Series C. Evidence of Synthalin being Inactive

Analysis of nine changes when synthalin was added and blood sugar rose.

Average total rise of blood sugar, 32 mg. per 100 c.cm. (15.5 per cent. of previous level).

Average previous level, 206 mg. per 100 c.cm.

Number of patients, 9 (2 male, 7 female).

Obese patients, 3; thin, 6.

Ages: 20-40 years, 1; 40-60 years, 5; over 60 years, 3.

Type: mild, 4; moderate, 4; severe, 1.

Total observations before adding synthalin, 11—an average of 1.2.

Total observations after adding synthalin, 13—an average of 1.4.

Total period off synthalin before change, 11 months—an average of 1½ months.

Total period on synthalin, 27 months—an average of 3 months.

Average gain in weight, 0.75 lb.

Notes: (a) The average total change in blood sugar was much less than in Series A and B, when synthalin appeared to be active. (b) It should be noted that moderate and severe cases totalled 5, approximately 56 per cent., whereas in the series when synthalin led to a reduction in blood sugar level the moderate cases were only 20 per cent. of the total.

Clinical: One case showed marked hyperpiesia, which appeared to account mainly for symptoms; this patient took insulin for a time later. One case was clinically well, and showed at other times a favourable response to synthalin. One patient reported feeling not so well when off synthalin, though synthalin did not constantly lower the blood sugar. One patient was a "bad dieter," and had symptoms suggestive of mild cholecystitis; she seemed better on synthalin, and at other times the blood sugar reacted favourably to the drug, with falls more marked than the rise included in this series. Two other cases later required insulin, one of which reacted favourably to synthalin on other occasions. One patient seems to be slowly deteriorating, and it appears that he will probably need insulin.

Series D

Analysis of eight changes when synthalin was withdrawn and the blood sugar fell.

Average total fall of blood sugar, 28.5 mg. per 100 c.cm. (10.25 per cent. of previous blood sugar level).

Average previous blood sugar level, 278 mg. per 100 c.cm.

Number of patients, 7 (2 male, 5 female).

Obese patients, 4; normal, 1; thin, 2.

Ages: 40-60 years, 4; over 60, 3.

Type: mild, 3; moderate, 4.

Total observations before adding synthalin, 19—an average of 2.4.

Total observations after adding synthalin, 8—an average of 1.

Total period on synthalin before change, 25½ months—an average of 3.2 months.

Total period off synthalin after change, 15 months—an average of 1.9 months.

Average loss of weight, 0.4 lb.

Notes: In this series when synthalin appears to be inactive it should be noted that, as in Series C, the moderate cases account for 57 per cent. Clinically, one patient, also in Series C, suffered with severe hyperpiesia. One patient was soon afterwards admitted as an in-patient suffering with ulcerative colitis; there was no reason to believe that this was due to synthalin, but the colitis may have disturbed the carbohydrate metabolism. Two patients reported as not being so well when off synthalin. Two later required insulin. In one patient delayed menstruation might possibly have disturbed the blood sugar level.

CONCLUSIONS

1. Used under the conditions outlined it appears that synthalin generally causes a moderate fall in the blood sugar level of adult out-patients with diabetes of mild or moderate severity, and that the general condition of such patients is improved by taking the drug.

2. Though we have used synthalin over long periods and in sufficiently large doses to produce a definite effect on the blood sugar in approximately 80 per cent. of sixty patients, we have found no evidence of toxicity, except in a few rare instances in which the toxic symptoms were only mild.

3. Our usual dosage has been 10 mg. three times daily after food for three consecutive days, with a "rest" on the fourth day.

4. We are not satisfied that synthalin B (the more recent product) has any material advantages over synthalin, which is the less expensive.

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ACTIVITY OF COMMERCIAL PREPARATIONS
OF HOG'S STOMACH

BY

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The increasing replacement of liver by hog's stomach in the treatment of pernicious anaemia^{1 2 3} makes it very important to ensure that the stomach preparations should be active and suitable for that purpose. During the last two years a large number of different preparations have become available, with the coincident possibility of unsuitable preparations being employed at grave risk to the patient. Obviously the palatability and ease of administration of a particular preparation is of no account if the preparation is inactive. As I have had occasion to examine one or two commercial preparations which were found to have an inadequate potency, it appeared advisable to investigate the activities of others. This was imperative, since the distribution of stomach preparations of uncertain value might continue and prove a potential danger to the class of patients concerned.

Of the sixteen preparations examined fourteen are in the form of powders (desiccated muscular or mucosal portions, or whole stomach), the other two being described as hog's stomach tissue "extracts." Their equivalence in fresh tissue is variously given by the manufacturers as four to seventy times the weight. Ten of these preparations are stated to be fat-free. The stomach preparations were supplied for clinical trial by the commercial houses which issue them, but a few samples were purchased in their original packages. Of some of the preparations further clinical samples were submitted by the suppliers after preliminary adverse reports, and it is believed that several active products have become available for general clinical use. Investigations showed that the commercial preparations

differ very considerably in their activities—some giving excellent responses consistently, while many others show inconstant or wholly negative results. It thus appears probable that the activities of many commercial preparations were being destroyed or reduced during manufacture. This may be due to insufficient knowledge of the essential details of manufacture and of the importance of controlling the products clinically. It is hoped, therefore, that the following details will serve the purpose of ensuring the widespread supply of active preparations of pig's stomach for the treatment of pernicious anaemia.

MANUFACTURE OF ACTIVE STOMACH POWDER

The following outline indicates the essential details:

1. The raw material is the whole hog's stomach. It has been shown² that such herbivorous animals as the cow and sheep do not furnish suitable potent preparations. It is desirable that the *whole* stomach be used.
2. The stomachs should be obtained as soon as possible after the pigs are killed, and then, if not to be dried at once, should be kept at 0° C. It is important that salt should not be added to preserve the stomachs.
3. The stomachs are freed from adherent fat, opened, and washed in cold running water at room temperature.
4. They are then examined for parasites, tumours, etc.; small nodules may often be found in the mucous membrane. Stomachs showing such abnormalities must be rejected.
5. The adherent water is removed by centrifuging, if necessary, and the whole stomachs are then minced as finely as possible by being passed several times through a mechanical mincer.
6. The finely minced tissue is desiccated in suitable driers, either *in vacuo* or at ordinary pressure.
7. Drying must be carried out at a temperature *not exceeding* 45° C. The time required for this operation varies according to the type and size of the plant employed, but rapidity has some importance.
8. The product so obtained is ground to the finest powder possible in a suitable pulverizer, but the temperature must not be allowed to rise during this stage.
9. The product is a light, biscuit-coloured powder, has a slight odour, and a faint fatty taste. It contains less than 6 to 7 per cent. of moisture, not more than 10 to 11 per cent. of fat, and usually less than 11 per cent. of total nitrogen. It appears to keep indefinitely if dry. The fat content can be very largely reduced by means of the usual fat solvents. This renders the preparation slightly more palatable but more expensive. *All traces of any such solvents must be carefully removed before it is issued for use.*
10. *Before issue for use* the product so obtained must be examined: (a) Bacteriologically, for pathogenic organisms; (b) Clinically, for its activity in producing remissions in pernicious anaemia (*vide infra*). Although one batch of a product may be quite potent it does not necessarily mean that all subsequent batches from that source will be active. Thus it is important that all batches issued for general use should have been clinically tested before release. On the other hand, the relative paucity of suitable cases of pernicious anaemia for such work renders it necessary that such testing should be kept to the minimum. (c) For its peptic activity (*vide infra*); this is only suitable as a rough laboratory control test of known samples, since it would be possible for pepsin to be added to an inactive preparation and yet be impossible to differentiate the two. The pepsin content appears to run parallel, in most cases, to the haemopoietic activity of this desiccated product.
11. In the use of desiccated stomach powders it should be remembered that the haemopoietically active substance

is very susceptible to temperatures above 45° C.; the product must not be administered, therefore, in hot liquids.

TESTING OF HOG'S STOMACH PREPARATIONS

It should be stated at the outset that, until a suitable reliable laboratory method is fully worked out, there is only one satisfactory method of testing these preparations of hog's stomach for their ability to induce remissions in pernicious anaemia—that is, by direct clinical observations on patients suffering from that condition. However undesirable the method may be, it should be remembered that it is for the ultimate benefit of the numerous patients under treatment for this disease. Obviously, the greater the number of cases used, the more accurate the estimation of the value of each preparation, but owing to the large number of these preparations available, the use of many cases for each is impracticable because of their scarcity. It was possible, however, to devote a few cases to the examination of each preparation in this particular investigation—certain preparations used as controls having featured in the treatment of more than 240 cases.

(a) Potency for Initiating Remissions in Pernicious Anaemia

For this test all samples are administered to cases of true pernicious anaemia under careful observation in hospital. The following rigid criteria are essential before any case is considered suitable for these tests:

- (i) The presence of the clinical signs and symptoms of pernicious anaemia, together with achylia gastrica, a high colour index, and typical blood picture.
- (ii) A red blood cell count of less than 1,500,000 per c.mm. (not increasing during the control period), so that satisfactory reticulocyte responses may be obtained with active preparations while not missing reduced responses for less active preparations.
- (iii) The absence of all complications (except postero-lateral sclerosis), including minor infections such as tonsillitis, etc.
- (iv) A reticulocyte count that has remained within normal values (below 2 per cent.) for at least seven days prior to commencement of treatment. This is important, since many cases are admitted to hospital in spontaneous remissions easily detected by a determination of the reticulocyte and red cell counts. Treatment in these cases, even with inactive extracts or preparations, gives misleading results.
- (v) No previous treatment has been or is being administered.

The preparation under investigation is fed to such a patient in doses of 30 grams per day, as has already been described,^{1,2} but occasionally doses of 40 grams are administered where there is any preliminary uncertainty as to possible potency. Other preparations, not in powder form, are given in doses greater than the equivalents of 30 grams of the desiccated preparations. After the preliminary control period of at least seven days, the preparation under trial is administered in the routine manner (with meals, in cold milk or water, or mixed with potted meat, etc.) until (a) the reticulocytes have "peaked," returned to normal, and the patient has been discharged from hospital with a good remission in progress, or (b) a minimum of fourteen days has elapsed without any signs of response on the part of the blood. In the latter case, a known active preparation is then administered in doses of 30 grams daily and the case shown to have been suitable for the test by the subsequent response obtained. If a response is not then obtained within twelve days the case is rejected as unsuitable for the test.

The progress of the condition of each patient is observed clinically and by regular estimations of the reticulocytes, red blood cells, white blood cells, and haemoglobin in the circulating blood. The reticulocytes are determined by the well-known vital staining method using brilliant cresyl blue. These are counted daily, and given as a

percentage of the concurrent red blood cell count. The red blood cells, haemoglobin, and white blood cells are estimated twice to six times per week, according to the condition of the patient.

An active preparation is characterized by a rapid clinical improvement, usually commencing in the first week, and the following measurable blood changes in a case of pernicious anaemia (cf. Chart, from 24th day onwards):

(i) A rise in the reticulocyte percentage within seven to twelve days of commencing treatment to a maximum of between 30 and 70 per cent. after a preliminary seven-day control period.

(ii) A progressive increase in the haemoglobin and red blood cell values after the reticulocyte "peak," without a relapse, to normal values.

Ultimately, an adequate dosage should maintain normal health.

Peptic Activity

The preparation of a suitable active desiccated preparation of hog's stomach necessitates the preservation of the natural enzyme activity of the stomach tissue. If this is destroyed the haemopoietically active substance in stomach is also destroyed. This is in contradistinction to liver. On the other hand, the presence of the known enzymes in stomach tissue is not a criterion of its activity for initiating remissions in pernicious anaemia, although it is certainly a good rough guide to its probable value. Too much stress, however, should not be laid upon this particular "value," since, as stated above, adulteration with pepsin would mask inactive preparations.

The estimation of the peptic activity is determined by two methods:

1. The egg-white method.
2. Edestin digestion method.

The most satisfactory technique is, using either of these, to compare the activities of equal weights of the unknown stomach preparation and a known preparation of desiccated hog's stomach, or known scale pepsin, simultaneously by noting the time required in minutes for them to digest equal quantities of egg-white or edestin. It is important to bear in mind that the pepsin values obtained in this test are influenced by the state of division of the desiccated preparations and the strength of acid employed for extraction.

Some comparative results obtained in a few of the preparations examined are shown in the Table. The pepsin contents given in Column 4 show the limits observed in

repeated tests made during the last two years; those in Column 5 with egg-white are the results obtained using the most recent samples of each preparation available. An equal weight of each preparation was employed, and the figures represent the time in minutes required for complete digestion.

ILLUSTRATIVE TESTS

Preparation A

A desiccated preparation of hog's stomach of a light biscuit-colour, and having a slight odour; it contained 11 per cent. of fat, and gave peptic activities of (a) edestin, 15 minutes, (b) egg-white, 14 minutes. A daily dose of 30 grams was administered in cold milk to a case

of pernicious anaemia after a control period of seven days (cf. Chart, 24th day onwards)—initial red cell count 1,400,000; haemoglobin 38 per cent. The reticulocytes reached a maximum of 42 per cent. on the eighth day of treatment, and the blood picture showed a progressive improvement to: red cells 3,200,000 and haemoglobin 77 per cent. on the sixteenth day. The

patient is still taking the preparation, and is in normal health.

Preparation H

A desiccated preparation of hog's stomach (H, i) almost white, no odour; contained 1 per cent. of fat and 2 per cent. moisture. Peptic activity is nil by both edestin and egg-white methods. It was administered in daily doses of 40 grams to a case of pernicious anaemia, after the seven-day control period—initial red cell count 980,000, and haemoglobin 38 per cent. After eighteen days there had been no response, and the blood count had fallen to: red cells 790,000, and haemoglobin 19 per cent. A known active preparation was substituted (30 grams daily) with good results (see Chart). The inactivity of this product was confirmed in two other cases. This report was referred to the manufacturers, who supplied a modified preparation after certain recommendations had been made. This second product (H, ii) was similar in appearance to the first, but the peptic activities were (a) edestin, 12 minutes, (b) egg-white, 12 minutes. The administration of 30 grams daily to a suitable case of pernicious anaemia gave a rapid reticulocyte response (38.5 per cent. on the tenth day) similar to that shown in the chart. This product is now quite satisfactory.

DISCUSSION OF RESULTS

As a result of this investigation it may be stated that (1) the active preparations of hog's stomach have shown good peptic activities at all times in the large number of samples examined, and (2) the inactive preparations have failed to show peptic activities. Three preparations had variable peptic activities in different samples, two of them being inconstant in their ability to initiate remissions clinically. It should be made clear that pepsin is not the active principle, but only serves as a rough laboratory guide to the possible presence or absence of the, as yet, unidentified active substance. Certain of these preparations have been described in the medical literature as giving satisfactory results, although I

Illustrative Examples of Results Obtained with Stomach Preparations

Preparation	Daily Dose, Grams	Remissions Produced	Peptic Activity: Digestion Time in Minutes	
			Edestin Method	Egg-white Method
A	15-30	+	14-24	14
C	15-30	+	23-32	12
D	30	+	19-44	17
H (i)	40	None	No digestion	No digestion
H (ii)	30	+	12	12

have previously criticized the lowness of the reticulocyte responses in some of the cases.³

It appears probable that the manufacture of these products has not been sufficiently standardized or controlled, so that batches of inactive material have been released for use before clinical trials have been carried out—an extremely serious matter where the life of a patient may be concerned. This may account for the occasional reports in the medical literature of cases of true pernicious anaemia "resistant to hog's stomach preparations."

Obviously, rigid clinical control of all material supplied to patients is essential if the safety of a large number of those under medical treatment is to be assured.

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A NOTE ON AORTIC VALVULAR DISEASE

WITH REFERENCE TO ETIOLOGY AND PROGNOSIS

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Disease of the aortic valves is generally due to rheumatism or syphilis; but the relative importance of these two conditions is very differently estimated. In some series most of the cases have been considered syphilitic, while in others nearly all under the age of 40 have been said to be rheumatic. In the following series of nearly 300 consecutive cases the cause was rheumatic in more than one-half, and syphilitic in about a quarter. Out of every six cases with disease of the aortic valves, acute rheumatism accounted for four, syphilis for one, while atheroma and all other causes were responsible for one or less.

The etiology is summarized below.

TABLE I.—*Etiology in All Cases of Aortic Valvular Disease*

	Acute Rheumatism	Syphilis	Atheroma	Other Causes
Guy's Hospital ...	100	29	9	12
Heart Hospital ...	100	26	11	9
Total ...	200	55	20	21

When rheumatic patients with marked mitral stenosis were excluded, out of every four patients with aortic disease, acute rheumatism was responsible for two, syphilis for one, and all other causes for one or less. Advanced atheroma was present in half of the cases which were not either rheumatic or syphilitic, and was probably the causal factor. Of the twenty-one cases due to "other causes," which will not be further discussed, primary infective endocarditis was responsible for six, and in most of the remainder the cause was unknown. The etiology was adjudged rheumatic when there was (1) a clear rheumatic history (177 cases), or (2) mitral

stenosis, even without this (23 cases). When there was mitral stenosis (confirmed by x rays), only routine inquiries were made for a history of syphilis, and the Wassermann reaction was frequently not done. In the absence of mitral stenosis, careful inquiries for any history of syphilis, and a Wassermann reaction and x -ray examination of the aorta, were included. Patients were placed in the atheromatous group when radioscopy suggested such changes in the aorta in those who could not be included in the two previous groups, or when there were advanced arterio-sclerotic changes in the brachial, radial, or retinal arteries.

Table II shows the different types of valvular disease in the rheumatic group. Of each six cases, roughly

TABLE II.—*Type of Rheumatic Valvular Disease*

	Males	Females	Total
Aortic stenosis and incompetence* ...	24	10	34
Aortic incompetence alone ...	27	15	42
Aortic stenosis and } with mitral stenosis ... {	9	26	35
Aortic incompetence }	37	52	89
Total ...	97	103	200

* Five cases with aortic stenosis had no evidence of aortic incompetence while they were under observation.

speaking, three had aortic incompetence and mitral stenosis, the fourth had aortic stenosis as well, and the fifth and sixth were clinically without mitral disease, one having aortic incompetence alone and the other aortic stenosis and incompetence.

AGE AND SEX INCIDENCE

There were equal numbers of men and women in the rheumatic group, but they were differently distributed. In those without mitral stenosis there were twice as many men as women; in those with mitral stenosis the proportions were two men to three women. In the syphilitic group there were three men to one woman. In the atheromatous group there were seventeen men and only three women. Of those with syphilis nearly 80 per cent. were between 40 and 60, there being no sex difference in the ages; in the atheromatous more than 90 per cent. were over 50. On the other hand, 90 per cent. of the rheumatic cases were between 10 and 50.

The etiology is well shown in Fig. 1; nearly all the

FIG. 1.—Age incidence of three main types of aortic disease.

Note.—Below 40, rheumatism is responsible for nearly all cases; from 40 to 50, it is still a more common cause than syphilis; from 50 to 65, syphilis is the most common cause; after 65, atheromatous changes.

cases under 40 were rheumatic, while after 50 syphilis was the responsible factor twice as frequently as rheumatism, atheroma occupying an intermediate position. With the rheumatic cases the incidence was more evenly spread from 10 to 45, but there was a group of men with aortic stenosis between 45 and 55.