ministered to the 3 subjects. Because it was not palatable in this form, and its ingestion caused nausea, it was discontinued. It was subsequently desiccated and given again in salol coated capsules.

Where the extract was taken regularly, there was effected a reduction in the size of the liver to normal within from 3 to 5 months. Upon discontinuing the medication the enlargement of the liver recurred in 1-2 months. In each case the decrease in the size of the liver was accompanied by a significant lowering of the total serum lipids and lipid phosphorus.

One can reasonably assume that the introduction of the specially prepared pancreatic extract given in addition to diet and insulin was responsible for the recession of the liver in these 3 juvenile diabetics, where careful control of diet and adequate insulin treatment had been unsuccessful.

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Suitability of Inulin for Intravenous Administration to Man.

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Attention has been called to the fact that, while some samples of inulin are physiologically innocuous, others, apparently of the highest chemical purity, may induce febrile reactions, accompanied in the more severe forms by chills, nausea and lumbar pain.[1] According to Co Tui, *et al.*,[2, 3, 4] the pyrogenic activity can be removed by passing the solution through a Seitz serum filter or EK filter, a fact which we have confirmed for the EK filter. Treatment with filter material (asbestos) in bulk is ineffective. Originally we removed the pyrogenic activity as follows: 750 gm. of dry inulin (8% water) are dissolved in 1500 cc. of hot distilled water and boiled for 5 minutes with 50 gm. of Norit A; the solution is filtered hot

1 Goldring, W., and Smith, H. W., PROC. SOC. EXP. BIOL. AND MED., 1936, **34**, 67.

2 Co Tui, McCloskey, K. L., Schrift, M. H., and Yates, A. L., PROC. SOC. EXP. BIOL. AND MED., 1936, **35**, 297.

3 Co Tui, Schrift, M. H., McCloskey, K. L., and Yates, A. L., PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 227.

4 Co Tui, McCloskey, K. L., Schrift, M., and Yates, A. L., *J. Am. Med. Assn.*, 1937, **109**, 250.

with the aid of suction, mixed with an equal volume of 95% alcohol, and chilled in the icebox. The inulin is filtered out by suction and well drained by hand pressure. If further purification is desired the moist inulin is dissolved in 1200 cc. of distilled water and the above process repeated; otherwise it is dried at 50° for 15 to 24 hours. This method was used by the Pfanstiehl Chemical Company to purify inulin on a large scale, the resulting preparations being non-reactive in man in doses of 100 gm., administered intravenously as a 20% solution in 1.0% NaCl, injected at a rate of 6 to 10 cc. per minute. But more recently Norit extraction has failed to work, both in our hands and in the Pfanstiehl laboratory, and until the method is corrected we are removing the reactivity by filtering the 5 or 10% solution through a Seitz EK serum filter.

Preliminary tests may be made upon dogs by giving the inulin intravenously in doses of 0.5 to 2.0 gm. per kg.; powerfully reactive inulin produces fever of 104 to 105°, usually accompanied by weakness, tremors, vomiting and diarrhea one to 4 hours later, while less reactive preparations produce only slight degrees of fever. It is as yet uncertain that the absence of a reaction in the dog is certification of the innocuousness of the material in man, and we prefer to examine every new lot in man by starting with small doses. The inulin is dissolved in hot, sterile saline, filtered, boiled, and administered by syringe or infusion in from 5 to 20% solution. Testing is begun with a 0.5 gm. dose and if negative the dose is doubled until 100 gm. are given. Hourly rectal temperatures are observed for 6 hours after the injection. Temperatures between 100 and 100.5° are suspect, while rectal temperature above 100.5° or definite subjective complaints are indicative of pyrogenic activity.

Tolerance to inulin reactions can be developed in both man and dogs, as shown by the following: 2 volunteer subjects received 2.0 gm. of inulin No. 684 (a highly reactive preparation) intravenously and both showed a reaction in the form of a severe headache, a chill lasting 20 minutes, increase in pulse rate, a temperature above 102° and perspiration; this dose was repeated on the second day with a diminution of symptoms, and again on the third day with no reaction other than a slight rise in temperature (101 and 100.4°); a fourth injection on the fifth day was again negative, the highest temperature being 100 and 100.4° with no subjective symptoms whatever. Two dogs injected with No. 684 and a third with No. 1382 (0.5 gm. per kg.) showed a marked reaction evidenced by vomiting, defecation, depression and fever. On successive identical injections, 2, 4, 6, 8, and 10 days later the reactions,

including fever, disappeared entirely. Five weeks after the last injection the same samples in the same dose again produced fever, vomiting, tremors and depression, indicating that tolerance had disappeared.

Since our previous report (loc. cit.) and prior to the introduction of the Seitz filter method, we have administered intravenous infusions of chicory or dahlia inulin in doses exceeding 20 gm., 168 times. Usually a priming infusion of 100 cc. of saline plus 15 gm. of inulin was given at the rate of 10 cc. per minute, followed by the slow infusion of 5% inulin in saline. The approximate total dosage of inulin has ranged as follows: 20 to 29 gm., 58 times; 30 to 39 gm., 50 times; 40 to 49 gm., 44 times; 50 to 80 gm., 12 times; 100 gm., 3 times. Excluding a few instances of mild afternoon headache, subjective complaints indicative of pyrogenic reaction have been made in 11 instances. In one instance the reaction was attributable to the saline; in a second, the reaction (chills and a slight fever) appeared to be due to urethral trauma; in 4 instances it is believed that the reaction was due to the administration of unduly warm infusion fluid, a circumstance that arose when we were not using a thermometer to check the cooling coil in the infusion apparatus, and it was possible for excessively warm solution to enter the arm.

The remaining 5 reactions were probably attributable to inulin. One of these consisted of a severe headache, but the maximum afternoon temperature was normal (99.6). Two subjects complained of abdominal-lumbar pain during or shortly after rapid infusion (10 cc. per minute), the pain disappearing when the infusion was stopped for a short time, and not recurring when the infusion was continued at a slower rate. The maximum afternoon temperature of these 2 subjects was also normal (99.2). The 2 remaining subjects showed an unmistakable reaction, as evidenced by chill, marked subjective conmplaints and fever, the afternoon temperature rising from 102 to 103°; it should be noted, however, that the same lot of inulin which induced these 2 reactions was administered 86 times without reaction to other subjects, some before and some after the time when these 2 reactions were observed.

In view of our inability to account otherwise for the 2 distinctly febrile reactions and the other instances of mild complaint recorded above, we infer that some subjects may show an unmistakable reaction with samples of inulin that produce no reaction in other individuals. However, we believe that if the material has been adequately tested untoward reactions accompanying the use of physio-

logically tested inulin are no more frequent than with other intravenous infusions of like duration. Scrupulous care must be observed with respect to the saline and the infusion apparatus. From experience with over 250 infusions carefully observed for reaction, we place considerable confidence in Sterisol saline bottled in pyrex ampoules. The rubber tubing, before being put into use, should be thoroughly cleaned by filling it with N NaOH, stoppering the ends and rolling it vigorously so that the lumen is cleaned by friction, which process removes astonishingly large quantities of particulate material from the best "intravenous" clear gum rubber tubing. It is then rinsed and sterilized by boiling. It must be washed at once and with particular care after use with inulin solutions to prevent the inulin from crystallizing out and adhering to the walls or in small crevices, since these slight incrustations may be a source of reaction.

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Hemodynamic Effects of Subcutaneous, Submucosal, and Subgingival Injections of Procaine-Epinephrine Hydrochloride Solutions.

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The investigations of Luckhardt and Koppanyi[1] were concerned with the pressor effects of epinephrine hydrochloride injected subcutaneously and the effect of massage thereon. In the present work, two problems and their ramifications have been and are being studied. First, the absorption of epinephrine from injections in subcutaneous areas as compared with submucosal injections in the oral cavity. Secondly, the effect of subgingival injections of procaine-epinephrine hydrochloride solutions. Conclusions were drawn from a comparative measurement of the blood pressure changes as evidenced from these injections.

Dogs, 38 in number, were used in the series of experiments. An area on the chest wall was selected for the subcutaneous injections, whereas a site in the dog's mouth at the mucobuccal fold offered an easily accessible area for the submucosal injections. In some of the

[1] Luckhardt, Arno B., and Koppanyi, Theodor, *Am. J. Physiol.*, 1927, **81**, 436.