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PANCREATIC DIABETES

A

Clinical and Experimental Enquiry

into

Its Nature, Causation and Treatment.

By

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Member of the Royal College of Physicians, London.

Edinburgh University Graduation Thesis.

1891.

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C O N T E N T S

LIST OF ILLUSTRATIONS

P R E F A C E

In this Thesis I propose to treat of the form of diabetes mellitus which has been found associated with disease of the pancreas: it being one not only of much clinical importance to the practitioner of medicine, but likewise of very considerable interest to the experimental pathologist.

Although I have gone, as will be seen, very fully into the clinical literature of the subject, and cited some interesting cases of the disease hitherto unpublished, the main value of the essay will, I think, be found in the new chemical, physiological, and pathological data I have been able to adduce explanatory of the nature and cause of the particular form of diabetes under consideration. And here, at the outset I desire not only to return my best thanks, but also to acknowledge my very great indebtedness to the several gentlemen in whose laboratories the experimental knowledge about to be put forth was obtained. For had it not been for the kind counsel and assistance I received from Professors Pasteur and Roux, at the Pasteur Institut; from Professor Dastre in the Physiological Laboratory of the Sorbonne; from Professor Hoppe-Seyler at the Chemico-physiological Laboratory of Strasburg, and lastly and more especially to Professor Sophus Torup at the Fysiologiske Institut of Kristiania, wherein by far the greater part of the experimental work about to be narrated was carried on, and who, as will

be seen in the text, rendered me invaluable aid in all of the more intricate parts of the research, I should never have been able either to have accomplished the work or collected the materials the Thesis embodies.

I have still further to acknowledge the obligation I am under to Professor Heiberg of Kristiania, for not only having furnished me with the medical history of, but the pathological specimens from the exceedingly characteristic, I might almost say typical, fatal case of pancreatic diabetes which occurred in a Medical student dueing the time I was experimenting on the subject in Professor Torup's laboratory.

While, lastly, I am indebted to the artistic skill of my friend, Dr Julius Nicolaysen, for the four water colour drawings of the morbid appearances met with in the case of the medical student.

It may, perhaps, be well for me here to state that no single experiment has been recorded in the following pages about the exactitude of which I entertained the slightest doubt; so that, as can easily be imagined, those narrated - numerous though they be - bear but a very small proportion to the actual numbers performed.

Vaughan Harley.

April, 1891.

SYMPTOMATOLOGY OF PANCREATIC DIABETES

With cases illustrative of its Clinical History

C H A P T E R I.

The signs and symptoms met with in cases of diabetes, either depending upon or associated with pancreatic disease, present in several respects a well marked difference from those usually manifested in the other forms of diabetes, entirely unconnected with any derangement of the pancreatic functions. This may be said to be particularly noticeable in those that have been described as typical examples of the disease. For in them the onset of the signs and symptoms of the diabetes is marked by the suddenness with which the characteristic thirst, voracious appetite and polyuria manifest themselves, in association with the presence of sugar in the urine in persons (usually) under the middle period of life, and generally at a time too when they are apparently in the enjoyment of the best of health. Moreover pancreatic diabetes differs still further from the ordinary forms of saccharine urine in the uninterrupted speed with which it marches on to a fatal termination. Marked nervous prostration and great muscular debility accompanied with a rapid emaciation, being quickly followed by a comatose condition, precipitately ending in a lethal collapse.

In addition to these differentiating signs there

is yet another, which ought, I think, to be regarded as more important than any of them. If it be true, as has been asserted, that in order to induce diabetes it is necessary that the pancreatic functions are completely in abeyance, In that case (as was pointed out by my father in the report of a case in his book on Diseases of the Liver and Pancreas (+).) from no pancreatic secretion finding its way into the intestines, the oily and fatty parts of the food appear in the stools not mixed with, but separate from and upon the excrements after cooling. The unemulsioned oleaginous matter in the form of a dirty whitish-yellow grease, the unemulsioned fatty substance as a hardened lard: not at all unlike in appearance to what is known as old brown Windsor soap. I consider that we ought to regard the appearance of oleaginous and fatty substances in the stools, in the manner above described, as an essential factor in the diagnosis of pancreatic diabetes. At least, until we have discovered some yet more crucial test for, or pathognomonic sign of the disease.

There is yet another point in the symptomatology of pancreatic diabetes which it is necessary for me to direct attention to. Namely, it not unfrequently happens that shortly before the death of the patient, the sugar which has hitherto been in the urine in

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(+) Jaundice: its pathology and treatment; with the application of Physiological Chemistry to the Detection and Treatment of Diseases of the Liver and Pancreas by Dr. George Harley. Walton and Maberley, London, 1863.

abundance disappears. The cause of this is probably not far to seek. For seeing that the foods partaken of, not having undergone the necessary chemical transformation by the pancreatic juice, are unfitted for the purposes of assimilation, the disappearance of the sugar from the urine may possibly be due to there being an absence of the necessary materials in the organism for its formation. The rapidity and extent of the emaciation at least favours such a view.

The above being, as far as I have been able to ascertain, the salient signs and symptoms of what have been looked upon as typical cases of Pancreatic Diabetes, I shall now proceed to cite illustrative examples of the diease. Before doing so, however, it may be well to mention that notwithstanding that I have gone through all the available French, German and English literature on the subject, and it is exceedingly copious, I have been somewhat surprised to find so few cases recorded which, in my opinion, have any right to the title of "typical". Consequently I conclude that true typical examples of the disease must be exceedingly rare. This is perhaps fortunate, seeing that the few I have come across have not alone all ended fatally; but rapidly so. I may further remark that not only have the autopsies of many of the cases that have been recorded as examples of pancreatic diabetes, revealed important structural lesions in other organs, but even although called by the compilers of cases of pancreatic diabetes examples of such, some

of them had no such title bestowed upon them by their original reporters.

The most typical case of Pancreatic Disease with which I am acquainted is that of a Medical Student, who died last September (1890) at Kristiania while I was working experimentally on the subject with Professor Torup in the Physiological Institute there. The case has never been published, and for the following notes of it, as well as for the pathological specimens of the pancreas, from which the accompanying coloured drawings were kindly made for me by Dr Julius Nicolaysen, I am indebted to the kindness of Professor Heiberg; under whose care the case was. I have further to acknowledge my obligations to Professor Gulberg, the Professor of Anatomy in the University, who took the trouble to prepare the microscopical sections from which the drawings were made.

Y.K., aged 23. As a child he had enjoyed good health, although pale and of a somewhat scrofulous appearance. He was a diligent boy at school, and always held a good place in his class. As he grew up he was mentally less bright, his eyes had a dull appearance, and that, with his large hanging lips, gave him a somewhat stupid look. On entering the University to study medicine, he was not well developed bodily, and seemed mentally languid; although he never complained of being ill, and was considered sufficiently strong to be accepted as a soldier for service in the summer of 1890. In June he entered upon his duties as a recruit which he found very trying, the drill tiring him so

much that, after only serving 14 days, he was discharged. In the middle of August he suffered from a catarrhal tonsilitis which weakened him very much, and on the 26th of that month, he complained of being very languid, sleepless and having headaches. About this time his great thirst and constant hunger led to his urine being tested, and to the discovery of sugar. He soon became drowsy and restless, constantly wanting to get out of bed, but when out of it, he was unable on account of his weak condition, to sit up for long. His thirst was very marked but not his appetite. The quantity of urine passed was from 4 to six litres a day, and it contained 2 per cent of sugar. His tongue was very dry, and his breath had a distinct aromatic apple-like odour. His weakness now rapidly increased and during the last few days of his life he was almost comatose, but up to the last day he could always be roused from his state of stupor.

He died quietly on the 6th September: that is to say, 11 days after the diabetic state was discovered.

At the autopsy, the heart and lungs were found perfectly normal. The liver was also normal in size and appearance. The same may be said of the Spleen. The kidneys were normal in size and their capsules easily stripped off. The surface was smooth and of a reddish grey colour, but marked with yellowish striae. On section the cortex had the same colour and the pyramids were of a bright red. A microscopic section

Fig. I.

The pancreas converted into an irregularly round mass, the size of duck's egg, closely adherent to the duodenum

of the fresh kidney showed the epithelial cells of the convoluted and straight tubules to be finely granular, and on the addition of Liq: Potas: showed fatty degeneration. Section after hardening showed some of the tubuli free from cells.

The pancreas alone shewed marked pathological alterations. Its head was entirely converted into a round mass about the size of a duck's egg: which adhered closely to the duodenum Fig. I. All that remained of the body and tail was merely a thin flat fibrous band. Within the head of the organ was found a cavity the size of a cherry, filled with semi-purulent fluid. The surrounding substance being of a greyish colour and filled with numerous small abscesses, from the size of a pea down to what was scarcely recognisable to the naked eye. All of these contained the same yellowish green looking semi-purulent fluid. (Fig. II)

Fig. II.

Section with remains of pancreas, showing various abscesses, filled with yellowish green pus.

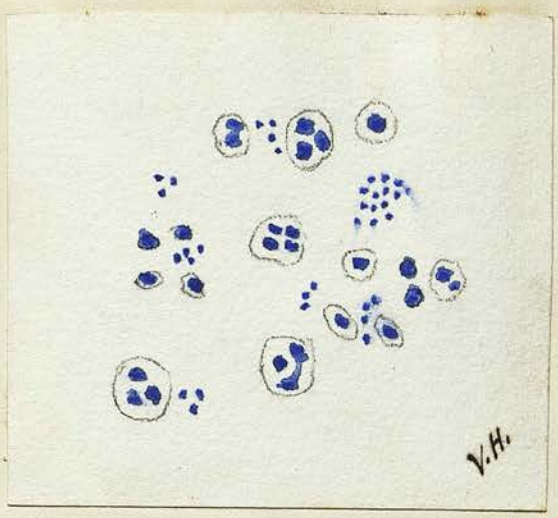

Fig. III.

Pus from abscess in Pancreas, showing leucocytes and micrococci. Stained by Löffler's methyl blue ($^1/_{12}$ homog. immers. Zeiss)

The pus examined microscopically showed numerous leucocytes and micrococci arranged in grpups or short chains. (Fig. III) Some fresh pus inoculated in rabbits caused local abscesses, Cultivations were made from the fresh pus. Gelatine tubes were rapidly liquified, depositing a yellow sediment. Agar agar tubes showed a yellowish gold band ay the striae of inoculation. (Fig. IV)

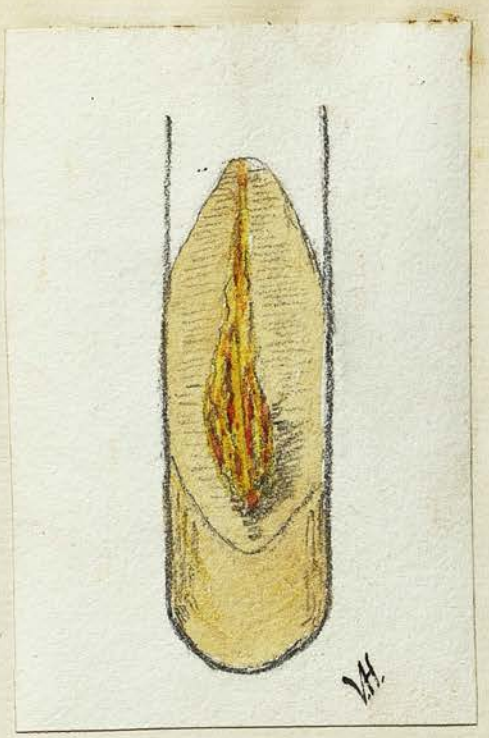

Fig. IV.

Cultivation in agar agar from pus of pancreatic abscess Staphylococcus pyogenes aurens.

In hopes of finding some tubercular bacilli some tubes to which glycerine was added, were inoculated which only yielded cocci, no bacilli being found on careful search.

From the above characteristics, evidently we had to deal with the staphylococcus pyogenes aurens. The common bile duct could be traced behind the head of the pancreas and unaffected by it. The duct of Wirsung could be traced into the substance of the gland, where however, it became lost, no calculi were to be found in it.

Microscopical examination of a section of the head of the Pancreas yielded the following (Fig. V).

The lobules are seen to be atrophied (A) and the gland cells were fatty. The interlobular connective tissue was greatly increased (C) and pressing on the atrophied lobules. Scattered throughout the section were

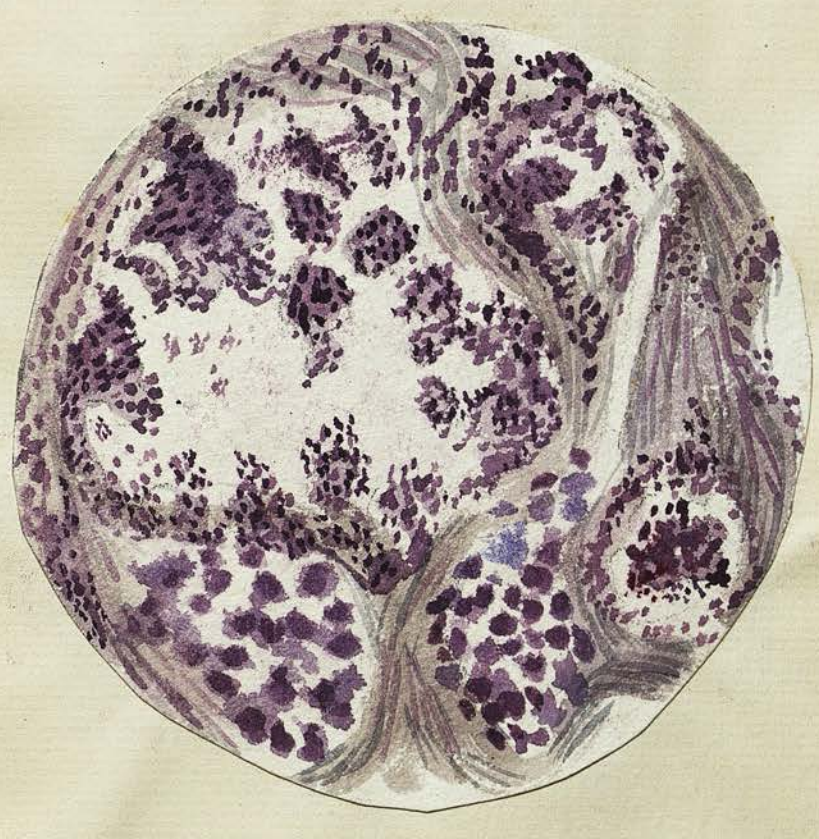

Fig. V.

Section through head of Pancreas. A. Atrophied pancreatic lobules. B. Abscesses of different sizes. C. Hypertrophied connective tissue.

Fig. VI.

A Section from another part of pancreas, in which fat globules removed, showing remnants of glandular and connective tissue.

seen small abscesses of various sizes containing leucocytes (B) The walls were formed by the interlobular connective tissue.

In another cut the glandular lobules were found to consist of a mass of fat globules, in which no structure could be recognised. After dissolving out the fat, remnants of glandular and connective tissue were seen, as shown in Fig. VI.

Other sections showed merely abscesses and no gland tissue could be recognised. The remnants of glandular and connective tissue are seen with gaps out of which the fat drops have been dissolved. A fresh specimen of this showed merely a mass of fat drops in which no structure could be recognised.

The next case is one recorded by Dr George F. Duffey in a paper "On the connection of acute diabetes with disease of the pancreas" in the Trans: Academy Medicine - Ireland, Vol. II, 1884. p. 405.

A Farm labourer, aged 24 but looking older, 6 feet in height and well made stated he had always enjoyed the best of health until about 5 weeks before his admission to City of Dublin Hospital, on 18th October, 1883. His parents were dead; he had 2 brothers and 2 sisters alive and healthy. The first symptoms he noticed were polyphagia, polydypsia, polyuria and emaciation.

After about a fortnight he began to feel languid and weak, did not sleep well and found he had lost a stone in weight. He could not assign any cause for his illness except having had to work very hard dur-

ing harvest.

On admission he presented the usual symptoms of an advanced case of Diabetes Mellitus. He seemed remarkably apathetic and rarely spoke unless in answer to a question. He preferred staying in bed to getting up, stating he did so because he got so easily tired. During his stay in Hospital, the amount of highly saccharine urine he passed in 24 hours varied from 215 to 170 ozs. and its specific gravity from 1045 to 1040. It had a sweetish odour and gave the reddish brown colour on the addition of Ferric-chlorides, due to Ethyl diacetic acid. For 10 days he continued much the same, when, without evident cause his bowels, which had been constipated, became exceedingly loose and vomitting occurred. He complained of pain in the epigastrium and the abdomen was tender on pressure. The diarrhoea persisted for a week. The stools were somewhat of a dysenteric character, being very frequent, but small in quantity, of a jelly-like consistence and extremely foetid. For the first 2 or 3 days they contained white masses resembling lumps of undigested caseine, but these disappeared on giving him peptonised milk. He had now completely lost his voracious appetite, but was even more thirsty than upon admission. The debility and emaciation increased, and he became extremely low and desponding. On the evening of 3rd November, his temperature, which had been previously normal, rose to 100°, but subsequently his extremities became very cold, his pulse quick and so

weak as to be almost imperceptible. He then sank into a state of coma, or more correctly speaking collapse, and died on the morning of 6th November. During this latter period his face was flushed. He lay on his back with his mouth open, and exhaled a sweet smell from his breath, but I cannot say it was a characteristic one of acetone. His respiration was rapid, but no physical signs of pulmonary disease were elicited on examination.

The autopsy was made the day after death, when although to the naked eye all the organs were normal with the exception of the pancreas, the microscopical examination showed that the liver and brain were not perfectly healthy. Mr Abraham (+) found a marked turgescence of the vessels of the Pons and Cerebellum. They are engorged with blood and the lymph spaces around them are, without doubt, considerably widened. A few blood-stained, irregular masses are to be seen peripherally in the pons in contiguity to the blood vessels. None are observed in the cerebellum.

Liver. The liver cells are comparatively small and the inter-cellular spaces large. In places there seems an inflammatory increase of connective tissue.

Pancreas. The proper substance of the gland is quite gone, and no where are to be found either ducts or alveoli. The mass is made up of loose connective

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(+) On some microscopical sections, from two cases of Diabetes Mellitus, Trans: acad: Med: of Ireland, Vol. II, 1884, p. 415.

tissue, trabeculae, with large tracts intervening. These meshes contain groups of large, irregular, nucleated cells, interspersed with smaller cells and nuclei. The latter are often crowded together, appearing like lymphoid tissue among the fibres of the trabeculae. There can be little doubt as to the carcinomatous nature of the growth.

Mesenteric Glands. Scattered among the lymphoid tissue are the same large, irregular, nucleated cells, singly or in masses.

Kidney. There is a great hypertrophy of the intertubular connective tissue, with dense inflammatory infiltration and some fatty degeneration in parts. The tubular epithelium appears for the most part unhealthy - sometimes broken up and often with the nuclei not taking the stain.

Lung. Portions of the hepatised patches of lung were examined, showing the usual appearances of pneumonia, but no evidence of fatty embolism.

Heart. Muscle. The fibres are rather granular but without fatty degeneration.

To these two cases with Autopsies, I will add two other even still more remarkable cases of Acute Diabetes, which were reported by Dr Daniel Noble in the Brit: Med: Jour: of the 17th January, 1863. Although from there having been no autopsy made in either of them they cannot be positively said to be examples of Pancreatic Diabetes, nevertheless, the rapidity of their course, as well as the mode of their termination

led to the conclusion that they were most probably examples of such. But even if they were not, as such acute forms of diabetes are exceedingly rare, it will be well for me to refer to them. The first was a boy, aged 17, who, without any assignable cause, while at a boarding school "became gradually listless and weak, incompetent alike for physical exertion and mental application." When Dr Noble first saw him he "had thirst, voracious appetite, dry skin and large discharge of urine." On the following day he was much weaker. The urine was of high specific gravity and contained a large proportion of sugar. On the succeeding morning, the debility and exhaustion had very alarmingly progressed. xxx Early the following morning the patient died "in a state of collapse" that is to say, within four days after the diabetes was diagnosed, and only a few weeks from the first signs of debility showing themselves.

The next case is equally remarkable. It is that of a young lady of about 13 years of age, who had been treated homaeopathically for some weeks on account of "losing flesh and strength" although she had an unusually good appetite. When Dr Noble was called in she complained of excessive thirst, abundant urine, dry skin and voracious appetite. These symptoms were followed by a rapid debility, and after three days' confinement to the house, and only ten after being first seen by Dr Noble, she expired.

I will now call attention to a set of cases,

which have been recorded as examples of pancreatic diabetes, although they differ very materially from what I consider the typical form of the disease. Not only have they run a much longer, as well as a more erratic course, but their autopsies have revealed other organs quite as much, or in some cases even more diseased than the pancreas itself. In these it being impossible to affirm how great or how small a rôle the diseases in the other organs, besides that in the pancreas, may have played in the production of the diabetic state and led to the fatal termination I designate as "Mixed Pancreatic Diabetes."

The first I will refer to is one that was published as long back as a hundred and three years ago; that is to say, at a time about equidistant from now and the date of the discovery, in 1674, of the presence of sugar as an abnormal product in human urine, by our countryman Dr. Thomas Willis.

It is narrated by Dr Thomas Cawley in the London Med: Jour: Vol. IX, p. 286, 1788, as "a singular case of Diabetes".

A. H. aged 34, strong, healthy and corpulent, accustomed to free living and country exercise. In December, 1787, suffered from gradual emaciation and debility. On March 20th. 1788, the urine was found to be sweet, and to ferment with yeast. Two pounds of urine yielded on evaporation five or six ounces of a sweet black extract, resembling molasses. Up to this period the quantity of urine was not noticed to be

above the normal. Various medicines were tried and at first he somewhat improved under tonic treatment, but soon afterwards every medicine disagreed and the patient gradually sank and died on the 18th of June.

The disease was at first attended with severe pain in the rectum, caused by piles. He suffered from constipation. Some time before his death he had slight hectic symptoms and intolerable thirst. His mouth and fauces were very clammy and the tongue deeply fissured. The skin dry and scaly. His appetite which was at first good, gradually diminished, and changed into aversion even at the sight of solid food. His only support being liquid nourishment. At this time he had on passing his urine, a sensation of sinking in the hypochondria, as if the urine came from those parts.

During the last three days of his life the quantity of urine was greatly increased, and the power of retention much diminished.

His right arm had frequently convulsive movements lasting a few minutes. Delirium and convulsions closed the scene.

In spite of the progressive fatal symptoms, the quantity of sugar daily decreased and the urine, from being of a pale straw, became of a deeper and more natural colour.

Autopsy. Kidneys of usual size, but seemed paler and softer than normal.

Liver was much wasted and externally of an ashy or nearly pipe-clay colour. It had a plastic consis-

tence, and could be moulded like dough, into any shape. On section it exhibited the usual colour.

The gall-bladder, centaining the normal quantity of bile, was adherent to the mesocolon.

The pancreas was full of calculi, which were firmly impacted in its substance. They were of various sizes, none larger than a pea; white in colour and made up of a number of smaller ones, like mulberry stones, and in this respect resembled those sometimes found in the salivary ducts. The right extremity of the pancreas was very hard and appeared to be scirrhous.

No other signs of disease were found in the abdomen, and the contents of the thorax were perfectly normal.

The next case I will give fully, as it is not only one narrated by Dr Richard Bright, whose name is so justly celebrated in connection with kidney disease, but it furnishes us with an admirable example of how carefully the distinguished Physicians of sixty years ago both studied and reported their cases.

It is recorded in the Med: Chir: Trans: London, Vol. XVIII, p. 3, 1833, under the title of: - "Diabetes - with supervening icterus from obliteration of the common bile duct, caused by disease of the pancreas - malignant ulceration of the duodenum - copious discharge of fatty matter with the dejections."

T. B., aged 49, a clerk, of sober and regular habits. In March, 1827, complained of immoderate thirst and appetite, with a constant pain in his loins. Passed urine frequently. These symptoms, together with

increasing emaciation, made him seek the advice of several medical men. It was not until August, however, that the case was pronounced to be diabetes mellitus. In the beginning of September he became jaundiced. It was unpreceded by any painful sensations.

When seen by Dr Bright on 4th of December, he was reduced to a state of great debility, although still by no means a thin man. He complained of constant thirst and hunger. Pulse 80 and soft; skin deeply jaundiced. Urine 9 pints in 24 hours. It was bile-stained, sweet and had a specific gravity of 1039. Evacuations by the bowels copious and light coloured. Put on animal diet and as little bread as possible. A bitter, aromatic mixture, containing bicarbonate of soda being given. Between the 5th and 8th of December, the urine gradually diminished in specific gravity and quantity. On the latter date the diabetes was considered so improved that attention was more particularly directed to the obstruction of the bile, and he was given mercury and taraxicum.

On December 24th, skin still of bright yellow colour, bowels regular - urine somewhat less highly coloured, had entirely lost its sweet taste, specific gravity 1015, quantity only 4 pints, he having drunk 6 pints. Liver was hard and solid, projecting three or four inches beneath the ribs; edge made out to be rounded. The distended gall-bladder could be plainly felt.

On 28th, without any notable change of symptoms, the patient began to pass by stool a quantity of yel-

lowish fatty matter resembling butter that had been melted and again become solid. This matter followed the faeces, and as it was evacuated in a fluid state it appeared on the surface of the dejections. The presence of this fatty matter could not be explained by diet, as he had taken no fats. He had now bicarbonate instead of liquor Potassae given to him in the tonic mixture.

On December 31st, the alteration made in the mixture had done away entirely with the oily character of the motions. Three copious motions were passed in the 24 hours. The urine had atill a specific gravity of 1015, but in spite of this the patient was growing weaker and more emaciated from the obstinate obstruction of bile and consequent defective assimilation of the nourishment. The stools,which consisted of half digested food, were pasty, deficient in colour, and of a feculent odour, and seemed more copious than if the usual proportion of nutritive matters had been abstracted. In consequence of hepatic pain, a large blister was applied over that part.

On January 8th, 1828, he was more debilitated, passed four or five stools in the 24 hours, somewhat loose, and now and again containing some of the fatty matter before described, as well as undigested meat. Appetite good but not voracious. Sleep disturbed,seldom lasting more than an hour and a half. Tongue somewhat brownish in centre. Pulse 84, soft. Urine high colohred, specific gravity 1020. For the relaxed bowels chalk and opium were given. The engorged liver

was treated with a mercurial blister. On 13th, number of dejections reduced to three in 24 hours, only two on previous day, which continued of a pasty, stringy consistence, but were not of a very light colour. The patient was more emaciated and duller. The edge of the liver and large, rounded extremity of the gall-bladder were still plainly felt. The rest of the abdomen was flaccid. Had severe pain on the right passing through to the left side, which almost wholly prevented sleep. Tongue clean and of a healthy colour, pulse 87, weak. Ordered to be cupped on the right side to eight ounces and to take four grains of blue pill. The following day the pain in the side was relieved. The quantity of urine was 4 pints in 24 hours, while 5½ pints had been drunk, the specific gravity was 1020 and that of the bloody serum collected from the cupping, 1030.

On the 16th the bowels again became relaxed; were of a dark colour and still contained a little oily matter. The pills discontinued, and an astringent mixture, containing haematoxylum, catechu and opium, was given. 21st much weaker, but still able to move slowly about the house. The bowels continued relaxed six motions a day. The feet, for the first time, were noticed to be somewhat oedematous, and the skin remained of a deep yellow. The emaciation was progressive and the rest continued much disturbed.

From the beginning of February he was evidently a dying man. On the 10th had a left pleurisy. On the 26th, the quantity of urine amounted to 2½ pints. The appetite now failed. The bowels which had been re-

laxed, were confined. He died without pain or struggle, on the 1st March, worn out with emaciation and want of rest, but he retained his senses and a perfectly collected state of mind till the last.

Autopsy. The limbs were remarkably flaccid, the whole skin of a dark yellow colour; there was general emaciation and the legs slightly oedematous.

The two pleura were coloured by bile. The lungs healthy, except the lower left lobe, where the recent pleurisy had formed a thick coating of gelatinous fibrine, which readily broke down on drawing the lungs forward. This was partly deposited on the lower surface of the diaphragm, and partly on the posterior part of the ribs near their angle, and it was highly tinged with bile. The lung itself contained a small abscess the size of an olive near the edge, where it rests upon the diaphragm. The pericardium was bile-stained, and the large vessels near the heart had a yellow colour throughout. Heart small and contracted, valves normal.

The abdomen contained rather more than a gallon of dark olive-coloured fluid. The gall-bladder distended with very dark bile, was seen projecting when the parietes were first removed.

The liver of a dark olive colour, ducts greatly enlarged. The common bile duct was large enough to admit the little finger, and terminated in a cul-de-sac in the diseased substance of the pancreas; at its extremity was a rough white deposit of fibrin or cholesterine.

The head of the pancreas formed, with some of the surrounding glands, a hard, globular mass, round which the duodenum turned, and to which both it and the pylorus were firmly joined. At two points - where the pancreas and duodenum were welded together - ulceration had taken place, penetrating the whole thickness of the intestine; one of them the size of a shilling, the other not larger than a silver penny. The pancreas was hard and cartilaginous to the touch, and of a bright yellow colour.

Stomach was slightly vascular.

The spleen normal structure, but its external surface mottled, with cartilaginous deposit.

The intestines tolerably normal, but somewhat opaque, and the internal lining rather pale.

The kidneys looked healthy, but when torn open, the tubular parts were more plain than usual, and in some of the tubes were white specks, either fibrinous or calcareous. The pelves of the kidney were bile-stained.

The lining membrane of the bladder healthy and free from all vascularity; but its net-like appearance bespoke more than usual action in the muscular coat. The aorta and common iliacs were in many points covered with bony deposits surrounded by dark spots, where the internal surface had been destroyed by ulceration or absorption.

Among the cases of obstructed pancreatic ducts that have been claimed by Dr Lapierre as examples of Pancreatic diabetes - in his book on Wasting Diabetes

in connection with changes in the condition of the pancreas (+) - is one entitled "Complete obstruction of the bile and pancreatic ducts", published in Vol. XIII (1862) of the London Pathological Society's Transactions by my father, and again in 1863 in his work Diseases of the Liver and Pancreas. He did not, however, on either occasion speak of the case as being in any way an example of pancreatic diabetes, but only as a case in which a saccharine condition of the urine was associated with liver and pancreatic disease. The case may be given in abstract as follows: -

The patient was a gentleman, aged 50, who died from the combined effects of occlusion of the bile and pancreatic ducts. The diagnosis of the pancreatic occlusion, as well as of the biliary one, had been early made in consequence of the frequent passage by stool of fatty matters - not mixed with the motions, but quite separate, though upon them. The fatty matters on cooling, solidified into a firm, brown matter closely resembling in appearance Windsor soap. And as it was in some respects not at all unlike some of the biliary products, it was, before it was analysed, supposed to consist in part of the fatty acids of the bile; but when subjected to chemical analysis it proved to be strangely modified fish oil - the olein of which had entirely disappeared. In fact, it turned

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(+) Sur le Diabête Maigre dans ses rapports avec les Altérations du Pancréas." Delahaye et Cie. Paris, 1879.

out to be nothing else than the but sparingly soluble fatty acids of cod-liver oil which the patient had been taking medicinally, from which all the liquid principles had been absorbed during its passage along the digestive canal. This, of course, at once negatived the idea of bile having reached the duodenum, and yielded its fatty acids to the faeces, and at once pointed to a stoppage of the pancreatic secretion. As soon as the absence of the pancreatic secretion from the intestines was discovered, one and a half grain doses of pure pancreatine - some of the first, it may be mentioned, that was ever prepared - was administered (+) to the patient, and it was thought to diminish the amount of fatty matters voided by the stools. The urine was frequently tested for sugar, but none was detected in it until after the patient had lost considerable flesh, after which its quantity slowly and gradually increased during a week or two, and then steadily continued in varying amounts until the patient's death. The urine found in his bladder at the post mortem was found to be highly saccharine.

A case of a somewhat similar kind is recorded by Dr H.F.Goodman - "Case of diabetes with fatty diarrhoea", Philadel: Med: Times 22nd June, 1878, p. 452.

Col. S.Z., aged 55. Entered the army in 1861, in excellent health, weight about 190 pounds. Had, in the summer of 1862, an attack of jaundice, diarrhoea,

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(+)See, Paper by Professor George Harley entitled "Experiments on Digestion" in the Brit: Assoc: Reports for 1858, also Brit: and Foreign Med: Chir: Trans: 1860.

cough, with fever, known as typho-malaria. A return of the diarrhoea in 1863 and again in 1865. In July 1863 his horse fell on him and he received an injury of the spine, causing severe pain in the back and limbs. After this he was subject to pain in the back and numbness in the limbs. He had had a so very severe attack of jaundice and diarrhoea some years before this that he was not expected to live.

From 1867 or 1868 he noticed his health gradually failing. I was first called to see him on the 16th of October, 1873. Found him emaciated; weight 125 to 130 pounds; diarrhoea so incessant as to confine him to bed; stools passed involuntarily and of the consistence of sweet oil, leaving greasy spots on bed clothes. He passed 2 gallons of water daily. Had no fever nor pain, only prostration.

October 16th. Urine had specific gravity 1044, an acid reaction, devoid of sediment. Urates and uric acid diminished; chlorides normal; phosphates and sulphates apparently diminished. Glucose very abundant; no albumen.

Faeces contained mucous and epithelial cells in various stages of disintegration and foreign matter; but the great bulk fat, in the form of spherical masses composed of dense aggregations of minute crystals, like margarine. Examined, together with Dr Da Costa: no tumour was felt in the abdomen. Put on diet excluding starch and fatty matters, with quinine and opium in small quantities. Under this treatment he gained flesh, the diarrhoea ceased, no fat was noticed in

faeces and the quantity of sugar diminished in the urine. Whenever he transgressed in his diet, the diarrhoea and fatty discharges would return, and urine increase in quantity. I looked after him for a year, during which time he attended to his business. He then went under the care of Dr McClintock, who treated him until his death, in June 1876.

Autopsy. Emaciated. Abdomen contained a small amount of serum. The pericardium contained 2 ounces of serum. Heart covered with a small amount of fat. Left ventricle hypertrophied. Aortic semi-lunar valves showed no marked changes. The orifice was rigid from atheromatous changes (one place was calcareous) just above the valves. The hydrostatic test showed slight incompetence at this orifice. Mitral valve was atheromatous in places.

Right pleura. One sac was obliterated by firm adhesions of the upper lobe, in which were found numerous ecchymotic patches; the lower part contained a collection of serum and a mass of recent flocculent lymph.

Left pleura. There were a few old adhesions of the left lung to the chest wall, a small collection of serum, but no recent lymph.

Lungs. Left was crepitant throughout, much congested posteriorly; its upper lobe normal; lower lobe on section exudes abundance of bloody, slightly frothy serum; its tissue unaltered in consistence. The right upper lobe showed a number of cheesy masses, and one cavity the size of a pullet's egg, containing thick yellowish-white matter; lower lobe was, to a great ex-

tent, carnified (compressed by inflammatory exudation) no cheesy masses.

Spleen was enveloped in a complete fibrous (inflammatory) capsule, was large (6 inches), pretty firm, regular in outline; on section, its tissue was found normal in appearance.

Kidneys. The left was much congested, the surface uneven and mottled, the capsule adherent. On section, the vessels were very conspicuous; the relation of cortex to medulla was normal. The whole organ was very considerably enlarged. The right presented about the same appearance. It was less congested, and its capsule was less adherent.

Supra-renal capsules were normal in size and consistence. The medullary portion was perhaps rather increased in amount.

Pancreas. On the left side of the vertebral column, behind and below the stomach, was found a rounded, firm mass, about the size of a large orange. It was tightly adherent posteriorly, especially to the connective tissue above the left kidney. The mass was carefully dissected out and found to be an enlargement of the tail of the pancreas. It was a cyst, with firm, rigid walls, so rigid that it did not collapse, nor could even be much indented, although its contents had escaped during the removal, at a point where the wall was thinned and adherent. Unfortunately, the fluid contents suddenly escaped, and none could be collected for examination. It was of a yellowish-green

colour, more fluid in consistence than white of egg. The tumour, together with the rest of pancreas, and about six inches of the duodenum were removed together, ligatures being placed on the intestine before its division.

Subsequently, dissection showed the cavity of the cyst had no communication with the pancreatic duct. The interior was lined with a dirty brownish material, thickly gelatinous in consistence, which could be readily scraped off, but had no tendency to separate of itself. Parts of this material were deeply coloured black. Within the cyst, attached to the right wall, was found a rounded mass the size of a large plum, having a short fibrous pedicle. The pancreatic duct was traced from the intestine through the length of the organ as far as the cyst wall, at which point it ended abruptly. The lumen of the duct was very large throughout the whole length of the body of the pancreas, and suffered but little diminution as it approached the cyst. The portion of the duct passing in or behind the head of the organ to reach the intestine was narrow, perhaps narrower than normal; the probe found difficulty in passing this portion of the duct as it approached the wall of the intestine. The duct was opened at the point where it passed from the head to the body of the pancreas, and here were seen two small sacs or pouches in which some calculous matter rested. The glandular tissue of the organ appeared to be entirely atrophied; the head of the pancreas was represented by a lump of fibrous tissue, which was

continuous with a mass of connective tissue (new growth) between the stomach, pancreas, duodenum and transverse colon. This connective tissue surrounded the blood vessels in this region, and received numerous small branches from them, and was evidently constricting and pressing upon the duct.

The common bile duct, which was also involved in the mass, was somewhat dilated; its entrance into the intestine, whilst somewhat narrowed, was less interfered with than the pancreatic duct.

The splenic artery was found passing along the border of the atrophied pancreas and then on the posterior wall of the cyst, to which it was adherent.

The vena porta and the termination of its principal branches were lying in looser parts of the connective tissue, and seemed not to be interfered with. The liver was large; its outline pretty regular; its capsule marked by occasional white patches or spots. On section its tissue appeared normal.

The gall-bladder contained golden-coloured bile. In it were found two small biliary concretions.

The stomach was contracted. Its mucous membrane showed very considerable post-mortem change, but nothing abnormal.

Seeing that there is so much to be learned and so many doubtful points to be cleared up regarding the nature of pancreatic diabetes, I think it will be as well for me to quote a few more cases which I have come across in my search through the literature of the subject. From the fact that it is still uncertain

how much or how little the derangement in the functions of the other internal organs than the pancreas may contribute to produce not only the saccharine condition of the urine, but several of the other more prominent signs and symptoms accompanying it. This appears to be all the more desirable, from recent researches having shown that a saccharine urine is associated with such a great variety of widely differing forms of pancreatic disease.

The first case that I shall quote as showing how widely differing may be the pathological conditions of the pancreas associated with diabetes, is one headed: - "General fatty degeneration of the pancreas(pathogence und Therapie des diabetes mellitus" recorded by Dr Harnack in the Deutsch: Archt fur Klinisch Medicine, Band XIII, 1874 - p. 593, u. diss. inaug. Dorbat 1873)

A peasant, aged 33, who had been in excellent health till within the last year, was admitted to the Hospital, 14th October, 1872. The clinical examination showed advanced diabetes; the quantity of urine 14,000 to 16,000 c.c. containing 600 to 800 grms of sugar. General wasting with constipation and meteorism. Slight enlargement of the liver with displacement above. Lungs suspicious. Later on he developed neuralgia and daily fever with evening exacerbations. The appetite became bad, and diarrhoea supervened. Temperature rose, dyspnoea occurred and the patient died 22nd December, 1872.

From 16th October to commencement of December the

quantity of urine fell from 16,000 to 4,000 c.c. The sugar from 671 to 92.4 grms, the urea from 124 to 51 grms. the density oscillated about 1030. The weight diminished from 62.3 kilo. to 56.3 kilo: - towards the end there was scarcely a trace of sugar.

Autopsy. Both lungs had pleuritic adherences and general hepatisation. Enlargement of liver and spleen Catarrh of stomach and of the mucosa of the intestine. On microscopical examination of the pancreas it showed a general fatty infiltration.

Dr Recklinghausen records a case of diabetes associated with a"Large dilated sacciformed tumour of the pancreatic duct - Drei Fälle von Diabetes mellitus" Arch: fur path: Anat: und Phys: Band 30, 1864, p. 360. (+)

K., hatter, aged 40 suffered from diabetes since 1859; was admitted into the Charity Hospital for serpiginous ulceration of the umbilicus and of the nose, without ever having had syphilis. His urine contained 4 to 5 per cent sugar, its specific gravity was 1030. Died 15th August, 1863.

Autopsy. The pylorus was compressed by a large tumour which passed above the transverse mesocolon. The stomach was slightly adherent to the tumour, merely presenting a slight thickening and a few haemorrhagic erosions of its mucosa. The duodenum was equally healthy, the bile duct free. The vena porta con-

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(+) The two cases by Dr Recklinghausen I have translated from Dr Lapierre's admirably written little book "Sur le Diabetes Maigre", already referred to.

tained black blood, little coagulated, was contiguous to the right border of the tumour, and was somewhat flattened at the point where it quitted the tumour; its branches were healthy. Between the right border of the tumour and the duodenum one could see the head of the pancreas of which the lobules were soft. The pancreatic duct had its opening into the duodenum free, entering normally the head of the pancreas, but irregularly into the tumour, and in such a manner that it no longer penetrated the glandular tissue, but the white hard tissue which went from the head of the pancreas to the tumour. The pancreatic duct which penetrated into the extremity of the tumour was obstructed by a concretion the size of a bean. The tumour itself was the size of a baby's head, almost spherical and was formed of a closed sac, containing a turbid yellowish liquid in which one could see crystals with the naked eye, (cholesterine and fatty needles) Microscopically it was composed of a granular mass with round cells and débris, The walls of the sac in almost its entire circumference were 3 mm. thick. At the posterior extremity of this sac one found a hard body about 6 mm. thick, which on section showed no lobules but had a glandular aspect. It seemed to be the remains of the tail of the pancreas.

In the lungs were large cavities of caseous pneumonia. The right superior vocal cord showed an ulceration.

In the large and small intestines were tubercular ulcerations. Slight sclerosis of the larger arteries.

Dr Recklinghausen also relates a case of pancreatic concretions with dilatation of duct and destruction of glandular parenchyma.

B., chimney-sweep, aged 26, died 6th July, 1863, after having suffered from diabetes for some time.

Autopsy. Left lung showed a recent pleurisy and caseous pneumonia, with large cavity. The bronchi had small ulcerations, the same were found in lower part of the ileum.

Brain normal.

In the place of the pancreas was a body which only resembled it in size and form; it was formed of lobules of ordinary fat and only contained healthy lobules in the head. In centre of this body the pancreatic duct, largely dilated, containing viscid white liquid holding in suspension bodies which on analysis were found to be carbonate and phosphate of lime. There existed in the middle of the duct a large fusiform calculus of 1 inch long by $^3/_8$ inch broad, at the side another 1 inch by $^3/_8$ broad. Both had a rough surface and were whitish in colour. The wall of the dilated duct was very thick and its internal surface resembled that of the common bile duct.

I now give some cases by Dr L. Baumal, who believes all cases of diabetes are associated either with macroscopic or microscopic changes in the pancreas.

The first I will cite is one headed "Calcul Pancréatique dans le Diabète." (Montpellier Medical, February 1881, p. 108)

M.J., a negro, aged 55, was admitted into Hospital on the 24th July 1880.

He had considerable gastric "embarrassment" was very feeble and thin. The only thing in his former history of any note was drunkenness, especially abuse of absinthe. On the 27th he was noticed to have polyphagia, polydipsia and polyurea. On the following day he passed 6,500 gram. of urine containing 400 grms. of sugar, no albumen. He coughed, and examination of his chest revealed bronchial râles and pleuritic friction at base of right thorax posteriorly. Epigastric pain on pressure.

29th July urine 5,500 grms, containing 409 grm. glucose
30th " " 4,225 " " 289 " "
31st " " 2,200 " " 150 " "

On this day he had diarrhoea which stopped on the following day.

1st August. Urine 5,200 grms. containing 422 grms. of sugar
3rd " " 4,000 " " 201 " " "

4th Diarrhoea returned, the motions being fatty.

7th Some oedema of lower limbs noticed. On the 9th had eclampsia, during which he passed his urine. He died at mid-day.

Autopsy. Brain normal. Lungs adherent on both sides, principally left. Caseating tubercles at left apex. Right apex in same condition but not so far advanced. Right base congested posteriorly.

Heart small, with concentric hypertrophy of left ventricle. Aorta atheromatous and fatty.

Liver of a deep brown colour, normal size. The microscope showed an increase of connective tissue in the portal spaces.

Spleen very small and sclerosed, vessel walls thickened.

Kidneys. Right congested and left pale and decolourised throughout. Both had a good deal of sclerosis and the glomeruli atrophied.

Pancreas to naked eye normal, on section found to be filled with calculi from head to tail. Calculi together weighed 1.2 grammes and were almost pure carbonate of lime. The largest of the size of a pea. The microscopical section of the pancreas revealed great hypertrophy of its connective tissue, starting from the blood vessels and ducts. extending to the finest glandular ramifications. The gland substance by this increase of the connective tissue was markedly atrophied.

In the same journal (November 1881, Vol 7,p.406) Dr Baumal gives another case of diabetes with pancreatic disease.

M.X., male, aged 50. Entered Hospital July 1880. The patient was of a lympho-sanguine temperament and "embonpoint considérable."

What was especially remarked was the excessive redness of his face, with intense fever, 40° C.(104° Fahr.) Owing to delirium his history could not be obtained. The left arm and leg painful. The leg, on examination, showed a swelling the size of a hen's egg above the patella, which was hot. Fluctuation not dis-

tinct. Pressure or movement increased the pain. In the arm, situated about the middle of the biceps, there was an exactly similar swelling. When or how those swellings arose could not be found out. In consequence of the pain the patient always lay on the opposite side. He coughed a little and left base posteriorly had the physical signs of pneumonia.

The urine, high coloured, had the characters of a febrile one. The excessive thirst, which tormented the patient was at first thought due to the fever; as it persisted the urine was tested and 60 grammes of sugar were found in the 24 hours' urine.

As fluctuation was recognised in the swelling of the knee, it was punctured and a ¼ glass of pus drawn off, which contained no sugar.

The symptoms increased, the delirium and dyspnoea becoming more marked, and he died 4 days after his entrance into the Hospital.

Autopsy. Effusion on left side, both lungs adherent and congested, left having in addition a patch of hepatisation in inferior lobe posteriorly.

The heart, covered with fat, was large and flaccid and fatty degenerated. Endocardium pale and contrasted greatly with the intense reddening which existed on mitral valve and its neighbourhood. The interior of the aorta was throughout its length markedly and uniformly red.

Liver very much enlarged and fatty.

Kidneys surrounded with an extensive cellulo-adipose covering and were slightly congested.

Spleen of normal size, soft and diffluent.

Pancreas. The vessel walls thickened with an increase of the connective tissue. The glandular cells fatty. In some of the acini the cells were almost entirely fatty, while others contained very few fat cells.

Dr Baumal relates another case in the same Journal for January, 1882. Vol. 48, p. 31.

O.R., a domestic servant, aged 52. Stated that towards end of July, 1880, she noticed feebleness in lower limbs, which soon after became painful. At the same time oedema, limited to the ankles, and most marked in the evenings, disappearing after a night's rest.

In youth she had severe colic, about once a month 8 days after the menstrual period, It lasted about 12 hours. When 15, she began to have fits after an attack of typhoid. They occurred frequently during the year, but ceased on the reappearance of menstruation, which had been suspended since the typhoid fever

At the age of 16 she had a soft, and at 18, an indurated chancre and at the same time sciatica. At 25 she suffered from articular pains and a syphilitic gumma of left tibia.

Had had four children, the first at the age of 16, born dead at 8½ months. The second at 18, an abortion at the 4th month. Third at 20, also an abortion at the 7th month. The fourth at 23, at term, still living.

When 40 she passed two urinary calculi.

For the first time, she came into Hospital in 1869. She vomited after eating and suffered great ab-

dominal pain.

When admitted a second time - for peritonitis - she was strong and fat.

In 1879, admitted for a third time, suffering from haematemesis and polydipsia. Since her peritonitis she had had, at intervals, diarrhoea. She complained of severe pains in the epigastrium; frequently micturated and passed a large quantity of urine in the 24 hours. Had a good appetite.

She came again into hospital with oedema of the face and hands. Had a soft cataract in the right eye for the last 15 days.

On the 10th October, while in Hospital, she passed 3½ litres of urine, containing 321.6 grammes of glucose.

18th, 1080 cc. of urine. containing 77.7 grms. of sugar.

29th, 625 cc. of urine, with 18.7 grammes of sugar.

On the 8th November, the sugar disappeared from the urine, reappearing on the 13th February, and on the 14th it contained 20.8 grms. of sugar.

3rd March. Emaciation became more and more manifest, until almost a skeleton; and she died in April from marasmus.

Autopsy. Skin of a yellow colour, especially marked on face.

Lungs. Right, adherent; superior lobe emphysematous; inferior, marked oedema. Left, voluminous and congested.

Heart. General fatty degeneration and valvular

lesion. A moderately sized calculus was found in gall-bladder. Abundance of fluid in peritoneal cavity and remains of chronic peritonitis.

Pancreas, stomach and spleen matted together in the adherences.

Liver of a considerable size and fatty degenerated The capsule adherent to environs; with milky patches.

Dr Baumal thinks although the pancreas was not microscopically examined it was diseased.

This is evidently a very mixed case, for there was in it pulmonary, cardiac, hepatic disease along with rheumatic and uric acid, diathesis, plus syphilis.

I now give a fourth case by the same author in the same journal (Mai, 1882, p. 442)

F., an agriculturist, aged 35. Admitted into hospital 11th August, 1881, complaining of considerable feebleness and progressive wasting, dating back about two years. He had polydipsia and polyurea. A thick white discharge from urethra. Had no alcoholic or venerial history. Had had numerous boils,and on admittance a commencing cataract with feebleness of sight.

Liver slightly enlarged. Always fed on vegetables, and smoked hard.

On the 13th, he passed 5 litres of urine, specific gravity 1035, with 193.5 grms. of sugar. On the 14th, was put on a nitrogenous diet. The following day had diarrhoea, which was stopped by opium on the 18th.

20th urine 3½ litres, specific gravity 1036 with 179.5 grms. sugar. As on the 23rd he had sweated pro-

fusely, he was given atropine. The respiration on right side posteriorly was loud and harsh, with prolonged expiration, on the left crepitant râles.

31st August 2½ litres of urine, specific gravity 1030, contained 139.9 grms. of sugar. He now quitted the Hospital for a month. On his re-admittance the 1st October, he was much more emaciated, Had a large boil in the neck, pus from which contained no sugar. Died on 12th October.

Autopsy. Left Lung small, carnified, did not crepitate between the fingers. Right lung-apex with tuberculous infiltration.

Heart - concentric hypertrophy of left ventricle.

Liver large and hyperaemic.

Pancreas. Head grated on section and was coloured yellow by bile. Throughout the whole head were many very small concretions. The tail of the organ was of a wine-red colour. The microscope showed the acini to be completely atrophied; in their place were a few fatty cells. Connective tissue increased and the walls of the vessels hypertrophied.

Kidneys. Left large and congested, especially the cortical part. Right discoloured in superior and inferior part, in centre markedly coloured.

Brain, pons and medulla had nothing abnormal. There was some oedema of the subarachnoid.

The next case I will cite is one of atrophy of the pancreas, published by Dr Lancereaux, in the Bull: de l'Academie de Med: 1877 (2nd series, Vol.VI.p.1215) under the title of "Coliques et vomissements; polyphagie et poly-

dipsie, glucosurie; amaigrissement rapide et excessive; lésions pulmonaires; muquet de la bouche et des grandes lèvres; mort. Destruction complète du tiers moyen du pancréas, atrophie des deux autres tiers. Hypertrophie des glandes de l'estomac et du duodénum."

A.P.B., female, aged 61. Family history good, no gout, or rheumatism. During 30 years she acted as concierge, living more or less in damp apartments. In spite of this her health was good till September 1875, at which time she was seized with vertigo, vomiting and colic which lasted, with intermissions, for 36 hours. On the 18th November, 1875, she was admitted into Lariboisière, under Dr Guyot, who found sugar in urine and put her on diet with gluten bread. During her stay in Hospital she first suffered from polyphagia and the presence of an epigastric swelling was found. Returning home, she drank 3 to 4 litres, her appetite was insatiable. Now and then she suffered from diarrhoea, progressive weakness and wasting, work becoming more and more irksome. In March 1877, she was admitted into Hospital St. Antoine, under Dr Anger. She was pale, wasted, with very little adipose tissue. She lost her hair, and her teeth were bad, skin thin and dry, the tongue furred. Appetite and thirst excessive. Liver enlarged. Spleen normal. The sight slightly feeble, intelligence and sensibility normal; but lethargic, and walked with difficulty; osseous pains. On 12th March, urine 4½ litres, acid, pale, slightly turbid, specific gravity 1035, containing 373 grms. sugar and 2.5 grms. of albumen.

Continued much in same state till 6th April, when pneumonia appeared, followed later by furuncles.. In September she suffered from diarrhoea for 3 weeks and for some days, without any cause, almost continuous somnolence.

7th October urine 3 litres, containing 150 grms. sugar and traces of albumen. Auscultation revealed implication of the left apex. Temperature 37° in morning, 38° C. (100.4° Fahr.) in evening. Thrush on the lips.

16th October there was a fresh eruption of furuncles (8 to 10)

18th October the urine (about 4 litres) contained only 35 grms. of sugar per litre. Specific gravity 1029. Anthrax of the sacrum occurred.

The following day the temperature rose to 40° C. (104° Fahr.) in the evening and coma set in. Died 25th October.

Autopsy. Slight oedema of legs. The anthrax 4 centimetres large, showed a black centre. Nothing special in brain or spinal cord.

Lungs. The left showed a caseous infiltration of the upper lobe with adherences. The right inferior lobe, three centres of lobular pneumonia. No tubercular grahulations.

Heart muscles friable and greyish. The aortic valve small, papilliform vegitations.

The stomach contained thick viscid mucus.

The pancreas was remarkably altered. being divided into three distinct parts. The first part consist-

ing of the tail, was firm, hard and manifestly atrophied. In the second part, which consisted of rather more than middle part of organ, the pancreatic tissue had entirely disappeared, and only with difficulty could the duct be found. The third part, consisting of the head, was small amd atrophied, nevertheless it retained its form and showed glandular tissues. A probe could not traverse the duct in the middle part. Microscopically the tail showed atrophy and fatty degeneration of the epithelium. The head, increase of the inter-lobular fibrous tissue with atrophy and fatty degeneration of the epithelium. The solar plexus normal. Liver weighed 1350 grms. Spleen 254 grms. firm. Two kidneys 360 grms. normal colour, consistence firm.

To this case Dr Lancereaux adds another interesting one, entitled: - "Diabète sucré, polyphagie et polydipsie: glucosurie, amaigrissement rapide; pneumonie lobulaire avec large excavation pulmonaire. Mort. Obstruction des deux canaux pancréatiques par les calculs de carbonate de chaux; dilatation de ces canaux et atrophie du tissu glandulaire; hypertrophie des glandes de l'estomac et du duodénum."

J.B., Cabinet-maker, aged 42. Had 4 children. His mother died insane, his father still living. Had syphilis at 20, afterwards he was in good health till spring of 1874, when he had anthrax of the back, about the same time he noticed increase of appetite and thirst. Soon afterwards he suffered from weakness which stopped his work. He had intense headaches in

1876, and caries of the teeth. In the summer insatiable appetite and great thirst; he stated that he passed 14 litres of urine during the day. In August he had oedema of the lower limbs, which lasted for a week. 28th November he was pale, very thin, and growing weaker day by day. He had inexhaustible thirst and hunger and polyuria. Examination of urine showed diabetes. All the organs seemed healthy, liver slightly enlarged, no vomiting, no diarrhoea.

During December he passed 6 to 8 litres of urine per day, acid and very pale. Specific gravity 1030 to 1039; 500 to 560 grms. of sugar; urea medium 20 grms. The 8th December he commenced coughing and showed the characteristic symptoms of acute pneumonia, which later developed into phthisis. In January his appetite diminished, gums became spongy, bleeding, and separated from the teeth. Quantity of urine and sugar diminished.

15th February had diarrhoea for first time, followed by constipation. He fell into a state of extreme marasmus and could not retain either faeces or urine. He became somnolent, ceasing to eat, and died on 8th March.

Autopsy. Brain normal. Both lungs showed caseous masses and cavities, with increased pigmentation and fibrous tissue. Liver weighing 1430 grms. hyperaemic. Spleen enlarged. Kidneys somewhat enlarged, the left containing a cyst the size of a chestnut, otherwise normal. Stomach dilated and its coats hypertrophied.

Pancreas considerably diminished in size, soft and flattened. The parenchymatous substance being transformed into a greyish or fatty granular mass. The duct, a little above Vater's ampulla, was dilated, containing numerous calculi; calculi also in the smaller ducts. Semi-lunar ganglia appeared hypertrophied.

While referring to these cases published by Lancereaux, I may as well mention that in L'Union Médical (7th February, 1880) he gives the following graphic description of what he regards as the characteristics of Pancreatic Diabetes.

"In the midst of apparent health the patient is surprised by frequent desire to micturate, an inordinate appetite, and an insatiable thirst, associated with a rapid loss of flesh. Polyuria, polydipsia and polyphagia are the earliest phenomena of the disease, though the principal sign is the saccharine condition of the urine. The quantity of sugar passed varying from 40 to 60 grammes, or even amounting to as much as from 80 to 90 per litre (= two pints) While the amount of water passed in the 24 hours may vary from 5 to 10 litres.

Along with these signs and symptoms there is at the same time a marked and a rapid diminution of the intellectual faculties as well as of the physical powers. The duration of the disease is short. Death is the constant termination. It may be due to a complication - as, for example, to phthisis, to inflammation, to anthrax, or to gangrene; but in any case it occurs within two years of the onset of the illness - and

the autopsy reveals atrophy with more or less complete destructive degeneration of the pancreatic tissues."

The next two cases in which an atrophied pancreas occurred with diabetes were found in the pathological note-book of Professor Worm Müller by Professor Sophus Torup. The clinical history was kindly translated for me by Dr Julius Nicolaysen from the case book of the Rigohospital Kristiania.

T.E., a female, aged 21. admitted on the 10th September, 1877. She had always been in good health until the spring of 1875 when she became thin and very weak; always felt cold, had increased hunger and thirst, with frequent and profuse micturition. Menstruation ceased, having been previously regular.

In May, 1877, she had amblyopia, due to soft cataract of both eyes.

The only thing in her family history was her mother died from consumption and a brother had epilepsy.

The patient was very thin, weight 35 kilos. Eat and drank a good deal. Felt cold. Temperature 36.1°C. (97° Fahr.) Pulse 100. Respirations 20. Tongue clean and teeth good.

The left apex - want of resonance, with râles on inspiration. Right apex - expiration prolonged and inspiration harsh. Urine from 5 to 6 litres daily, pale colour, specific gravity 1030, containing 5 to 6 per cent of sugar and a trace of albumen. Chlorides normal, phosphates abundant. Microscopically a few leucocytes but no tube-casts.

12th September put on diet containing 2 rusks, 30

grms. butter, 750 cc. of coffee, 500 cc. bouillon, 4 rissoles, 2 eggs, and 250 cc. of claret; the quantity of urine fell as did also the sugar.

20th September the appetite failed and had fish instead of meat.

26th September, only took water and a litre of bouillon for one day. Then continued with diet. 23rd November abdominal pain and vomiting, which recurred on 27th.

On the 28th November, had a feeling of oppression over the chest. Respirations 28. Pulse 136, small and hard. Died in the night.

Analysis of the urine.

Date	Quantity in cc.	sp. gr.	Sugar per cent
11th September	5000	1030	5.7
20th "	2500	1035	3.3
27th "	1540	1022	2.0
30th "	1335	1029	3.2
1st October	1345	1031	3.7
8th "	2750	1032	4.7
15th "	3000	1025	3.1
20th "	2250	1020	3.2
24th "	2750	1020	2.7
31st "	3125	1022	2.9
7th November	3125	1024	3.4
12th "	1750	1028	3.8
21st "	2500	1028	3.3
26th "	1750	1020	1.8
28th "	1500	1018	1.7

It is seen the quantity of sugar greatly decreased towards the fatal termination, as so often happens in pancreatic cases.

Autopsy. Very emaciated, rigor only in upper limbs.

Cranium - Dura normal. Pia mater hyperaemic and some oedema posteriorly. Convolutions normal, the white substance contained some small haemorrhages.

Ventricles somewhat dilated; right cornua the size of little finger; the left obliterated by adhesions. Pons normal.

Thorax - Heart's substance anaemic and fragile. Pleural cavity contained a small quantity of fluid. Left Lung - Superior lobe pale. Inferior lobe of a brown red colour, due to hypostasis. In centre an infiltration the size of a nut, which on section showed a caseous centre surrounded by fresh foci yielding a whitish fluid; but no distinct tubercle. Right lung slightly adherent, of normal appearance, except inferior lobe which was oedematous. Bronchi somewhat hyperaemic amd containing a sero-mucoid fluid.

Abdomen. Spleen of normal size but anaemic. Kidneys - left of normal size, capsule easily removed, on section cortical parts somewhat yellow. The epithelium was fatty degenerated, especially the convoluted tubes. Right slightly enlarged. Capsule not adherent. Scattered over its surface were a few yellow nodules, which were found to be composed of an infiltration of leucocytes. Pelvis contained a few small erosions.

Bladder dilated, mucous membrane injected and in parts eroded.

Liver normal. Stomach - mucous membrane thickened and yellowish grey. Intestimes normal.

Pancreas very small and flattened.

The next case, from the same source, is that of:-

A.T., a youth, aged 17. Admitted 22nd January 1878.

The patient stated that when 4 years old he was confined to bed for a cardial pain. Otherwise always in the best of health, until two years ago. The cause he believed to be extra hard work, getting frequently wet and sleeping in a cold room. He then noticed that he was continually drinking and had to rise two or three times in the night to micturate. Soon became weak and was unable to work. Had had furuncles on neck and cheek, some as large as apples. In spite of the great appetite he grew very thin. On consulting a doctor he was told he had diabetes and was given a mixture and ordered a diet.

In the summer, 18 months ago, his abdomen swelled, apparently without cause, and in the same manner went down again in the autumn. A year ago his sight became dim. Shortly before Christmas, he had two attacks of violent pain in the upper part of his abdomen, lasting some hours. They were so severe that he believes he lost his reason during the seizure. There was no diarrhoea or obstruction to account for them. The patient on his admission was very weak and thin, could not sit up without support. The teeth carious, tongue moist, and furred. Appetite bad, and did not like meat.

Bowels regular.

He was narrow chested. The supra-clavicular regions hollowed, jugular veins prominent. Percussion gave dulness and auscultation râles over right apex. Abdomen large, ralaxed and veins dilated. Oedema of right foot. Pulse 104, very small. Respirations 32. Temperature 37° C. (98.6° Fahr.)

He passed in the day 4.7 litres of clear, light coloured urine. Acid, specific gravity 1020, containing 5.7 per cent of sugar, no albumen. Chlorides normal, phosphates abundant.

23rd January. Had not slept owing to cough. Sputum muco-purulent. He was put on a diet.

On 9th February his breath had a peculiar odour like onions.

On the 20th thirst diminished. Cough increased. Headache and oedema of eyelids and scrotum.

On March 1st, Slept well during the night, but at 5 a.m. taken suddenly ill. Breathing heavy; face congested, moist and red. Mouth firmly closed but he was quite conscious. Pulse 132 only just able to be counted. At 6 a.m. his face became pale, pupils dilated. Respiration very slow, pulse could not be counted, and he died at 6.45 a.m.

Urine analysis gave as follows: -

Date	Quantity in litres	sp. gr.	Sugar per cent
23rd January	4,750	1020	5.7
26th "	1.750	1020	1.6
29th "	1.250	1018	0.2
1st February	1.500	1012	traces

9th February	1.000	1022	1.3
13th "	1.750	1024	1.7
19th "	1.500	-	1.2
23rd "	1.500	-	0.5
25th "	1.750	-	1.2
27th "	1.000	-	1.8

The urine collected after death, contained neih ther sugar nor albumen.

Autopsy. Extreme emaciation, weight only 25 kilos.

Pericardium adherent (½ - 1 millimetre thick) easily separated, showing some haemorrhagic points. The muscular substance of heart pale and translucent, but not fatty. Valves normal. Microscopically, finely granular and in parts the transverse striation wanting.

Both pleura contained a limpid red fluid.

Lungs. Left, superior lobe anaemic; inferior lobe in lower part airless and of a blue-black colour; rest hyperaemic and oedematous. Right, upper lobe adherent, containing a cavity size of a hen's egg, half full of purulent pus; walls in part smooth and in part formed by débris of lung tissue, covered with a fibrinous membrane in which the ends of numerous small bronchi could be seen. Deeper in same lobe some small cavities filled with pus, the walls formed of degenerated lung tissue. No tubercles. Surrounding parts airless. Middle lobe anaemic and oedematous. Inferior lobe, lower part of a bluish colour and collapsed. Bronchi contain purulent matter. Bronchial glands enlarged, pigmented but not caseous. In the region of the bifurcation of

the trachea was situated an abscess, the size of a pigeon's egg; containing yellow pus, and surrounded by a grey wall of necrotic tissue.

Peritoneal cavity contained ½ litre of limpid fluid. Spleen, enlarged, of a brownish-grey colour, 125 grms. Liver weighed 1,360 grms. On section lobules not well defined. Very little fatty tissue round kidneys.

Kidneys. Left, weight 178 grms. Capsule slightly adherent, surface smooth. On section somewhat hyperaemic. Right, weight 135 grms. otherwise as left. In both pelvises some of the papillae covered with uric acid.

Bladder, prostate and testicles normal.

The pancreas only weighed 65 grammes (about 2½ ounces) Stomach and duodenum normal.

The examination of the cranium showed nothing abnormal.

Seegen in his work on diabetes at p. 116 gives the following case.

Herr W., a native of Vienna, aged 58. Two sisters died of melancholia. He had always been of sound mind, and had good health, although very stout. For some years was in France and whilst there noticed great thirst, which he attributed to change in the manner of living, and he now remembered that he had eaten a quantity of sweet things there. During the war of 1866 he was very excited, and in the autumn noticed that he was much thinner. In October, 1866, while in Paris, he again suffered from great thirst.

In the night of October 25th, he voided a large quantity of urine and on rising in the morning had great vertigo so that only with assistance could he keep upright. He returned to Vienna. His urine on 28th October contained 6 per cent sugar. During winter and spring of 1867, urine analysis was: -

24 hours' urine.	Sp.gr.	Sugar		Urea	
		p.cent	per diem	p.cent	per diem
14.Feb. 3200 cc.	1031	2.95	94.4	2.78	88.9
15.Apr. 2880 cc.	1035	4.58	132.0	2.30	66.2

In May, 1867, he went to Carlsbad. His condition was as follows: - Face pale, anxious expression, eyes somewhat staring. Body not emaciated, weighing 132 pounds. Skin dry. Great appetite, dryness of mouth. Tongue on both sides fissured. Thoracic and abdominal organs normal. Some muscular weakness.

Urine	24 hours	sp.gr.	Sugar	
			per cent	per diem.
11th May	2500 cc.	1035	4.5	113.0
15th "	2880	-	3.1	90.4
24th "	3520	-	1.4	49.2
31st "	3200	-	2.5	80.0
7th June	2800	1015	0.7	19.6

Weight at the end of course 130 pounds. In the winter of 1867-8 he got continually weaker and thinner. Appetite remained good, but he had a very bitter taste in mouth and sometimes so much so that he could not eat.

Urine	Daily quantity	Sugar per cent	Sugar per diem
3rd February	3540 cc.	4.55	166.2
3rd March	3480	4.00	139.0

3rd April	3700	3.26	124.3

On his return to Carlsbad, in May 1868, he was markedly thinner; weight only 103 pounds.

19th May	Urine	4500 cc.	3.5 p.c.	157.5 grms. sugar
2nd June		5250	3.5	183.7
14th "		5650	3.8	213.7
25th "		4875	3.8	185.2

In 1869, his weight on arrival at Carlsbad, was 103 pounds.

11th May	Urine	4420 cc.	Sugar 4.0 per cent.
19th "		5100	4.2
25th "		4080	2.2
1st June		4040 (12 hrs night)	2.4
		3060 (12 hrs day)	4.2
8th June		2040 (12 hrs.night)	3.8
		3060 (12 hrs.day)	4.1.

Weight increased to 106 pounds. Patient found himself better. In October, 1869, he died suddenly in the night, after having spent the evening as usual in his Club.

Autopsy Caseous infiltration in both lungs. Liver small and withered.
Pancreas shrunk to half its size and soft. Ganglia of solar plexus small and withered. Cranium not opened.

The following pancreatic cases complicated with disease in other organs have been recorded by Dr Fr. von Frerichs in his work on "Diabetes."

The first is entitled a case of "Diabetes with disease of the Pancreas."

C.W., workwoman, aged 27. In the spring of 1880

suffered from pain in the gastric region, with great thirst and weakness. The patient came into Hospital in June. She then passed 8 litres of urine daily, containing 6 per cent of sugar. Had bleeding from swollen gums, the epigastrium was both painful on pressure and distended. Temperature 36° C. (96.8° Fahr.) She was put on a carefully regulated diet and given opium. Later appetite failed, there was increased swelling in region of stomach, sleeplessness, sweet smell of breath, the urine containing acetone. Chloral hydrate given for the sleeplessness; urine increased to 8700 cc. with 7 per cent of sugar. Oedema of feet supervened. Painful cough, bronchial râles at both apices, and profuse expectoration. Thrush of mouth. Acetone disappeared from the urine before death on 8th November.

Autopsy. Both lungs contained cavities with caseous infiltration.

Heart very pigmented, no fat.

Pancreas. Above transverse colon and bound to the stomach was situated a sharply defined tumour, the size of a goose's egg. It was firmly connected to the posterior wall of stomach, in the position of the pancreas, of which only the head remained. This cyst contained 300 grms. of turbid, clayish fluid. Behind it, and surrounded by a false membrane, was situated an atrophied bit of pancreas, containing haematoidin crystals and granular cells.

The gastric mucosa thickened, folded and dry. Liver of a brown colour and atrophied. Spleen anaemic.

Vault of cranium thin, brain substance anaemic, oedema of pia mater.

A further case of diabetes equally associated with pancreatic disease is the following: -

E.B., needlewoman, aged 31. Was suddenly taken ill in July, 1875, after an over-indulgence in haricot beans. Three days later she had jaundice, which lasted 14 days, accompanied by cardiac weakness and vomiting. This was followed by diarrhoea and wasting, great hunger and thirst. The urine 11300 cc., specific gravity 1030, contained 596 grms. of sugar. Weight 35.5 kilos. Was put on a diet of meat and eggs, the quantity of urine fell in 6 days to 3600 cc., specific gravity 1015 and contained 1.3 per cent (46.8 grms.) of sugar. The weight decreased to 33.5 kilos.

On a mixed diet for the next 6 days, the urine rose to 5600 cc., specific gravity 1032, containing 4648 grms. of sugar. The weight increased to 34.5 kilos.

The patient was again put on an animal diet, the urine falling to 3000 cc., specific gravity 1015, containing 43.2 grms. of sugar. Weight fell to 33.9 kilos. The diet could not be continued, owing to lung mischief and fever. The phthisis lasted 4 months, the weight falling to 28.5 kilos. The urine during the last week for several days contained no sugar. Before death the sugar was 1.2 per cent, and at last 0.3 per cent. The urine of cadaver free from sugar.

Autopsy. Lungs contained cavities. Heart soft and small. Liver, spleen and kidneys normal. Mucosa

of stomach and intestine loosened, the intestine contained small yellow nodules.

Pancreas. The head converted into an abscess the size of an apple, containing a thick yellow pus. This abscess was not connected with the duct. A small portion of the tail remained.

Dura mater posteriorly and on left side pachymeningitis. In the substance of the cerebellum a small calcareous tumour the size of a hazel nut.

Dr Frerichs refers to another case, belonging to the same class. It is entitled: - Carcinoma of head of Pancreas. Closure of bile and pancreatic ducts. Jaundice. Haemorrhage from intestine. Diabetes Mellitus. Dysentery. Death from marasmus. Old capillary blood extravasations in Pons Varolii.

W.V., brick-layer, aged 50, admitted into Clinic 13th February 1854, died 9th April. He had had transient pain in the region of liver during the previous year. To these pains he did not pay special attention, as they did not materially affect his health. Since the beginning of December, i.e., three months, he became gradually jaundiced, the pains were more marked and radiated from the hepatic region towards the right shoulder, During this time his stools were sometimes tarry, which could not be attributed to his food.

On examination the skin was of a yellow brown colour, the abdomen soft, slightly distended, without pain on pressure. Liver somewhat enlarged. A round tense tumour was situated in the region of the head of the pancreas, which was painful on pressure, above

and to the left of this, another tumour was found on deep pressure, nodular and movable, but its boundaries could not be distinctly defined. His appetite continued good, there was no vomiting. Pulse small and 60. Heart normal. At the apices of both lungs were râles and dulness on percussion. The urine 3400 to 5000 cc. Specific gravity 1009 to 1018, contained 1.08 to 3.8 per cent of sugar. No albumen.

In spite of various treatments, he gradually lost flesh. The stools contained blood without admixture of bile. From the 7th April his urine was acid, containing biliary pigments, without a trace of sugar and on 9th at 1 o'clock in the morning, he died from marasmus.

Autopsy Skin jaundiced, no oedema.

Cerebral meninges yellow and mediumly rich in blood, the cerebral substance the same. In the Pons were brownish red aglomerations of pigment due to old capillary haemorrhages.

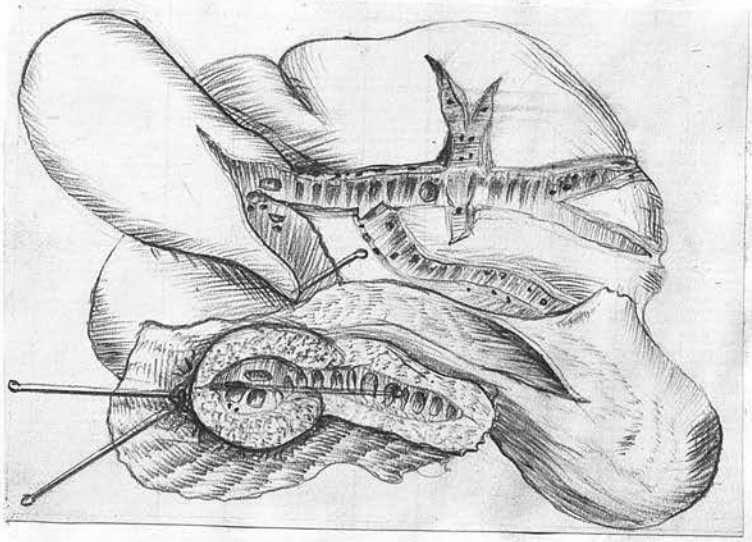
Tubercular infiltration of lungs. Heart normal.

Peritoneal cavity contained 1½ pounds of bile stained fluid.

Spleen adherent to colon, of normal size, capsule thickened, its parenchyma soft.

Liver, situated lower than normal. Not enlarged, sharp border and smooth surface. Gall-bladder enormously distended, contained 11 oz. of black-brown bile, in which floated large crystals of cholesterine. The bile ducts were so greatly dilated as to give the surface of the liver a feeling of fluctuation. Their

mucous membrane had lost its cylindrical epithelium and in its place were squamous cells in a state of fatty degeneration. The liver substance moist and soaked in bile. The liver cells for the most part not fatty.



- Fig. VII.

Carcinoma of head of Pancreas. Closure of bile and Pancreatic ducts

Pancreas connected with pylorus and duodenum. Its head converted into a medullary cancer. Inside the cancerous mass the duct of Wirsung dilated into a cyst, contained a colourless mucoid fluid. The rest of gland markedly atrophied. (See Figure VII)

Kidneys jaundiced, otherwise normal.

I will cite yet another case from Frerich's work as it is equally interesting: - entitled - Diabetes; phthisis; choroidal plexus adherent to calamus scriptorius; slight nephritis; complete atrophy of pancreas with marked dilatation of the duct of Wirsung, which

was filled with chalky concretions.

B., chimney-sweep, aged 26. Was first seen September, 1862, complaining of thirst and emaciation. Under treatment with opium, somewhat improved. In June, 1863, great emaciation and muscular weakness. Dulness of both apices; right with bronchial breathing and consonating râles, the left prolonged vesicular expiration..

Saliva acid. Mouth and pharynx red and swollen. Painful sensation in epigastrium and loss of appetite. Bowels regular. Liver unaltered. Spleen enlarged. Had hectic fever.

Urine 6 to 7 litres, specific gravity 1031 and rich in sugar. Treated with Carlsbad water and opium. At first remained much the same, only suffering from night sweats and intercostal neuralgia.

On July 3rd lost his appetite, marked diarrhoea. The urine, which had been pale, became dark red and fell to 1700 cc., specific gravity 1027.

On 6th July urine only 400 cc. specific gravity 1027. Sugar had disappeared and albumen and casts occurred. At this time both apices had physical signs of cavities. Dyspnoea set in, and the patient died from exhaustion on the 7th July.

Autopsy. Both lungs contained cavities. Heart normal. Dura mater thickened. Pia oedematous. Brain substance pale. Spleen enlarged. Kidneys both enlarged, cortex and medulla reddened. Epithelial cells fatty, capsule of glomeruli thickened, interstitial tissue increased, but loose.

Liver enlarged, brownish-red; cells small.

Small ulceration of ileum, follicles swollen. Mesenteric glands enlarged.

Pancreas. The whole gland converted into lobules of fat, only at the head some lobules of gland tissue remained. The pancreatic duct greatly dilated and varicose, contained a colourless fluid, in which was suspended small particles of carbonate and phosphate of lime. In the middle of the duct, a spindle-shaped concretion 1 inch long by $^3/_8$ inch thick, and nearer the duodenum another $1\frac{1}{2}$ inches long by $^3/_8$ inch thick were found. The walls of the duct were thickened; its branches ended in blind processes in the connective tissue separating the lobules of fat. The whole secreting substance of the gland being destroyed.

The next two cases are from the work of Edward Küly "Reiträge zur Pathologie und Therapie des Diabetes Mellitus" (Marburg, 1874)

E.D., aged 26, servant girl. Only remembered having measles as a child. Had menstruated regularly since she was 18. Four weeks before Christmas, 1890, she menstruated, the day after, when washing the house she got her feet and clothes wet, which was followed by sudden cessation of menses. She continued working although feeling ill. Had great thirst and had to rise 2 or 3 times during the night to micturate. She had some derangement of vision and said she could not collect her thoughts. On 7th January she stayed in bed, and as she daily got worse she entered the Hospital on 12th January. Her appearance was as that of

one suffering from typhoid. Temperature 36.8° C. (98.4° Fahr.) Muscles flabby. Skin rough and dry. Examination of her eyes revealed nothing. Her voice was whiney. No physical signs of disease. She was melancholy and somewhat inclined to cry. She excreted sugar even when taking no carbo-hydrates. The menses which had so suddenly ceased, never returned. She died suddenly, 12th February, 1872, the disease having lasted one year and two months.

Autopsy. Lungs pigmented, indurated, and dry on section, some emphysema. The kidneys seemed macroscopically fatty. The liver normal in size. Pancreas small. Brain bloodless, the convolutions somewhat flattened, the ventricles almost free from fluid. In the plexus small cysts.

J.U., aged 55, miller. Had suffered from typhus in 1848 and pneumonia in 1860, otherwise he had always had good health. He was not able to give any cause or time of commencement of present illness, but found he was not able to work as well as formerly. He had never noticed any furuncles. In 1863 he found he could not see as well as formerly, and since 1865 he had been completely blind. Soon after entrance into Hospital he became somewhat deaf. On examination he was found to be very emaciated. Skin withered and desquamating. Subcutaneous fat diminished. He never had swollen glands. Muscles flabby. Both eyes had marked opacity of lenses. He was deaf in both ears, only hearing when loudly spoken to. Examination of ears showed no cause for deafness. Thorax very rigid

and flattened in front on left side. The percussion note more dull on right side anteriorly than on left. Auscultation throughout harsh vesicular breathing with prolonged expiration, but no râles. Circulatory system normal. Tongue clean. Great thirst and appetite. The liver was normal in size, and the bowels sluggish. The patient had taken very little notice of his illness, only being discontented when not able to get as much food as usual. He only passed sugar when he took carbo-hydrates in his food. The patient died from marasmus in August, 1871.

Autopsy Lungs altered as so often found in diabetes. Microscopical examination of liver, kidneys and medulla showed no alteration. The middle part of the Pancreas was small and narrow.

If the diabetes is to be taken from the time of the changes in the eye, it had 8 years' duration.

This case, although one that I attach comparatively little importance to, I think it right to quote, as the pancreas is said to have been small and atrophied.

Lécorché - De la cataracte diabétique. Arch: Gen: de Med: 1861, Vol. XVIII, p, 70. Amblyopie diabétique grave, due à l'atrophie des rétines; cataracte diabétique striée survenue deux ans après le début du diabéte, chez un sujet de 45 ans; etc.

X., aged 45, piano-maker, was admitted into l'Hopital de la Charité, under M. Rayer, 8th June. Died 28th August, 1858. The patient never suffered from any serious disease. At the age of 20 he suffered from a gonorrhoea, which occurred three or four times. La-

ter he had a chancre and mucous plaques. In 1856 he had sore throat which recovered without treatment; the same year he had intestinal trouble which he could not definitely specify. It had marked effect on his health and left him with intense thirst. His general health became worse, emaciation became pronounced in spite of excellent appetite, and he became gradually weak and lost sexual powers.

In September, 1857, X. was taken with severe headache, lost his sleep and noticed that his sight was defective; at the distance of 4 or 5 metres he could only see objects indistinctly. This amblyopia persisted some time when, without known cause, it gradually improved. A Doctor whom he consulted found him to be diabetic and advised him to go to the Hospital.

In the commencement of 1858 he entered the Lariboisière, but he was unable to continue the Gluten diet because of frequent diarrhoea. The urine contained much sugar, but no albumen. In May, 1858 the emaciation was more marked; he had profuse sweats and cough, without haemoptysis, although auscultation revealed tuberculosis of both sides. The appetite had almost entirely disappeared, the thirst always intense Micturition frequent and abundant deprived him of sleep. The gums were soft, the teeth brittle, diarrhoea continuous.

The defect of vision was more pronounced than ever, He showed signs of atrophy of retina as well as commencing cataract in the left eye.

In June he was admitted into "La Charité", but he

had so severe a diarrhoea he was unable to be subjected to any treatment.

The tuberculosis, which hitherto had been latent, hastened its progress and he was soon unable to leave his bed. His urine, which was frequently examined, contained large quantities of sugar; towards the end of June it contained only traces and at this time it became albuminous and his legs oedematous. This condition continued without any material change till his death from phthisis.

Autopsy. The abdominal veins seemed abnormally large and the sub-peritoneal tissue very injected. Liver showed marked injection of its large capillaries; colour normal; consistence somewhat hardened. The section was a dark reddish brown and the branches of the vena porta were a considerable size. Spleen showed nothing abnormal. The Pancreas was small, as if atrophied. The left kidney large, weighed 210 grammes. Capsule not adherent, on section showed the second stage of Bright's disease.

The right kidney very small, weighing 35 grammes; part of this organ was atrophied and fibrous, and there only remained 5 or 6 pyramids of Malpighi intact, the others having disappeared. The ureters and the bladder were unaltered.

The lungs contained numerous tubercles. In the left, a little above the root of the lung there existed a large cavity containing foetid pus, but not entirely gangrenous. The right, the tubercles the most advanced were situated in the middle lobe.

Central nervous system contained no special lesions. In the lens was a soft cataract. The retinae showed varicosity of the arteries and augmentation in the volume of the veins; the texture of this membrane was not altered; the recent amblyopia was not accompanied by the characteristics of advanced atrophy.

The following case is of great interest, as in it not grape-sugar but maltose was found in the urine. It is, in fact, the only case in which maltose was found in diabetes accompanying pancreatic disease that I have come across. It was described by Dr Friedr. van Ackeren, entitled "Ueber Zuckeraussheidung duret den Harn bei Pankreaserkrankensgen." (Berliner Klin. Wochenschrift 8th April, 1889, p.293)

W.S., a male, aged 49. In his youth suffered from measles and scarlet fever, otherwise enjoyed good health until the spring, 1885, when he suffered for 8 days from gastric pain, which had no relation to the taking of food. Followed by vomiting and constipation. In June, 1888, the gastric pain recurred, which was continuous, vomiting and eructations as well as constipation. The patient rapidly emaciated and entered the hospital 7th August. He was of medium stature, of delicate build, with lax muscles, withered skin without subcutaneous fat. The skin was dry and of a pale yellow colour. He weighed 48 kilos! Nothing abnormal was found in the circulatory or respiratory systems. Liver dulness small.

To the right and above the umbilicus, there was made out on palpation an irregular, hard, and very

painful tumour. This tumour did not alter its position on respiration, although it was slightly movable sideways. After the passage of the oesophageal probang, the patient brought up about ½ litre of a dirty brown liquid, and immediately the tumour had changed its position and now lay between the umbilicus and left ribs. On the stomach being filled the tumour again returned to the right side. The examination of the contents of the stomach gave a very marked hydrochloric acid reaction, but no lactic acid could be recognised. On some days, blood was mixed with the stomach contents. The urine was scarce, cloudy, alkaline, specific gravity 1016, containing neither sugar or albumen.

The patient was then treated for some time by washing out the stomach, and for the constipation glycerine enema was employed. The gastric pain was lessened, but the vomiting did not improve. In the beginning of September oedema of the ankles set in, which soon disappeared, to recur again in December, when it extended to the scrotum and hands. The skin was very dry and peeling. In the beginning of January ascites and hydrothorax set in.

Throughout the whole time the tumour had so slightly increased in size, as to be inappreciable by palpation. The examination of the stomach washing, even as late as the 10th January, gave a marked hydrochloric acid reaction. On the 18th it no longer gave the reaction by the many tests in use, although it now gave a distinct lactic acid reaction.

In January the quantity of urine was 1800 cc.,

daily, and specific gravity 1028 to 1030. For the first time, on the 10th January, a substance was recognised in the urine which reduced Fehling's solution some time after boiling. This substance, after a most careful chemical analysis, was found to be Maltose, and also another carbo-hydrate.
The urine was rich in indicase, but no bile pigments.

The faeces, although frequently examined, never contained fat, but were rich in muscular tissue.
The patient progressively emaciated and died the 22nd January.

Autopsy - Revealed primary carcinomatous ulceration of the pylorus, with metastatic carcinomatous nodules in the peritoneal glands. In the pancreas were found two large carcinomatous lymphatic glands, one in the tail, another in the head.

The last case of pancreatic diabetes I will refer to is that of a case not hitherto published, for the notes of which I am indebted to Professor Sophus Torup. The history of the patient is so instructive that I will give a verbatim and literal translation of the record Professor Torup furnished me with.

A rich Banker died in October, 1886, at the age of 64, from diabetes and cancer of the pancreas. The case has several most interesting features about it; seeing that it not only occurred in a much more elderly person than usual, but the disease ran a much longer course than usually happens, and was only towards the end associated with the two most characteristic of the signs of pancreatic diabetes, namely ex-

treme emaciation and fatty stools. In addition to these important features the case has an exceptional clinical interest, in as much as during the whole four years the disease lasted, the urine was not only repeatedly examined for sugar, but a correct quantitative analysis made of the amount present in it from the very beginning of the disease in 1882 until its termination in 1886. Besides which we have the report of a carefully conducted examination of the organs and the morbid appearances met with in them after death.

Family Medical History. Father died of a vesical urinary calculus. One of his father's brothers died of diabetes, complicated with cancer of the stomach. His other brother also died of cancer. The patient himself considered himself a healthy man until the summer of 1882, when he had an attack of boils. At this time his urine was found to contain sugar. It had been on one or two occasions examined for sugar during 1881, without any having been found. The amount of sugar present in the urine was at this time 1 per cent. In the summer of 1883 the sugar had increased to 5 per cent. So he went to Carlsbad and took a course of the waters. On his return the amount of sugar was found to have greatly diminished, being only 0.5 per cent. But during the winter it rose to 6 per cent. So in the summer of 1884, as it had risen to 7 per cent, he again went to Carlsbad with the result that the quantity of sugar was, for a second time, reduced to 0.5 per cent.

In the summer of 1885, as the sugar in his urine

had once more considerably increased (the amount is not stated), he again repaired to Carlsbad and took a third course of the waters with the effect that the sugar fell to 1 per cent, which, although twice as much as on the two former occasions, was still regarded as satisfactory. And except that he began to complain of being thirsty, he felt well and vigorous. There was no perceptible loss of flesh and he had neither pain, nor any physical symptom of disease about him. Both heart and lungs were perfectly sound, so that he did not diet himself after he returned from Carlsbad until the sugar again began to increase in the urine. He then found it was easy to reduce its amount to from 1 to 2 per cent by a strict albuminoid dietary.

In the beginning of 1886 he commenced to lose his appetite and get sensibly thinner, while at the same time the sugar little by little increased; till it had by the summer time risen to 9 per cent, when he again went to Carlsbad. His visit on this occasion was, however, unattended with beneficial results. On his return home he gradually lost more and more flesh and his vigour and strength steadily decreased. His appetite equally notably diminished.

In the month of August a deep seated, slightly irregular-surfaced tumour was detected in the middle line, about midway between the ensiform cartilage and umbilicus. It was somewhat tender on pressure, and slightly mobile. About the same time quantities of unemulsioned fats of the food were noticed in the

stools. Of the existence of pancreatic disease consequently there could be no doubt. By the month of September the skin of the whole body had assumed an icteric tint, which got more and more marked up till the day of his death on the 5th October.

Autopsy. Skin deeply jaundiced. Rigor mortis marked. Scarcely a trace of subcutaneous fat. The pericardium contained a little yellow bile-stained serum. The heart itself was normal in size, very pale and without any fat about it. The valves were normal.

The pleural cavities contained about 100 cc. of bile-stained serum. The lung tissues were emphysematous. On section they otherwise appeared to be normal.

The lymphatic glands were mostly normal: but a few of them showed signs of commencing caseous degeneration. The abdominal cavity contained a considerable amount of yellow bile-stained, somewhat turbid serum, with here and there fibrinous coagula floating in it; while the peritoneum itself, more especially at the lower portion of the abdomen, had thin fibrinous deposits on its surface. The stomach was normal. The intestines somewhat dilated and slightly injected. In the lower portion of the duodenum there was an ulcer of a diameter of 3 centimetres with red edges. In its centre was a fistulous opening, through which a probe could be passed into a cavity behind, and on the withdrawal of the probe and the application of pressure there flowed out a whitish, viscid fluid somewhat resembling cream in appearance. There were two other smaller fistulous openings close to the large one.

Behind and closely adherent to the duodenum and vena cava was a tumour the size of a man's fist, implicating the duodenal orifices of the common bile and pancreatic ducts. The tumour was so adherent to, and so embodied in the head of the pancreas that it was impossible to distinguish between the limits of the proper pancreatic tissue and that of the tumour itself. On section the tumour was found to have a different constitution and consistence in different parts. One, a white portion, was hard and resisting to the knife. Another, of a yellower colour, was soft and almost gelatinous. While scattered throughout the tissues of the tumour were several more or less big cavities filled with the same whitish-yellow viscid, cream-like liquid as that which oozed from the fistula.

The sound could be made to enter the common bile-duct for about 5 or 6 centimetres; but there it impinged upon a stricture, caused by the pressure of the tumour on the walls of the canal. The gall-bladder contained three gall stones and about 50 cc. of bile.

The liver was of normal size; but its ducts were all dilated and its surface on section deeply stained by the pent-up bile.

The Pancreas. The head of the pancreas was completely permeated by the tumour. The remainder of the gland, from the outside, appeared to be normal; but on section its interior was found to contain a number of differently sized cavities, all filled with the same yellowish-white cream-like fluid already spoken of. At about 8 centimetres distant from the duodenum the

pancreatic canal opened into a cavity considerably larger than the other, which was full of the same kind of creamy liquid.

The spleen and kidneys were perfectly normal..

Here then, the autopsy of the man who had suffered from diabetes for four years, and latterly with great loss of flesh,and fatty stools, reveals, one might say, nothing abnormal in any of his organs except the pancreas, the tumour in the head of which completely obstructs both the orifice of the bile and pancreatic ducts, so as to arrest the entrance into the duodenum of either bile or pancreatic fluid. Moreover, as the tissues of the pancreas were greatly diseased, while those of the liver appeared healthy, except in so far as they were saturated with the pent-up bile, one cannot venture to blame the liver or any of the other organs, but the pancreas alone, as being the cause of the diabetes in the patient, with a cancerous family history associated in one instance - that of a paternal uncle - with diabetes.

It cannot fail to have been noticed in the foregoing cases, collected from such a variety of sources, both as regards their narrators and the countries in which they occurred that the diseases of the pancreas, with which the diabetic state was found associated, were extremely diverse in their characters. From being cases of merely partial disease of the gland, to complete fatty, cancerous or atrophic degeneration of its entire tissues - from a partial to a complete obstruction of its ducts by calculi, tumours or cica-

triced ulcerations. And this must of necessity appear all the more surprising from the fact that physiological experimental inquiry has shown that in no case can an artificial pancreatic diabetes be induced in animals unless the organ be totally extirpated or otherwise destroyed.

CHAPTER II

THE BEHAVIOUR OF SACCHARINE MATTER IN BLOOD.

As Medical Science, and in that term I include what is usually called Practical Medicine, has arrived at a stage in its career when, in order to make further advances along the road of progress, and arrive at the goal of exactitude, it is absolutely necessary that experimental enquiry should go hand in hand, if not actually precede, or even in some respects supersede empirical observation in investigating the etiology as well as the therapeutics of disease. I shall now proceed to refer to my experimental chemical and physiological researches into the causation of saccharine urine in cases of Pancreatic Diabetes.

Seeing that before any sugar can be excreted by the kidneys in the urine, it must not only have been present in the blood, but have actually been present there in excess, it naturally follows that any enquiry into the causes of saccharine urine must be preceded by the acquirement of some knowledge as to how the saccharine matter behaves itself in the blood and circulation. In this chapter I only treat with the behaviour of sugar in the blood itself.

According to Otto normal blood contains, on an average, from 1 to 1½ per cent. of sugar; there being less in venous than in arterial blood, and Claude Bernard said that until the amount of saccharine matter in the blood exceeded 0.3 per cent, none whatever is eliminated by the kidneys.

Hoppe-Seyler has still further added to our knowledge by showing that in some cases of diabetes the quantity of sugar present in the circulation may even reach to as much as 0.9 per cent. These facts of themselves are, I think, sufficient to show how necessary it is for any one working at the subject of diabetes to try and discover the part played by sugar during its sojourn in the blood, if he hopes to add anything to our knowledge of the subject. My being conscious of this led me to attempt doing so in the way presently to be described, although there are many difficulties besetting the path of enquiry, as will be seen in my experiments.

Schenk (+) recently stated the whole amount of sugar in the blood cannot be correctly determined by any single one of our present methods of analysis. This conclusion was arrived at from the results obtained from a series of experiments he made, not only with blood itself but with pure serum and also with solutions of the albumens of the blood. It may be well to mention that his experiments were performed as follows.

After ascertaining by a quantitative analysis how much sugar a measured amount of defibrinated calf's blood contained, he added to it a definite quantity of grape sugar, stirred it, and after waiting for a period of five minutes, acidulated the mixture by the addi-

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(+) Ueber das Verhalten des Traubenzuckers zu Eiweiskorper des Blutes. Archiv. fur die Gesammte Physiol. Band 46, p. 607.

tion of acetic acid, added from 4 to 5 vols. of water, and boiled it, so as to coagulate the albumens. The coagulum was thrown upon a filter and thoroughly washed. The filtrate and wash-water evaporated to a convenient quantity - thereby coagulating the remaining traces of the albumen, which were then separated by fresh filtration and washed. The sugar was now estimated according to Knapp's method of analysis, and the result was he found he lost from 45 to 80 per cent of the total sugar in the defibrinated blood and 46.2 per cent in the case of the serum. He further found that when he boiled the coagula with hydro-chloric acid, neutralised the filtrate, and tested it, there was always a considerable quantity of sugar present; so that on adding the sugar extracted by the hydro-chloric acid from the coagulum to the amount that had been previously obtained, only from 1 to 3 per cent of the original known quantity of the sugar was actually lost. The loss he regarded as due to a certain quantity of the added sugar having entered into chemical combination with the albumens of the blood. Schenk's paper was soon followed by one by F. Röhmann (+), whose experiments were made in a different way, in as much as he put into a vessel (capable of holding 50 cc.) 15 cc. of a saturated solution of sodium sulphate, and after being weighed, a quantity of blood was allowed to flow direct from the artery of a living animal into the

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(+) Ueber die Bestimŭng des Zŭckers im Blŭt. Aus dem Physiŏlogische Institut zŭ Breslaw. Centralblatt fŭr Physiol. Band 4, No. 1, p. 12. April 1890)

soda solution and the vessel with its contents was again weighed. The sodium and blood mixture was now emptied into a glazed iron capsule, and after being acidulated with acetic acid, was kept on a hot water bottle - with constant stirring - until the albumens were coagulated. The coagulum was then thrown on a filter and well washed with hot water acidulated with acetic acid. Both the filtrate and the wash -water were slightly coloured, and in order to obtain from them the last traces of their albumens, 2 grammes of acetate of soda and chloride of iron were added, and after the mixture was neutralised with sodium hydrate it was well heated over a free gas flame. This last precaution was, however, quite uncalled for, as the presence of traces of albumen is found not to interfere with Knapp's titration method. By this method Röhmann found that only from 5.6 to 21.6 per cent of the sugar was lost and did not consider Schenk right in saying that a chemical combination takes place between the albumens and saccharine matter in blood.

These contradictory conclusions led Seegen (+) to repeat the experiments, and employing Fehling's method of calculating the sugar instead of Knapp's. The results he obtained were almost identical to those of Röhmann. This being the case and knowing that it was absolutely necessary for me to have definite views on the subject before I could hope to do anything towards

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(+) Seegen. Zŭr Zŭckerbestimung im Blŭt. Centralblatt fŭr Physiol. Band 4, No. 8. July, 1890.

the elucidation of etiology of Pancreatic Diabetes, I resolved to investigate the matter for myself, and the following is briefly the result of the seven months I devoted to the research in the Fysiologiske Institut, Kristiania, along with Professor Torup who not only kindly counselled, but otherwise assisted me in the investigations in every way in his power.

The chief points I endeavoured to solve were: - Firstly, if sugar really enters into any kind of chemical combination in the constituents of blood? and Secondly, if by any mode of analysis it be possible to ascertain with exactitude the quantity of saccharine matter contained in any given amount of blood?

In order, if possible, to obtain reliable replies to these questions three different modes of research were adopted.

1st That of coagulating the albumen in the blood by Heat and Acetic Acid.

2nd That of coagulating the albumen in the blood by Mercuro-potassic iodide.

3rd That of coagulating the albumen in the blood by Mercuric chloride.

Before proceeding to adduce the results of the investigation, it may be as well to state that in order not only to mimimise, as far as possible, the danger of errors occurring in the methods of operating, but likewise to insure harmony and exactitude in the results, every precaution that suggested itself was taken. Thus, not only was there on every separate occasion a fresh volumetric analysis of the sugar em-

ployed made, but in every single instance when the quantity of saccharine matter was estimated, either in blood or water, it was done by the titration method and in no case were ever less than three titrations made. And not only so, but whenever one of the titrations failed to correspond to within 0.1 cc. of the solution in the burette it was not alone at once rejected, but the titration repeated even, it might be, to the extent of seven times, until the required degree of harmony in the result was obtained. Then and then only was the calculation proceeded with and the average struck. In order to prevent repetition, it will be well to mention that in all cases when not otherwise stated, the blood of a different animal of the same species was used, and that was generally the blood of the calf obtained as speedily as possible from the abattoir. The sugar employed in the experiments was chemically pure grape sugar, being repeatedly re-crystalised from alcohol of a specific gravity 0.837, and invariably titrating it afresh every time it was used. And when the quantity of sugar existing in the blood at the time of the addition of sugar is not stated, it is because it was found to be too small to be estimated. The experiments are, for the sake of easy reference, numbered consecutively, quite irrespective of the dates of their performance, and divided into sectional groups illustrative of the different points investigated. The first series I will refer to were made with the view of confirming or negativing Schenk's idea of the sugar entering into a chemical

combination with blood albumens and were conducted as follows: -

The blood (after having been obtained and prepared in the manner presently to be described in each of the cited analyses) was allowed to fall, drop by drop, into a measured quantity of briskly boiling, and constantly stirred distilled water, acetic acid being added until the mixture has an acid reaction. On the coagulation of the albumens being considered complete, the liquid was separated from them by filtration, and the coagulated albumens then well washed with hot acidulated water. In order that every particle of the saccharine matter existing in the blood might be got out of the coagulated albumens, the coagula were next boiled in a fresh quantity of water, replaced on the filter and again washed. This re-boiling and re-washing process being invariably repeated seven, and even occasionally more times. The collected filtrates and wash-waters were then evaporated down to a convenient working quantity, usually from 100 to 150 cc., and the sugar in it estimated by Knapp's method, as modified and improved by Worm Müller and Otto (+).

The improvement is founded on the fact that grape sugar has the power of reducing the cyanide of mercury in alkaline solutions to the state of metallic mercury and the mode of applying it is as follows: -

A titration liquid is made with 10 grammes of chemically pure and dry cyanide of mercury, along with

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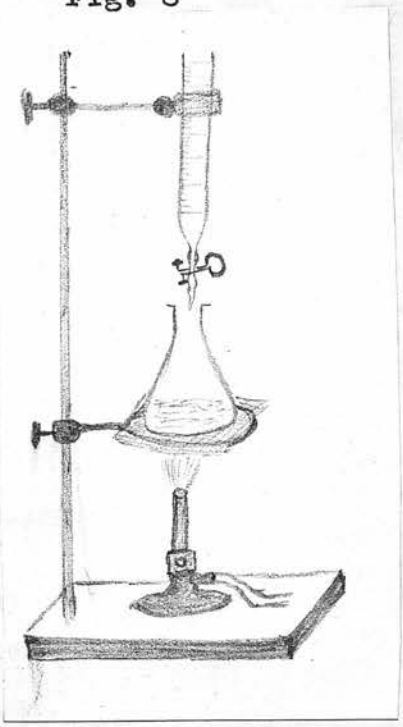
(+) Hammarsten - Lehrbuch der Physiol. Chemic. p. 349. 1891.

100 cc. of sodium hydrate solution of a specific gravity of 1.45 in a litre of distilled water, every 20 cc. of which is equal to 0.05 grammes of grape sugar. But the quantity of sugar in the liquid to be tested must never exceed 1 per cent.

The analysis is conducted by putting the liquid to be tested into a burette (as shown in Fig. 8) and 20 cc. of the volumetric solution into a flask below it, and setting it boiling. Then into the boiling solution is allowed to flow, drop by drop, from the burette the liquid - after the addition of each few drops half a minute's pause being allowed to elapse. Then when the process is nearly finished - as is known by the solution in the flask beginning to clear and quicksilver to be deposited - a drop of the boiling liquid is taken into a pipette and allowed to fall on a piece of white Swedish filter paper. The paper is then first held over an open flask of fuming hydrochloric acid, and next over one of strong sulphuretted hydrogen solution. So long as any mercuric salt remains in the test liquid, the paper is turned of a goldish-yellow colour, whereas so soon as the test is finished it remains white. The quantity of the sugar solution used is now read off from the burette, and the calculation made.

Fig. 8



This being the mode of operating, I will now give the results: but as the analyses made are far too numerous to admit of their being given in detail, I shall merely give what I deem are the best illustrative examples of the results obtained in each separate series of experiments. And to begin with, I will give six of those where the albumens of the blood were coagulated by the aid of heat and acetic acid; two of the samples being those that yielded average results; two of those yielding the best results, and two of those giving, as was supposed, the worst. For in this way I think the value of the research can be more readily assessed.

With these preliminary remarks I shall now proceed to relate the illustrative samples of the results from each series of experiments.

Experiment I.

To 50 cc. of freshly defibrinated calf's blood - after the amount of its own animal sugar had been ascertained to be so small as to be incalculable - 10 cc. of distilled water, containing 0.264 grammes of grape sugar, was added and the mixture immediately coagulated (in the manner previously described). No interval of five minutes having been allowed to elapse between the adding of the sugar and the commencement of the coagulation as in Schenk's mode of experimenting. This immediate action was had recourse to in consequence of its having been found - as will be afterwards shown - that the mere element of time has an

important influence on the results obtained when estimating the quantity of saccharine matter present in blood that has stood aside for some time.

The experiment yielded -

Amount of sugar in the blood	0.264
" " " found by analysis	0.251
Failed to detect	0.013 = 4.9 per cent.

That is to say, that for some reason or another yet to be determined, 4.9 per cent of the sugar that had been actually added to the blood could neither be recognised nor estimated by the chemical reagents employed in the analysis.

Experiment 2.

To 50 cc. of another calf's blood treated exactly as in the preceding case, and equally containing only an insignificant trace of sugar was added 10 cc. of water holding 0.264 grms. of grape sugar in solution.

Quantity of sugar present in the blood	0.264
" " " found by analysis	0.249
Failed to detect	0.015=5.6 p.c.

The next two experiments I will cite show the largest loss of sugar that I met with. They were performed exactly as the preceding, even to the minutest detail, so I see no reason to attribute the difference in the results to the mode of operating.

Experiment 3.

To 50 cc. of a calf's defibrinated blood, known to contain 0.032 grms. of sugar, 10 cc. of water holding 0.496 grms. of grape sugar were added, and the co-

agulation, etc., done as before.

Total quantity of sugar present in the blood	0.528
" " " " found	0.476
" " " " lost	0.052=9.8 p. c.

Experiment 4.

To 50 cc. of defibrinated calf's blood, which contained only insignificant traces of sugar were added 10 cc. of water containing 0.792 grms. of sugar

Quantity of sugar in blood	0.792
" " " found	0.671
" " " lost	0.117 = 14.8 p.c.

Having here shown the worst results obtained, I shall now cite what, in contrast, may be equally appropriately named the best of this series of analyses.

Experiment 5.

To 50 cc. of defibrinated calf's blood in which no sugar was detectable, 10 cc. of water holding in solution 0.562 grms. of sugar were added, and the mixture coagulated and otherwise treated as before.

Amount of sugar in blood	0.562
" " " found	0.501
" " " lost	0.061 = 1.1 per cent.

Experiment 6.

To 50 cc. of calf's defibrinated blood found to contain 0.048 grms. of sugar per cent, were added 10 cc. of water containing 393 grms. of sugar.

Total quantity of sugar in the blood	0.417
" " " " found	0.417
" " " " lost	nil.

The discrepancy in the results in these two last sets of analyses is so marked that it is impossible to imagine that there does not exist some important cause for it. What that cause may be I find it difficult to explain. From the fact that the only differences observable in the two different sets of analyses having been in the behaviour of the albumens during their coagulations. As that difference, however, may turn out to be the actual cause of the discrepancy in the results, I will refer to it. The difference consisted in the albumens in the latter set of analyses coagulating in the form of loose, fleecy, flocculent curds, and in the former separating in the shape of little, dense, firm clots; so that while the saccharine matter was readily extractable by washing from the fleecy curds, it was proportionally difficult to remove it entirely from the firmer clots in the interstices of which it had probably become entangled during the solidifying process.

In order not only still further to test this point, but to ascertain if possible the behaviour of sugar in the living animal, an entire change was made, not, however, in the mode of operating, but in the material operated on - viz. the blood. Instead of any longer employing defibrinated calf's blood, obtained at the abattoir, the undefibrinated, arterial blood, taken directly from the carotid artery of a living animal was used. And as this blood was not only withdrawn from the blood vessel of a healthy living ani-

mal; but from a vessel which ensured that its constituents had undergone no deteriorating changes (by performing any nutritive function) after they had passed through, and been oxidized in the lungs. It might be regarded not only as a good representation of living blood, but of living blood in the full entirety of its nutritive vigour. Consequently if the constituents of living blood really possess chemical action upon sugar, they would scarcely fail to manifest it on the grape sugar they were brought into immediate contact with in the process of analysis.

The results obtained in this way were the following: -

Experiment 7.

10 cc. of blood was withdrawn directly from the carotid of a living rabbit, and at once analysed exactly as in the preceding cases. Having found that it contained 0.0199 grammes of sugar ~~per mil~~., that is to say, 0.199 per cent, a further 10 cc. of the same rabbit's blood was directly withdrawn from the carotid, and 10 cc. of distilled water charged with 0.562 grammes of sugar added to it. The mixture was then immediately coagulated and examined for sugar by Knapp's method precisely as before.

The result of this analysis was: -

Total quantity of sugar in blood					0.5819
"	"	"	"	found	0.5780
"	"	"	"	lost	0.0039=0.6 p.c

Experiment 8.

To another 10 cc. of the same blood, which after

having been withdrawn from the living animal had been placed aside for four hours, 15 cc. of distilled water charged with 0.843 grammes of sugar were added, and immediately coagulated and analysed as in the previous instance. It gave the following result: -

Total quantity of sugar in blood					0.851
"	"	"	"	found	0.789
"	"	"	"	lost	0.062 = 7.2 p. c.

Here again is noticed a marked disagreement in the quantities of sugar found in the two cases. For 0.6 per cent only having been lost in the one, and 7.2 per cent in the other, that is to say, 12 times more, if the mode in the coagulations of the albumens be not accountable for it, the difference may be due to the factor of time. Seeing that while in the first case the blood was at once coagulated, and in the other it was permitted to stand aside for a period of four hours before having had the sugar added to it. With the view of obtaining more light upon this point, yet another alteration in the mode of experimenting was made. This time in the chemical part of the procedure, by substituting the mercuric iodide of potassium process (Brücke's solution) for the acetic acid and boiling method of coagulating the albumens. The change being as follows: -

The blood was first rendered faintly acid with hydrochloric acid, and then Brücke's solution added. The coagulum separated by filtration and to the liquid that passed through more of Brücke's solution added, this process being repeated again and again till

the filtrate no longer yielded a precipitate. The whole of the coagula were now washed, taken out of filter paper, and ground in a mortar, again acidulated and Brücke's solution reapplied to it, then filtered through same filter and washed.

The process being gone over five or six times in order to make sure that all the sugar was extracted from the coagulum, the whole of the obtained liquid was now concentrated over a water-bath and sulphuretted hydrogen, then passed through it, in order to get rid of the mercury. The mercurial precipitate collected and washed, and the sulphuretted hydrogen got rid of from filtrate by passing air through, then neutralised by sodium hydrate and the quantity measured. Titration by Knapp's method as in the other cases. The doing of this took an exceedingly long time.

Experiment 9.

To 50 cc. defibrinated calf's blood, containing mere traces of sugar, were added 10 cc. of water charged with 0.522 grms. of grape sugar, and the mixture at once analysed according to the above described method of Brücke.

Quantity of sugar in blood		0.522
" " "	found	0.515
" " "	lost	0.007 = 1.3 p.c.

Experiment 10.

Another analysis was made in the same way on 50 cc. of defibrinated calf's blood to which 0.264 grms. of sugar dissolved in 10 cc. of water were added, and yielded the following result: -

Quantity of sugar in blood			0.264
"	"	"	found 0.249
"	"	"	lost 0.015 = 5.6 p.c.

These results being very similar to those I obtained by the Acetic acid method of analysis, I now proceeded to employ mercuric chloride mode of coagulating the albumens, the process being in all other respects identical to Brücke's.

Experiment 11.

To 50 cc. of defibrinated calf's blood containing only an insignificant amount of sugar, was added 0.522 grms. of grape sugar dissolved in 10 cc. of distilled water, and the mixture immediately coagulated by the mercuric chloride process. The result was: -

Quantity of sugar in blood			0.522
"	"	"	found 0.521
"	"	"	lost 0.001 = 0.2 p.c.

Experiment 12.

Another experiment conducted precisely as the last in every single particular gave a still smaller loss.

Quantity of sugar in blood			0.5220
"	"	"	found 0.5214
"	"	"	lost 0.0006 = 1 p.c.

From the results of these various groups of analyses, it is seen: - Firstly, that the quantity of sugar remaining unaccounted for, bears no relative proportion to the quantity known to have been actually in any individual specimen of blood; while, secondly, not only the results of the analyses I have quoted, but

those of others that are left unquoted, point clearly to the fact that the actual quantity of the sugar lost in each case stands in a marked relationship to the behaviour of the albumens during the coagulating process, the loss being greatest when they separate in the form of dense little clots, and smallest when the albumens coagulate as loose flocculent curds. These facts have consequently led me to believe that the loss of the sugar is not due to a chemical combination having taken place between it and the constituents of the blood, but rather to the fact of the saccharine matters having become entangled with the albumen during its solidification, and being retained so firmly that it cannot be all regained by the washing out process. I see that even Schenk (+) himself has found reason to abandon his chemical combination theory since he repeated his original experiments, employing Brücke's method of coagulating the albumens. He found that instead of the enormous losses he had had with the method of heat and acetic acid previously recorded of from 45 to 80 per cent, he lost as little as 1.1 per cent on one occasion; 0.6 per cent on another; while on a third, instead of having a loss he actually had a surplus of 0.4 per cent, as well, as having found by means of the behaviour of the mixture, to dialysis no chemical combination could have possibly occurred.

As the cause of the sugar loss from blood is a question of great importance in studying the patho-

(+) Ueber Zückerstimung im Blut. Pflüger's Archiv: f. Physiol. Vol. 47, p. 621. 1890.

genesis of diabetes, I considered it well not to rest satisfied with the above Mechanical Retention theory until I had tested the value of some of the other factors that might possibly have equal influence. The first that suggested itself for consideration was the factor of "time" - be its mode of action what it might.

Accordingly the following experiments with the view of elucidating the point were undertaken; the albumens being in this instance coagulated by means of acetic acid and boiling.

Experiment 13.

To 200 cc. of freshly drawn and defibrinated calf's blood was added 40 cc. of distilled water, containing 1.112 grms. of grape sugar and the mixture simply placed aside in the laboratory. At the end of an hour 40 cc. of it which ought to have contained 0.2224 grms. of sugar were analysed with the result: -

Quantity of sugar originally present in the blood 0.2224 grms.

" " " found after 1 hr. 0.1397

" " " lost in " 0.0827= 37.18 p.c.

Experiment 14.

Again at the end of another hour a similar quantity of the blood was examined and this time the result yielded was: -

Quantity of sugar originally present in the blood 0.2224 grms.

" " " found after 2 hrs. 0.1251

" " " lost in " 0.0973=43.75 p.c.

Experiment 15.

At the end of six hours a similar quantity of the

the same blood was examined in precisely the same way, with the following result: -

Quantity of sugar originally present in the blood 0.2224 grms.

" " " found after 6 hrs. 0.1146

" " " lost in " 0.1078 = 48.47 p.c.

200 cc. of equally fresh and defibrinated blood from another calf, to which 1.10 grms. grape sugar had been added, was treated in exactly the same way, as regards having been placed quietly aside. The analysis of 50 cc. of it yielded: -

Experiment 16.

At the end of one hour.

Quantity of sugar originally present in the blood 0.220 grms.

" " " found after 1 hr. 0.193

" " " lost in " 0.027 = 12.27 p.c.

Experiment 17.

At the end of two hours: -

Quantity of sugar originally present in the blood 0.220 grms.

" " " found after 2 hrs. 0.179

" " " lost in " 0.041 = 18.63 p.c.

Experiment 18.

At the end of seven hours: -

Quantity of sugar originally present in the blood 0.220 grms.

" " " found after 7 hrs. 0.127

" " " lost in " 0.093 = 42.27 p.c.

Two more groups of experiments were performed, one in every particular as in the last, the other as will be presently seen, slightly changed.

200 cc. of calf's blood after having added to it 40 cc. of distilled water, charged with 1.10 grms. of grape sugar, was allowed to stand aside in the laboratory under the same conditions, and then 50 cc. of it analysed at identically similar spaces of time, the results being:

Experiment 19.

At the end of one hour.

Quantity of sugar originally present in the blood 0.220

" " " found after 1 hr. 0.141

" " " lost in " 0.079 = 35.90 p.c. in 1 hour.

Experiment 20.

At the end of two hours: -

Quantity of sugar originally present in the blood 0.220

" " " found after 2 hrs. 0.126

" " " lost in " 0.094 = 42.72 p.c. in 2 hours.

Experiment 21.

At the end of seven hours.

Quantity of sugar originally present in the blood 0.220

" " " found after 7 hrs. 0.109

" " " lost in " 0.111 = 50.45 p.c. in 7 hours.

In the other similar, though slightly changed controlling set of experiments which were undertaken, the modification in the method of procedure was simply to slightly increase the percentage of sugar employed, and reduce the volume of blood used to one half; and limit the experiments to a one and a two

hours' analysis. In all other respects the mode of operating was identical.

Experiment 22.

50 cc. of the mixture was analysed at the end of one hour.

Quantity of sugar originally present in the blood 0.264 grms.

" " " found after 1 hr. 0.216

" " " lost in " 0.048 = 18.2 p.c. in 1 hour.

Experiment 23.

Same as above analysed after two hours' standing.

Quantity of sugar originally present in the blood 0.264 grms.

" " " found after 2 hrs. 0.193

" " " lost in " 0.071 = 26.8 p.c. in 2 hours.

As the results in these different groups of experiments all are seen to point in one direction, the disappearance of the sugar from the blood being under the influence of "time." It had a strictly progressive character, although the quantity disappearing in the different groups varied greatly, the mechanical retention theory is quite inapplicable in these cases. The information I acquired in 1889, while working in the Pasteur Institut at Paris, regarding the mode of action of certain ferments on sugars, suggested to my mind the idea: - That this irregular. but always strictly progressive disappearance of the sugar from the blood might possibly be in some way or another connected with the presence in the blood of varying quantities of bacteria, as it would hardly be the

blood per se that acted with such a different destroying power in these cases.

Not only had ample opportunity existed for the blood to become contaminated with the bacteria floating about in the air of the abattoir during the time it was being defibrinated, but likewise of its obtaining any amount of bacteria from the air of the laboratory during the different stages of the experiment. Not only so, but there also existed the possibility of a chemical combination having taken place through the intermediary of the important element of "time" between some one or other of the normal constituents of the blood - albuminoid or other - and the artificially added grape sugar. While, lastly, the destroying oxidation of the sugar by the contact of the free oxygen in the blood, although not a very likely cause, was still one not to be entirely overlooked in an enquiry of this kind. So I determined to put these points to the test of experiment.

Firstly: - The possible action of bacteria was tested in the following manner.

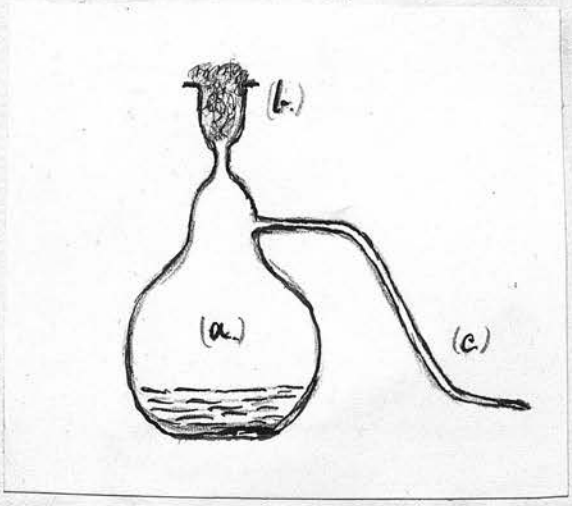
Experiment 24.

A Pasteur-flacon (fig.9) containing 0.132 grms. of sugar dissolved in distilled water, after being sterilised in the usual way by heat and pressure in an autoclave, was carefully weighed. That being ready, the carotid artery of a healthy rabbit was exposed. The sealed end of the receiving tube (a) attached to the flacon, after being heated and broken off, was inserted into the exposed carotid of the animal, and

the blood allowed to flow directly into and through it into the flacon, careful aseptic precautions having been taken in order to prevent the blood coming into contact with any bacteria in its transit from the blood vessel into the saccharine solution. It is consequently unlikely that any bacteria obtained access to the flacon, unless they existed in the blood itself. The blood employed in the following series of experiments may therefore be regarded, not only in the light of living blood, but living blood at the most active period of its existence. For the reasons assigned in the remarks prefacing the group of experiments with arterial blood beginning with Experiment 7, p. 92.

When a sufficient quantity of this arterial non-defibrinised blood from the living animal had entered the flacon, the end of tube (a) was again sealed and the whole re-weighed. So by subtracting the original weight of the flacon and sugar solution from its weight, after the addition of the blood, the exact quantity of the latter was ascertained.

Fig. 9.



(a) Pasteur-flacon with contents. (b) neck of flacon stopped with sterilized cotton wool. (c) blood receiving tube. The flacon having been well shaken, so as to prevent the blood

from coagulating in one mass, was placed aside in the laboratory. At the same time as this was done 11.3 grms. of the blood that had been immediately afterwards withdrawn from the carotid of the rabbit, was analysed in order to see how much sugar was present in the blood that was being used in the experiment. It was found to contain 0.0264 grms. So the 6.87 grms. of blood known to have entered the flacon was thus ascertained to contain 0.0160 grms of sugar.

After the flacon had stood for 2 hours in the laboratory its contents were analysed with the following result.

Quantity of sugar in the Rabbit's blood	0.016 grms.
" " " " " distilled water	0.132
Total quantity of sugar	0.148
Quantity of sugar found	0.128
" " " lost	0.020=13.5 p.c. in 2 hours.

Experiment 25.

24.8 grammes of blood from the carotid of another healthy rabbit was obtained, and treated in a Pasteur-flacon along with a similar quantity of distilled water containing the same amount of sugar, namely 0.132. The method of treatment throughout being identical to that followed in the previous case, except that the flacon was allowed to stand in the Laboratory for 26 instead of only for 2 hours before its contents were analysed.

The 27 grammes of the rabbit's blood that was examined for sugar was found to contain in this case

0.052 grms. of sugar = 0.192 per cent. The result found was:

Quantity of sugar in rabbit's blood	0.047
" " " in the distilled water	0.132
Total quantity of sugar in flacon	0.179
" " " " found	0.140
" " " " lost	0.039 = 21.8 p.c. in 26 hours.

Before venturing to draw any conclusion from the results thus obtained, I thought it prudent to make a comparative set of experiments with the blood of another species of animal, and that of the dog was selected for the purpose. I modified the experiment still further by using the same dog's blood a second time instead of as in the case of the rabbit, using the blood of another individual each time. In all other respects the experiments were conducted in the same way as regards the mode of collection and sterilization, etc.

Experiment 27.

61.5 grammes of blood freshly drawn from the carotid of a well fed and healthy dog, contained 0.0973 grammes of sugar - 0.15 per cent.

25 grammes of the same blood, containing consequently 0.039 grammes of sugar was kept in the Pasteur flacon along with 0.264 grammes of sugar dissolved in distilled water, during 21 hours in the laboratory. On analysis at the end of that time the following result was obtained.

Quantity of sugar in dog's blood	0.038 grms.
" " " distilled water	0.264
Total " " " in mixture	0.303
Quantity of sugar found	0.265
" " " lost	0.038=12.5 p.c. in 21 hours.

Experiment 28.

48.5 grammes of arterial blood obtained from the same dog in the same way, and treated exactly as the foregoing in all respects, except that it was kept in the laboratory for 70 instead of 21 hours - that is to say, three times as long, yielded on analysis, the following result: -

Quantity of sugar in dog's blood	0.077 grms.
" " " distilled water	0.264
Total " " " mixture	0.341
Quantity of sugar found	0.282
" " " lost	0.059=17.3 p.c. in 70 hours.

It is thus seen that with the dog's, as with the rabbit's blood, when the element of "time" is brought into play the disappearance of the saccharine matters from sterilized non-defibrinated, almost living, blood, is equally progressive. Although in a less marked degree than in the case of defibrinated, non-sterilized and consequently blood unprotected from the influence of bacteric action. It cannot therefore be said that the disappearance of sugar from blood under the influence of "time" is wholly due to the saccharine transforming power of bacteria, any more than it can be wholly accounted for by the mechanical retention

theory.

Hence one is forced to admit that there must exist in the blood some other sugar destroying factor. This is probably due to the direct action of some one or other of the normal constituents of the blood itself on the saccharine matter, either by a process of oxidation or the sugar being split up by unorganised ferments, i.e., enzymes. I will enter more fully into this point when I come to the discussion of the Pathogenesis of Pancreatic Diabetes.

CHAPTER III.

THE BEHAVIOUR OF SUGAR ARTIFICIALLY INTRODUCED INTO THE CIRCULATION.

Having shown in the last chapter how sugar behaves itself in the blood, I will now try and show experimentally how sugar that has been artificially introduced into the living circulation comports itself. Before saying anything regarding my own investigations, however, I will first briefly sketch the position in which the question stood when I entered upon the enquiry.

The most important knowledge of this subject is due to a series of researches conducted in Professor Ludwig's laboratory at Leipzig, by Dr v. Brasol, with the view of ascertaining how an excess of sugar was got rid of when artificially introduced into the jugular vein of animals. (1) Previous to this Falk Limpert (Virchow's Archiv. Vol. IX) and Forster (Zeitschrift für Biologie, Vol. XI) had shown that although a part of the sugar thus introduced into the circulation was excreted by the kidneys, the greater portion of it remained behind in the body. After them Luchsinger, (2) Forster, (3) Külz (4) and Heidenhain (5)

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(1) Leo. v. Brasol. "Wie entledigt sich das Blut von einen Uberschus am Traubenzucker?" Archiv. f. Physiol. 1884, p. 211.
(2) Pflüger's Archiv. 1883
(3) Sitzung's berichte der Münchener Akademie, 1876.
(4) Pflüger's Archiv. Vol. 24.
(5) Maly's Jahresbericht, 1874.

further showed that a portion of it was also transformed into glycogen by the liver.

Brasol's results are of great interest as they showed not only that the sugar excreting power of the kidneys in different animals of the same species varied, but that they went on excreting sugar when the quantity in the blood was normal.

Experiment A.

38 grms. of sugar injected into the jugular vein of a dog weighing 39 kilograms was eliminated from the urine as follows: -

In first 3 hours (collected by catheter)	1.6	grms.	sugar
" next 3 "	4.0	"	"
" " 18 "	2.9	"	"
Total eliminated in 24 hours	8.5	"	"

Experiment B.

Injected 40 grms. of sugar into jugular vein of a dog weighing 14 kilos.

In 1 hour and 5 minutes	6.7	grms.	sugar
" next 3 hours and 55 minutes	0.6	"	"
" rest of day	0.2	"	"
Total elimination in 24 hours	7.5	"	"

Experiment C.

Dog 28.5 kilos. Injected 60 grms. sugar.

In 5 hours	12.04	grms.	sugar
Next 5 "	1.88	"	"
Rest of day	0.99	"	"
Total eliminated in 24 hours	14.91	"	"

From these results it is seen that the greater part of the injected sugar is not excreted by the kid-

neys, but remains behind and is used up in the animal economy..

The next series of experiments show how quickly the excess of sugar is got rid of from the circulation and the quantity present in the blood is again restored to normal.

Experiment D.

Dog, 39 kilos. Injected 38 grms. of sugar. In 24 hours 8.58 grms of sugar were found in the urine.

Before injection, the serum contained	0.137	p.c. sugar
In 2 minutes afterwards	0.805	" "
In 1 hour, 7 minutes	0.072	" "
In 20 hours	0.101	" "

Experiment E.

Dog 33 kilos. Injected 100 grms. sugar. In 4¼ hours 21.38 grms. of sugar were found in the urine.

Before injection the blood contained	0.108	p.c. sugar
In 2 minutes after injection	1.054	" "
In 2 hours "	0.159	" "
In 4½ hours "	0.054	" "

Here it is seen that not only the excess of sugar is rapidly eliminated by the kidneys, and the quantity in the blood reduced to normal within the short period of two hours, and that the excessive excretion does not always stop here, but goes on still further, even until it has reduced the amount of sugar in the blood to much below the normal standard. This anomalous fact is explained in Brasol's paper on the theory that the kidneys, having once been over stimulated by the excretion of the excess of saccharine matter, still go

on excreting the sugar from the blood even after it has ceased to contain any excess of saccharine matter.

After the injection of sugar into the circulation Brasol states that if we calculate, as is usually done, the quantity of blood as being equal to 7 per cent of the weight of the animal's body, his results show that only from a quarter to a half of the injected sugar can be accounted for by analysis within the brief space of 2 minutes.

In order to see if this enormously rapid disappearance of the sugar from the circulation could possibly be due to an augmentation having taken place in the quantity of blood, by an influx of fluid from the tissues; the quantity of haemoglobin was estimated before and after the injection. This was done by Welcker's modification of Hoppe-Seyler's method, taking the quantity of haemoglobin before injection as 100, it was found to have fallen in nine experiments to from 31.4 to 81.02. While in using the more accurate spectrophotometric method of Vierordt and Hüfner in two of the analyses made by Professor Bohr, it was found to have fallen to 66 and 70.

It is thus seen that there is a great increase of fluid in the blood vessels, though not quite sufficient to account for all the sugar lost. This probably may, to some measure, be accounted for by the loss sustained during the coagulation, as shown in the last chapter.

The sudden increase of fluid in the blood vessels,

causes, as might naturally be expected, a corresponding rise in the arterial pressure. This will be seen in the following experiment.

Dog, 14 kilos. Injected during 6 minutes, 184 ccm. of saline solution containing 110 grms. sugar.

	Colouring matter in blood.	Pressure in Carotid artery
Before injection of sugar	1.00	132 m.m. Hg.
1 minute after	0.69	165 " "
11 minutes after	0.87	160 " "
2 hours, 41 minutes after	1.20	136 " "

Brasol's results and views expressed upon them, seemed to me so important that I made the following experiment. But before relating it, it may be well to take this opportunity of explaining under what conditions my experiments on living animals were performed. Not only were all the animals operated upon anaesthetised, except in those instances in which the employment of an anaesthetic agent would interfere with the value of the results obtained, but I always before administering the chloroform gave the dogs and rabbits a hypodermic injection of atropine and morphine, a mode of procedure I learned while working with Professor Dastre, in 1889, at the Physiological Laboratory of the Sorbonne in Paris, which has the power of rendering animals exempt from the lethal effects of chloroform. This fact I have had ample opportunity of verifying by the results following upon its adoption in my experiments on dogs and other animals in Paris, but also while working with Professor

Hoppe-Seyler at Strasburg and Kristiania. It has the great advantage too of not only diminishing the quantity of chloroform required to render the animal insensible, but it makes the animal so quiet that no trouble is experienced in administering the anaesthetic to it, or even in fastening it to the operating table. (+)

Experiment 29.

Into the right carotid artery of a dog (weighing 5½ kilos.) after being anaesthetised, was inserted one of Ludwig's metal cannulae, connected to Ludwig's improved Kymograph by means of a lead tube filled with a saturated solution of sodium carbonate. And while the animal was kept tranquilly insensible 17.52 grms. of pure grape sugar, dissolved in 30.cc of a 7 per mil ~~cent~~ saline solution, was slowly (during ten minutes) injected into his left crural vein. Immediately - before the injection was completed - the blood pressure in the carotid rose.

The quantity of sugar in the dog's blood, analysed by heat, acetic acid, and Knapp's method, was found to be -

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(+(Of such utility do I consider the atropine and morphine injection, that I herewith give Professor Dastre's formula for its preparation.

Chloride of morphine	2.00	grms.
Sulphate of atropine	0.20	"
Water to	100.00	

Every cubic centimetre contains { H.D. 2 centgr. morphine; 2 m/mgr. atropine }

The dose to give is for every kilogramme of the animal's body-weight a cubic centimetre of the solution, and administer if about half an hour before the intended operation.

Sugar in the blood,	before the injection of the sugar	0.144 p.c.
In 2 minutes	after the injection "	0.700 "
" 2 hours	" " " "	0.202 "
" 6 "	" " " "	0.139 "

The amount of haemoglobin in each specimen of blood withdrawn was estimated by Hüfner's spectrophotometric method, and found to fall at first as in Brasol's experiments.

The urine was collected by means of a catheter tied in the bladder, and the presence of sugar determined by Fehling's method, the quantity by Knapp's.

Sugar in urine	before the injection of the sugar	none
5 minutes	after injection of the sugar sufficient to give	Brown colorisation, but no precipitate.
2 hours	" " 55 cc. contained	1.59 grms.
6 "	" " 27 " "	0.518 "
7 "	" " 5 " "	0.203 "

The small quantity of urine obtained for the last analysis was due to an unfortunate accident having occurred, which caused the dog's death. As is seen, however the results obtained, as far as the experiments went, completely confirmed those published by Brasol and seeing that Brasol's experiments were so carefully performed and so ably recorded, I did not deem it necessary to repeat the experiment which even confirmed, as is seen, his observation that the kidneys continue to excrete sugar when grape sugar is injected into a blood vessel, even after the quantity present in the

blood has reached the normal. This apparently anomalous fact I will now comment upon. For, as I already said, Brasol's explanation of it is, to my mind, not a satisfactory one, namely, that it arises from the kidneys having been, from the sudden influx of sugar into the circulation, so over stimulated by the unusual amount of work temporarily thrown upon them, that they go on excreting sugar after the quantity in the blood has arrived at the normal or even below it. To me it seems likely that the reason why the kidneys go on excreting saccharine matter after the quantity in the blood has been reduced to normal limits is because one of the functions of these organs is to eliminate from the circulation all foreign soluble matters that find entrance there. And although chemists speak of grape sugar and the sugar found in the animal body as being identical, and no doubt they are so chemically, it is possible that "vegetable grape sugar" differs as much from "animal grape sugar" as the urea prepared in the laboratory does from the urea formed by the human body and excreted in the human urine; or as much as the alcohols that are distilled from maize, rice and barley differ from one another. For though all are isomerically the same, each of them has, to some extent, different physiological actions and exerts a different series of effects on the animal economy. Consequently it seems to me as if the "vegetable grape sugar" that was injected into the animal's veins was not only eliminated because it raised the percentage of the saccharine matter in the blood to above normal,

but, likewise because not being so easily used up in the economy, it played the part of a foreign material in the circulation, which it is part of the duty of the kidneys to get rid of.

As no theory is worth the paper it is written upon unless it be based on demonstrable facts, and as physicians are more concerned with sugar as it appears and exists in the urine of their diabetic patients than with its behaviour elsewhere, I thought it desirable to make some experiments with the view of discovering how quickly "vegetable grape sugar" makes its appearance in the urine after having been injected into a blood vessel. Imagining that the result obtained from them would most probably not only answer the question as to the rapidity with which sugar is eliminated, but at the same time, show if I am right in my supposition that "vegetable grape sugar" is not really identical with, but has only an isomeric relationship to the so-called "grape sugar" manufactured in the animal body itself. Accordingly, I made a number of injections with a solution of pure "vegetable grape sugar" dissolved in distilled water into the external jugular veins of rabbits, and tested their urine both before and immediately after the performance of the operation, in order to see how quickly it was excreted from the circulation by the kidneys. The result was that I found that the sugar in most of the cases appeared in the urine within the brief space of two minutes, as the following illustrative experiment made upon a rabbit, weighing 1 kilo. 930 grms. shows:

Experiment 30.

Having inserted a glass cannula into the external jugular vein, through it 38.5 cc. of a saline solution containing 13.861 grms of grape sugar were introduced into the blood vessel. The whole process, from the beginning to the end of the injection, lasting about twenty minutes.

The urine collected immediately before the commencement of the experiment, contained no trace of sugar whatever, but no sooner was the injection process begun than the water which flowed from the end of the catheter showed traces of sugar, and by the time five minutes had elapsed, it contained 0.800 per cent of saccharine matter. Between that and the end of fifteen minutes more, it had increased to 0.860 per cent. The object in view having been now attained, the experiment was interrupted.

The above results, proving as they do, that the excretion of "vegetable grape sugar" begins as soon as it reaches the circulation, seems to me to show that it plays to some extent the part of a foreign body, precisely in the same way as soluble poisonous salts do. Even the excretion by the kidneys of the iodide of potassium - which is known to be one of the most rapidly eliminated of the mineral salts is not one whit more speedy. Hence, I think I am justified in believing that "vegetable grape sugar" plays, to some extent, the part of any other foreign material in the circulation and gives rise, as I above said, to the fact of the kidneys continuing to eliminate with

the urine a quantity of saccharine matter even after the amount of sugar in the blood has fallen below the normal.

Now comes the question: -

Is sugar met with in Normal Urine? This is a question very far from being as yet settled, and it being one of considerable importance for us to have clear ideas regarding, I will here insert the results of experiments I made on the subject three years ago, when practically engaged upon the solution of a different physiological problem. As the matter at present stands, the idea that normal human urine contains sugar is supported by Brücke, Bence Jones, Abeles and Kühne.

While against the idea stand Külz, Seegen, Moscatelli.

Dr Pavéy considers that he has been able to find traces of sugar in the normal human urine by forming a lead saccharine compound which he considers he has isolated. (+) This being the position in which I found the matter, I instituted a number of experiments on different species of what I considered to be normal urine. The agents employed for testing in the saccharine substance being Fehling's, Moor's and the Yeast test, particularly the latter; for without evidences of fermenting I should hesitate to say that any specimen of urine whatever incontrovertibly contained sugar, first because, with a standard solution of

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(+) "On Certain Points connected with Diabetes." London, 1878.

caustic potash of a specific gravity of 1060, many human urines passed by apparently healthy men and women give on boiling the light sherry or orange coloured reaction of sugar. While again, healthy rabbits' urine contains a substance which acts like sugar in reducing Fehling's liquid, yet when tested with yeast does not ferment like sugar.

Having satisfied myself that healthy dogs' urine is devoid of sugar, I tested my own under a great variety of conditions, and although I occasionally got a sherry or orange coloration on boiling it with caustic potash alone, as I never succeeded in either getting a typical reduction with Fehling's liquid or anything like a saccharine fermentation with yeast, I concluded that my normal urine contains no sugar at any period of digestion when I am living on ordinary diet.

The next point was to give a superabundance of saccharine matter along with the food and see if the excess thus introduced into the animal economy would be absorbed into the circulations, expelled from them by the kidneys, and make its appearance in the urine, as had been stated by Worm Müller (1) and Seegen (2). The former observer states that he found from 0.7 to 0.8 per cent of sugar in the urine of a healthy man after feeding him with 250 grammes of cane sugar, while Seegen says that he found sugar in the urine of

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(1) Worm Müller. Die Ausscheidung des Zuckers im Harn. Pflüger's Archiv. Band XXXIV.
(2) Seegen. Ueber Zucker im Harn bri Rohrzuck fütterung. Pflüger's Archiv. Band XXXVII.

dogs upon a highly saccharine diet. Both of these statements I put to the test while working with Professor Dastre in 1889 in the laboratory of the Sorbonne at Paris, on the influence of sugar on the excretion of uric acid.

Experiment 31.

To more than half a dozen dogs (I should say about 8) I daily gave 50 grms. of cane sugar along with their ordinary diet, and although I continued the experiment on some of them for 27 days, I never on a single occasion was able to make the urine to ferment with the yeast test, nor obtain a typical sugar-reduction with Fehling's solution. Therefore I arrived at the conclusion that the whole 50 grammes of cane sugar I had given to the dogs was used up in their systems as nourishment, and there existed no excess in the circulation for the kidneys to eliminate.

Experiment 32.

I at the same time performed, in the same way, a number of experiments upon myself. I will not, however, do more here than refer to the result, as I intend to publish the experiments in detail, in a paper "On the relationship of sugar to gout, with reference to its influence on uric acid formation." Suffice it then here to say that even after I had for four days taken at the rate of 400 grammes, that is to say, no less than 13 ounces of cane sugar per diem, and even so completely upset my digestion, and made myself so ill by so doing, that I had to abandon the experiment, I never found any sugar in my urine when it was care-

fully tested either by Fehling's liquid or yeast.

Seeing then that I had, as I thought, already obtained sufficient evidence that cane sugar taken as food, both by men and dogs, is in some way or another used up in the body, so that none of it re-appears in the urine, it was necessary to try and see how sugar behaves itself when it does not enter the animal body by the digestive canal, but is injected directly into the portal veins and by them transported straight to the liver, and passed through it before being allowed to enter the general circulation. I may mention that this is not only a generally recognised fact, but one that has received experimental demonstration by Von Mering, (1) who showed that none of the saccharine matter that reaches the intestines as food, is taken up by the lacteals, but all is absorbed by the branches of the Portal vein. And already in 1855 Claude Bernard (2) has stated that grape sugar behaves itself quite differently when it is injected into the portal vessels, from what it does when injected into those of the general system. For no sugar is found in the urine of starving animals when grape sugar is directly introduced into the portal vein, - a statement subsequently confirmed by Schröpfer (3). What then, it may be asked, becomes of the grape sugar under these circumstances?

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(1) Von Mering. Ueber die Absergswege des Zuckers aus dem Darmcanal du Bois - Reymond's Archiv. 1877
(2) Cl. Bernard. Leçons de Physiol. experimental. Paris, 1855. 7 Leçon.
(3) Schröpfer. Archiv. für experim. Pathol. I.

The solution of this question appearing to me to be a point of very great importance in an enquiry of this kind, I made the following series of experiments; and most fortunately, as it proves, I did so, for it has led to the unexpected discovery that when grape sugar is injected into the portal blood vessels and passed through the liver before it is allowed to get into the general circulation a new substance is formed, which is excreted by the kidneys along with the urine. This new substance, although not itself saccharine, is, by boiling with dilute hydrochloric acid, at once converted into sugar.

The results I obtained from the first experiments, which were made upon rabbits, completely accorded with those published by Bernard and Schröpfer. For on injecting grape sugar into the portal vein, I was neither able to get the urine to reduce Fehling's solution nor ferment with yeast. This seemed in agreement with the view that it was held back in the liver as glycogen. It occurred to me, however, that it was quite possible even if the sugar was transformed by the liver into some other carbo-hydrate, some of it might escape from this organ into the general circulation and on reaching the kidneys be eliminated by them as such a carbo-hydrate, therefore it might be well for me specially to test the urine for carbo-hydrates and see if it did or did not contain any.

Experiment 33

I accordingly boiled some of the urine (which had not given any reduction with Fehling's solution)

with dilute hydrochloric acid and after neutralized it with sodium hydrate. I then found on again boiling it with Fehling's solution, that it gave the typical reduction of sugar. As this is an important observation, I will quote in illustration one experiment on a well fed rabbit.

Experiment 34.

The rabbit weighed 1 kilo. 655 grms. As the urine collected before the experiment did not reduce Fehling's solution, either before or after boiling it with hydrochloric acid, it could not have then contained any carbo-hydrate.

So soon as this fact was ascertained a cannula was inserted into the splenic branch of the portal vein, and 20 cc of a saline solution, containing 15 grms. of grape sugar, slowly allowed to enter it from a burette (during fifteen minutes) The urine on being tested for sugar by boiling it with Fehling's solution, gave only a brown coloration, but no precipitate; whereas the very same urine, after having been boiled with hydrochloric acid and neutralized with sodium hydrate, on then being boiled with the Fehling's solution, gave the typical precipitate of sugar.

I next repeated these experiments on starving rabbits, so as to make sure that at the time of injection there would be no glycogen in either the animal's liver or in its muscles. For glycogen always disappears from the liver and the muscles of rabbits after 5 days' starvation, and even earlier. This fact I have repeatedly verified.

In searching for glycogen I always employ the method of R.Külz, and in doing so a portion of liver or muscle is removed as quickly as possible (either before or after death) weighed and then immediately plunged into briskly boiling water. It is next as fast as possible, with a pair of scissors, cut up into small pieces while in the boiling water, and allowed to boil for about five minutes. The pieces are then taken out, put into a mortar, and after being ground down to a pulp, replaced in the boiling water, to which is added from 3 to 4 per cent of potassium hydrate. This mixture is now concentrated over a water-bath, and on cooling it is rendered acid with hydrochloric acid, after which all the albumens it contains are precipitated by the addition of mercuro-potassic iodide and separated by filtration through thick filter paper. To the colourless filtered solution more hydrochloric acid and mercuro-potassic iodide are added, and if there be any precipitate, it is again filtered, and the whole process again and again gone through, until on adding hydrochloric acid and mercuro-potassic iodide there is no longer any precipitate.

When a quantitative analysis is made the precipitate is washed, taken out of the filter, placed in a mortar, hydrochloric acid added, then mercuro-potassic iodide along with water, and after the whole is well bruised, it is thrown on filter paper and the liquid filtered off as before. This process has to be repeated at least 4 or 5 times. To the filtrate and

wash water absolute alcohol is now added until all the glycogen is precipitated. In merely qualitative testing the repeated washings are uncalled for.

I may mention that according to my experience when one is searching for very minute quantities of glycogen, it is much better to use absolute alcohol than to rely upon the iodide test.

Experiment 35.

The liver of another rabbit, weighing 1 kilo. 835 grms., which had had nothing except water for 5 days, was examined for glycogen in the following manner. Its abdomen was opened in the middle line, one of the lobes of the liver was drawn out by the wound, a firm ligature passed carefully round it, and the lobe removed. It weighed 3.6 grms. After being treated by Külz's method and tested, it was found to be absolutely devoid of glycogen.

Experiment 36.

I now slowly injected 15 grammes of grape sugar dissolved in 60 cc. of saline solution, into the rabbit's vena porta. The injection took half an hour, and at the end of this time another piece of liver, weighing 10 grms. was removed. It likewise was treated after the method of Külz and found still to contain no glycogen, notwithstanding that grape sugar had been injected into the portal vein. The urine gave no reduction either on being boiled at once with Fehling's solution, or after it had been previously boiled with hydrochloric acid and neutralized with soda solution.

Experiment 37.

From another rabbit, weighing 1 kilo. 638 grms., which had been kept fasting during six days, 2.5 grms of liver was removed in the same manner as in former experiment, treated after method of Külz, and as it was found to contain no glycogen, I slowly injected into its portal vein 15 grms. of grape sugar, dissolved in 60 cc. of the usual strength of saline solution. The injection lasting over a period of 40 minutes. When it was finished, that is to say, 40 minutes from the time the sugar must have begun to enter the liver along with the portal blood, 5 grms. of it were removed and after being treated and tested as before, was found to contain no glycogen.

Urine collected during whole experiment, and for 10 minutes after it, gave no sugar reduction with Fehling, even after boiling with hydrochloric acid.

In these two experiments we thus not only find no reducing substance in the urine; consequently no saccharine matter, not even after boiling with hydrochloric acid, but no evidence even of the formation of glycogen - a diametrically opposite result to what one might have expected, and one probably due to the fact of the animals being in want of saccharine nourishment they used up the sugar at once as sugar without allowing it to be transformed into glycogen in the liver.

I now repeated the same kind of experiment on a previously well fed dog, in order to see if any carbo-

hydrate appeared in the urine.

Experiment 38.

Dog, weighing 20.8 kilogrammes, anaesthetised. The abdominal cavity was opened by an incision in the middle line, and a loop of intestine drawn out. A small glass cannula having been inserted into one of the mesenteric veins. The urine collected up to this point of the operation gave no sugar reaction with Fehling's solution, either before or after boiling with dilute hydrochloric acid, merely a slight browning due to uric acid or creatinin. By means of a graduated burette 100 cc. of saline solution, containing 30.0 grms of grape-sugar, was now gradually injected during 1 hour and 20 minutes. The urine collected during this time, on being boiled with Fehling's solution merely gave the same brownish coloration; another specimen was then boiled with dilute hydrochloric acid and neutralized with sodium hydrate when it yielded, on boiling with Fehling's solution, the brownish yellow precipitate of sugar. A third portion of urine collected during the next hour and a half, that is to say, 2 hours 50 minutes after the commencement of the injection, on being boiled with Fehling's solution, gave a brownish red precipitate, which was much more marked after having been boiled with hydrochloric acid.

This can be tabularly represented, thus: -

Time during which urine collected	Sugar injected	Quantity of urine in cc.	Sugar before boiling in HCl.	Sugar after boiling in H Cl.
40 minutes		20	none	none
1 hr. 20 min.	30 grms. in 100 cc.	60	none	present
1 hr. 30 min.		35	present	copious

It is thus seen when grape sugar is injected into the circulation, so as to have first, to traverse the liver slowly, it does not appear in the urine as such for some time after, but appears as a carbo-hydrate the same as had been previously found in well fed rabbits. Its later appearance in the urine may be due to one or other of two causes. Either as the consequence of the anaesthetic employed, or it had had time after being first converted into a carbo-hydrate in the liver, to be reconverted into sugar. The first I do not consider likely, since a very small quantity of chloroform was used, and only during the time of operative procedure. It appears to me most probable the sugar on reaching the liver was in part transformed into some other carbo-hydrate, some of which would remain in the liver, but the rest passing into the general circulation. This form of carbo-hydrate, when not utilized in the animal economy, would be at once excreted as such by the kidneys. The other part of the injected sugar, which had not been transformed, having accumulated in the blood, was also now excreted as sugar in the urine. This explains the results in the experiment. First the carbo-hydrate alone appearing in the urine, and second, when the sugar had had

time to accumulate in the blood, both it and the other carbo-hydrate appeared, as seen in the results of the analysis.

Here unfortunately these experiments were abruptly brought to an end, from my having a poisoned dissection wound in the hand while making the autopsy of a dog that had died of acute septic peritonitis. The blood poisoning was sufficiently severe as to prevent my again entering the laboratory for three weeks, and even then I was so weak that it was thought advisable for me to leave Kristiania and return to England. However, Professor Torup was kind enough to perform two experiments for me, to see the effect of rapid and slow injections of sugar through the portal vein.

In a dog, weighing 20.5 kilos., the urine collected before the operation contained no sugar. A cannula was inserted into one of the duodenal veins, into which a solution of sugar was injected, (contained 28.0 per cent of sugar) - The following table gives the result: -

Time	Sugar solution cc. injected	Time during which Injection made	Quantity of urine in cc.	Sugar per cent.	Sugar in grms.
		Commencement of Injection			
8 minutes	19.5	8 minutes	55.0	1.8	0.99
27 "	14.0	19 "	33.0	5.05	1.67
40 "	24.0	13 "	43.0	4.88	2.12
53 "	22.0	13 "	52.5	4.67	2.45
69 "	32.0	16 "	29.0	4.72	1.37
81 "	23.0	12 "	6.5	4.54	0.30
1 hr. 21 m.	134.5		219.0		8.90

The injection being now stopped, the dog, however, remained attached to the table for the next two hours, during which time he passed 246 cc. of urine, containing 5.48 per cent of sugar, or 13.48 grammes. Then placed in cage, and during the next 10 hours, 195 cc. of urine containing 3.55 per cent or 6.92 grammes of sugar. After this the urine contained no more sugar.

The solution of sugar injected contained 28.00 per cent, therefore in the 134.5 cc. employed there was 37.66 grms. of sugar.

Excreted in the urine	29.30 grms.
Lost	8.36 "

The next experiment made on the same dog, after he had recovered from the effects of the previous operation, was made in the same manner. However, the injection in this case was much slower and not into a duodenal vein, but into one of the mesenteric veins low down in the intestine.

Time	Sugar solution injected cc.	Time during which injection made	Quantity of urine in cc.	Sugar per cent.	Sugar in grms.
		Commencement of injection			
15 min.	59.0	15 min.	11.2	no sugar	
36 "	74.2	21 "	19.0	1.75	0.33
70 "	60.8	34 "	27.0	7.44	2.01
127 "	80.7	57 "	50.6	5.59	2.83
173 "	76.5	46 "	31.2	7.00	2.18
216 "	Injection finished		20.9	3.64	0.76
279 "			12.7	none	
Total	351.2				8.11 grms.

After this time no sugar could be recognised in the urine.

The solution injected contained 7.65 per cent of grape sugar. There was consequently injected in all

	26.86	grms. sugar
Excreted in urine	8.11	" "
Lost	18.75	grms.

In these two experiments we find a great difference in the results obtained. For in the first only 8.36 grammes of sugar could not be accounted for in the sugar excreted in the urine, while in the second we find so great a quantity as 18.75 grammes not to be recoverable as sugar in the urine. Also in the first sugar continued to be excreted by the kidneys for more than two hours after the injection of sugar had been discontinued, while in the latter it was unable to be recognised in less than the brief space of two hours (106 minutes)

The question naturally arises, how can we explain this great difference?

The difference of situation had recourse to in these experiments could have little or no effect, for whether the sugar be injected into a duodenal or mesenteric vein, it is conveyed direct to the portal vein and liver without traversing any other organ, which could modify it in any manner whatsoever.

The great difference, however, lies in the rapidity of the injection, and by this alone it seems to me we can explain the apparently difficult problem. It will be remembered I have already given reasons for

suspecting "vegetable grape sugar" differs physiologically to "animal grape sugar" although it is chemically the same. Now in the latter experiment the sugar was so slowly introduced into the portal system, that it could have time to be in the greater part modified in the liver, as would have befallen it if absorbed from the intestine. In my experiments on dogs and myself, I found that no sugar was excreted in the urine on a diet rich in cane sugar, which differs widely from grape sugar and therefore from animal sugar. Now in this experiment the sugar most probably reached the liver far quicker than it would if it had been absorbed through the intestinal walls, so that all was not transformed into glycogen (or other substances) and of that part of it which passed through the liver (without being converted into some other carbo-hydrate form) had possibly been modified so as to be in the greater part easily split up and used in metabolism in the same manner as animal grape sugar, in consequence of which the greater part of the sugar, 18.75 grms., injected was either used up in the animal economy or stored there for future use; while only 8.11 grms. of the injected sugar were excreted by the kidneys and that too very quickly, as is seen in the table; for no sugar was recognisable in the urine in this experiment in less than two hours. If this is to be accepted as the true explanation of the last experiment, we can readily understand how in the first, when the sugar was rapidly introduced into the portal

system, very little had time to be converted into glycogen by the liver in its rapid transit through this organ, and still less to be modified so as to act as the easily split up and utilised animal grape sugar, consequently it was in the greater part excreted by the kidneys and only 8.36 grammes were not to be found in the urine, this having been utilised in the animal economy.

CHAPTER IV.

EXPERIMENTAL PATHOLOGICAL EVIDENCE IN FAVOUR OF THE EXISTENCE OF PANCREATIC DIABETES

Great difficulties unfortunately beset the path in a pathological enquiry regarding the possibility of producing pancreatic diabetes artificially in animals by means of direct experiment, in consequence of the severity and fatality of all those operations on the pancreatic gland which entail either its whole, or its partial destruction. The direct effects of the operation itself - even when skilfully and carefully performed - often leading to the death of the animal within a few hours. And the after effects being such that even in the most fortunate of cases none of these animals can be kept alive longer than two months, a period which scarcely suffices for a definite and perfectly conclusive set of results being obtained.

Having already adduced the clinical evidence in favour of the view that pancreatic disease is a most important agent in producing one form of diabetes mellitus in man, I shall now give a resumé of all the experimental facts that have been published regarding the effects of extirpation of the pancreas and then detail the results of my own physiological and pathological researches upon it, in connection with the subject of pancreatic diabetes.

The Experimental literature of Pancreatic Diabetes is exceedingly limited. It may be said to begin

with what Claude Bernard (1) published in 1856, regarding the effects of producing an interruption to the flow of the pancreatic juice into the intestines by blocking up its duct with solid paraffin. All the animals he operated upon died, which led him to believe that the removal of the pancreas must inevitably be a fatal operation. He noticed that all the dogs he experimented upon became thin; that the fatty parts of the foods were not absorbed from the intestines into the blood, nor all the starchy matters changed into sugar. But he makes no mention of having examined the urine for sugar. Although Schiff (2) injected paraffin in the same manner as Claude Bernard, he states that the dogs so operated on remained in perfect health.

Bérard and Collin extirpated the pancreas from various species of animals, and the most successful of all their operations were upon pigs, which they said could live without the gland; but some doubt has been entertained regarding the completeness of the removal of the organ in those cases in which the animals apparently suffered but little from its extirpation; which has led them to entirely disagree with the published opinions of Bernard, It may not be out of place to mention that when, in 1857, Professor Bérard exhibited to my father, among other of the pigs

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(1) Cl. Bérnard. Mémoire sur le pancréas etc. Compt rendus. Vol I. 1856, and Leçons de physiologie experimentale, Vol II, p. 274. 1856
(2) Schiff. Med. Centralb. 1872, p. 790.
(3) Bérard et Collin. Memoire sur les effets de l'extirpation du pancreas, Gazette hebdom. de med. et de Chir. Vol V. p. 59. 1858.

he had operated upon, two such miserably lean animals that on seeing them passing along the side of the courtyard wall on which the sun was shining brightly, he jokingly remarked that he thought if they got any thinner they would be sufficiently transparent not to be able to cast a shadow on the wall! Though I am not aware that any sugar had ever been looked for or found in their urine, as extreme emaciation is one of the most notable signs in pancreatic diabetes, it is not improbable that as the pigs my father saw were so exceedingly lean, their urine too might have been saccharine.

Klebs and Munk (1) extirpated the pancreas in dogs but never found sugar in their urine, and consequently they considered that when diabetes mellitus occurred in man associated with pancreatic disease, it was due to implication of the solar plexus,, However, in a foot-note to v. Mering's paper Klebs remarks that they did not remove the whole of the pancreas, so this may account for their not finding sugar in the urine.

Finkler (2), in his cases of extirpation of the pancreas, did not find diabetes mellitus follow upon the operation.

Senn (3), in his excellent work on the surgery of the pancreas says that on operating on both cats and

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(1) Klebs and Munk. Tageblat. der 43 Versammlung deutscher Nat. und Aeryte. Innsbruck, 1869.
(2) Finkler. Verhand. des Congress für innere Medicine. Wiesbaden, 1886, p. 172.
(3) Senn. Die Chirugie des Pankreas. Volkmann's Sammlung Klinischer Vorträge. No.313-314, Leipzig, 1888.

dogs he found that when he extirpated the whole of the gland they only lived from a few hours to 9 days, and gives the following table as the causes of their deaths after the total extirpation of the organ.

1. Dog died in 9 days from peritonitis
2. " " 4 " " gangrene of duodenum
3. Cat " 5 hours " haemorrhage and shock.
4. " " 1½ " " " "
5. Dog " 4 days " suppurating peritonitis.
6. Cat " 2 hours " haemorrhage.

In none of these cases was the operation performed with the view of inducing diabetes and consequently sugar was not searched for in the urine. Nevertheless it is well to call attention to the fact that the dog that lived 9 days, in spite of good feeding, lost in this short time 2.5 kilos. in weight. And it is also well to direct attention to the fact that a dog which lived 76 days, at the end of three weeks, after a partial extirpation of the organ, was noticed to have developed a remarkable appetite, and that the part of the pancreas which remained was found atrophied. Another dog for the first four weeks remained in comparatively good health. Then it began to fall off and in spite of eating as much as four normal dogs would, lost flesh and died 126 days after the operation. Both these dogs were thought to have been in good health, until atrophy of the remaining portion of the pancreas supervened. In spite of sugar not having been looked for in the urine, as they lost so much flesh it is just possible they might have had diabetes.

Martinotti (1) likewise extirpated the pancreas almost completely. His observations being directed to Lieberkuhn's glands, which he considered after extirpation of the pancreas, took on the functions of that organ. He, too, did not examine the urine, but he mentions incidentally that in one dog there was a well marked faulty nutrition, and great loss of flesh.

V. Mering and Minkowski (2) were the first to call attention to the fact that after complete removal of the pancreas there is always a diabetes mellitus and that too, of a very severe form.

In some of these dogs sugar appeared in the urine as early as from 4 to 6 hours after the operation, while in others not until the following day. It reached its maximum of from 5 to 11 per cent in about two days, and so it continued until death, even when the dogs had received no nourishment. One dog, weighing 8 kilos., fed on bread and meat, passed from 70 to 80 grms. of sugar daily. The sugar was proved to be grape sugar by the quantity estimated by Fehling's liquid, and the Polariscope being exactly the same.

The diabetic dogs suffered from great thirst and some were so hungry as even to eat their own faeces. Polyuria was a marked symptom. From 1000 to 1700 cc. of urine being voided daily. Rapid loss of flesh followed by great feebleness occurred in all, in spite

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(1) Martinotti. Sulla extirpazione del pancreas. Giornale della R. Academia di Medicine dei Torino, 1888. p. 348 and 383.

(2) v. Mering and O. Minkowski - Diabetes mellitus nach Pankreas - extirpation. Archiv. für exper. Pathol. und Pharmakol. Vol XXVI, 1890, p. 371.

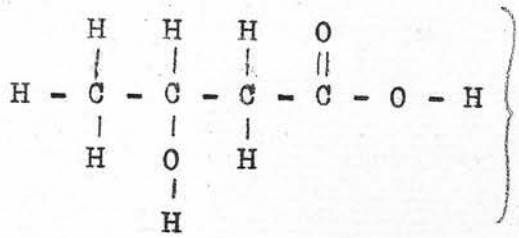
of good feeding, the dogs which lived as long as 3 weeks being unable to walk.

In the urine of the dogs were found both acetone, aceto-acetic acid, and Beta-oxybutyric acid. At first there was only sufficient acetone present to render it detectable by Lieben's and Legal's tests; but just before the animals died it had sufficiently increased to be recognisable by the chloride of iron test alone.

Acetone, aceto-acetic acid, and Beta-oxybutyric acid are three substances at the present moment of so much importance in connection with the question as to the cause of the sudden coma which often supervenes and most unexpectedly terminates life in cases of diabetes, that I shall require to devote some space to them, especially as I have, in the clinical part of this Thesis, related cases in which it occurred, and it is said these three substances are constantly met with in cases of pancreatic diabetes, I think it well to take the present opportunity of briefly stating what is at present known about them.

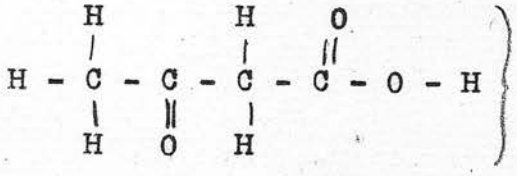
They were at first recognised only in the urine of cases of diabetes mellitus, (Peters, Kaulich, v. Jaksch and Gerhardt) and were considered to be confined to that disease. V. Jaksch further stated that acetone was to be met with in normal urine in quantities of not more than 0.01 grms. Then Le Nobel said he found acetone in the urine of comparatively speaking healthy people, who were taking either alcohol or albuminous foods in excess. Now a great step in ad-

vance has been made: but before referring to it, I may mention that acetone, aceto-acetic acid and Beta-oxybutyric acid can be formed from one another in the way illustrated by the following graphic formulae.



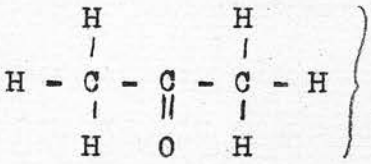
= Beta-oxybutyric acid

Beta oxybutyric acid is by oxidation converted into



= Aceto-acetic acid

While aceto-acetic acid, in its turn, readily splits up into Acetone and Carbonic acid.



Acetone + O = C = O Carbonic acid

Acetone and aceto-acetic acid not improbably originate in the same manner in the animal body. They are indeed most probably in no way the direct consequence of the diabetes, but merely result from some of the complications which so frequently accompany the disease. This idea originates in the fact that acetonuria has now been observed to occur in most diseases wherever there is wasting of the tissues and general marasmic cachexia, as, for example, in cases of fever, carcinoma, in some form or another, of the digestive tract, and in certain chronic forms of insanity, more especially in cases of children. Acetonuria has also

been observed to occur in starvation. (+) In fact, it appears that the further the subject is gone into, the more evident it becomes that the presence of any one or other of these three substances in the urine is indicative of no single form of disease, for they seem to be present in the urine in almost every case of disease accompanied with an excessive waste of the nitrogenous tissues. Although it must be admitted that this is particularly the case in the form of diabetes depending upon disease of the pancreas, I think I have adduced sufficient facts to prove that even acetone cannot any longer be regarded as pathognomonic of any form of diabetes whatever. Now ought it to surprise one when he finds the urine has a more or less fruity apple-like odour in cases of wasting diabetes, seeing that pancreatic disease is a form of affection which, as has been shown in the clinical, and this, the experimental, part of the Thesis, is invariably attended with an exceptionally rapid loss of flesh. In which case acetone, aceto-acetic acid, and beta-oxybutyric acid may appear.

Seeing that the clinical significance of the presence of not only acetone, but of its precursors in the urine, is gradually assuming a diagnostic importance, I shall briefly narrate the best methods for their detection.

Firstly, as regards Acetone - $C\,O\,(C\,H_3)_2$ - which is a colourless liquid, mixing readily with water, alcohol and ether, with a fruity apple-like odour, when in

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(+) Cetti "Hungerkunstler" Berliner Klin. Wochenschrift. Vol. 24, p. 434. 1887.

quantity in the urine is easily recognised by giving a well marked red colour on the addition of chloride of iron solution (Gerhardt's test). When present in the urine in small quantity, may be detected by Lieben's (+) method, which is the following. After rendering the urine alkaline, a solution of iodine, dissolved in water containing potassium iodide, is added and the mixture gently warmed. If acetone be present a yellow precipitate separates.

Legal, again, tests for acetone by adding to the suspected liquid a few drops of a freshly prepared nitro-prussate of sodium solution, then a little caustic soda or potash, which causes the liquid in the presence of acetone to assume a bright red colour. As creatinine, however, gives the same reaction, it is necessary to proceed further and acidulate the mixture with acetic acid, which causes it to become of a fine carmine or purple tint, whereas with creatinine it merely assumes a yellow colour.

Aceto-acetic acid $C_2H_3O.CH_2.COOH$ must be tested for when the urine is fresh, as aceto-acetic acid on standing is converted into acetone. Its presence is recognised by its giving with the chloride of iron Gerhardt's red reaction. The test is very simple: to from 10 to 50 cc. of urine, a dilute solution of chloride of iron is added, until it gives no longer any precipitate. The thus precipitated phosphate of iron is filtered off, and more chloride of iron added.

(+) Hammersten. Lehr. Phys. Chir. 1891.

If aceto-acetic acid be present, it gives a claret red colour. A second portion of the urine, of a strongly acid reaction, is next heated to boiling, and on cooling it ought to give negative results. A third portion of the urine is acidulated with sulphuric acid and then shaken with ether, which takes up the acid. On now shaking the ethereal mixture with dilute chloride of iron solution, if aceto-acetic acid be present the watery layer will be coloured of a violet red or claret hue, which colour again disappears on warming.

As Beta-oxybutyric acid, $CH_3 . CH(OH).CH_2.COOH.$ is a left-rotator of light, and consequently interferes with the right-rotation of grape sugar in the urine, when less sugar is found by polarisation than by titration, one may ordinarily put it down to the presence of Beta-oxybutyric acid.

Another test is that of Külz. The urine is evaporated to a syrup and then an equal volume of concentrated sulphuric acid added to it. When, if any Beta-oxybutyric acid be present, it is converted into Alpha crotonic acid. Thus: -

$$CH_3.CH(OH).CH_2.COOH = H_2O + CH_3.CH:CH.COOH.$$

and on being crystalised alpha-crotonic acid has a melting point + 72° C.

To return to the experiments. I may further mention that vom Mering and Minkowski found the dogs continued permanently diabetic up till the time of their deaths in all those cases in which the pancreas had been totally removed, and that they even continued excreting sugar along with their urines when kept without food.

This form of diabetes Von Mering and Minkowski assert is the direct consequence of the removal of the pancreatic gland, and not due to any injury to the nervous system by the operation; for they never could discover at the autopsies of them any evidence of injury to the nerves. This fact was confirmed by Recklinghausen in the case of a dog he examined after death. But in further proof of the statement in one case that although they separated the pancreas entirely from the mesentery and left it merely attached to the duodenum, and had consequently done quite as much injury to the nerves near it as if they had extirpated the organ, there was nevertheless no diabetes. While again in two other dogs they applied a double ligature to the pancreatic duct and likewise separated the pancreas from the duodenum, so that the gland was only connected with the mesentery. Yet neither of these two dogs became diabetic, although one of them suffered from a transitory glycosuria, which they thought was probably due to merely a temporary interference in the pancreatic circulation.

That any merely partial extirpation of the pancreas was not followed by diabetes was proved, they said, by the following experiments.

In a dog they separated the horizontal part of the pancreas, leaving only the vertical; and no diabetes occurring within the next three weeks, they removed the vertical portion of the gland, after which the animal became diabetic and remained so until its death, from lung disease, 20 days afterwards. In an-

other dog they removed the middle part of the pancreas and again no diabetes followed until after the rest of the gland had been removed a month later.

Heyden (+) removed the pancreas from 22 dogs, and in in all of them found diabetes within from one to two days after the operation. The quantity of sugar passed in the urine was, as a rule, 5 per cent, and the animals showed all the ordinary signs of diabetes, i.e., polyphagia, polydipsia, with a marked loss of muscular power. He says that they generally died of marasmus in from 20 to 30 days.

These being briefly all the experiments I have found recorded by others, I will now cite the results obtained from my own, all of which were performed in the Physiological Institute of Kristiania, under the eye of Professor Torup, who, as I before said, kindly aided me in every way in his power, and without whose valuable counsel and assistance, I would never have been able to accomplish as much as I did in the seven months I spent there.

As the anatomy of the pancreas of the dog is quite different from that of the human being, in order that my modes of experimenting may be readily understood, it is advisable to briefly explain by the accompanying diagramatic sketch (Fig, 10), that the organ in the dog consists of two almost entirely separated portions, joined together at the head.

(+) Heyden. Extirpation du pancréas et diabête. Société de Biologie, Paris. 25th October, 1890.

Fig. 10

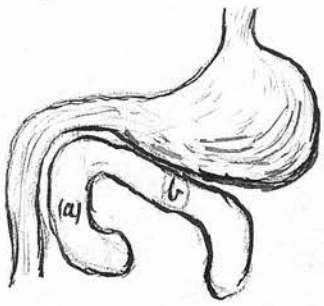


Diagram of Dog's Pancreas.

(a) Duodenal or vertical portion
(b) Subgastric or horizontal portion.

One, a duodenal or vertical (a) with its extremity lying in the mesentery, quite away from the intestine, runs in close connection with the duodenum for merely from 5 to 10 c. and then joins with the other horizontal, (b) or subgastric portion, to form, as it were, the head of the gland, opposite the gastro-duodenal junction. It receives its blood supply from the pancreatico-duodenal vessels. The subgastric or horizontal portion is longer than the duodenal. It runs from the point of union (head) of the pancreas horizontally below and somewhat behind the stomach, as far as the spleen. It then turns downwards and ends in a mesentery of its own about the middle of the left kidney. In this horizontal portion the splenic vessels run, and it is necessary to separate them from the gland substance in extirpating it. To all the dogs I operated on was given a hypodermic of atropine and morphine about half an hour before performing the operation.

The strictest antiseptic precautions were always taken. The instruments, after being freshly boiled, were kept until used in a carbolic acid solution, while a freshly made 2 per cent boracic acid solution, after having been likewise boiled, was used to wash

the intestines with and flush out the peritoneal cavity after the operation.

In order to avoid unnecessary repetition, I will here, once and for all, describe the mode of operating which it may be taken for granted was strictly followed, unless special mention is made to the contrary.

The skin over the abdomen was shaved and well washed with corrosive sublimate solution, the rest of the abdomen being covered with antiseptic cloths. An incision was made in the middle line from the xiphoid cartilage downwards for about 3 or 5 inches. The duodenum was then drawn forward, and the gland separated from its intestinal attachments, the vessels having a double ligature applied to them. The horizontal or subgastric portion was found by raising the spleen, and great omentum. (+) The splenic vessels were separated from the gland tissue as much as possible, and all the branches from them going to the gland were doubly ligatured. The gland thus isolated by ligatures, was now removed by merely cutting it out from among them. Having finished with the extirpation of the organ, the peritoneal cavity was well washed out with the hot solution of boracic acid. The wound was closed and then dressed with iodoform and collodium.

Experiment 39.

A large dog, weighing 18.7 kilos., from which the

(+) As a rule the great omentum was removed, as I had found it expedient to do so in making biliary fistules, etc., while I was working in the laboratory of the Sorbonne.

whole of the pancreas was removed, (there having been very little haemorrhage during the operation) was placed in a urine collecting cage. On the following morning he seemed very well, the wound looking healthy. In the collecting box there was 100 cc of urine which gave a distinct reduction with Fehling's solution and fermented, consequently it contained sugar. He was given some milk. The day after this I found him very quiet. He took no notice when patted, and the pulse being weak, I gave him a hypodermic injection of ether, but he died within an hour after it, about 20 hours after the operation. Autopsy an hour later. Wound looked healthy. The peritoneal cavity contained 50 cc. of a brownish coloured fluid. Peritoneal surface of both the intestines and mesentery was injected, and here and there were small haemorrhages. No pancreas remained. Liver congested and a large quantity of bile in gall-bladder as well as in the larger ducts of liver. Kidneys somewhat congested. Bladder contained 30 cc. of high coloured, cloudy, acid urine. It gave both a well marked reduction with Fehling's solution and fermented. The urine neither contained albumen, blood, bile acids nor bile pigment; but on adding to it a saturated solution of zinc chloride and ammonia, it gave a distinct urobilin reaction. Urobilin was also proved to be present by a spectroscopic examination. This fact might be accounted for by the peritonitis.

Here then we have evidence of sugar being excreted within 24 hours after complete removal of the pan-

creas.

Experiment 40.

From a dog weighing 11 kilos. the pancreas was completely removed, but had great difficulty in detaching it from the duodenum. Following day dog seemed pretty well, although somewhat quiet. 50 cc. of urine had been passed during the night. As it gave a reduction with Fehling's solution and likewise fermented with yeast, it contained sugar. Next morning the dog was found dead in his cage. No urine had been passed. Autopsy. No signs of peritonitis. About 1½ inches of the duodenum a little below the pylorus was of a dark purple colour, evidently a commencing gangrene. Liver, spleen and kidneys normal. No pancreas remained Bladder contained only 2 cc. of urine, which gave a distinct reduction with Fehling's solution. Here again there was an excretion of sugar within 24 hours after removal of the pancreas.

Experiment 41.

Removed the pancreas from a dog weighing 13 kilos. Again had the same difficulty in separating the duodenum from the gland. The vessels were very short and the gland was closely bound down to the duodenum. On the following day the dog seemed well. He had not been put in cage for collecting urine, it having been thought better to allow him to remain in his kennel in order that he might quicker recover from the effects of the operation. On the second day he seemed so well that he was given some milk. Wound looked healthy. On the third day he was quieter than before, but took

his milk. He was no better next day, and on the morning of the fifth after the operation he was found dead. Autopsy. No pancreas remained. Liver and spleen normal. Kidneys somewhat congested. Middle part of duodenum of a dark purple, almost black colour; but there were no signs of peritonitis visible. Bladder contained 8 cc. of pale, acid urine, which gave a copious precipitate on boiling with Fehling.

Experiment 42. Pancreas removed from a dog weighing 13.5 kilos. From the mesentery being very short in this case, I had great difficulty in getting the duodenum forward, and in consequence there was some haemorrhage into the peritoneal cavity. It was soon stopped, however, and was washed out until the boracic solution returned colourless. After waiting a few minutes as there seemed to be no longer any haemorrhage the wound was closed as usual. The dog was, however, found dead next morning, having passed no urine. Autopsy. Pancreas absent. Liver, spleen and kidneys very anaemic. Peritoneal cavity contained a large quantity of almost pure blood. The bladder contained no urine.

Experiment 43 .

Pancreas extirpated from a dog weighing 10 kilos. From the splenic vessels being very closely adherent to the gland, had great difficulty in removing it. The next day he seemed well, though quiet. Had only passed 10 cc. of urine during the night. It, however, gave a distinct reduction with Fehling. Had not sufficient for the fermentation test. The morning after

he was found dead in the collecting cage.

Autopsy. The organs all normal. No trace of the pancreas remained. Peritoneal cavity contained blood-stained fluid, but not sufficient blood to account for death. No urine in the bladder.

Experiment 44.

Pancreas was removed from a dog weighing 14.5 kilos. Towards the end of the operation there was a good deal of haemorrhage, but no bleeding point could be found, so placed two drainage tubes in the wound and dressed it with the usual antiseptic dressings. The dressings being noticed to be blood-stained in the afternoon, it was considered advisable to search for the bleeding point. On opening the abdominal cavity, found haemorrhage had stopped. The dog died during the night, having passed no urine.

Autopsy. Pancreas entirely removed. Liver somewhat anaemic looking. All the other organs being healthy the dog seemed to me to have died from the shock of the operation, as the loss of blood was far too insignificant to account for death.

Experiment 45.

Removed pancreas from a dog weighing 12 kilos. Considerable haemorrhage and he never properly recovered from the operation.

Autopsy showed no cause for death. No urine found in bladder.

Experiment 46.

Pancreas removed from a dog weighing 12.3 kilos. He died immediately after the operation, apparently

from the effects of the shock.

Before detailing the results of any of the other experiments I made on the pancreas of the dog, I will cite some of those I performed on the rabbit, the anatomy of whose pancreas is entirely different from what it is in the dog, in as much as it extends over a far greater area from its being, as it were, spread out into a number of fine ramifications in the mesentery. The rabbit's pancreas consequently presents insurmountable anatomical difficulties in the way of its removal by the knife, and this being the case I tried the effect of destroying it piecemeal with the galvanic cautery; by touching with the galvanic cautery and thus destroying each little branch of the gland separately, and any small haemorrhages that were threatened during the course of this procedure were stopped in the same manner.

Before citing any of the experiments I must first remark that in examining the rabbit's urine for saccharine matter, it was never forgotten that, as Worm Müller stated, normal rabbit's urine contains a substance with a reducing nature which turns Fehling's solution of so distinct a brown colour, that unless care be taken the coloration might be mistaken for that arising from the presence of sugar. However, so far as I have been able to ascertain the organic substance in normal rabbit's urine which gives this reaction does not possess the power, as sugar does, of giving a distinct precipitate of reduced copper on cooling. But to make sure that no error could occur

on this head, I invariably employed the yeast test as confirmatory of either the presence or absence of sugar in all the experiments. The nature of the substance in the rabbit's urine which gives the brown colour with Fehling's liquid is a disputed point. It has been thought that it might possibly be either uric acid or creatinine, both of which products are met with in the urine of the rabbit. Indeed, the former in quite as great a quantity as in the urine of man when the diet is identical. I found this to be the case by actual experiment.

Experiment 47

For at Kristiania on an average of 23 analyses of the urine of rabbits on bread and water diet, 0.0064 grammes of uric acid were daily excreted and this per kilogramme of bodily weight, is equal to $^1/_{13}$ of a grain ~~of~~ for 2 pounds' bodily weight per 24 hours.

Experiment 48.

And while I was working at the question of uric acid in connection with gout, at the Sorbonne in Paris, I found that while I excreted 0.0092 grammes of uric acid per kilo, equal to $^1/_7$ of a grain per 2 pounds of bodily weight in 24 hours while indulging in a rich Parisian diet, but when I restricted myself to a diet of bread and water, I only excreted 0.0043 grammes per kilo, i,e., $^1/_{15}$th of a grain of uric acid for 2 pounds of my weight in 24 hours.

We therefore by this see that rabbits pass more uric acid on a bread and water diet than a human being does and this fact together with the presence of

creatinine in their urine may perhaps be, as has been stated, the cause of the decoloration that occurs on boiling their urine with Fehling's solution.

The results were obtained by making the quantitative analysis of the uric acid by Salkowski's method with a slight modification which I will now give.

One requires for the analysis of Uric acid by the method of Salkowski three standard solutions.

A. An ammoniated solution of Nitrate of Silver 26 grammes to the litre. One dissolves 26 grammes Ag NO_3 in 600 cc. of water, add ammonia until the precipitate at first formed is dissolved and make the solution to one litre.

B. A Magnesian mixture consists of 100 grammes of magnesian chloride dissolved in water and ammonia added until the mixture smells strongly of it. Then ammonium chloride is added until the precipitate which at first forms is completely dissolved. Water is then added to make the whole up to one litre.

C. A solution of Sodium Sulphide. This is made by dissolving 10 grammes of caustic soda in one litre of water. Through 500 cc of this solution sulphuretted hydrogen is passed until saturation, and then it is mixed with an additional 500 cc. of the caustic soda solution = Na OH, Na SH.

With these three solutions one proceeds as follows: - Mix in a glass 10 cc. of the silver solution, with 10 cc. of the magnesian solution, these add to 100 cc. of urine and then sufficient ammonia to make

the mixture clear. Allow it to stand for one hour, then filter and wash with feebly ammoniacal cold water.

The contents of filter are put into a becher glass and then 10 cc. of the alkaline sulphur solution added to it along with an equal quantity of water. It is now heated until it boils. Filter it again through the same filter, into the becher glass containing the silver precipitate. Wash the filter with boiling water and let the washings flow into the becher glass. Then heat latter for some hours in a water bath. When cooled filter, and wash into a porcelain capsule. Acidify the contents of capsule with hydrochloric acid and evaporate them to about 15 cc. Then add a little more hydrochloric acid and allow it to stand 24 hours. The crystallised uric acid is now collected on a weighed filter, washed first with a little cold water then with alcohol, ether, and lastly with bisulphide of carbon. The filter dried at 100 - 110°C. and weighed. The increase of weight + the following correction, gives the quantity of uric acid in 100cc. of urine.

Correction - for every 10 cc. of wash water used in the last washing, add 0.00048 grammes of uric acid.

A still better plan is, instead of weighing, to estimate the quantity of nitrogen in the filter paper (the filter-papers used having been first proved to be free of N) by the method of Kjeldahl presently to be described.

Experiment 49.

A rabbit weighing 1,894 grammes, was anaesthe-

tised with Ether, and as much of the pancreas destroyed as could be reached with the Galvanic cautery. On the following morning it was found that it had passed no urine, but on the second day 30 cc of urine of an acid reaction was found in the collecting box. It gave a distinct precipitate with Fehling's solution, and likewise fermented with yeast, so there was no doubt that it contained saccharine matter. On the third day 15 cc. of urine was obtained, which was also found to contain sugar. The rabbit died in the afternoon.

Autopsy. Abdominal wound healthy and firmly closed. On opening the abdominal cavity an acute peritonitis was discovered. The cause of it was found to be a perforation in the duodenum, 15 c. from the pylorus, of about the size of a threepenny piece, through which the intestinal contents had entered the peritoneal cavity. The perforation was probably caused by the galvanic cautery having injured the peritoneal coat of the duodenum and led to a slow perforating ulceration of them. The animal had in the four days lost 279 grammes in weight, notwithstanding that he had been given as much bread and water as he would eat.

Experiment 50.

In a large rabbit under Ether, weighing 2,327 grammes, the pancreas was destroyed with the galvanic cautery. The next morning at 11 a.m. as he seemed tolerably well, he was given some bread and milk. He commenced to eat it immediately. Four hours later he was found lying on the side and he soon after died.

The bladder contained 50 cc. of acid urine. It gave the sugar reaction readily both with Fehling and yeast. The quantity of grape-sugar found in it amounted to 0.706 grammes.

Estimated by titration 1.412 p.c. of sugar

" by Polarisation 1.450 " "

This urine, therefore actually contained grape-sugar and not maltose.

The quantity of Nitrogen estimated by Kjeldahl's method was found to be 0.5712 grammes. No albumen.

Autopsy. Wound healthy. No haemorrhage. Adhesions found commencing around parts destroyed by galvano-cautery. All the other organs seemed healthy. No pancreas appeared to have been left between the duodenum and caecum. The death was supposed to be due to shock, as no other cause for it was discoverable.

Experiment 51.

A rabbit weighing 1.882 grammes, anaesthetised with Ether, had its pancreas destroyed by the galvanic-cautery. The following day it was so well that it had some milk. The urine passed during the night was unfortunately lost. On the second day 83 cc. of acid urine was collected. It contained no albumen, but gave the sugar reduction with Fehling's liquid and fermented with yeast. The urine contained 1.200 grms. or 1.5 per cent. The quantity of nitrogen found by Kjeldahl's method was 1.7196 grammes.

Third day. Drank milk but would eat nothing. 43 cc of acid urine contained 0.681 grammes of sugar or 1.7 per cent.

The nitrogen estimated by Kjeldahl's method amounted to 0.6239 grammes. Fourth day 83.5 cc of acid urine. It contained a much smaller quantity of sugar, only 0.5 per cent.

The nitrogen found by Kjeldahl's method was 0.4210 grammes. The urines of the next three days were useless owing to their getting mixed with milk, therefore I only gave him water bread and greens, Obtained on the eighth day 46 cc. of acid urine which gave a reduction with Fehling's solution but the presence of sugar was not confirmed by the yeast test. Had the same result on the ninth day. The rabbit had then lost 62 grammes in weight, although it had been feeding well for the last 4 days. The urine which was tested from time to time for sugar by the fermentation test, but always with a negative result. The animal lived for 61 days after the operation, and from his having died during an excessively cold night, and being greatly emaciated at the time, his death was attributed to the effects of cold. He had lost no less than 737 grammes of flesh in the 61 days, and this too notwithstanding that he had been latterly taking his food remarkably well. The fact of the sugar only being met with in his urine during the first four days after the operation, and none subsequently, and yet the emaciation being so markedly progressive, and that one often meets with great emaciation in the human subject, suffering from pancreatic disease when there is no concomitant diabetes, the idea naturally arises: may this be due to a sufficiently healthy portion of

the pancreas being left to prevent the occurrence of the diabetes though not sufficient to prevent the emaciation?

If some of the pancreas was accidentally left intact in this case, it is quite possible that it might not have been sufficient to split up or destroy the sugar, and hence its appearance in the urine, but that when the immediate effects of the shock had passed off, this portion was quite sufficient to prevent the diabetes. The great wasting might easily be explained by the ducts having been destroyed with the greater part of the gland and consequently no pancreatic juice was poured into the intestines to aid in the proper digestion of the food and render it fit for assimilation, and hence the extreme emaciation.

Autopsy. Liver, spleen and kidneys normal. Pancreas - there was not sufficient of the glandular tissue remaining to be recognisable among the many adhesions, although I felt there might have been remnants of the pancreatic tissues here and there that were undetectable to the eye. Throughout the body most marked signs of emaciation, no fat recognisable. Muscles very lax.

Experiment 52.

Destroyed with the galvanic cautery as much pancreas as could be found in a rabbit weighing 2,300 grammes, while it was anaesthetised with ether. On the following morning it was found dead in its cage.

Autopsy. No fluid in peritoneal cavity, Liver and kidneys normal. Lower part of duodenum of a some-

what dark colour. All of the pancreas seemed to have been destroyed. The bladder contained 42 cc. of pale acid urine. The urine was saccharine and contained no albumen. The quantity of sugar (estimated by Knapp's method) was 0.314 per cent, and by the polariscope from 0.25 to 0.30 per cent.

Death had evidently been caused by the shock of the operation, at least there appeared no other cause to account for it.

Experiment 53.

Operated on another rabbit, weighing 2,160 grms. as in the former case. It, however, never properly recovered from the narcosis, so that may have been the cause of its death.

Autopsy. All the pancreas seemed to have been destroyed. No urine having been passed, nor any having been found in bladder after the animal's death, no search for sugar could be made.

Experiment 54.

Operated on a pure white rabbit, 1,365 grammes in weight, in same manner as in the case of Experiment 53. After the operation he lay quiet in his cage, with the eyes closed. Died in the evening without having passed any urine.

Autopsy. No cause of death found. There seemed to be some of the pancreas left below the duodenum and between it and the caecum. The bladder contained 4 cc. of pale urine, which contained neither sugar nor albumen.

Experiment 55.

Destroyed the pancreas of a rabbit weighing 1,622 grammes, as in the other cases. It died during the night. The acid urine (30 cc.) was of a decidedly red colour and contained 0.10 per cent of sugar. The red colour on spectroscopic examination was found to be due to the presence of oxyhaemoglobin.

Autopsy. Peritoneal cavity contained a blood stained fluid. Some of the pancreas was recognised on separating caecum from mesentery near to the duodenum. Liver and kidneys somewhat pale. The sugar in urine may possibly have been in the blood that was found mixed up with it.

Experiment 56.

Pancreas was destroyed in a rabbit weighing 1,345 grammes, but it never recovered from the narcosis. Passed no urine.

Autopsy. On separating the mesentery from the caecum some of the pancreas was found remaining. No urine in the bladder.

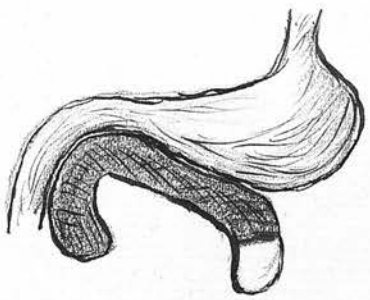
I now come to the consideration of another set of experiments on the pancreas, namely those that were performed with the view of ascertaining the effects of a partial destruction on sugar excretion.

Experiment 57

The pancreatic duct of a large dog, weighing 23½ kilos. was doubly ligatured and the portion between the ligatures excised. The remaining portion of the gland was then isolated by ligaturing - all except

the subgastric part which could not be reached.

Fig, 11.



Pancreas of dog.
Shaded portion isolated by ligatures.

On the following day the dog remained very quiet - did not so much as even move. She died in the evening, that is to say about 30 hours after the operation. The amount of urine collected was 300 cc. It was acid. It contained no sugar.

Autopsy. A little blood stained fluid in abdomen. The part of the pancreas shown shaded in the diagram which was the part that had been isolated by the ligatures, was of a dark purple colour. It was found to have been completely isolated and to have no connection with the circulation, and consequently for all practical physiological purposes it was as useless as if it had been entirely removed from the animal's body. The end of the subgastric portion, forming about $^1/_8$ part of the whole gland, was of the normal colour, and presumably had continued to perform its functions. To this fact may be attributed the absence of sugar in the urine.

As all the other organs were apparently healthy the death of the dog was attributed to the shock of the operation.

Experiment 58.

A dog, weighing 20.9 kilos., was operated on ex-

actly as in preceding experiment,, leaving only a very small portion of subgastric, not more than the size of a nut. The urine collected in first 6 hours amounted to 280 cc. it had probably got accidentally mixed with some of the drinking water. It contained 0.131 grammes of sugar = 0.046 per cent.

The urine collected on the following morning gave no sugar reaction. It died at mid-day, that is to say 20 hours after the operation.

Autopsy. All the organs were very anaemic. The abdominal cavity contained some blood-stained fluid. All the pancreas that was surrounded by the ligatures was of a dark purple colour. The tip of the subgastric portion of a normal colour. The upper $^1/_3$ of duodenum of a dark colour, as if commencing gangrene. Urine in bladder 2 cc, gave no reduction with Fehling's solution.

Experiment 59.

A dog weighing 10.1 kilos. Operated on exactly as the above. Died during night. Urine of night gave no reduction of Fehling.

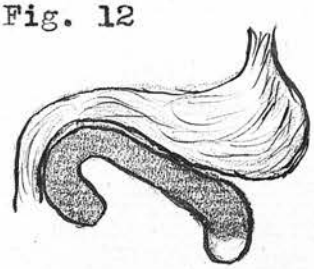
Autopsy. Showed no cause of death. Pancreas included within ligatures of a dark purple colour. The extremity of subgastric portion of a normal colour.

Experiment 60.

In another dog, weighing 16.9 kilos, the pancreas was operated on in the same manner. It passed during the afternoon and evening 150 cc. of acid urine. It gave no reduction with Fehling, nor fermentation with yeast. During the night there had been some haemor-

rhage from the dog having torn off the dressings. Died in the afternoon. Urine was so much mixed with blood, that it could not be examined for sugar.

Fig. 12



The shaded part of pancreas was the part included in the ligatures.

Autopsy. The part of pancreas included in the ligatures was of a dark reddish-black hue. Only the tip of the subgastric portion remained of a normal colour. Liver, spleen and kidneys somewhat pale. Bladder contained a few drops of urine, which gave no reduction with Fehling.

Experiment 61.

On a dog weighing 12 kilos the operation was slightly modified. The main duct of the pancreas was doubly ligatured and the portion lying between the ligatures removed. The free end of the duodenal portion was next removed, and the main artery supplying the subgastric portion ligatured.

On the following day the dog seemed well, but he refused food. 225 cc. of a pale yellow coloured acid urine was collected. It contained sugar as it not only reduced Fehling's solution, but fermented with yeast. The amount of nitrogen it contained was found by the method of Kjeldahl to be 2.097 grammes. On the second day the dog not only refused to eat, but he drank nothing. 160 cc. of a high-coloured acid urine was collected, but contrary to the specimen of the day before, it neither reduced Fehling's liquid

nor would it ferment, so that it contained no sugar. The amount of nitrogen in it was ascertained to be 2.437 grammes. On the third day the dog was exceedingly quiet, and although he took notice when spoken to, he could not be induced to eat. He died in the afternoon, having passed 220 cc. of a high-coloured acid urine, which, like that of the previous day, was totally devoid of sugar. The quantity of nitrogen was not estimated on this occasion.

Autopsy. Lungs congested. In the part of the pancreas that remained were some small abscesses from the size of a pin's head to a pea. Liver and kidneys congested. There was a very diffuse peritonitis in this case.

Experiment 62.

In the above case the quantity of nitrogen in the urine was calculated according to the method published by Kjeldahl of Copenhagen, which consists in converting all the nitrogen present into ammonia and then estimating the amount of the engendered ammonia. This method possesses the double advantage of accuracy and simplicity. (+) This I know from my having often employed it, and I prefer it to all the other methods, not only for the before stated reasons, but also because in many other analyses the quantity of nitrogen thus formed furnishes the data necessary to recognise the substance being analysed, as, for ex-

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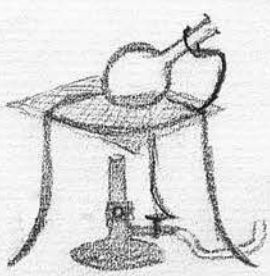
(+) In the Physiological Institute of Kristiania we could easily do 18 of these analyses at the same time, which was of course an immense advantage.

ample, in the case of uric acid.

The mode of procedure in analysing urine is the following: - Take 5 cc. of diluted urine - the urine must be diluted until it will not yield more than 0.5 grammes of nitrogen, for the smaller the quantity the more delicate is the test - put it in a small glass flask, and add to it from 10 to 15 cc. of pure concentrated sulphuric acid (S.G.1.85). The sulphuric acid must have been previously ascertained to contain neither nitrogen nor any nitrogenous products by boiling and adding more soda than is enough to neutralise it. If no nitrogen be present in it, it will give off no ammonia. The presence or absence of the ammonia is recognised by receiving the products of distillation into a solution of sulphuric acid, which is dosed both before and afterwards with a standard solution of sodium hydrate. To the flask containing the urine is now added a drop of mercury. This, with the sulphuric acid forming sulphurous acid, the oxidation and transformation of the nitrogenous matters into ammonium sulphate, is facilitated. The flask, inclining on its side is now heated on a wire-gauze over a gas-flame, at first very gently in order to prevent frothing. It is kept boiling until its contents are perfectly decolorized, which takes from 2 to 3 hours.

Fig. 13



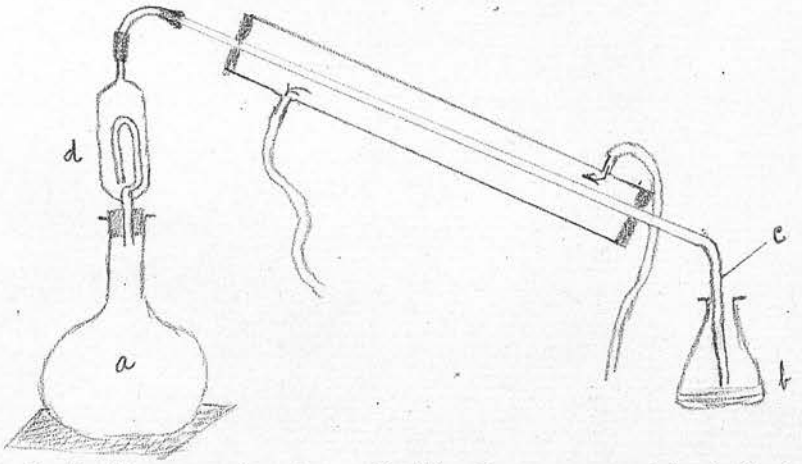
Position of flask for destruction.

During destruction leave flask inclined. Fig. 13

The gas-flame is now extinguished, the flask placed in an upright position, and to the still boiling contents permanganate of potash is added until a green colour is obtained, which shows that complete oxidation has taken place.

All that is necessary to be done now is to dose the sulphate of Ammonia. For this purpose the flask is allowed to cool while covered with a watch glass.

Fig. 14.



When cooled the contents of flask are emptied into a flacon (capable of containing about 1 litre) and flask well washed, emptying into flacon until about 300 cc of liquid. Allow flacon to cool and then put into it about 1 gramme of powdered zinc (free from nitrogen) A solution of soda is now added quickly (a little more than enough to neutralise the sulphuric acid) and the flacon closed by attaching it to a distillation apparatus (see diagram, Fig. 14) Its contents are then distilled into a conical vase (b) containing a solution of sulphuric acid, of known concentration. Now heat flacon (a) and distil off the ammonia into conical vase. One must heat sufficiently long to allow all the ammonia to distil over. When this is done a

piece of red litmus paper will not be turned blue when held at opening of tube (c). Tube (c) must be kept always just above the level of sulphuric acid solution in conical vase by gradually lowering the latter. If too much liquid distils over, the flame is removed from beneath the flacon, and by means of a syphon arrangement at (d) any excess of the fluid flows back from (d) into flacon. The ammonia having all been distilled over, the quantity of sulphuric acid that remains in the conical vase (b) is now titrated, and the loss of acidity gives the quantity of ammonia and from it is estimated the quantity of nitrogen. This is the way in which the results I have given were arrived at.

The next experiment I will relate is another of partial removal of the pancreas, which was performed on a cat. I may remark that the anatomy of the cat's pancreas is very similar to that of the dog's.

Experiment 63.

Removed the head and duodenal portion of the pancreas from a large and healthy cat. On the following morning it was found dead in its cage. The acid urine obtained from the bladder did not ferment with yeast, so that it contained no sugar.

Autopsy. The subgastric portion of the pancreas was the only part found remaining. There had been no haemorrhage, and as everything else appeared normal the animal's death was attributed to nerve shock.

Experiment 64.

Destroyed the greater part of the pancreas of a

rabbit, weighing 2,365 grammes, with the galvanic cautery. The animal only lived till the evening. No urine got.

Autopsy. Haemorrhage into the abdomen had taken place from some of the mesenteric veins. A portion of the pancreas, and all the other organs were found normal.

Experiment 65.

Destroyed nearly the whole of the pancreas of a rabbit, weighing 1.672 grammes, with the galvanic cautery. 15 cc. of acid urine was collected on the following morning. It contained no sugar. The quantity of nitrogen was found to be 0.4587 grammes. He was fed on bread and milk. In the next four and twenty hours 42 cc. of acid urine was obtained. Like that of the previous day it contained no sugar. The quantity of nitrogen was now 0.5374 grammes. During the following night the animal died.

Autopsy. No apparent cause of death could be found. The part of the pancreas that remained seemed normal.

Experiment 66.

The greater portion of the pancreas was destroyed in a rabbit, weighing 2.080 grammes, in the same way as before, but it only survived the operation 6 hours, during which time it passed no urine.

Autopsy. A Haemorrhage had occurred from the mesenteric vessels. The whole of the pancreas lying between the duodenum and caecum remained. No urine found in the bladder. There would therefore

seem to have been a complete suppression of the renal secretions in this case.

The following is a short table of the operations and their results: the conclusions I draw from them may be briefly summed up as follows: -

Diabetes mellitus invariably follows on complete destruction of the pancreatic gland, while if only a small portion of the gland tissue remains, it appears to be sufficient to prevent the occurrence of the diabetes mellitus.

Ligature of the pancreatic ducts is not followed by diabetes until the gland tissue has become completely destroyed by atrophy of its gland cells and hypertrophy of its connective tissue.

From these results it is seen that the appearance of the diabetes mellitus has nothing to do with the pancreatic juice reaching the intestines. The great importance of this fact will be more lengthily discussed in the next chapter, when its physiological explanation will be given.

That this diabetes occurring after the extirpation or destruction of the pancreas, is not due to any nervous injuries caused by the operative manipulations, but to the obliteration of the pancreatic functions alone.

The diabetes mellitus arising from the experimental destruction of the pancreas is the most severe form, and always has a fatal termination. Its symptoms being polyphagia, polyurea, polydipsia, extreme emaciation, and muscular weakness, and the occurrence in the urine

of acetone, aceto-acetic acid and oxybutyric acid the results of the great proteid destruction, often terminating in fatal coma.

We see that the experimental pancreatic diabetes corresponds in all its points with that of the clinical, and hence is of the greatest value to all physicians.

Expt.	Animal.	Weight	Kind of operation.	Sugar and Nitrogen	Lived	Cause of death
39	Dog	18.7 k.	Complete removal	Found sugar next morning	20 hrs.	Shock
43	"	10 "	"	"	36 "	"
44	"	14½ "	"	No urine obtained	12 "	"
45	"	12 "	"	"	4 "	"
46	"	12.3 "	"	"	¼ "	"
42	"	13½ "	"	"	died during night	haemorrhage
40	"	11 "	"	Sugar found in night's urine & up till death.	46 hrs.	gangrene
41	"	13 "	"	"	5th day	"
49	Rabbit	1.894 g.	As complete removal as was possible	Sugar found in the 24 hours & up till 3rd day	4th "	perforation & peritonitis
50	"	2.327	"	In night's urine Nitrogen = 0.5712 grm.	22 hrs.	Shock
56	"	1.345	"	No urine		Did not recover from the anaesthetic
53	"	2.160	"	"		"
51	"	1.882	"	In night's urine & up till 4th day = 1.7 per cent N = 0.421 grammes.	61 days	marasmus + extreme cold

Expt.	Animal.	Weight	Kind of operation.	Sugar and Nitrogen	Lived	Cause of death
61	Dog	12 kilos	Partial removal	Sugar during 1st 24 hours only N=2.097 grammes.	3 days	Paritonitis.
57	"	23½ "	"	No sugar	30 hrs.	shock
60	"	16.9	"	"	24 "	"
58	"	20.9 "	"	In 1st 6 hours 0.131 grms. of sugar comtinued till death	20 "	haemorrhage
59	"	10.1	"	No sugar	16 "?	Cause doubtful
55	Rabbit	1.622 gr.	"	Sugar in urine but might have been from the blood mixed with it.	16 "?	Haemorrhage.
52	"	2.300	"	0.314 p.c.	16 "?	Shock
64	"	2.365	"	Obtained no urine.	8 "	Haemorrhage
66	"	2.080	"	"	6 "	"
54	"	1.361	"	No sugar	6 "	shock
65	"	1.672	"	N.at 1st day=0.4587 grammes N.2nd day =0.5374 grm.	48 "	unknown
63	Cat		"	None	16 "?	Shock

CHAPTER V.

THE PATHOGENESIS OF PANCREATIC DIABETES

To attempt to give the pathogenesis of almost any disease is invariably a more or less difficult task, but it is exceptionally difficult in a case like the present, where the nature of the affection is still imperfectly understood. Seeing, however, that pancreatic diabetes is apparently what is called a chemical disease, from its symptoms and course being in a great measure traceable to a defective nutritive chemistry connected with the pancreatic functions, I shall endeavour to show how far physiological chemistry explains why, when the pancreas is diseased, sugar is met with in the urine.

As was previously stated, normal urine either contains none, or but the faintest traces of saccharine matter, whereas when patients labour under diabetes the out-put of sugar in the urine may rise to from a few ounces to a couple of pounds in the twenty four hours. Moreover, the sugar excreted by the kidneys, and eliminated in the urine is almost invariably (+) of the same kind, namely, dextro-rotatory grape sugar. In all the experiments I made on animals I found that it was grape sugar that appeared in their urines after removal or destruction of the pancreas.

The appearance of sugar in any urine whatever can only be due to one of two causes. Firstly, from the

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(+) In two cases J. Seegen found laevo-rotatory sugar in the urine. Centralb. f. d. Med. Wissen. No.43, 1884. Ackerm, Berliner, Klin. Wissen. 8th April, 1889.

kidneys excreting the normal blood sugar, or, Secondly, the kidneys excreting the sugar that has increased in the blood to an amount beyond what the organism can make use of. The latter cause is undoubtedly the one at work in all cases of diabetes, for if the first assigned cause were the correct one, the quantity of sugar in the blood of a diabetic animal would be always less than normal. Whereas, the quantity found is always above the normal. The blood of a man or a dog normally contains from 0.1 to 0.15 per cent of sugar, while in the case of dogs rendered diabetic by extirpation of the pancreas, it contains from 0.3 to 0.46 per cent. Von Mering and Minkowski (1) in one dog, 6 days after the pancreas was extirpated, found that the blood contained 0.3 per cent of sugar and the urine 7.1 per cent. In another dog, 27 days after the same operation, the blood contained 0.46 per cent, and the urine 7.5 per cent of sugar. As was before stated, Claude Bernard (2) found that when the quantity of sugar in dog's blood was artificially increased to 0.3 per cent by the intravenous injection of a sugar solution, it passed at once through the kidneys into the urine. Brasol (3) showed that the kidneys, when once stimulated to excrete sugar, from being increased in the blood to above 0.3 per cent, they continued to eliminate sugar until it had again fallen back to the

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(1) Von Mering and Minkowski. Diabetes Mellitus nach Pankreas extirpation. Arch. für Exp. Pathol. u. Pharmakol. Vol. 26, p. 371. 1890

(2) Cl. Bernard, etc. Chapter p.

(3) Brasol - Archiv. für Physiol. 1884. p. 211.

normal standard or even lower. My explanation of this fact has already been fully given at page 115, so it is unnecessary for me to repeat it.

It seems therefore certain that the presence of sugar in the urine in cases of diabetes is due to its being abnormally increased in the blood. As was pointed out by my Father in his book on "Diabetes" (+) all the various forms of diabetes may be explained as a consequence of one or other of the two following factors.

Firstly - As a consequence of an excessive formation of sugar in which the patients do not lose flesh.

Secondly - As a consequence of a diminished assimilation of sugar giving rise to its accumulation in the blood, which is always accompanied by a loss of flesh.

In a condition of health there must always be an equilibrium between the formation of sugar in the animal body and its assimilation by the tissues. It naturally follows therefore that anything which upsets this equilibrium will cause an increase of the sugar in the blood, and as a sequence the appearance of sugar in the urine.

Before discussing which of these factors is at work in the case of pancreatic diabetes, I will briefly give the views most generally held by physiologists at present, regarding the formation of sugar in the animal body.

Since Claude Bernard discovered the glycogenic

(+) George Harley "Diabetes" Walton and Maberley, London 1866

function of the liver that organ has been regarded as regulating the amount of sugar in the blood. Unless we admit the existence of some mechanism for regulating the quantity of sugar in the blood, it would be next to impossible to explain the fact that so many investigators, under the most varied conditions, have found that the quantity of sugar in the blood of healthy animals varies very little. The explanation of this fact generally is, that if the quantity of sugar taken up by the portal rootlets, during the digestion of carbohydrates, be in excess, the liver stores it up in its cells as glycogen; and so soon as the quantity of sugar in the blood sinks below the normal, the liver gives up sufficient of the stored up glycogen and thus brings the amount present in the circulation to normal. This power is supposed to be possessed by the liver in consequence of its containing a ferment which can convert its stored up glycogen into sugar. If this were true the quantity of sugar in the hepatic vein would be sometimes greater and at others smaller than in the portal vein, and this has been proved by experiment to be actually the case. For that the quantity of sugar in the portal is greater than in the hepatic vein during the digestion of carbohydrates, has been demonstrated by von Mering. (1) This statement, however, has been contradicted by Bleile (2).

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(1) Von Mering. Archiv. f. Phys. (de Bois Reymond) p. 410 - 415. 1877.

(2) Bleile. Ueber den Zuckergehalt des Blutes. Du Bois Reymond's Archiv. 1879.

It must be remembered that in the collecting of blood from the hepatic vein, the manipulation itself must necessarily stimulate the liver, and as the blood from the portal vein is first collected, the stimulation of the liver resulting from the operation may cause it to set some of the glycogen free as sugar, and this may be the cause of the contradictory statements of these two experimenters. Again, in animals fed on a non-carbohydrate diet, as well as in starving animals the quantity of sugar has been found to be greater in the hepatic than in the portal vein; exactly what one would expect if v. Mering's observations be correct, which I incline to think they are.

The following table gives the results obtained by T. Seegen (1) in different bloods under different food conditions.

No. of Experiments.	Mode of Feeding	Percentage of sugar in blood of Carotid Artery.	Portal Vein	Hepatic Vein	Sugar plus in Hepatic vein Absolute	relative in perc.
8	Starvation	0.157	0.147	0.260	0.113	76
9	Starch	0.150	0.147	0.261	0.114	77
6.	Sugar	0.165	0.186	0.265	0.079	42
4	Dextrin and sugar	0.176	0.258	0.327	0.069	26
8	Meat	0.155	0.141	0.281	0.140	99
8	Fat	0.128	0.114	0.217	0.113	90

Seegen considers the increase in the quantity of sugar in the hepatic vein does not arise from the gly-

(1) Die Zuckerbildung im Thierkorper. Berlin, 1890. p. 176.

cogen being changed into sugar, but from the formation of sugar from the proteid and fat of the liver.

That glycogen can be formed from a non-carbohydrate diet was long ago shown by Bernard, who found glycogen in the livers of animals fed solely on albumen.

Seegen's views are still further strengthened by the fact that starving animals can be rendered diabetic, that is to say, at a time when glycogen is not to be found either in their livers or muscles. (1)

Von Mering (2) has given yet additional evidence of the truth of the idea from his having found that after an animal's system has been completely drained of all its glycogen, either by starvation or by causing it to have a diabetes by Phloridzine taken internally, it can again be made to pass sugar in its urine by giving it a fresh dose of the phloridzine. In one case he brought on a glycosuria in a dog after 21 days' starvation: consequently the sugar excreted in this case must have been formed out of the proteids or fats, or probably out of both. That the production of sugar from proteids and fats is a vital process is, I think, shown by the results furnished by the following experiments I made on the livers of starved animals.

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(1) I have found on starving rabbits 5 to 10 days, no glycogen either in the liver or muscles, although the blood still contained sugar, This sugar must have been formed from the proteids of the animals.

(2) Von Mering. Zeitschr. f. Klin. Med. Vol. XVI, p. 431 to 446.

Experiment 67.

A rabbit weighing 2.450 grammes, after having nothing given to it but water for 10 days, weighed only 1.972 grammes. It had therefore lost in that time 478 grammes. The blood from its carotid artery contained 0.043 per cent of sugar. The abdominal cavity was opened, and a cannula inserted into the portal vein and a cold, iced saline solution (NaCl 7 per mil) allowed to flow through the liver. The stream of saline solution was kept up until all the liver was washed free of blood. This washing had a double purpose to perform: firstly - by freezing the liver, it prevented any glycogen that might be present in it from being transformed into sugar; while, secondly - it prevented the possible error of any of the sugar contained in the blood from complicating the analysis. After this washing out the liver was removed and divided into four nearly equal parts.

One portion, weighing 15.7 grammes, was immediately plunged into boiling water and analysed by the method described at p. 124, for glycogen or sugar. No reduction was obtained with Fehling's solution, and no fermentation with yeast. This negatived the presence of sugar. No glycogen was detected either by alcohol or iodine (by method before described) A second portion, 14.5 grammes, was simply kept exposed in the laboratory for 15 minutes. On this being analysed no sugar or glycogen was found in it. A third portion, weighing 19.5 grammes, after having been kept

in the same way for 6 hours gave equally negative results. A fourth portion, weighing 18.5 grammes, after 27 hours' similar exposure, gave no sugar or glycogen reactions.

Experiment 68.

A rabbit after having been starved 7 days, weighed 1.300 grammes. The carotid blood was found to contain 0.077 per cent of sugar. The liver was washed as in the former experiment. A portion, 15.4 grammes was immediately analysed for glycogen, and found to contain none. A second portion, 14 grammes, was immediately plunged into boiling water rendered slightly acid with acetic acid, and the albumens coagulated. The coagulum filtered and well washed. Filtrate and wash water evaporated to 20 cc. gave no evidence of sugar, either by Fehling or yeast test. A third and fourth portion, weighing respectively 19.6 grammes and 12.9 grammes, treated with acetic acid as the last after 7 and 20 hours' respective exposures in the laboratory, contained no sugar. 50 grammes of muscle, taken from the rabbit immediately after it was killed were treated after the method of R. Külz and found to contain no glycogen.

Experiment 69. A rabbit after 8 days' starvation, weighed 1,525 grammes. 52 grammes of blood taken from the carotid artery, contained 0.021 grammes of sugar, i.e., 0.0404 per cent.

The liver was operated on as in the last two experiments. First portion of the liver, 7 grammes, examined for glycogen; but none present. Second portion

16.5 grammes, after having stood for 12 hours at the temperature of the laboratory, was boiled with dilute hydrochloric acid for 15 minutes. After neutralization of filtrate got no reduction with Fehling or fermentation with yeast. Third portion, 17 grammes, treated in same manner with hydrochloric acid, after standing 20 hours in the laboratory, gave no sugar. The fourth portion, 13.5 grammes, after having been kept for 12 hours at a temperature of 37°C., contained no sugar. The fifth portion, 14.5 grammes, was kept for 20 hours at the same temperature, and yet contained no sugar.

The Muscles, analysed by the method of R. Külz, contained no glycogen.

Experiment 70.

A rabbit, weighing 1,846 grammes. After 6 days' fasting the blood taken from the carotid artery contained 0.023 per cent of sugar. Liver washed as in experiperiment 67. A piece of liver, 80 grms, was found to contain no glycogen. Another piece, 20 grms, after having been quickly thrown into boiling water and boiled in it, was pounded in a mortar; again boiled and extracted with water. Filtrate and wash water concentrated over a water bath. Gave no reduction with Fehling or fermentation with yeast. A third piece, 20 grammes, was boiled, pounded in a mortar and boiled again. Dilute hydrochloric acid was then added, and the whole placed in a water bath for 20 hours. Neutralized and filtered. Filtrate gave no reduction with Fehling or fer-

mentation with yeast.

Three portions of muscle from the hind legs were treated in exactly the same manner at the same time. The first contained no glycogen; and the second and the third no sugar, after having been treated in exactly the same manner as the third and fourth specimen of liver in this experiment.

In these four experiments it is seen that the blood of the starving animals contained sugar; and that, as they received no food, the sugar could not possibly have been obtained from without. Hence, the inevitable inference is that it was manufactured out of some material or other in the animal body, seeing that the sugar existing in the body at the commencement of the starvation process must have long since disappeared. Plenty of experiments have been published which show that, from saccharine matter being used up in metabolism it very quickly disappears from the blood. Sugar being one of the materials from which bodily heat and muscular work spring, higher animal life is impossible without it.

In the animals experimented upon, the sugar found in the blood could not possibly have come from any glycogen stored up, either in the liver or in the muscles, seeing that none was found in either of them. In fact, I found that as glycogen entirely disappears from the livers and muscles of rabbits after 3 or 4 days of total abstinence from food, there was no likelihood of its being present in the livers or muscles of the cases here experimented upon.

In Experiments 67 and 68 no sugar was generated in the liver after it had been removed from the animal, although kept at the temperature of the laboratory for 27 and 20 hours; while in Experiment 69, portions of the liver were kept at the temperature of the animal's body, and even after 20 hours had formed no sugar. And in Experiment 70, although the portions of liver and muscle were acted on by hydrochloric acid, still no sugar was formed. Yet, as is well known, hydrochloric acid not only converts glycogen and starch into sugar, but many other substances such as those contained in mucus.

As in the foregoing experiments no reduction was obtained on boiling with Fehling's solution, it shows that not only there was no sugar, but not even jecorin; which is a substance about which very little is as yet known. That, like sugar, reduces Fehling's solution, and it is of interest to know that it also disappears from both the liver and muscles of animals during starvation.

I may mention that Jecorin was first discovered by Drechsel (1) in the liver of horses and dogs. Later Baldi (2) a pupil of Drechsel's showed that it could be found in the liver, spleen, muscle and blood of different animals and also in the brain of man. Its chemical composition is not yet known, but it contains phosphorus and sulphur. It is soluble in ether, from

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(1) E. Drechsel. Berichte der Kgl. sächaischer Gesellschaft der Wissenschaften. Sitzung von 8. Feb. 1886.

(2) Dario Baldi. Du Boid Reymond's Arch. 1887.Supp. p. 100

which solution it can be precipitated by alcohol. From the above characteristics, it is considered to belong to the Lecithin group. As jecorin is soluble in water and reduces Fehling it would have, in these experiments, given a reduction if it had been present. In support of the view that sugar is formed in the liver, as has been long generally believed, we have the results yielded by the analysis of the blood of the heart obtained before and after extirpation of the liver.

Bock and Hoffmann (1) having ascertained, for example, that the normal heart-blood of rabbits contained 0.07 to 0.1 per cent of sugar, ligatured their portal veins, and found no change in the quantity of sugar contained in the blood. But on removing the whole liver from rabbits that survived 30 minutes, they found that the heart-blood now only contained 0.02 per cent of sugar, while in the heart-blood of those that lived 40 minutes, no sugar was found at all.

Minkowski (2) found that geese live a considerable time after the extirpation of their livers, and that in the case of a goose that lived 20 hours after its liver was removed, the sugar had entirely disappeared from the blood.

Seegen (3) ligatured the aorta and vena cava and so shut the liver from out of the circulation.

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(1) C.Bock and F.Hoffmann - Exper. Studien über Diabetes, Berlin. 1874.
(2) Minkowski. Ueber den Einfluss der Leberextirpation auf Stoffwechsel. Arch. für exp. Path. und Pharmokol. Vol. XXI
(3) Seegen. Zuckerbildung in Theirkorper p.185 Berlin 1890.

Three dogs thus operated upon lived from 30 to 70 minutes, and he found a rapid decrease took place in the quantity of sugar contained in the blood of their carotid arteries.

It must not be forgotten that the muscles also contain glycogen, which varies in the same manner as liver glycogen. (1) That the muscles can form glycogen from grape-sugar was proved by E.Külz (2) injecting a solution of grape sugar subcutaneously, after the removal of the liver, and finding that an increase in the muscle glycogen occurred.

This muscle glycogen may perhaps be one of the principal factors in the diabetes of the over fed and under-exercised persons among the upper classes, especially seeing that in many of those cases much muscular exercise gets at once rid of the sugar in the urine. Numbers of the cases related in Bomchardat's book on Diabetes, cannot, I believe, be explained by any simpler supposition.

The glycosuria produced (Cl. Bernard) by puncturing the floor of the 4th Ventricle, between the origins of the auditory and pneumo-gastric nerves, only occurs while the liver contains glycogen. If a rabbit so operated on, be killed as soon as it ceases to pass sugar in its urine, no glycogen is to be found in the liver. In animals whose livers have, by starva-

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(1) Nasse. Physiol. au contract. substanz. Pflüger's Arch. Bd, II and Physiol. der Kohlenhyd. Pflüger's Arch. Bd. XIV.

(2) E. Külz. Bildet der Muskel selbständig Glykogra? Pflüger's Arch. Vol. XXIV.

tion, been rendered free of glycogen at the time of puncture, it is found that no sugar appears in their urines after the operation. (+)

This form of nerve stimulating diabetes is merely due to a disturbance of the normal innervation of the liver causing a too rapid transformation of glycogen into sugar, and from the saccharine matter being suddenly increased in the blood to beyond what the wants of the system require, the excess has to be excreted by the kidneys and eliminated from the body along with the urine. So it might be said that this nerve form of diabetes furnishes us with a typical example of what is called the diabetes of an excessive formation.

With these observations, I now turn to the consideration of the many and varied theories that have been advanced by different writers regarding the probable pathogenesis of pancreatic diabetes.

By far the majority of persons who have attempted to explain why disease of the pancreatic gland should be accompanied with diabetes, and that too of a most severe character, assume that there is an excessive formation of sugar in the body on account of the pancreatic functions being arrested, although they differ very considerably as to why and wherefore the arrest produces an excess of sugar. This being the case, in quoting the different theories adduced, I

(+) See foot-note in Bunge's Lehrbuch Physiol. Chemie, 1889. p. 380. Pavey, etc.

will give a brief criticism of all of those which appear to fail to explain themselves.

Popper (1) considers that the fatty acids, which are normally formed from the fats by the action of the pancreatic juice, no longer reach the liver; and consequently they cannot combine with its glycogen to form biliary acids, and as a result there is in the liver an excess of glycogen, and this excess of glycogen in the liver, it its turn leads to there being an excess of sugar in the blood, and thus the diabetes is induced. But this theory is somewhat opposed to physiology, for the biliary acids are supposed by Physiologists to arise from the proteids and not from glycogen. Consequently Popper's view can hardly be regarded, in the present state of our physiological knowledge quite a physiological explanation of the pathogenesis of pancreatic diabetes.

Bonchardat (2) again endeavours to explain pancreatic diabetes by a most ingenious assumption. He thinks that the diastatic action of the pancreas being suppressed, the action is vicariously performed by another organ, and that it is the stomach which, by producing the diastatic ferment in excess, causes the starchy matters of the food to be changed into sugar in too large quantity, and consequently that this excessive formation of sugar is the cause of the diabetes.

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(1) Popper. Das Verhaltniss des Diabetes zu Pankreasleiden w.s.w. Oesterr Zeitschr. f. prakt. Heilkend. Vol. XIV. 1868.

(2) Bonchardat. De la Glycosurie et Diabête Sucré. Paris, 1875.

My answer to this is, that it has not yet been proved that the stomach specially excretes at any time or in excess a diastatic ferment. It is to be remembered, however, that all living tissues have a weak diastatic action, the stomach like the rest, but it is much too feeble a one to explain an excessive formation of sugar from the starchy matters of the food, and thus the pathogenesis of pancreatic diabetes in the way Bonchardat has tried to explain it.

Cantari, on the other hand, believes that the diabetes is due to the diastatic ferment of the pancreas becoming so changed by disease that instead of forming glucose it forms a paraglucose, which paraglucose is not suitable for the purposes of nutrition, and consequently, although in no great amount, it is not all made use of and a diabetes is the result. Unfortunately for Cantari's theory of the diabetes being due to the formation of para-glucose, on account of the absence of the normal pancreatic ferment, there are, as far as I am aware, no scientific data that can be adduced in support of it. Even supposing it be true that there really exists such a substance in the blood as para-glucose, it appears to me that such a mal-formed, unassimilable sugar, such as it is said to be, would play the part of a foreign substance in the blood, and consequently would be eliminated, as quickly as it was formed, in an unchanged state.

Baumal, (+) of Montpellier, takes quite a different

(+) Baumal. Montpell. Med. Vol. VI. P. 213. 1881.

view of the case, for he considers that the arrest of the pancreatic secretion allows the diastatic ferment to be reabsorbed by its own blood vessels and be carried by them into the portal circulation, which takes it direct to the liver, and no sooner does it reach the hepatic organ than it converts all the glycogen it contains into sugar, which is immediately poured into the general circulation, and, being in superabundance, induces the diabetic state. I have, unfortunately, however, here also to point out a most formidable objection to the theory, in as much as what he states could only occur in the limited number of cases in which there exists an obstruction to the outlet of the pancreatic secretion into the intestines. While still more potent against it stands the fact that complete obstruction to the out-flow of pancreatic juice has been frequently met with in the human subject without any diabetes having occurred; and not only so, but where the pancreatic duct has been artificially obstructed in dogs no sugar has appeared in their urine until the whole pancreatic gland has become disorganized, and consequently rendered completely useless as a secreting organ. Besides which, were the theory tenable, from the physiological facts I have already cited, the obstruction of the duct could only cause a diabetes so long as the liver or the muscles contained glycogen for the ferment to transform into sugar. Consequently there would be no diabetes when the animals were starved. Yet, as has been shown that is exactly a thing that occurs in the cases of

complete removal of the gland from starving animals. Baumal's theory, therefore, in its turn must be abandoned.

I think I have now arrived at the stage in this enquiry when it becomes necessary for me to show, if possible how pancreatic diabetes may arise from a diminished assimilation - that is to say, be the product of a faulty nutrition. And for this purpose I must almost solely rely upon the evidence which experimental pathology and physiological chemistry furnishes.

Bouchard (1) calculated the amount of sugar used up in the animal economy by comparing the difference in the quantity found by Bernard in the arteries and veins, and arrived at the conclusion that an ordinary healthy man of 60 kilos. weight, uses up on an average 1.850 grammes of grape sugar daily, so that if it be true, as has been estimated, that not more than 800 grammes can be oxidised, it is clear that the 1.050 grammes surplus must be assimilated by the tissues every 24 hours.

There are only two ways known by which sugar entering the blood disappears in the circulation, namely: one by direct oxidation; the other by a splitting up into more assimilable matters.

With the question of excretion I have at present nothing to do. First then, as regards oxidation. The little we know about it may be said to be the following:

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(1) Ch. Bouchard. "Leçons sur les Maladies par Kalentissement de la Nutrition." at p. 155.

1. Pettenkoffer and Voit, (1) by means of an admirably devised respiratory apparatus, carried out some experiments on the gaseous changes of a diabetic patient. The man, aged 21, weighing 50 kilogrammes, who had for some time suffered from diabetes, was put on different diets, and his expired gases compared with those of a healthy man on the same diet. It was found that the diabetic not only expired less carbonic acid and watery vapour, but took up less oxygen from the air than the healthy man.

2. Professor Dastre, of Paris, found that when a dog was made to breathe in a confined space, sugar was excreted in the urine.

3. Lépine (2) repeated this experiment, and on taking the blood of a dog thus asphyxiated, found that when it was mixed with sugar, far less was destroyed in it than in the case of normal blood.

The same observer also found that on adding sugar to normal blood and shaking it up with carbonic acid, far less sugar was destroyed then when merely left standing exposed to air.

4. While working with Professor Hoppe-Seyler at Strasburg, I was able to watch some experiments performed by Araki, in which dogs were placed in a confined space, and allowed slowly to use up the oxygen of the air while the carbonic acid was continuously removed, the result being that both sugar and lactic acid appeared in their urines.

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(1) Pettenkoffer and Voit. Zeitschr. f. Biolog. Vol. 3. p. 428 to 432. 1867.
(2) Lépine. Semaine Medical. 21 Mai, 1890.

5. That the mere want of oxygen can produce saccharine urine has undoubtedly been proved, but unfortunately this fact by itself does not help us in explaining the cause of the form of diabetes which we meet with in cases of pancreatic disease, for the pancreas is not known to have any action whatever either on the pulmonary or on the internal respiratory changes.

6. The appearance of substances which might be regarded as products of a defective oxidation in the urine of dogs rendered diabetic by extirpation of the pancreas, can be explained in a much more simple manner. I refer to the appearance in the urine of acetone, aceto-acetic acid, and oxybutyric acid, which, as we saw (page 139) were found in the urine of some of the dogs experimented on by von Mering and Minkowski. (1) These substances undoubtedly arise from the proteids. They have no relationship to the carbohydrates, for they are not found in all cases of diabetes, but only in those in which there is a great increase in the destructive metabolism of the proteids. And as in no form of diabetes is there a greater waste of proteids than in the pancreatic, we cannot feel surprised at their appearance in it.

Having already, while speaking of the methods of detecting acetone, aceto-acetic acid and Beta-oxybutyric acid, shown how the former substance springs from, and can be artificially made out of the other two, I will at once pass on to the next point in the chain of the pathogenesis of pancreatic diabetes.

(1) Von Mering and Minkowski. Archiv. f. Exp. Path. u. Pharmak. Vol 26. p. 371. 1890.

An increased decomposition of the proteids seems invariably to accompany diabetes, at least, it has been found to occur in those cases in which it has been carefully sought for. Thus, it was shown by Gachtgens (1) Pettenkoffer and Voit (2), and Frerichs (3) that in the cases they examined (one by each author) that the patients excreted more nitrogen than healthy persons on the same diet. Consequently there must have been an increased destruction of the proteids to have furnished the extra quantity of nitrogen excreted. While, again, in pancreatic diabetic patients, we have, as we know, an actual starvation to contend with in addition, arising from the want of the pancreatic secretion to aid in the digestion and preparation of the food for assimilation; for of all the various digestive secretions in the animal body none is so powerful or so varied in its modes of action on the different kinds of food as that of the pancreas.

That the increased breaking up of the proteids in ordinary diabetes may be in great measure, if not even entirely, due to the sugar not being assimilated, is explained by Bunge (4) in the following manner: - "The increased decomposition of proteids in diabetes is due to the inadequate breaking up of the sugar, that is to say, from the chemical potential energy of

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(1) Gachtgens. Ueber den Stoffwechsel eines Diabetikers u. s. w. Diss. Dorpat. 1866.
(2) Pettenkoffer and Voit. Zeitschr. f. Biol. Vol. 3. p. 400 - 425. 1867.
(3) Frerichs. Ueber d. Diabetes. p.276. Berlin 1884.
(4) Bunge. Lehrbuch der Physiol. Chemie. p. 376. Leipzig, 1889.

the sugar not being completely utilized, the proteids have to assist in supplying the kinetic energy which is necessary for the maintenance of the functions of the body. This is analogous to the behaviour of normal muscle, which has recourse to its own store of proteids, so soon as its supply of carbohydrate nourishment runs short."

As may have been seen from the previously cited data, that although much may be advanced in favour of the view of a deficient oxidation being the cause of the mal assimilation of the sugar in the ordinary forms of diabetes, it is quite insufficient to explain the rationale of that form which is met with and is supposed to be caused by disease of the pancreas. A far more plausible view is, in my opinion, that it is the result of a defective splitting up of the sugar molecule. I have been led to adopt this opinion from physiological chemistry having taught us the important rôle sugar plays in the metabolism of the animal tissues. Carbohydrates being absolutely necessary not only for the development of heat, but also of muscular energy, two essential factors in what we denominate higher animal life. And that grape sugar is one of the most important of the carbohydrates both in producing heat and muscular power might even be inferred from the large quantity of it that is daily used up in the animal body. For example, Bunge states that a man when on a potato diet will form out of their starch from 600 to 1000 grammes of sugar per diem, and every partical of this large quantity will be used up

in his system and there will be actually no excess to be excreted by the kidneys and make its appearance in the urine.

Moreover, we must remember that sugar is not only being continually brought into the body as food, but likewise formed in the economy itself, not only from the starchy substances of the body, but from proteids, and probably even fats as well. Consequently it cannot surprise us that any defect in its assimilation will lead to its accumulation in the blood.

Bouchard, as already stated, calculates that a healthy person assimilates daily 1850 grammes of sugar. Consequently, from all these facts taken together, as Bernard has shown, whenever the quantity of sugar in the blood rises to above 0.3 per cent, it is of necessity eliminated by the kidneys, we may legitimately, I think, infer that if anything should happen either to cause such an excessive formation of sugar in the body as to be beyond the requirements of the system, or, on the other hand any reason should exist to prevent the normal amount of sugar entering the blood from splitting up and being assimilated, sugar will equally accumulate in the circulation, and so soon as it rises beyond 0.3 per cent, be excreted by the kidneys and appear in the urine: in either case equally giving rise to a diabetes, although from diametrically opposite causes. Here then, I think, we have the key to the theory of the two distinct forms of diabetes - the one arising from an excessive formation -

in which the patients do not lose flesh; the other from a defective assimilation - in which more or less emaciation is a constant concomitant.

As pancreatic diabetes belongs apparently to the defective assimilation class of cases, I shall now discuss the cause of defective assimilation when the pancreas is diseased or extirpated. In the case of pancreatic diabetes the defective assimilation cannot, as already shown, be the result of defective oxidation and hence, must arise from the other only known manner in which sugar disappears from the circulation, that is, by its splitting up into more assimilable matters. As nothing takes place without a cause, the easiest way to account for the splitting up of sugar is to suppose it to be due to the action of a ferment. I will now consider this point.

The unorganized ferments occurring throughout the body have been called enzymes by W. Kühne, in order to distinguish them from such organised ferments as yeast, bacteria, etc. They are probably produced within the body by the vital activity of tissue cells. Many have been separated in an impure state by dissolving them in water or glycerine and precipitating them by alcohol. Their chemical composition is unknown, as also, if they have really a distinct and independent existence. It may be only a vital activity of the atoms which make up any living animal substance. When we talk of the ferment action of the organised ferment yeast, it must be remembered that it is not the yeast cell, but the vital activity of its

contents that produces the fermentation. Although physics and chemistry are of great aid in helping us to unravel physiological and pathological problems, the further we advance the more importance we are forced to attach to the unknown, but so-called vital or organised activity of living animal matter; and until we know what the attribute of life really consists of we cannot hope to be able to explain many of the difficult problems which beset us in our endeavours to understand many of the changes and transformations occurring in the organism. I have already shown that sugar, when added to normal blood, slowly diminishes in quantity, even when no bacteria are allowed to reach it. This may, to a certain extent be due to direct oxidation; but most probably it is principally due to its being split up and destroyed by an enzyme. (1) For were oxidation the cause, it is perfectly evident that the blood from a pancreatic diabetic dog would do so likewise. While, on the other hand, if the destruction (the splitting up) of the sugar be due to an absence of the enzyme-which is always present in normal blood, and normally destroys or splits up the sugar contained in it - the absence of this enzyme from the blood of the dog from which the pancreas had been removed, would, naturally at once appear to be a sufficiently intelligible explanation. I will

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(1) I here employ the term enzyme in its broadest sense. From feeling that until an unorganised ferment has been absolutely and undeniably isolated, its independent existence must be regarded as only being problematical.

therefore now try to find sufficiently reliable scientific evidence in support of this view of the case.

Lépine and Barral (1) have demonstrated by experiment that the blood of dogs rendered diabetic by the removal of the pancreas, no longer possess the power of destroying sugar. They found that the blood of a healthy dog, when mixed with grape sugar, destroyed from 4 to 6 per cent of the sugar, when it was allowed to stand for an hour. Whereas, the blood taken from a dog rendered diabetic by removal of the pancreas, destroyed in the same time practically no sugar at all.

As it is well known to every biologist that the higher a vegetable or an animal is in the scale of organisation, the more and more subdivided become the functions of its component parts, it cannot be regarded as going a step too far if it be suggested that it is well within the range of possibility that the pancreas, among its other functions, possesses that of manufacturing an enzyme, which plays the chief rôle in the splitting up of the sugar in the circulation, and thereby fitting it for the purposes of bodily nutrition. This idea does not, of course, necessitate the belief that other things in or other parts of the body do not likewise possess a similar power. In fact, we know that such is actually the case. For Lépine and Barral found that when they allowed normal defibrinated blood to circulate through an isolated kidney of

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(1) Lépine and Barral. Compt. Rendus Academie des Sciences, p. 1314. No. 25. Paris 25 Juin, 1890.

a dog by means of Jacobi's artificial blood circulator at least 15 per cent more sugar disappeared than when the same amount of sugar and blood was kept merely standing still for the same length of time at the same temperature. While, when they employed in the same way, not normal blood but the blood of a dog rendered diabetic by the extirpation of its pancreas, only 6 per cent of the sugar disappeared. This proved that the tissue substance itself has a sugar transforming or destroying power.

When added to this we remember (as was pointed out by Chauveau) that the renal tissues destroy far less sugar than do those of the other organs, probably from the fact that the only work the kidneys have to perform is that of eliminating effete products from the system. In the second place, some of the scientific facts already adduced have shown that it requires but a very slight disturbance in the normal equilibrium between the sugar supply and the sugar destruction, to give rise to an excess of sugar in the blood, and that whenever the amount rises above 0.3 per cent, it is excreted by the kidneys, and a saccharine condition of the urine is the result.

In the next place I have to call attention to the fact that Lépine (1) thinks that the pancreas manufactures an enzyme which is being continuously conveyed by the lymphatics of that organ into the general cir-

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(1) Lépine. Compt. Rendus Academia des Sciences. 8 Avril. 1890. p. 742.

culation, which opinion he endeavours to prove rests on a demonstrable basis. As is shown, he says by the result of the following experiment.

A dog weighing 16 kilos. was starved for 36 hours. The pancreas having been then removed (at 4. p.m.) it was kept without food until its death. The urine passed during the night was lost. The urine obtained at 8 a.m. contained 83.3 grammes of sugar per litre.

The urine was then collected hourly and gave the following results.

	Urea grammes	Sugar grammes	Quantity of sugar to 100 of urea.
8 to 10.30 a.m.	0.425	0.833	199
10.30 to 1 p.m.	0.750	1.666	222
1 to 2.30 p.m.	0.946	2.222	233

It is here seen that in spite of the dog receiving no nourishment, both the sugar and urea steadily increased after the removal of the pancreas. At 2.30 p.m. he injected into the jugular vein, a saline mixture containing 18 cc. of chyle collected from a fistula of the thoracic duct of a dog, which had received one litre of milk in the morning. The urine of the pancreatic diabetic dog, collected from 2.30 until 3 p.m. showed a slight diminution in both the quantity of sugar and urea. This was more marked from 3 to 4 p.m. While the urine collected from 4 to 5 p.m., contained 0.510 grammes of urea, 0.125 grammes of sugar, the quantity of sugar to 100 of urea being only 24.

The following day the diabetes is said to have been intense and the dog died at mid-day from haemor-

rhage.

From the above results he considers the lymph to have been the channel by which the enzyme reached the blood from the pancreas. Chyle in a fasting animal is nothing more than lymph, and during digestion only contains fat particles in addition. This being the case Lépine really only injected lymph with some fat particles in addition. Consequently, the lymph would contain the same ferment as blood itself.

So early as im 1864 Grohe stated that chyle contained a sugar destroying ferment; but it still remains to be proved that it contains more of the ferment than normal blood.

Lépine and Barral (1) in a yet later communication further endeavoured to substantiate their view that the chyle is especially rich in the sugar destroying ferment from their having found that with sugar added to blood they only lost from 4 to 6 per cent in an hour, while with sugar treated in the same manner with chyle they lost from 8 to 10 per cent. At the same time they found, as already stated, that when the blood of dogs, rendered diabetic by extirpation of the pancreas, was treated in the same manner practically no sugar was destroyed by it; two sets of facts which, when regarded conjointly, seem to me strongly to support the theory I am now advocating. Moreover, Von Mering and Minkowski (2), who I regard

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(1) Lépine and Barral. Compt. Rendus. Académie des Sciences. Paris 25 Juin 1890. No. 25, p. 1314.
(2) Von Mering and Minkowski. Arch. f. Exp. Path. u. Pharmak. Vol. 26. p. 371. 1890

as most careful observers and shrewd reasoners, equally support the idea that the diabetes in animals deprived of the pancreas, is the direct result of an "unknown function of the gland." From the fact that on transfusing blood from the crural artery of a dog, after its pancreas had been removed for 26 days and while it was passing 7.5 per cent of sugar in its urine, into the crural vein of a healthy dog, the latter passed no sugar whatever with its urine. From this result they concluded that there was a something in the blood of the healthy dog, which was not in the blood of the dog without its pancreas. And this something I regarded in the light of an unorganised ferment - an enzyme. All of these facts appear to support the theory that Pancreatic Diabetes is due to defective sugar assimilation on account of the absence from the blood of an enzyme, whose normal function is to split up the sugar in order that it be properly prepared to be assimilated by the organism. Consequently anything which either hinders the formation of the sugar-splitting-up enzyme, or prevents it after it has been formed from getting into the general circulation, will give rise to diabetes.

Lépine's view that this unorganised ferment reaches the circulation by means of the lymphatics, is, to my mind, far from proved. I therefore hold the more easily explained view that the enzyme reaches the circulation directly by the blood taking it up, during its course through the pancreas.

The pancreas, therefore, seems to have at least

two distinct functions; one, the formation of pancreatic juice, the other, the formation of an enzyme for the splitting up of sugar to render it more easily assimilated.

These two functions correspond to the two principal functions that the liver is known to possess. In order to render my views more clear, I will state first the two well known functions of the liver, and show how they appear to exactly correspond with those less known although just as important functions of the pancreas. Not only does the liver form bile, which it throws directly into the intestines, but it has the no less important "glycogenic function", which yields sugar direct into the circulation. Now this latter function corresponds to the enzyme one of the pancreas, and we must see how much further the analogy can be carried.

This formation of sugar by the liver, is not the only source of sugar in the organism (although, as I have previously shown, it is the principal one) for, as has been shown by various experimenters, the muscles have a glycogenic function. Yet derangement of the liver may lead to diabetes from the excessive formation of sugar.

Now turning to the pancreas, we find it also has at least two distinct functions. It forms pancreatic juice which is thrown directly into the alimentary canal, in the same manner as the liver does its bile; while, on the other hand, it forms an enzyme (whose

function it is to split up sugar to render it more easily assimilated) which reaches the circulation directly by the blood, in the same way as the sugar does from the liver.

That the pancreas is the only seat of formation of this sugar-splitting-up ferment, any more than the liver is the only seat of the formation of sugar, cannot be for a moment upheld, for, as already shown in this Thesis, the other tissues have this power although to a lesser extent. The pancreas is merely the principal source of the sugar-splitting-up ferment, as the liver is the principal source of sugar formation.

When we remember how small an upset of the equilibrium between the sugar formation and the sugar assimilation causes an increase of the sugar in the blood and its appearance in the urine. There can be no surprise that disease or artificial destruction of the pancreas, by preventing the sugar-splitting up enzyme (the natural product of the pancreas) from reaching the circulation, will upset the equilibrium between sugar formation and sugar assimilation, and consequently lead to an increase of the sugar in the blood and its appearance in the urine.

This explains the otherwise inexplicable fact that ligature of the pancreatic duct does not cause diabetes until the gland tissue itself is destroyed ; for in ligaturing the duct we only prevent the action of one of the functions of the gland, and get conse-

quent emaciation, while the sugar-splitting-up function can be still carried on and no sugar consequently reach the urine, until the gland tissue is completely destroyed and no longer forms any sugar-splitting-up enzyme.

Having thus explained, as I hope satisfactorily, one of the principal factors of pancreatic diabetes, namely, the cause of the appearance of sugar in the urine, I will now turn to another equally important factor, namely, the cause of the great emaciation.

The excessive emaciation, which is an invariable concomitant of pancreatic diabetes, is due to the absence of the other function of the pancreas, that is to say, the pancreatic juice not reaching the alimentary canal to assist in the preparation of the food so that it may be properly assimilated. This is especially the case as regards the action of the pancreatic juice on the most important of the nutritive elements of the food, namely, fat. The want of it will consequently materially aid the non-assimilation of the sugar in bringing about the rapid emaciation whish is so characteristic of the pancreatic diabetic state.

It will be remembered that in the clinical part of the Thesis I called special attention to the fact, that the presence of unmodified oils and fats in the stools was one of the leading signs in the diagnosis of pancreatic diabetes; for before fat can be carried through the intestinal walls, it is absolutely necessary that they should first be emulsionised; and be-

fore the neutral fats can be emulsionised, they require to be split up into glycerine and fatty acids. This is done by means of an enzyme. One fat molecule takes up three molecules of water, and splits up into glycerine and its corresponding fatty acid (Bernard (+),) The transformation being thus represented: -

$$C_3 H_5 O_3 R_3 + 3 H_2 O = C_3 H_5 O_3 H_3 + 3 (H O R)$$

neutral fat + water = glycerine + fatty acid

In the case of artificial digestion, this splitting up of the neutral fats goes on very slowly, while in the animal it is known to go on quickly. It has been found that so soon as a small part of the neutral fat is split up, the whole of the fat is rendered capable of being converted into a fine emulsion, and thus speedily absorbed.

Neutral fats can only be saponified; i.e., split up into glycerine and salts of fatty acids to form soaps by free alkalies. The carbonates of the alkalies having no action on neutral fats, but only on free fatty acids, the carbonic acid is driven out of the salt by the stronger acid, and a salt is formed by the fatty acid combining with the alkali. Fatty acids and neutral glycerides are mixable in every proportion. If a mixture of fat and a small quantity of fatty acids be acted on by a solution of sodium carbonate, a soapy solution is formed everywhere between the molecules of the neutral fats. The whole mass of fat is in this manner converted into a fine emulsion

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(+) Bernard. Assoc. de Chim. et de Physique, sér. III. Vol. XXV. p. 474. 1849.

of microscopically small drops.

Perfectly fresh neutral fats cannot be converted into an emulsion by a solution of sodium carbonate, consequently when they are given to a person with pancreatic diabetes, in whom the pancreas is no longer functioning, they reappear unaltered in the faeces. This is, I believe, the true explanation of the appearance of the fat that is so frequently noticed in the stools in the clinical cases such as I referred to, as well as also noticed by von Mering and Minkowski in the stools of dogs in which the pancreas was removed. Still further, from the tripsin not reaching the alimentary canal, the conversion of the proteids of the food into the diffusible and no longer coagulable peptones will, in like manner, be hindered. The only remaining point now left for me to consider, in connection with the pathogenesis of pancreatic diabetes, is the sign or symptom usually denominated Diabetic Coma.

A comatose condition is often the fatal termination in other forms of diabetes than the one I am discussing; but as it happens that it is more especially the usual ending of those diabetics who suffer from the defective assimilation form of the disease, and as we have seen there are good grounds for believing that to it pancreatic diabetes belongs, I cannot leave the subject without attempting some explanation of the etiology of diabetic coma.

To begin with, I may remark that the coma of dia-

betes is something quite sui generis from the more ordinary forms of coma set with in a variety of different diseases. For example, it bears no relationship to the coma of apoplexy, either in its symptoms or origin. Being, as a rule, quite unattended with stertorous breathing, loss of sensibility and paralysis, it much more closely resembles the coma of poisoning, more particularly that of uraemic poisoning, in as much as it is in general associated with vomiting, intense headache, and convulsions of the voluntary muscles. Moreover, it is never recovered from; but usually terminates fatally within forty hours after the commencement of the attack.

The exciting cause of the comatose state is also entirely different; for while in the case of apoplexy the stupor is due to the effects of mechanical pressure on the nerve substance, in diabetes it is the result of a chemical disturbance of the nerve nutrition by a poison brought to it in the circulation. And what the nature of the poison is, it now behoves me to try and explain. Before attempting to do this, however, I must remark that the diabetic coma I have under consideration has nothing whatever to do with the various comatose conditions which occasionally arise in the course of diabetes, and lead to an equally fatal termination. Such, for example, as that which arises from cardiac disease, acute nephritis or cerebral haemorrhage, as these are merely accidental concomitants of the diabetic state and in no way depend upon it.

The coma of pancreatic diabetes, like the comas that occasionally supervene in some of the other forms of disease, associated with, or giving rise to diabetes, is no doubt due to the formation in the blood of a poisonous product. Professor Bunge's (1) views on the subject being those I am inclined to adopt, I will give them in brief abstract along with the additional views I have been led to adopt from the opinions expressed by other writers on the subject.

As has been already stated, acetone, aceto-acetic acid and oxybutyric acid have been frequently noticed in the early stages of pancreatic diabetes and gradually to increase in the urine as the disease advances. With a marked increase of these substances the cerebral symptoms have been found to arise. Consequently many authors have endeavoured to explain the advent of the coma as the direct result of the narcotic action of the acetone, which acts on the brain in somewhat the same manner as alcohol and ether. The acetone, as already pointed out, being formed from the proteid waste, the quantity generated would not be sufficient to cause the coma; for it is calculated that in order to poison a man weighing 70 kilos, from 500 to 600 grammes of acetone (2) would be necessary.

Besides this, it has been found by Wolpe (3) that

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(1) Bunge. Lehrbuch der Physiol. Chdmie. p. 384. Leipzig, 1889.
(2) Albertoni. Arch. f. exper. Patho. u. Pharm. Vol. 18. p. 218. 1884.
(3) Wolpe. Unters. üb. d, Oxybuttersäure des diabet. Harnes. Diss Konigsberg, 1886.

in the last stage of diabetes, at the very time when the coma sets in the amount of acetone in the urine has become diminished, while at the same time, however, there is an increase in its precursirs, the oxybutyric acid and aceto-acetic acid. But these substances have no known narcotic action on the brain.

A satisfactory explanation to these apparently anomalous facts has, however, been offered by Stadelmann (1) and Minkowski (2). They refer to the results arising from a saturation of the alkalies of the blood by these acid products.

This is explained by Walter (3) who states that when he injected dilute hydrochloric acid into the stomach of a rabbit, dyspnoea occurred; that the animal lost the power of motion, and died with the signs of collapse. While, when sodium carbonate was subcutaneously injected, after the poisonous symptoms had begun to appear, the animal recovered. And on estimating the quantity of carbonic acid in the blood of rabbits thus poisoned, he found only from 2 to 3 per cent by volume. This, ~~by~~ is merely the usual amount of carbonic acid that is found in an uncombined state, that is to say, simply held in solution in the blood. In consequence of the alkalies that would have otherwise combined with acid and fixed the carbonic acid having been

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(1) E. Stadelmenn. Arch. f. Path. u. Pharm. Vol. 17. p. 433. 1883.
(2) Minkowski. Mittheilungen aus d. Med, Klin. zu Königsberg. p. 174. 1888.
(3) F. Walter. Archiv. f. exp. Patho. u. Pharm. Vol. 7. p. 148. 1877.

unable to do so on account of their having already become united with the hydrochloric acid he had injected into the stomach of the animal. From the blood having been thus deprived of its carrier of carbonic acid, the carbonic acid gas accumulates in the blood of the brain, as elsewhere, and causes, he thinks, the symptoms of dyspnoea and collapse. The same author likewise showed that the combining of the alkalies in the blood with an acid causes at the same time an increase in the amount of ammonia in the urine.

The effect of the artificially introduced hydrochloric acid on the animals thus experimented upon is identical with that of the oxybutyric acid generated in the blood itself in cases of diabetic coma; for we have, in diabetic coma, not only dyspnoea as a symptom, but likewise an increase of the ammonia in the urine as well as a fatal collapse.

Lastly, I have further to call attention to the fact that Minkowski found that the amount of carbonic acid in a diabetic patient, while in a comatose condition, was only 3.3 volumes per cent, and that the blood taken from the body after death had not only an acid reaction, but likewise contained large quantities of oxybutyric and sarcolastic acids. I think, therefore, in the present imperfact state of our pathological chemical knowledge of diabetic coma, we are bound to accept the above explanation of it in the absence of a better. As regards my explanation of pancreatic diabetes, that it may not satisfy, or even

that it may meet with opposition will in no way surprise me seeing that all I can say in its favour is that of all the theories that have been propounded on the subject, it appears to me to be the least open to objection, and I am fully aware that there never was a novel theory advanced on any medical subject whatever which, when first promulgated, gave universal satisfaction.

CHAPTER VI.

THE TREATMENT OF PANCREATIC DIABETES.

If it be true, as I believe it is, that "Science is the key to wise Practice", I think I am justified in attempting to show what the chemistry, physiology, and clinical observations unfolded in the foregoing pages teach us is the most likely way of benefiting patients labouring under pancreatic diabetes.

It is but little more than a quarter of a century ago since cases of diabetes were regarded as hopelessly incurable. Fortunately this can no longer be said to be the case for since the two different forms of diabetes were differentiated a great improvement has taken place in the mode of treatment. From it being soon discovered that the same lines of procedure were not applicable to both, and that the form of the disease originating in an Excessive Formation of sugar, had to be treated very differently from that arising from Diminished Assimilation. From this improvement in the treatment of the two forms of the disease it became evident that, contrary to all previously entertained belief, about 50 per cent of the whole cases of diabetes, if not actually curable, were nevertheless so markedly under control that the sufferers could be kept alive in a state of comparative comfort for many long years. The best example of this kind with which I am acquainted, is the case of the brother of a well-known London practitioner,

which came under the care of my father in 1860, and full details of which were given in his book on urinary derangements in 1872 (+) who only died last year. That is to say, thirty years and more after he was known to labour under diabetes, and that too, most probably, of a hereditary form, seeing that two of his sons became affected in the same way before they reached the seventh year of their age. This case was diagnosed and treated as one of diabetes arising from "Excessive Formation", 75 per cent of which cases my father thinks are amenable to treatment. It is not however, with that form of the disease I have at present to do, but solely with the other and far less tractable one, viz., that of Diminished Assimilation; to which class, I think, I have successfully shown, Pancreatic Diabetes belongs. But even here, though, as we cannot remove the cause, we cannot hope to cure, we must try and do our best at least to minimize the prejudicial effects upon the constitution which emanate from the morbid condition, and thus be enabled to retard the fatal issue which it is our misfortune to be unable to arrest. With that object in view, the chapter on the pathogenesis of the disease appears to me to suggest the following lines of treatment. The fons et origo of pancreatic diabetes exists apparently in there being an absence from the circulation of a substance possessing the power of splitting up, and so transferring the sugar that finds its way into the

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(+) "The Urine and its Derangements". Walton and Maberley. London, 1872.

blood, into other and more easily assimilable materials. And that is seemingly an enzyme, which is normally formed by the healthy pancreas, consequently it is clear that if we consider it hopeless to expect to be able to restore to the circulation the normal enzyme, we at least ought to try to do the next best thing for the patient, namely, find some substitute capable of supplying the place of the absent enzyme in the splitting up of the sugar, so as to counteract in as far as possible, the detrimental effects its absence occasions, more especially in the shape of progressive emaciation, loss of bodily and mental energy and the formation of the poisonous substances which engender the coma and fatal collapse.

First then, as to combating the emaciation, which no doubt arises from no pancreatic juice reaching the intestines, there to perform important digestive functions, namely: (a) The splitting up of neutral fats into glycerine and their corresponding fatty acids, and forming a permanent emulsion; (b) The transforming the starchy ingredients of the food into grape sugar; and (c), Assisting by its tryptic action, the digestion of proteids, so as to enable them to be more readily absorbed by the intestines into the blood.

1st. As regards the emulsionising of the fats of the food. This part of the digestive process being for the most part accomplished by the pancreatic juice. whatever interferes with its coming in contact with the fats of the food will necessarily greatly affect

the nutrition of the body. In order to remedy this defect therefore, , various preparations of the pancreas of the pig, are made and administered along with the food. But this plan of supplying the deficiency is scarcely, I fancy, as philosophic a one as it looks. Seeing that all of the proposed substances are necessarily themselves proteids and that from their having to remain for some time in the stomach before they can reach the duodenum - where their special action alone comes into play - and from gastric juice being a potent digester of all albuminoid matters, it seems to me to be questionable if the pancreatic emulsions, or extracts administered as remedies, may not themselves be so acted upon by the gastric juice, during their sojourn in the stomach, as to have their special properties destroyed, and thereby be rendered perfectly inert as duodenal digestive agents, before they arrive at their destination. If such should unfortunately happen to be the case, then their administration can scarcely be expected to be of much use to the patient. In his work on Liver and Pancreatic disease, published in 1863, my father described the preparation of what he called pancreatin, as well as gave an account of its administration in the form of pills, but he long since abandoned the use of it, for the above-named reasons, as well as from the fact that although he could demonstrate out of the body, its power of both transforming starch into sugar, and aiding in the digestion of albumens, he failed to obtain any reliable

evidence of its possessing a fat-emulsionising power.

Abelmann, (1) one of Minkowski's pupils, found by experiments on dogs that if pigs' pancreas is given to them along with fat, the fat is so acted upon as to be rendered capable of being absorbed during its passage through the intestines. If such be the case, it appears to me that it would be an improvement on this plan, to emulsion the fats with the pigs' pancreas outside of the body, so that the pancreatic emulsionising process might be completed before it had the chance of being interfered with in the stomach, by the action of the gastric juice upon the pig's pancreatic tissues.

Fortunately we are now in possession of some important physiological chemical facts which enable us to do a great deal towards emulsionising fats quite independently of artificially prepared pancreatic products. For example, we know that free fatty acids emulsion readily with alkalies like the carbonate of soda or liquor potassa, and that when so emulsioned they are absorbable into the ~~blood~~ system from the intestines. Moreover, rancid oils or fats are remarkably easily emulsionised by virtue of the fatty acids they contain. (2) And seeing that there are whole nations, as well tribes of peoples in different parts of the globe, who use rancid oils in preference to fresh as food, there would scarcely, I think, be any great difficulty in getting

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(1) Ueber die Ausnützung, d. Nahrstoffe nach Pancreas extirpation, &c. Inaug. Diss. Dorpat, 1890.

(2) Minkowski says that the absorption of fats greatly depends upon the form in which they are administered. "Zur Lehre der Fettresorption." Berlin. Klin. Wockensch. No. 15, 1890.

patients to use them as remedies, particularly when they have the misfortune to labour under such a grave form of disease as pancreatic diabetes. For be it remembered it is not alone the half savage Laplander that enjoys eating rancid oil, but even the refined and cultivated Spanish Grandee won't eat salad oil until it is quite rancid, and strong smelling. Taste is a mere matter of fashion. One can not only accustom oneself to eat what at first sight appears repellant, but rapidly become fond of it. Consequently, I do not hesitate to recommend the use of rancid oils and fats in the treatment of pancreatic diabetes.

Cod Liver Oil, as all know who have had much experience in the treatment of cases of diabetes arising from Diminished Assimilation, is a most useful remedy, more especially when it is administered along with alkalies in the form of an alkaline emulsion. So I would, on physiologico-chemical grounds strongly recommend its free employment in cases of pancreatic diabetes. The whole benefit derived from the use of mineral waters, such as those of Carlsbad and Vichy, in diabetic cases is, I imagine, entirely due to their aiding in emulsionising the fats of the foods by reason of the alkalies they contain. In the last clinical case I cited, the advantage of Carlsbad waters was strikingly manifested, and in order to prevent repetition, I beg to refer to its perusal at p. 74. The case was one of those I call cases of Mixed Diabetes, for it evidently began - probably hereditary - as one of

Diabetes from Excessive Formation, and it was only within the last two months of his life, that it actually drifted into one of pancreatic diabetes, and so long as it remained a case of the former kind, the influence of the mineral waters was most strikingly marked, seeing their use actually reduced the sugar from 7 p.c. to 0.5 p.c.

Lépine (+) advised the use of pilocarpin, in the hope that it would stimulate the secretion of the pancreatic gland, just as it does that of the salivary glands. But how it could possibly do any good in pancreatic diabetes I am at a loss to see, from the fact (as has been shown in the experimental physiological part of this thesis) that when any of the pancreas is left in a sufficiently healthy state as to be able to carry on its functions, there exists no diabetes, and that the diabetes does not actually occur until there is no healthy pancreatic gland-tissue left for the pilocarpin to act upon. Therefore I am unable to say anything in favour of Lépine's proposed remedy. The next question we have to consider is - Can we in any way supply this want of the pancreatic juice in transforming the starchy matters of the food into sugar? This is, I believe, well within our power, simply by giving pancreatin either in the form of pill or powder. Now-a-days, a form of pancreatic powder is sold under the name of Fairchild's pancreatin, and although not so strong in its action, as it is much less expensive and more readily obtained than the pure pancreatin

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(+) Lépine. "La Semaine Médicale. 21 Mai, 1890.

originally used by my father, it might be well to give it a trial in cases of pancreatic diabetes, where no stone should be left unturned which offers the remotest prospect of prolonging the life of the patient.

It may be mentioned however, that the diastatic ferments which exist in other parts of the alimentary canal, act powerfully enough to allow of a great part of the Carbohydrates being absorbed into the blood.

Next as regards triptic digestion. Here it is that pancreatin, artificially administered, finds its greatest use; and it is for this reason, as well as for its possible advantage in rendering the fats more readily absorbed, that I would advise its use in all cases of Pancreatic Diabetes.

I now approach what I regard as the most difficult problem in the treatment of pancreatic diabetes, seeing that it is the supplying of the second great function of the pancreas in the nutrition of the body. The one indeed whose absence is not only the cause of the appearance of sugar in the urine, but also of the appearance of the other prominent diabetic signs and symptoms. So that the question now to be considered is - Can we by any possibility remedy the want of the pancreatic enzyme, whose duty it is to split up the sugar in the blood, and thereby fit it for purposes of nutrition? Here, I must confess, our therapeutical acquirements are sadly deficient, for as yet nothing of much practical value has been suggested in the way of finding a substitute for the sugar transforming power of the absent enzyme.

It was shown in a previous chapter that there are as yet only two methods known ~~only two methods~~ by which sugar is used up in the animal body, are by oxidation, and by the splitting of it up by an enzyme into more easily assimilated substances.

There being no therapeutic means as yet known by which we can supply the place of this enzyme in the blood, we must endeavour by a carefully regulated hygiene to increase the vital activity of the tissues, for by increasing the activity of the tissues, as has already been shewn, we may hope to increase their power of splitting up the sugar, so as to render it more easily assimilated. I have already shewn in the study of the pathogenesis of pancreatic diabetes that all the tissues of the body have the power of destroying sugar. We must, however, never lose sight of the danger we encounter of at the same time increasing the proteid destruction, and thus hastening the fatal poisoning by increasing the products of proteid waste.

I will now turn to the consideration of the other manner by which sugar is utilised in the animal economy; namely, by oxidisation. The only suggestion hitherto made on this point was that of Dr. Day, (+) who thirty two years ago recommended the employment of peroxide of hydrogen in cases of diabetes, a method of treatment which seemingly receives support from the experimental evidence adduced in this paper. For it

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(+) Day. Lancet, 20 January, 1868; and 20 March 1869.

has been seen that blood mixed with sugar destroys much less of it, if it be deprived of its oxygen by having it expelled by carbonic acid being driven through it. Besides which, we have in addition the experimental evidence of Professors Hoppe-Seyler, and Dastre, already referred to, of the appearance of glycosuria in animals when they are deprived of oxygen.

For a report of the practical application of the peroxide of hydrogen I extract the following remarks from my father's book on Diabetes already alluded to, (p.175) where in speaking of Dr. Day's proposal to use ozone in the form of ozonised ether, he says that not only he, but his colleagues, Sir William Jenner, and Drs. Fox and Russell Reynolds gave it a trial on several cases of diabetes in University College Hospital without any very satisfactory results. He mentions however, a private case which was diagnosed as one of diabetes arising from an Excessive Formation of sugar, when the same line of treatment appeared to be most exceptionally beneficial. The case was that of an Anglo-Indian Judge aged 47, who while taking a drachm and a half of ozonised ether had his urine diminished from 80 to 50 ounces per diem, and the sugar in proportion, notwithstanding that he was on ordinary diet during the time; and so improved was he in the short space of six weeks that he then returned to India and resumed his judicial duties. This case is however, the only example he records of an exceptionally beneficial result having attended the administration of

ozone. Dr Rienzi (1) on the other hand found ozone useless in his cases.

The administration of ozone appears to be quite unnecessary, as all the benefits of oxygen can be obtained by simply allowing the patient to breathe pure air, for that ozone merely acts as ordinary oxygen, I will show by the following known facts.

One third atom of oxygen existing in ozone (O_3) is so loosely combined with the other two, that it readily detaches itself in the presence of oxidizable substances. (2) So easily indeed, that ozone can actually oxidise substances at a low temperature, which can only be oxidised by simple oxygen at a high one. From the atoms of oxygen in the latter case requiring the intervention of the kinetic energy of heat to separate them, whereas in the case of ozone, the tendency to atomic separation is so strong that ozone cannot exist free in the living organism, simply on account of there being in it so many oxidizable substances. It therefore never reaches the blood as ozone, and when it gets there can only act as ordinary oxygen does.

I should advise sea-air and cheerful surroundings to encourage respiratory changes. We all know how much freer we breathe when in a good humour, and by these means we would obtain all the advantages we can hope to from the oxygen.

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(1) Rienzi. Virchow's Archiv. Vol. 104.
(2) Clausius. Poggendorff's Ann. Vol.121, p.250. 1864.

I now come to the consideration of opiates. As is well known, opium in some form or another, has long been held in high esteem in the treatment of diabetes, and I think that the scientific data now at my disposal will admit of my throwing a new light on the mode in which narcotics act in benefitting patients labouring under diabetes.

From Professor Seegen (1) having found by experiment upon dogs that when they are under the influence of opium the quantity of sugar is actually increased - instead of being diminished in the blood - as one would naturally enough expect it to be, if opium reduces the quantity of sugar in the urine of diabetic patients, one is somewhat surprised at the apparently paradoxical assertion that opium is beneficial to human beings when they are eliminating large amounts of sugar. I think, however, I shall be able to show that there is even harmony in this apparent discord, at least I shall try, and the remarks I am about to make on the mode of action of opium in diabetes, I desire should be considered equally applicable to all the forms of narcotics that have been found useful in the treatment of diabetic cases, no matter whether the narcotic be in the form of opium, morphia, codeia, hyoscyamus, antipyrin, sub-phonal, or bromides. For quite recently almost the identical same remarks have been made by Lépine (2) regarding the physiological

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(1) Zur Zuckerbutimung im Blut. Centralblatt fur Physiol. Bd.4. No.8. July 1890.
(2) L'Archiv. de Med. Exper. January 1899.

action of antipyrin on the sugar in the circulation as was made by Seegen regarding opium. So that if I can give a plausible explanation of the mode of action in the one case the same explanation will be equally satisfactory in the other, and the seeming paradox will disappear.

In order to illustrate my view of the way of in which narcotics act in reducing the amount of urine excreted, as well as the quantity of sugar eliminated I will refer to the effects of cordeia in certain forms of diabetes.

It is I believe, pretty generally known, that when cordeia is given, either simply by the mouth, or administered hypodermically in the form of phosphates, it has within the short space of twelve hours the power (in the vast majority of diabetic cases) of diminishing both the quantity of urine and sugar expelled from the body. And no sooner do we begin to analyse the character of the cases in which the cordeia appears to act thus beneficially, than we perceive that they almost all belong to the same class of cases; and that class is, with but rare exceptions, always the one recognised as arising from Excessive Formation. And if we proceed a step further and ask ourselves what is the pathology of such cases? the inevitable reply is - that the majority of them are the offspring of a super-hepatic activity in the transformation of Glycogen into sugar in the liver. Here then is the key, I believe, to the enigma, from its being a well-known fact that no drugs are so potent in reduc-

ing not only hepatic but renal activity as those belonging to the opiate group. Opium itself will not only so retard the secretion of bile as to give rise in some cases to white stools, but will even in perfectly healthy individuals greatly reduce the flow of urine. So in this fact lies, I think, the explanation of the paradox that even while opium diminishes the destruction of sugar in the blood, it acts beneficially by possessing the still more important power, in such cases, of impeding the transformation of glycogen into sugar by the liver, while it at the same time diminishes the renal secretion, by virtue of its narcotic action on both the hepatic and renal nerves. If such be the case there is little difficulty in understanding why a remedy which proves to be so useful in cases of Diabetes arising from Excessive Formation is of little or no use in those arising from Diminished Assimilation. And seeing, as I have tried to show, that pancreatic diabetes belongs to the latter or malnutritive class, I fear that the administration of opium, codeia, antipyrin, and other narcotics will prove but of little service, in so far at least as the saccharine condition of the urine is concerned.

Having now disposed of the various remedies which appear to be of doubtful efficacy in the treatment of pancreatic diabetes, I will next try and point out what the chemico-physiological facts narrated in the previous pages of this essay seem to suggest as the most appropriate lines of treatment to be adopted.

In the first place, seeing that loss of flesh and

energy are the two most marked features of the disease it naturally occurs to one that it would be wise to try and raise the general standard of the patient's health by fresh air, nourishing food, warm clothing, gentle exercise and the employment of tonics if they seem needful.

In the next, should the patient have constitutional tendency to any other enfeebling disease, that tendency should if possible be corrected. If, for example, there be anything like gouty or rheumatic signs or symptoms, they ought to be counteracted by a judicious course of salicylates, bromides, or iodides of the alkaline class.

Thirdly. As the beneficial effects of alkalies in emulsionising the fats has been already pointed out the use of soda and potash, even in the form of alkaline mineral waters is strongly indicated as likely to be highly useful to the patient.

Fourthly. A carefully selected diet roll in which oils and fats play a leading part, particularly in the form of fatty acids, no matter whether they be of the vegetable or the animal variety, must be regarded of paramount import.

The following general directions for diet is likely, I think, to be found useful, always bearing in mind that individual cases may require a special dietary.

MAY EAT.

Meats. Beef, veal, mutton, lamb, pork, venison,

hare,rabbit and all kinds of feathered game and poultry, sweetbreads, fat bacon, ox-palate, tongue and tripe. Eggs - raw, bioled, poached or fried. Butter Devonshire cream, and cream-cheese.

Fish. All kinds of sea and fresh-water fish - boiled, fried, stewed, or broiled, including eels, smelts, whitebait, crabs, lobsters, prawns, shrimps, as well as sardines and anchovies - fresh, and in oil or butter.

Soups. Animal soups of all varieties - oxtail, gravy, hare, turtle, prawn, clam, chicken, grouse, and other game soups. Beef tea, Liebig's extract, Valentin's meat juice, Brand's essence, Bouillon Fleet, and such like animal soup preparations.

Vegetables. Cabbage - white and red, cauliflower Brussels-sprouts, spinach, turnip-tops, greens, sorrel artichokes, brocoli, tomatoes, onions, and mushrooms.

Puddings. Egg-custard, calve's foot, gelatine, isinglass, Irish and Iceland moss jellies and blancmanges, flavoured with salt, or sweetened with glycerine or sugar. The amount of sugar taken in this way is so small as to have no deleterious influence on the disease.

Breads. Gluten and bran breads - plain or toasted gluten rolls, cracknels, almond, cocoa-nut and bran biscuits, gluten sponge cakes, as well as rusks.

N.B. If the bread be well prepared and free from starch, it does not become of a dark violet or a blue or blue-black colour, but only of a reddish brown,

when iodine water (¼ tinct. iodine + ¾ distilled water) is applied to it. The depth of colour indicates the amount of starch present.

Fruits. Oranges, limes, lemons, shaddocks, olives, pine-apples, bilberries, raspberries, blackberries, red and white currants.

MAY DRINK.

Milk, tea, coffee, lemon-squash, koumiss, soda, potash and alkaline mineral waters.

SHOULD AVOID EATING.

All wheaten, barley, oatmeal, or other forms of ordinary bread; pastry, pie-crust, dumplings, pancakes, porridge, as well as all kinds of farinaceous puddings - sago, rice, semolina, cornflour, arrow-root revalenta, malts, and maltine. Asparagus, potatoes, peas, beans, lentils, beetroot, parsnips, carrots and turnips, Jerusalem artichokes, rhubarb - stewed or in tarts, chestnuts, grapes, raisins, prunes, and dried figs.

AVOID DRINKING.

Alcoholic beverages, distilled as well as fermented. Whisky, brandy, rum, gin, arrack, port, sherry, Madeira, Marsala, Champagne and Burgundy. Ale, stout, porter and cider, as well as all varieties of liqueurs, except when the patient is weak, in which case the use of a stimulant of some kind may prove beneficial, and even ale or stout is not prohibited in pancreatic diabetes as they are in cases of diabetes from Excessive Formation. Instead of peptonising the foods before being eaten, if they are to be prepared

at all before being used, let it be done by adding to them finely chopped up, or better still the expressed juice of a fresh pig's pancreas, at a temperature of 99° Fah. for 10 minutes, so that the pancreatic constituents may act upon the foods out of the body just as they do in the duodenum.

The fats and oils again, can be emulsioned by mixing them with bi-carbonate of soda or potash, or with liquor potassa, and be rendered more easily assimilable in that way.

As will be noticed in the case of the Banker already referred to (p. 74) the strict dieting ceased to have any effect on the progress of the disease so soon as the diabetes had changed from being one the result of excessive formation to that of pancreatic diabetes. For no sooner did that happen than from the vice lying in the mal-assimilation of the sugar, the cutting off the saccharine supply was no longer attended with the same beneficial results. In fact the late Dr Budd of Bristol treated all cases of diabetes attended with emaciation by giving them large quantities of cane sugar, and contrary to what his colleagues had anticipated, some few of them actually improved under the treatment. Perhaps these may have been cases of the pancreatic form of diabetes, for seeing that in them the vice lies in a diminished power of assimilation, and not in an excess of saccharine supply, the giving of a superabundance of sugar might in reality be attended rather with beneficial than baneful results to the patient, in so far at least as his nutritive pro-

cesses were concerned.

Having in the pathogenesis chapter called attention to the fact that muscular activity has been found to be a potent agent in favouring the assimilation of sugar (p. 85) in the animal economy, I am led to think that regular muscular exercise, if kept well within the bounds of fatigue, would prove useful in retarding the downward progress of pancreatic diabetes. But if muscular exertion is to be used as a remedial agent, it must be used, as just said, within the margin of fatigue; for anything that lowers the vital powers - which fatigue either of body or mind most assuredly does - would be highly detrimental to the patient. Moderate foot or horse exercise I would therefore recommend to be tried, as well as gymnastics, Swedish exercises, or even massage, when the patient is weak; for no doubt everything that produces muscular movement is likely to increase the destruction of sugar in the animal organism. Though it is not to be forgotten that in cases of pancreatic diabetes it is not so much the destroying of the excess of sugar that is required, but the assimilation of other transformed or so-called destroyed saccharine matter that is in reality the goal to be aimed at in treatment.

Lastly. As regards the treatment of the diabetic coma, unfortunately it appears that but little can be done for it, for although it has been found that alkalies injected into the blood of rabbits poisoned by hydrochloric acid was successful in restoring them from

the comatose state; if alkalies were similarly employed in the case of a diabetic comatose patient, they would only neutralise - for the time being - the oxybutyric and aceto acetic acid in the blood, without however, attacking the primary cause of the comatose condition, the comatose state being due to the alkalies of the blood, having become saturated with the acids formed by the proteid waste, and thus from the blood being unable to carry to the lungs a sufficiency of carbonic acid, the carbonic acid by accumulating in the tissues, and more especially in those of the brain produces the fatal coma. What we must therefore attempt is in the form of prophylaxis, and to do this we must try to diminish as far as possible the proteid waste by employing the various hygienic remedies and means already pointed out.