on the other hand a solution of protein e. g. a solution of actomyocin.

When producing coatings of carbohydrates e. g. a mixture of finely powdered agar-agar and a solution of dextrin or finely powdered starch and a solution of agar-agar or tragacanth may be used. In the case of fats, e. g. a hardened fat and mutton fat, in the case of proteins, casein and actomyocin can be used. The advantage of this method is that the coatings may be prepared in materially shorter periods of time.

The formed bodies, which have if necessary been after-treated by heat and such-like, can subsequently be coated in a known manner with a layer of sugar or such-like also in a coating drum.

So that a doctor can distinguish the three different basic foodstuffs on the X-ray film or image during the radiation of the digestive organs with simultaneous use of X-ray contrast preparations containing the three different basic foodstuffs, it is advantageous to choose a different outside appearance e. g. outer form for each of the three different X-ray contrast preparations, for example, a lentil, pea, and bean form. From similar considerations the three differently formed X-ray contrast preparations can be made in a differentiating size. The same formed X-ray contrast preparations with a different thickness of layers may be characterized by a different form or size

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and/or colour. The following examples serve to illustrate the invention without limiting it in any way.

#### Example 1

Several highly curved lozenges containing within their core 83% of barium sulphate which are coated with a layer 0.45 mm. thick consisting of beef fat of melting point 43° C. and treated with a conserving agent and keratin, are swallowed with a little water. The X-ray picture obtained from a person under examination who has a normal fat digestion, i. e., who possesses the normal amount of fat splitting enzymes, shows up to about 3 hours after swallowing black, round or oval discs, according to their internal position (the images of the lozenges), after which time the lozenges begin to dissolve. A dark, fogged shadow which continues to increase in density begins to spread out from the lozenges which assume uneven shapes, become smaller, disintegrate into single particles and finally vanish altogether. Persons suffering from defective fat digestion require a time of 4, 6, 8 or more hours in order to decompose the lozenges, or do not decompose the lozenges at all.

#### Example 2

Pills containing barium sulphate which are evenly coated with a layer 3 mm. thick of laminated fibrin and also possess a dyed sugar layer, are used. Persons possessing a normal protein digestion will already exhibit after about 170 minutes similar phenomena to those described in Example 1, which can be observed and photographed.

#### Example 3

Lozenges which contain within their core barium sulphate and which are coated with a layer consisting of agar-agar, high molecular dextrine and pasty starch, and which have been after-treated by formalin vapours and by the effects of heat, and which possess a protective layer consisting of sugar, are used. With persons under examination who have a normal carbohydrate digestion, the lozenges begin to decompose after about 2½ hours.

#### Example 4

A pill mass, from which 1000 pills are formed with the use of a mixture of equal parts of starch and barium sulphate as scattering agent, is prepared from 250 g. of barium sulphate, 75 g. of powder sugar and 25 g. of wheat starch with the aid of sugar syrup. After drying the pills in warm air, they are immersed in beef fat which has been warmed to just above its melting point, and which contains 1% of keratin concentrate and 0.5% of a mixture of the methyl and propyl esters of p-hydroxybenzoic acid. After leaving the pills in the fat for a short time they are taken out with the aid of a sieve and placed into a cooled coating drum. Powdery beef fat dyed with keratin concentrate and conserved with p-hydroxybenzoic acid ester is then added in the coating drum. The coated pills obtained possess a smooth yellowish surface. The thickness of the fatty layer amounts to 0.4 mm.

#### Example 5

Lentil-like tablets weighing 0.125 g. are prepared in the usual manner from 2 kg. of barium sulphate, 380 g. of wheat starch, 100 g. of talcum, 20 g. of magnesium stearate and 30 g. of gelatin. The cores are placed into a coating drum and coated by the addition of molten fat with a melting point of 48° C. which has been prepared from vegetable oil by hydrogenation and which is sprayed onto the cores contained in the rotating and slightly cooled coating drum by means of a spray gun until a coating layer of 0.3 mm. has been obtained. The cores thus obtained are then coated in a second coating drum with a sugar layer which has been dyed red.

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#### Example 6

Lentil-like cores similar to those described in Example 5 are then coated with a layer approximately 0.1 mm. thick consisting of sugar and agar-agar. A layer consisting of a concentrated solution of mutton tallow in ethyl acetate 0.4 mm. thick, is subsequently sprayed on with simultaneous blowing in of air into the coating drum. Finally the tablets are again coated with a sugar layer.

#### Example 7

Uncoated pills prepared according to Example 4 are repeatedly dipped into a solution of fibrinogen. After each immersion the pill is briefly dipped into distilled water which contains a little thrombin and dried. This process is repeated until a layer of about 0.2 mm. thickness has been formed. The pills thus coated are finally well dried and after-treated in a coating drum with a mixture of talcum and a brown, insoluble dyestuff.

#### Example 8

Uncoated lentil-like tablets prepared according to Example 5 are placed in a coating drum. A 1.5% solution of actomyocin is sprayed onto the lozenges by means of a spray gun with such a velocity that the lozenges do not stick together. A stream of warm air is simultaneously blown into the coating drum. After a layer of 0.45 mm. thickness has been obtained the coated lozenges are after-treated in a drying cupboard at 60° C. Finally, they are coated in a further coating drum with a sugar layer dyed green.

#### Example 9

Uncoated lentil-like tablets prepared according to Example 5 are placed in a coating drum. With simultaneous blowing in of warm air into the coating drum a solution of agar-agar and dextrine, which also contains a little lactose and a trace of glycerine, is sprayed onto the tablets. After a layer of 0.3 mm. thickness has been obtained they are dried at 60° C. in a drying cupboard and finally a sugar layer dyed orange is added in a further coating drum.

What we claim is:

1. The method of diagnosing malfunctioning of the digestive process in humans by testing for the presence and activity of a human digestive ferment *in vivo* which comprises orally administering a diagnostic agent comprising a core of a water-insoluble X-ray contrast agent, incapable of resorption, said core being coated with a continuous layer of water-insoluble, non-water-swelling foodstuff specifically digestible by said ferment, and measuring the time of disintegration of said foodstuff layer in the human alimentary tract by X-ray observation.

2. The method set forth in claim 1 wherein said foodstuff layer comprises a fat and said digestive ferment tested is a fat-splitting ferment.

3. The method set forth in claim 1 wherein said foodstuff layer comprises a carbohydrate and said digestive ferment tested is a carbohydrate-splitting ferment.

4. The method set forth in claim 1 wherein said foodstuff layer comprises a protein and said ferment tested is a protein-splitting ferment.

#### References Cited in the file of this patent

##### UNITED STATES PATENTS

1,815,902 Ellzey \_\_\_\_\_ July 28, 1931

##### OTHER REFERENCES

Lesser, The Drug and Cosmetic Industry, vol. 49, Aug. 1941, pp. 151-154 and 161.

J. Am. Pharm. Assn. (1) Sci. Ed., Thompson et al., May 1945, pp. 135-142.

J. Am. Pharm. Assn. (2) Reprint, by Worton et al., Jan. 1938, pp. 21-28.