debility, shortness of breath, and cough. At present she has no expectoration; her respiratory capacity is one inch. Although the apices of both lungs in front are resonant, there is distinct flattening of the percussion note at the bases. The respiratory murmur at the apices and mid-lung is coarser than usual, and the expiratory murmur is prolonged. At the right base the respiratory murmur is feeble, and small dry friction sound is heard. Towards the base of the left lung and extending into the axilla are heard small moist tinkling sounds, suggestive of cavitation having taken place; here also small friction sounds can be heard. Similar physical signs prevail posteriorly. The apex beat of the heart is displaced upwards and outwards; it is felt external to the nipple, a circumstance which, combined with marked accentuation of the second sound of the heart heard over the pulmonary artery, suggests that fibrotic changes have already occurred in this lung. Although the patient states that she has no expectoration, this was present six weeks ago, and when examined was found to be free of tubercle bacilli. There is no enlargement of the external glands.

The other patient, aged 39, has been an asbestos worker for eighteen years. She had no illness until four years ago, when she developed cough and attacks resembling bronchial asthma. After remaining away from the factory for three months she returned to her employment, and followed the occupation for three years, when she married, and as in the early months of her pregnancy she lost considerably in weight she retired from the factory. Although reduced considerably in weight, and the subject of cough all through her pregnancy, her infant daughter, who is 14 months old, is healthy and well developed.

The patient complains of a dragging in the chest without actual pain. There is noticeable shortness of breath on slight exertion, and she complains of morning cough with expectoration. The sputum has been examined and is negative as regards tubercle bacilli. Her appetite is poor. She weighs 8 st., a drop of 3 st. having occurred within the last two years. Her heart is healthy; the apex beat is not displaced, but the second sound over the pulmonary artery is distinctly accentuated. The apices of her lungs are resonant. Here the respiratory murmur is coarser than usual and the expiratory is prolonged, so that the inspiratory and expiratory murmurs approach each other in equality. Moist râles are heard in mid-axillae and small friction with crepitation is heard at the bases. This woman's mother, who is aged 60, is still working in the factory.

From what I have seen clinically of pulmonary asbestosis it resembles silicosis of the lungs in the marked shortness of breath on slight exertion, deficient respiratory capacity, physical debility, and, in examination of the sputa of not too far advanced cases, absence of tubercle bacilli, but since fibrotic changes are developing in both of the patients to whom I have alluded, there is almost sure to develop, if such has not already taken place, pulmonary tuberculosis.

The clinical picture of pulmonary asbestosis differs slightly from that presented by a patient the subject of ordinary tuberculosis of the lungs, in so far as there is a pronounced deadening of the skin varying from mild bronzing to slight blueness, a degree of shortness of breath in excess of the physical signs, a greater amount of general disability, little expectoration, and comparative absence of night sweats.

AN ACTIVE CONSTITUENT OF THE PREPARATION CALLED "GLUKHORMENT."

BY

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AND

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IN May of this year Professor von Noorden published in the *Klinische Wochenschrift* an account of a new pancreatic preparation which had a controlling effect on carbohydrate metabolism, but, unlike insulin, was effective when administered by the mouth.¹ To this preparation the name "glukhorment" had been given, and the title of the paper made it clear that the substance was regarded by the author as containing a new anti-glycosuric principle, naturally preformed in the body. On information, evidently supplied to him by the chemist responsible for devising "glukhorment," Professor von Noorden stated explicitly that, in spite of indications in the patent specification, which might suggest some connexion of the active principle with a guanidine derivative, no such derivative, and in particular no synthalin,* had been added; and, further, that the finished preparation contained no guanidine derivative of any kind in recognizable amount. Professor von Noorden drew the cautious conclusion that, if the activity were due to a guanidine derivative, it would have to be one of extremely high activity. In July of this year one of us (H. H. D.) received a communication from the Horment Company, who were manufacturing glukhorment, stating that they were sending material in the hope that clinical trials of it could be arranged. In due course this and several subsequent consignments of glukhorment were sent by the Horment Company, with a request for their trial.

A consideration of preliminary reports, on the mode of action of this preparation on the human being and on laboratory animals, suggested a strong similarity between its effects and those with which we had become familiar, through experiments then for some time in progress, on the action of synthalin. Some of the glukhorment

was immediately placed in the hands of one physician, who will presumably report his experience with it in due course. The physiological resemblance to synthalin was so pronounced, however, that, before the question of wider clinical trials was considered, it was thought desirable to make a simple chemical examination, in order to confirm the fact that the preparation was free from synthalin and similar guanidine derivatives, as stated in the paper by Professor von Noorden, of which copies had been submitted by the Horment Company in support of their request. The result of this first test showed clearly that a guanidine derivative strongly resembling synthalin was present in substantial amount in the glukhorment tablets as submitted for trial. The evidence thus early obtained was at once so clear and so surprising that it was considered desirable to use a further quantity of the material submitted, in order to obtain precise information as to the nature of the substance in question. The isolation of the substance was made easy by the fact that the nitrate of synthalin is a remarkably insoluble salt.

Chemical Isolation from Glukhorment of a Guanidine Derivative closely resembling Synthalin.

Two hundred glukhorment tablets were powdered; the powder, weighing 60 grams, was thrown into 1 litre of boiling water and the mixture was kept gently boiling for fifteen minutes. The liquid was then filtered, while still hot, from a large mass of insoluble protein.

The filtrate was evaporated *in vacuo*, with the addition of octyl alcohol to prevent frothing, to a volume of 120 c.cm. On standing, it set to a jelly; this was warmed to 40°, when it became fluid, and concentrated nitric acid was added until the reaction of the liquid was strongly acid to Congo red. A white crystalline nitrate separated from the solution on standing, and the liquid no longer set to a jelly when cold. The crystalline material was collected by centrifuging, washed in the centrifuge with a small quantity of dilute nitric acid, and dissolved in about 25 c.cm. of hot water. This solution was boiled with charcoal and filtered. To the hot filtrate 0.5 c.cm. of 6 per cent. nitric acid was added, and the nitrate crystallized on cooling. This was filtered off and dried; it weighed 1.135 grams. It was then converted into the picrate by dissolving it in water and adding a saturated solution of sodium picrate until no further precipitate was produced. The picrate was filtered

* "Synthalin" is the synthetic compound, decamethylenediguanidine, introduced by Frank, Nothmann, and Wagner, as an antidiabetic remedy for oral administration, and already the subject of numerous reports.

off, washed with water, and recrystallized from 1,200 c.cm. of boiling water: yield of recrystallized picrate 1.681 grams.

The picrate was then warmed on the water-bath with 15 c.cm. of a mixture of 75 per cent. alcohol with 25 per cent. of 5 per cent. aqueous hydrochloric acid. To the clear warm solution were added 250 c.cm. of acetone, which precipitated the hydrochloride. This was filtered off and washed with acetone and ether until free from picric acid: yield of hydrochloride 0.806 gram.

This salt was crystallized from 12 c.cm. of water and 0.2 c.cm. of concentrated hydrochloric acid: yield 0.680 gram. From this salt the picrate (fine, curved needles), the chloroaurate (thin, long rectangular plates), and the mercurichloride (prismatic needles) were prepared.

Through the courtesy of Messrs. Schering we were in possession of a specimen of Kahlbaum's pure synthalin hydrochloride. This was compared with the hydrochloride isolated from glukhorment, and the above series of salts was also prepared from Kahlbaum's specimen for comparison. Both synthalin hydrochloride and the hydrochloride isolated from glukhorment gave identical purplish red colours when tested by Sakaguchi's reaction for guanidine derivatives, and in each case the corresponding salts had identical physical properties (solubility, crystalline form, and melting point). Mixed melting point determinations showed no depressions.

	Source.	Melting Point.	Mixed Melting Point.
Hydrochloride ...	Kahlbaum's synthalin ...	202°	202°
" ...	From glukhorment ...	200°	
Picrate ...	Kahlbaum's synthalin ...	196-8°	195-8°
" ...	From glukhorment ...	195-8°	
Chloroaurate ...	Kahlbaum's synthalin ...	156-8°	156-8°
" ...	From glukhorment ...	156-8°	
Mercurichloride ...	Kahlbaum's synthalin ...	172-6°	172-6°
" ...	From glukhorment ...	172-6°	

The chloroaurates were analysed and found to contain the same percentage of gold, which, moreover, is precisely that calculated for decamethylenediguanidine (synthalin) dichloroaurate—namely, 42.1 per cent.

Chloroaurate (from Kahlbaum's synthalin): Contained no H₂O of crystallization; 0.2146 gram, dried at 102°, gave 0.0901 gram Au. Au=42.0 per cent.

Chloroaurate (from Glukhorment): Contained no H₂O of crystallization; 0.2125 gram, dried at 102°, gave 0.0894 gram Au. Au=42.1 per cent.

It will be seen from this fairly thorough chemical comparison that the substance isolated from glukhorment is indistinguishable, by the tests applied, from synthalin as prepared by Kahlbaum. It must be either identical with synthalin, or so closely related to it that an elaborate analytical investigation with large amounts of material would be required to distinguish between them. A sample from a batch of glukhorment submitted quite recently, with the suggestion that this would prove to be better than earlier batches, contains the same synthalin-like substance in about the same proportion.

Physiological Tests of the Substance Isolated from Glukhorment.

We are indebted to Mr. H. P. Marks for investigating the action of this substance on two rabbits. The animals (each weighing 2 kg.) fasted for twenty-four hours; then into (1) 20 mg. and into (2) 50 mg. of the substance, in aqueous solution, were injected subcutaneously.

Rabbit.	Blood Sugar Percentage (Hours after Injection).						
	0	1	2	3	4	5	6
(1)	0.44	0.262	0.327	0.385	0.179	0.134	0.069
(2)	0.141	0.310	0.251	0.090	0.073	—	—

Rabbit (1) developed convulsions after six hours and rabbit (2) after four hours. When in convulsions they were killed, and samples of their livers taken for glycogen determinations.

Rabbit (1) had 0.05 per cent. liver glycogen.
Rabbit (2) had 0.02 per cent. liver glycogen.

These results are closely similar to many which have been obtained in this laboratory by similar injections of synthalin into rabbits.

These experiments establish beyond question the fact that the glukhorment tablets, as issued for therapeutic use, contain either synthalin itself, or a substance so closely related to synthalin as to be indistinguishable from it, by the chemical and physiological tests applied. The information on which Professor von Noorden had based his published statement, that glukhorment contained neither synthalin nor any other guanidine derivative in recognizable amount, was clearly incorrect. Substantially more than 1 per cent. of a guanidine derivative, indistinguishable from synthalin, was easily extracted from the tablets; and it was quite certain that the process would not yield, in pure form for weighing, more than a part of what was originally present.

The point obviously had a practical interest, and we decided that it was our duty to inform Professor von Noorden of the results of our investigation, and to place at his disposal the details of our experiments.

Professor von Noorden's reply, dated November 17th, 1927, made it clear that he had already received somewhat similar information from another quarter, and that he had taken the first opportunity of making a public statement concerning the position, as thus for the first time revealed to him. At his request we give the following translation of an extract from a lecture which he delivered on November 8th in the Berliner Fortbildungsinstitut für Aerzte. He informs us that this same part of his lecture will be published in No. 23 of this year's volume of the *Zeitschrift für ärztliche Fortbildung*, about December 1st.

"The Position of the Glukhorment Question."

(Extract from a lecture delivered on November 8th, 1927, by Professor C. von Noorden.)

Concerning substitutes for insulin I will only report briefly, since nothing of a final nature can be said concerning them.

The insulin-like nature of the guanidine derivative synthalin is not contested by anyone, provided that sufficient doses are given; but the curative dose and the injurious dose lie close together; the dividing line is often indistinct, scarcely recognizable, and shows wide differences in individuals. From month to month communications concerning synthalin accumulate. The contraindications become constantly more frequent, and stronger in comparison with those in its favour. That is the position of synthalin to-day.

Concerning glukhorment you will wish to hear something more definite. You must not, however, expect to hear anything final. I reported on it at the end of May, since, already one month earlier, before the conclusion of the preliminary experiments, a communication concerning it had reached the daily press, through a deplorable indiscretion.

The favourable conclusions which I then published in the *Klinische Wochenschrift* (No. 22)¹ are based on incontestable facts. The preparations which I received at that time, and on which I remained dependent until the beginning of the actual manufacture in July, were prepared on the smallest scale, and, according to the assurance on word of honour, which I then demanded and received, were prepared by strong tryptic digestion of fresh pancreas substance for about eight days, without any kind of addition. To which part of the fermentation mixture, rich in peptides, the undoubted antglycosuric action was attached, remained uncertain. I left the question open at that time, as to whether through the powerful tryptic digestion a very potentially active guanidine derivative might have been produced.

As happens also in other departments of chemistry, the preparations obtained by the later development of manufacture on a large scale failed by far to attain the activity of those obtained in small-scale working. They satisfied neither myself nor others. When, after a long absence, I again took up the investigation a few weeks ago, I received for the first time preparations from the large-scale manufacture, which, indeed, were inferior in activity to the original ones, but were nevertheless usable. Now Wiechowski has stated a few days ago, in the Medical Union of Prague, that he has found a guanidine derivative in glukhorment, which corresponds with synthalin in important reactions and in its pharmacological properties,

As to whether it is a case of true identity or not, Wiechowski obtained no definite evidence, according to his letter to me. Assuming identity, scientific logic would present only two possibilities:

Either, in spite of assurance to the contrary, without my knowledge and against my will, the guanidine preparation known as synthalin is added to glukhorment. In that case, we should be dealing with at least a gross breach of trust in relation to myself and to the public. According to the assurance repeated to me a few days ago, on the word of honour of the responsible chemist, at no time, either earlier or recently, has synthalin been mixed with glukhorment.

Or, the remarkable fact would be presented that from the pancreas, together with other products of decomposition, a substance chemically and pharmacologically at least very similar to synthalin can be obtained—a fact which would be of great importance for the study of intermediary metabolism. I recall in this connexion that I indicated in advance, as a possibility, the formation, together with numerous other decomposition products, of a guanidine derivative of great activity, exceeding that of synthalin.

You will see that I speak quite openly. Given the identity of the two active chemical substances present in synthalin tablets and in glukhorment tablets, the decision between these two possibilities must not be a matter of impression. These are questions for experimental investigation, of which, on my part also, there shall be no lack.

We need add but little to Professor von Noorden's frank statement. This publication of our own findings is made at his explicit request, and may be regarded as a contribution to the experimental investigation which he himself indicates as imperative. The details of the work done in Professor Wiechowski's laboratory have appeared since we communicated with Professor von Noorden, and learned from him of this other investigation of glukhorment.² Dr. Langecker's evidence of the chemical identity or close chemical similarity with synthalin is much less convincing

than that which we have been able to obtain. The physiological comparisons made in Prague are, on the other hand, more thorough than those which we thought it necessary to make. The conclusions are practically the same as our own.

Our evidence, of course, provides no means of discriminating between the two possibilities which Professor von Noorden mentions. If a substance, so different in structure as synthalin from any hitherto known to occur in the body, were produced by tryptic digestion of pancreatic tissue, the fact would obviously have an interest far beyond that of the immediate question concerning the nature of the active constituents of glukhorment. The point of practical importance, and the one which imposes upon us the necessity of publication, is that glukhorment cannot be regarded as free from synthalin, or similar guanidine derivatives. On the contrary, it contains either synthalin or a substance so closely allied as to be indistinguishable without prolonged investigation; and it contains this substance in sufficient quantity to play an important part in whatever therapeutic or other actions the preparation may possess.

It should, perhaps, be added that we are not in a position here to discuss the therapeutic value of glukhorment as such, or the possibility that the action of a substance like synthalin might be modified by the presence of the known constituents of a pancreatic digest. Our concern is to ensure that the physician, in charge of a patient who has shown intolerance to synthalin, should not be led to administer glukhorment by the mistaken supposition that it contains no synthalin or similar substance.

REFERENCES.

¹ *Klin. Woch.*, 1927, No. 22, p. 1041. ² "Der wirksame Bestandteil des Glukhorments," Hedwig Langecker, *Klin. Woch.*, 1927, No. 47, pp. 2238, 2239.

Memoranda:

MEDICAL, SURGICAL, OBSTETRICAL.

GALL-STONE FORMATION.

The following is rather an unusual case and worth reporting.

An unmarried woman, aged 30, a cook, was operated on in hospital in 1924 for gall stones. The stones were removed and the bladder was drained. During the last year she had recurrent attacks of colic. In September, 1927, I was called, and found her in a definite attack of colic. When this had subsided I operated and removed the gall bladder. On opening it after the operation I found two stones inside, which had formed round the purse-string suture inserted at the first operation, the suture running through the whole length of the stone.

Eastbourne.

E. WILSON HALL, F.R.C.S.Ed.

PREGNANCY COMPLICATED BY MITRAL STENOSIS.

The following details of a case of pregnancy, associated with mitral stenosis and terminating fatally, appear to be worthy of record.

A woman, aged 26, who had had a normal pregnancy and labour eighteen months previously, was admitted to hospital six and a half months pregnant with malaise which had lasted for some weeks. She had had rheumatic fever as a child, and, on admission, was found to have mitral stenosis without any signs of failure of compensation. The temperature, pulse, and respirations were raised; there was some abdominal tenderness, especially over the gall-bladder region, in the left iliac fossa, and in both renal angles. The spleen was doubtfully palpable; the urine negative. On the following day her condition was obviously worse, slight albuminuria had appeared and there was oedema of the

feet and back; the renal tenderness was less, and repeated examination of the lungs revealed nothing pathological. On two occasions she had syncopal attacks and nearly died; three days after admission, therefore, labour was induced by means of a prostatic catheter, no anaesthetic being employed. Delivery followed normally within six hours; a live and healthy foetus was born, but died a few hours later owing to prematurity. During the twenty-four hours following delivery the patient's condition was very much better, apart from an irritating cough which prevented sleep until heroin was given, when she had a good night. On the following morning the temperature had dropped to 96°, the patient felt better and complained only of slight nausea. At mid-day she had haematemesis, quickly followed by the passage of a quantity of blood from the rectum; two hours later she died.

At the necropsy all organs showed chronic venous congestion; there were large vegetations on the heart valves, especially the mitral, but no signs of emboli anywhere. At the junction of the middle and lower thirds of the oesophagus a small ruptured vein was found, without evidence of varicosity. About one inch of clot was drawn out from the vein and was found to be a *post-mortem* clot and not thrombus.

I am indebted to Dr. Statham and Dr. Herapath for permission to publish this case.

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AN EARLY CYSTOSCOPIC SIGN OF RENAL TUBERCULOSIS.

The following is a sign occasionally seen with a cystoscope before the bladder picture becomes typical.

The sign may be described as a rebound of the coloured urine on the pathological side (methylene blue or indigo-carmin being used). The accompanying diagram explains it. The rebound is caused by the

stream impinging on the lower edge of the ureter opening, which is slightly raised, hardened, and thickened.

Liverpool.

FRANK JEANS.