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APPLICATION DATED

19th July, 1923.

Applicant (Assignee of Actual Inventors) ... THE GOVERNORS OF THE UNIVERSITY OF TORONTO.

Actual Inventors ... ... FREDERICK GRANT BANTING. CHARLES HERBERT BEST. JAMES BERTRAM COLLIP.

Application and Complete Specification ... Lodged 19th July, 1923.

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Classes 09.9; 87.1.

No drawing.

COMPLETE SPECIFICATION.

"A product obtainable from the mammalian pancreas, the related glands of fishes, and other sources, useful in the treatment of diabetes mellitus, and a method of preparing it."

We, THE GOVERNORS OF THE UNIVERSITY OF TORONTO, of the City of Toronto, in the County of York, and Province of Ontario, Dominion of Canada, hereby declare this invention and the manner in which it is to be performed, to be fully described and ascertained in and by the following statement:—

Carbohydrate, such as the starches, taken in the food, is converted into simple sugars, such as glucose. In this form it is absorbed by the intestine and carried to the liver where most of it is stored as glycogen. The remainder is carried to the muscles and other tissues where it is either immediately oxidized or stored as glycogen. Prior to its conversion into glycogen, or to its oxidation, glucose probably becomes altered in chemical structure so as to make it more reactive. It becomes changed from an inactive into an active form. In diabetes mellitus the sugar absorbed from the intestine is no longer properly changed into the active form so that it cannot be stored in the liver as glycogen, nor oxidised in the tissues, but circulates in increased quantities in the blood (hyperglycemia) and is excreted in the urine (glycosuria). It therefore becomes lost to the body as a source of energy. As a result the store of glycogen is rapidly exhausted and protein is attacked as a source for glucose. As carbohydrate is necessary for the normal metabolism of fat in the body, incomplete combustion of fat occurs in diabetes mellitus, resulting in diabetic acidosis and coma. Diabetes mellitus must, therefore, be considered as a disease of metabolism in which carbohydrate is not efficiently utilized by the body, thereby causing a derangement of the normal metabolism of proteins and fats as well as carbohydrates. This derangement of metabolism is recognized by voracious appetite, hyperglycemia (increase in the percentage of sugar in the blood) and glycosuria (sugar in the urine).

As a result of the experiments of Von Mering and Minkowski, in which they

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showed that extirpation of the pancreas in dogs was followed by persistant glycosuria and other symptoms of diabetes, the important relation between this gland and diabetes was established. The pancreas consists of two types of tissue; the acinar portion secreting the pancreatic juice (the external secretion) which reaches the intestine through the pancreatic duct, and groups of cells scattered throughout the gland known as "The islands of Langerhans". These cells possess a rich supply of blood vessels. As the islands of Langerhans show pathological changes of varying degree up to complete destruction in the majority of cases dying of diabetes mellitus, Opie and others have considered that the insular portion of the pancreas is the one related to diabetes mellitus. They believed that it probably furnished an internal secretion necessary to normal carbohydrate metabolism, and several investigators, among whom might be mentioned Hédon, Lepine, Fraser and Rennie, Zuelzer, Forsbach, Scott, Murlin, and Clark, attempted to obtain from the pancreas this internal secretion.

As a result of the work of these investigators it was suggested that not only the ductless portion (islands of Langerhans) of the mammalian pancreas but also the pancreas of cartilaginous fishes, and the related glands (principal islets) of boney fishes contains this active anti-diabetic principle or hormone and that it is capable of alleviating diabetic symptoms in patients and laboratory animals, and other investigators conducted experiments in which diabetic patients and diabetic laboratory animals were given extracts obtained from these glands containing this active anti-diabetic principle or hormone.

The results of these experiments, however, were not considered sufficiently satisfactory to justify the continued use of these extracts in the treatment of diabetes in man because of the presence in the extracts of toxic substances, and no definite progress was made towards the preparation of an extract sufficiently pure to be safely administered to human patients until the investigations were continued by us. From our knowledge of the results in the early experiments we concluded that the presence of toxic substances in the extract caused local irritation followed by general reactions unrelated to the physiological and therapeutic effects of the hormone and these conclusions were confirmed by our early clinical observations.

The work of the previous investigators had shown that if the duct of the pancreas was ligated, degeneration occurred much more rapidly in the acinar portion that in the islands of Langerhans and we conceived the idea that if an extract was prepared from the pancreatic tissue remaining some time after ligation of the ducts, it should contain the supposed internal secretion of the islands of Langerhans, because there would not be enough of the digestive ferments to destroy it. Working upon this hypothesis we prepared an extract of the degenerated pancreas and injected it into diabetic dogs. Following the injection a definite lowering of the blood sugar and a decrease in the amount of sugar excreted in the urine was found to occur, and we were able to show that if sufficient extract was injected at proper intervals, completely depancreatized dogs could be kept alive and free of diabetic symptoms for a long period of time. These experiments proved that the islands of Langerhans in the pancreas contained a substance which lowers the blood sugar and diminishes or abolishes the excretion of sugar in the urine of diabetic dogs. Later, by extracting the foetal or adult normal pancreas with alcohol, we prepared an extract which contained the active anti-diabetic substance or hormone, in concentrated form, the alcohol evidently preventing the destruction of the active principle by the digestive ferments. This extract was injected subcutaneously into a boy suffering from severe diabetes mellitus. A definite lowering of the blood sugar and of the amount of sugar excreted in the urine, resulted. Unfortunately the extract contained other substances which caused considerable local irritation, making repeated injection impossible. We, therefore, deemed it advisable before further clinical trials were undertaken to prepare a potent product containing the active anti-diabetic principle or hormone free or practically free from toxic substances, and to devise suitable means for obtaining the maximum yield of it.

This was done by extracting the gland with a solvent capable of preserving the activity of the anti-diabetic principle or hormone and then separating it free from injurious substances including inert associated gland tissue, proteins, proteolytic enzymes, salts and lipoids.

The solvents which we used in the early period of our investigations were ethyl alcohol, methyl alcchol, methylated spirits, and acetone, which we found were not only capable of extracting the gland but were also capable of preserving the activity of the anti-diabetic principle or hormone by largely preventing or inhibiting the deletericus action on it of such proteolytic enzymes as trypsin, erepsin, and the proteases and of other catalysts present.

During the later periods of our investigations we discovered that other reagents could be used as solvents which tended to retard or inhibit the digestive action of the gland tissue and prevent the injurious substances going into the extractive solution and among these reagents we found that boiling water produced satisfactory results both in regard to the maximum yield of the potent substance and the small amount of proteins and other gland substances in the extractive solution and that copper sulphate solution produced substantially the same results as boiling water.

Following filtration for the removal of the inert associated gland tissue we precipitated the proteins by various reagents. Among these we used fractional precipitation with alcohol, precipitation at the isoelectric point by the use of dilute acid or alkali, precipitation with colloidal iron, and heating to a suitable temperature.

Fractional precipitation with alcohol yielded a product of sufficient purity for repeated subcutaneous administration without causing local irritation and the purified and potent substance obtained by this method was administered to a large number of patients suffering from diabetes mellitus with satisfactory results in every instance where it was properly administered.

While it has not been proven that the product containing this active anti-diabetic principle effects a permanent cure of the disease it has been noted in the results of the clinical tests that the patients after being treated with it for a short time require smaller doses than at the commencement of the treatment, but it has been proved for the first time in the history of medical science that a product can be obtained from the pancreatic glands of mammalia and cartilaginous fishes and from the related glands (principal islets) of boney fishes, which will, and has, saved the lives of a number of diabetic patients, many of whom were in a state of coma before the substance was administered.

It has since developed that it is possible, by substantially the same methods of extraction, to obtain a substance from other sources, (animal and vegetable), such as blood of slaughtered animals, yeast, potatoes, molluscs, and so forth, that will function in the body in a manner similar to that obtained from the pancreas of mammalia and the related glands of fishes, that is by promoting combustion of sugar in the tissues and the storage of glycogen in the liver. These, however, are only a few of the sources from which it is thought that a substance can be obtained having the power to function similarly to the active anti-diabetic principle or hormone of the pancreas of mammalia and the related glands of fishes. It has also been discovered since the early period of our investigations that stability, purification and potency of the final product is dependent at least in part on the hydrogen ion concentration of the solution containing it and that if this hydrogen ion concentration is properly adjusted a product of great purity and potency with a considerable degree of stabilization can be obtained.

Having found a method for the preparation or extraction of the active anti-diabetic principle or hormone of a purity and potency which permit of its repeated administration to human patients, it was possible to test its value in the treatment of diabetes mellitus. In various clinics to which it was distributed, and further investigations on the administration of the product in diabetic dogs and in severe cases of diabetes mellitus have shown that its injection restores to the body the lost ability to oxidise carbohydrates, and glycogen is again stored in the liver. This it evidently does by converting glucose into the active form and if the extract is given in sufficient quantity and at proper intervals the blood sugar is maintained at a normal level and the urine remains free of sugar. Fat is also completely burned. Acetone bodies disappear from the urine and diabetic acidosis and coma are prevented. In brief, the artificial administration of this product restores to the body a normal metabolism of carbohydrates, fats and proteins.

Although the administration of the product is capable of relieving the cardinal symptoms and signs of diabetes mellitus, one must not conclude that it can replace

the dietetic treatment of the disease. In diabetes there is a decreased production by the pancreas of the active anti-diabetic principle or hormone due to the weakened function of the islands of Langerhans. As all cases of diabetes mellitus are capable of metabolizing a certain amount of carbohydrate the degree of damage to the islands and their capacity to produce the active anti-diabetic principle or hormone may be ascertained by estimating the tolerance of the patient for carbohydrate. The etiological factor or factors causing this damage to the pancreas have not been discovered. It is known, however, that diets containing excessive quantities of carbohydrates, or proteins, fats and carbohydrates in improper proportions or quantities as well as infections, further weaken the function of the already damaged pancreas. The object of treatment and the administration of the product should be to give rest to the damaged islands and conserve their power to produce the active anti-diabetic principle or hormone. Before the introduction of this product this was accomplished best by dietetic treatment outlined by a number of diabetic specialists. By marked restriction in diet, combined with periods of fasting, it was demonstrated that even in severe cases of diabetes, the urine could be kept free of sugar and the blood sugar maintained at a normal level for long periods of time. Later, many patients remained aglycosuric without the necessity of fasting. This method of treatment gave a maximum of rest to the damaged pancreas and allowed it to maintain, or even to increase its power to produce the active anti-diabetic principle or hormone. The lives of severe cases of diabetes were definitely prolonged, and mild cases regained sufficient tolerance for carbohydrates to allow them to take a more liberal diet and yet remain free of symptoms. Unfortunately the extreme under-nutrition resulting from the prolonged use of the restricted diet with fasting caused a marked loss of weight and strength and made the continuation of the treatment difficult.

The introduction of the product containing this active anti-diabetic principle or hormone in the therapy of diabetes makes it possible to begin the treatment of even severe cases with a palatable diet of protein, fat and carbohydrate in adequate quantities to meet the requirements of the body at rest in bed or with moderate exercise, and at the same time afford adequate rest to the damaged islands of Langerhans. After the glycosuria and ketonuria have disappeared and the blood sugar level has returned to normal the diet may be gradually raised until the patient is receiving sufficient food to maintain the body weight slightly below normal, and sufficient calories are being supplied for the body to perform the ordinary duties of life. In some cases the pancreas has so regained its power to produce the active anti-diabetic principle or hormone that the daily dosage need not be increased; in other cases where the damage to the pancreas is more permanent, a sufficiently additional quantity must be given to keep the urine of the patient free of sugar on the increased diet.

Overdosage of the product is followed by the development of serious signs and symptoms demanding immediate treatment. The patient complains of a sense of weakness and fatigue associated with sweating. In the more severe forms there is acute distress with mental disturbances and even unconsciousness. These reactions are due to a fall in the blood sugar below the normal level of 0.1 per cent. When the blood sugar falls to 0.07 per cent., symptoms develop and if it falls to 0.035 per cent. the patient becomes unconscious. The symptoms, although alarming both to the patient and those in attendance, are completely relieved if glucose is given immediately.

The indiscriminate use of this product in the treatment of diabetes mellitus is a real source of danger. At the beginning of treatment all cases of diabetes mellitus except those suffering from severe acidosis and coma, should be put to bed and given a basal maintenance diet. This diet contains protein sufficient to replace the daily wear and tear of the tissues of the body, approximately 0.3 gm. per pound of body weight. Additional calories in the food are supplied by carbohydrate and fat in proper proportion to prevent the production of acetone bodies and in adequate amount for the height, weight and sex of the patient. If the urine of the patient becomes free from sugar on this diet it should be gradually raised until he is receiving an adequate diet for the performance of the ordinary duties of life. Should the patient remain aglycosuric on this diet the treatment with this product is not indicated. Approximately seventy-five per cent. of diabetics may be controlled by dietetic treatment.

If, at the end of a week's treatment on a basal diet the urine is not free of sugar the patient requires to be treated with this product. The amount of the product to be injected daily is dependent upon the total amount of glucose found in the urine at the end of the preliminary period of observation. It is given in divided doses, injected subcutaneously, usually before breakfast and supper or, in more severe cases, before each meal. Under combined dietetic and this product treatment the patient usually improves rapidly. As the body is supplied with an adequate amount of the active anti-diabetic principle or hormone carbohydrate is properly metabolized—sugar and acetone bodies disappear from the urine and the blood sugar returns to a normal level. The patient enjoys his food, feels stronger, and the mental depression so characteristic of the severe diabetic is replaced by cheerfulness. Some patients have been able to resume their former occupations after a month's treatment.

Probably the most brilliant results obtained with the use of the product containing this active anti-diabetic principle or hormone have been in the treatment of diabetic acidosis and coma. In the treatment of these cases this product must be given immediately. All cases of acidosis and threatened coma react favourably to combine dietetic and this product treatment. In uncomplicated cases of advanced coma the majority—four out of six—have recovered after being given repeated intravenous injections of the product combined with an adequate amount of glucose to prevent the blood sugar from falling to a dangerous level. All the other fatal cases of coma treated had an associated infection sufficiently severe to cause death apart from the diabetic conditions.

Diabetes mellitus can be successfully treated in the less severe form by giving a properly balanced diet; in the more severe, by proper diet and an adequate daily dosage of this product. The success of treatment is dependent upon the physician for the institution of proper treatment; upon the patient for the continuation of the treatment prescribed.

In the manufacture of this product from slaughter house material and from the related glands of fishes we found that extraction followed by fractional precipitation with alcohol yielded a highly purified and potent substance and for the information of biochemists we will describe the manufacture of the product in connection with the pancreas of mammalia and the related glands of fishes by the use of alcohol as an extractant followed by the purification of the extractive by fractional precipitation with alcohol, but we wish it to be understood that other extractants and other reagents for the purification of the extractive solution can be used to obtain a product containing this active anti-diabetic principle or hormone either from the pancreas of the mammalia and the related glands of fishes or from other sources, in as highly purified and potent state as by the alcohol method, and that the invention is not to be confined solely to the particular processes or sources herein outlined.

A potent preparation of the extractive of the internal secretion or hormone of the pancreas of mammalia was prepared as follows:—

The fresh pancreas of the ox was minced and then mixed with an equal volume of alcohol. The mixture was strained and filtered to separate the insert associated gland tissue from the substances which had gone into solution in the alcohol. The filtrate was treated with two volumes of the same solvent and allowed to stand several hours with occasional agitation. The greater bulk of the protein was precipitated by this treatment and the resulting precipitate was removed by filtration and this filtrate subjected to vacuum distillation to obtain a concentrated aqueous solution. A buffer solution of 1/2 cc. of 4% $NaHCO_3$ solution was added for every 5 litres of filtrate before distillation was commenced, to keep the hydrogen ion concentration within the p H range 4 to 7. The concentrated aqueous solution was twice extracted with ether. The lipoid substances were removed by this treatment. The ether was separated mechanically and the aqueous solution was returned to the vacuum still and concentrated further. Alcohol was then added to make this concentrated solution 80% alcohol and the mixture was thoroughly agitated. The greater bulk of the saline substances were "salted out" by this treatment and there was also precipitation of more protein. It was then centrifuged. After centrifuging four distinct layers were manifested in the tube. The uppermost layer was perfectly clear and consisted of alcohol holding all the internal secretion or hormone in solution.

Below this in order were a flocculent layer of protein, a second clear or watery layer saturated with salt, and a lowermost layer consisting of crystals of salt. The uppermost layer was next syphoned off and treated with several volumes of 95% ethyl alcohol. The foregoing treatments with alcohol caused fractional precipitation in which the earlier fractions were composed of precipitated proteins and salts and the last fraction was the internal secretion or hormone. The mixture was allowed to stand some hours. The precipitate was caught on a Buchner funnel washed with 95% alcohol and finally dissolved in distilled water. The resulting aqueous solution of the precipitate was then concentrated to the desired degree by vacum distillation at low temperature and filtered through a Berkfeld filter to sterilize it. A preservative such as tri-cresol was added the concentration of the same not exceeding 0.7 per cent.

A potent preparation of the extractive of the internal secretion or hormone of the pancreas of cartilaginous fishes and of related glands, (principal islets), of boney fishes was obtained as follows:—

The fresh gland was removed, cut in small pieces and placed in an equal volume of commercial alcohol. The mixture was allowed to stand at low temperature for several hours, after which the fluid was decanted and the gland tissue or solid residue ground to a fine pulp. The decanted fluid was then added gradually to the pulp with which it was thoroughly mixed by trituration to extract the internal secretion or hormone. The mixture was then strained to separate the pulpified gland tissue from the substance which had gone into solution in the alcohol, and the strained fluid filtered. The residue from this treatment was again extracted as above with fifty per cent. alcohol and strained and filtered and the filtrate added to the first one. The alcohol was removed from the combined filtrates by distillation. The resulting aqueous solution was extracted by the use of ether for the removal of lipoids. The clear lipoid-free aqueous solution was then run off from under the ether and transferred to a wide beaker placed on a boiling bath so as to rapidly raise the temperature of the aqueous solution to between 70° and 75° C. at which it was maintained for 3 minutes with constant agitation of the beaker. By this treatment a flocculent precipitate of protein was thrown down and that portion of the ether which went into solution in the water was got rid of. The heated aqueous solution was then cooled, and filtered first through paper and then through a Berkfeld filter to sterilize it.

From each of the above mentioned glands we obtained by the foregoing methods, a potent product or extract in sufficiently pure concentrated form for repeated administration to human patients and which had the physiological and therapeutic characteristic of removing the cardinal objective symptoms of diabetes mellitus in patients and reducing the percentage of blood sugar in laboratory animals, and which has a distinct value in the treatment of diabetes mellitus, lowering blood sugar, decreasing urinary sugar, checking acidosis and raising the carbohydrate tolerance of a diabetic individual to whom it is suitably administered.

In the extraction of the active anti-diabetic principle from the blood of animals and from other vegetable and animal material we employ the same general principles as outlined in the extraction of the substance from the pancreatic glands of animals and the related glands of fishes, and we therefore wish it to be understood that the invention is not limited to the production of the active anti-diabetic principle from the sources mentioned, and also that in view of the fact that we can use a large number of extractants and a large number of reagents for the purification of the extractive solution, the invention is not to be limited to the particular solvents and precipitants set forth.

Having now fully described and ascertained our said invention and the manner in which it is to be performed, we declare that what we claim is:—

1. A product containing in concentrated form a substance necessary to normal carbohydrate metabolism.

2. A product, containing in concentrated form an active anti-diabetic principle or hormone, sufficiently free from injurious substances for repeated administration and having the physiological characteristic of causing a reduction of blood sugar.

3. A product containing in concentrated form an active anti-diabetic principle or hormone which upon proper administration is capable of restoring to the diabetic animal its lost ability to oxidise carbohydrate and to store glycogen in the liver.

4. A product as claimed in Claim 2 characterized by the fact that it is suffici-

ently free from injurious substances for repeated administration and has the physiological characteristic of causing a reduction of blood sugar.

5. A product containing in concentrated form an active anti-diabetic principle or hormone which will relieve the cardinal symptoms and signs of diabetes mellitus.

6. A product such as claimed in any of the preceding Claims characterized by the fact that it will not cause local irritation or toxic symptoms.

7. A product according to any of the preceding Claims characterized by the fact that the active anti-diabetic principle or hormone is obtained from either the pancreas of mammalia and other slaughter-house material, from the related glands of fishes, or other sources.

8. A method for obtaining a potent product, from the pancreatic glands of mammalia, and other slaughter-house material, from the related glands of fishes and from vegetable matter and other sources, in concentrated form having the physiological characteristic of causing a reduction of blood sugar and which method consists of extracting the active anti-diabetic principle or hormone with a solvent capable of preserving the activity of the anti-diabetic principle or hormone and then precipitating the anti-diabetic principle or hormone from the solution practically free from injurious substances and making a sterile aqueous solution of said substance.

9. A method for obtaining a product, containing an active anti-diabetic principle or hormone capable of alleviating the symptoms and signs of diabetes mellitus, which consists of extracting the anti-diabetic principle or hormone from the pancreatic glands of mammalia, and other slaughter-house material, from the related glands of fishes, and from vegetable matter, and other sources, and then purifying and concentrating the extractive.

10. A product prepared from fresh pancreatic or related glands containing in concentrated form the extractive from the ductless portion of the glands sufficiently free from injurious substances for repeated administration and having the physiological characteristic of causing a reduction of blood sugar useful for the treatment of diabetes mellitus.

11. A product prepared from fresh pancreatic or related glands containing in concentrated form the extractive from the ductless portion of the gland, practically free from injurious substances and having the physiological characteristic of causing a reduction of blood sugar useful for the treatment of diabetes mellitus.

12. A product prepared from fresh pancreatic or related glands containing in concentrated form the extractive from the ductless portion of the gland practically free from inert associated gland tissue and injurious substances and having the physiological characteristic of causing a reduction of blood sugar useful for the treatment of diabetes mellitus.

13. A product prepared from fresh pancreatic or related glands containing in concentrated form the extractive from the ductless portion of the gland practically free from proteins and other injurious substances and having the physiological characteristic of causing a reduction of blood sugar useful for the treatment of diabetes mellitus.

14. A method for obtaining a potent substance from the ductless portion of pancreatic or related glands in concentrated form and practically free from impurities having the hereindescribed physiological characteristic, which consists of extracting said substance from a fresh gland with a solvent capable of preserving the activity of the substance, precipitating said substance from the solution practically free from injurious substances, and making a sterile aqueous solution of said substance.

15. A method for obtaining a potent substance from the ductless portion of pancreatic or related glands in concentrated form and practically free from impurities having the hereindescribed physiological characteristic, which consists of extracting said substance from a fresh gland with a solvent capable of preserving the activity of the substance, precipitating said substance from the solution practically free from injurious substances, and making a concentrated sterile aqueous solution of said substance.

16. A method for obtaining a potent substance from the ductless portion of pancreatic or related glands in concentrated form and practically free from impurities having the hereindescribed physiological characteristic, which consists of extracting said substance from a fresh gland with a solvent capable of preserving the activity of the substance, precipitating said substance from

the solution practically free from proteins and other injurious substances and making a sterile aqueous solution of said substance.

17. A method for obtaining a potent substance from the ductless portion of pancreatic or related glands in concentrated form and practically free from impurities having the hereindescribed physiological characteristic which consists of extracting said substance from a fresh gland with a solvent capable of preserving the activity of the substance, fractionally precipitating said substance from the solution practically free from injurious adherent substances, and making a sterile aqueous solution of said substance.

Dated at the said City of Toronto, this eighth day of June, A.D. 1923.

THE GOVERNORS OF THE UNIVERSITY OF TORONTO,

By

B. E. WALKER, Chairman.

(SEAL)

F. A. MOURÉ, Bursar.

Witnesses—

Annie Mark Gall.

Madeline Mary Burns.

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Letters Patent Sealed.

References to the following numbers must include the year of application for the patent, which is indicated in heavy type.

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1917.—3531. 5652. 5726.

CHAS. V. WATSON,
Commissioner of Patents

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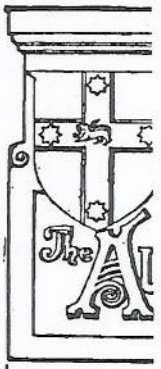

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