Cancer Association of South Africa (CANSA)

Research • Educate • Support

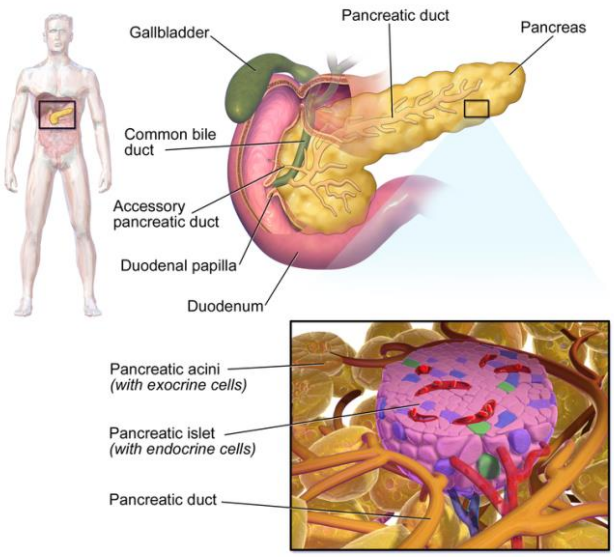
Fact Sheet on Insulinoma

Introduction

The pancreas is about 15 centimetres long and lies across the back of the abdomen, behind the stomach. The head of the pancreas is on the right side of the abdomen and is connected to the duodenum (the first section of the small intestine) through a small tube called the pancreatic duct. The narrow end of the pancreas, called the tail, extends to the left side of the body.

The pancreas is made up of exocrine cells and endocrine cells. These cells have different functions.

[Picture Credit: Pancreas]



Pancreatic Tissue

Most of the cells in the pancreas are exocrine cells. Exocrine cells make and release pancreatic juice. The juice travels through the pancreatic duct into the duodenum. Enzymes in the pancreatic juice help digest fat, carbohydrates and protein in food.

A small number of the cells in the pancreas are endocrine cells. They are arranged in clusters called islets, or islets of Langerhans. The islets make, and release, insulin and glucacon into the blood. These hormones help control the level of sugar, or glucose, in the blood.

Insulin lowers the amount of sugar in the blood when the blood sugar is high. It also stimulates the liver, muscles and fatty tissues to absorb and store the extra blood sugar.

Glucagon increases the amount of sugar in the blood when the blood sugar is low. It stimulates the liver and other body tissues to release stored sugar into the blood.
(WebMD; Canadian Cancer Society).

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Insulinoma

An insulinoma is a tumour of the pancreas that is derived from beta cells and secretes insulin. It is a rare form of a neuroendocrine tumour. Most insulinomas are benign in that they grow exclusively at their origin within the pancreas, but a minority metastasise. Insulinomas are one of the functional PanNET group ("functional" because it increases production of insulin; "PanNET" as an abbreviation of pancreatic neuroendocrine tumour).

Beta cells secrete insulin in response to increases in blood glucose. The resulting increase in insulin acts to lower blood glucose back to normal levels at which point further secretion of insulin is stopped. In contrast, the secretion of insulin by insulinomas is not properly regulated by glucose and the tumours will continue to secrete insulin causing glucose levels to fall further than normal.

As a result patients present symptoms of low blood glucose (hypoglycaemia), which are improved by eating. The diagnosis of an insulinoma is usually made biochemically with low blood glucose, elevated insulin, proinsulin and C-peptide levels and confirmed by localising the tumour with medical imaging or angiography. The definitive treatment is surgery. (Wikipedia).

Incidence of Insulinoma in South Africa

The National Cancer Registry (2013) does not provide any information regarding the incidence of Insulinoma.

According to the National Cancer Registry (2013) the following number of pancreatic cancer cases was histologically diagnosed in South Africa during 2013:

Group - Males 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	176	1:726	0,49%
Asian males	8	1:381	1,00%
Black males	50	1:1 928	0,46%
Coloured males	23	1:567	0,55%
White males	95	1:298	0,47%

Group - Females 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	152	1:1 314	0,42%
Asian females	8	1:703	0,79%
Black females	32	1:4 435	0,20%
Coloured females	22	1:631	0,53%
White females	90	1:418	0,57%

The frequency of histologically diagnosed cases of pancreatic cancer in South Africa for 2013 was as follows (National Cancer Registry, 2013):

Group - Males 2013	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	0	0	2	13	59	59	38	5
Asian males	0	0	0	1	0	3	4	0
Black males	0	0	1	7	20	14	5	1

Coloured males	**0**	**0**	**0**	**1**	**9**	**7**	**4**	**1**
White males	**0**	**0**	**1**	**3**	**28**	**24**	**24**	**2**

Group - Females 2013	**0 – 19 Years**	**20 – 29 Years**	**30 – 39 Years**	**40 – 49 Years**	**50 – 59 Years**	**60 – 69 Years**	**70 – 79 Years**	**80+ Years**
All females	**1**	**0**	**6**	**11**	**39**	**49**	**34**	**10**
Asian females	**0**	**0**	**0**	**0**	**3**	**3**	**2**	**0**
Black females	**1**	**0**	**2**	**4**	**9**	**9**	**4**	**0**
Coloured females	**0**	**0**	**2**	**1**	**5**	**7**	**6**	**0**
White females	**0**	**0**	**2**	**5**	**22**	**29**	**20**	**10**

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Signs and symptoms of Insulinoma

- Insulinomas are characterised clinically by the Whipple triad, as follows:
  - Presence of symptoms of hypoglycaemia [low blood sugar] (about 85% of patients)
  - Documented low blood sugar at the time of symptoms
  - Reversal of symptoms by glucose administration

- About 85% of patients with insulinoma present with one of the following symptoms of hypoglycaemia:

  - Diplopia (double vision)
  - Blurred vision
  - Palpitations
  - Weakness

- Hypoglycaemia can also result in the following:
  - Confusion
  - Abnormal behaviour
  - Unconsciousness
  - Amnesia (memory loss)

- Clinical Picture
  - Adrenergic symptoms (from hypoglycaemia-related adrenalin release): Weakness, sweating, tachycardia (rapid pulse), palpitations, and hunger
  - Seizures
  - About 85% of patients present with symptoms of hypoglycaemia (low blood sugar) that include diplopia, blurred vision, palpitations, or weakness
  - Other symptoms include confusion, abnormal behaviour, unconsciousness, or amnesia
  - About 12% of patients have grand mal (major) seizures
  - Adrenergic symptoms (hypoglycaemia causes adrenalin release) include weakness, sweating, tachycardia (rapid pulse rate), palpitations, and hunger
  - Symptoms may be present from 1 week to as long as several decades prior to the diagnosis (1 month to 30 years, median 24 months, as found in a large series of 59 patients). Symptoms may occur most frequently at night or in the early morning hours
  - Hypoglycaemia usually occurs several hours after a meal
  - In severe cases, symptoms may develop in the postprandial period (occurring after a meal). Symptoms can be aggravated by exercise, alcohol, hypocaloric diet, and treatment with sulfonylureas

- Weight gain occurs in 20-40% of patients. Because of hyperinsulinism, many patients may be overweight

(Medscape).

Diagnosis of Insulinoma

The biochemical diagnosis is established in 95% of patients during prolonged fasting (up to 72 hours) when the following parameters are found:

- Serum insulin levels of 10 µU/mL or more (normal <6 µU/mL)
- Glucose levels of less than 40 mg/dL
- C-peptide levels exceeding 2.5 ng/mL (normal <2 ng/mL)
- Proinsulin levels ≥22 pmol/L, or greater than 25% (or up to 90%) that of immunoreactive insulin
- Screening for sulfonylurea negative

(eMedicine).

Treatment of Insulinoma

The main treatment for insulinomas is surgery. This cures most insulinomas. But surgery is not always possible. Some cancerous insulinomas have already spread when they are diagnosed. If one cannot have surgery one will have drug treatment to control blood sugar levels and other symptoms.

The treatment depends on:

- Whether one has one or more tumours
- Whether the tumour is benign or malignant
- Whether the tumour has spread to other parts of the body
- Where in the pancreas the tumours are
- General health of the patient
- Whether the patient has a familial cancer syndrome

Other treatments may include:

- Treatment to control symptoms
- Chemotherapy

<u>Surgery</u> - the type of surgery the patient has will depend on:

- Whether he/she has one or more tumours
- Where in the pancreas the tumour is
- The size of the tumour

If the tumour is less than 2cm the surgeon may remove just the tumour. They call this enucleation. If the tumour is in the body or tail of the pancreas the patient may be able to have the operation with a laparoscope. This is also called keyhole surgery. It is a small operation where the surgeon puts a flexible tube filled with optical fibres (a laparoscope) into the body through a small cut. The surgeon looks through the laparoscope to find and remove the tumour.

If the tumour is in the head of the pancreas, is larger than 2cm, or the patient has more than one tumour, he/she may need to have open surgery. This means having an abdominal operation. Patients will also have an ultrasound scan during the operation, to check for other tumours.
Some people need to have some or all of their pancreas removed. The patient may also have nearby organs removed. The types of surgery used include:

- Removing the whole pancreas (total pancreatectomy)
- Removing the head of the pancreas (pylorus preserving pancreaticoduodenectomy – PPPD)
- Whipples operation – PPPD with part of the stomach removed
- Removing the tail of the pancreas (distal pancreatectomy)

These are major operations and there are risks with having this type of surgery. But the aim is to try to cure the insulinoma so the patient may feel it is worth some risks.

If the patient has MEN 1 or von Hippel-Landau syndrome, he/she is more likely to develop more tumours after having one removed. The surgeon may suggest to have more of the pancreas removed than if one did not have a family cancer syndrome. This is to reduce the risk of getting more tumours. The patient is also more likely to need to have an abdominal operation.

The specialist may suggest that the patient has surgery even if the malignant insulinoma cannot be completely removed. Taking away as much of the tumour as possible can help with symptoms because there will be less insulin produced.

Before one has surgery one will need to have good control of one's insulin levels. The patient may need to start on one of the drug treatments that control symptoms, for example, diazoxide. If the patient has MEN1 and has other symptoms because of that, such as a high calcium level, he/she will also need treatment to control the symptoms.

If a malignant insulinoma spreads to another part of the body, the most common area it goes to is the liver. The patient may also have surgery to remove tumours in the liver. As this is a major operation and there are risks, one needs to think carefully about the benefits. Will it improve quality of life enough to make it worth having such a big operation? The surgeon will discuss the risks and benefits and answer any questions the patient may have.

Instead of having a major open surgery for a cancer that has spread to the liver, the patient may be able to have radiofrequency ablation, cryotherapy or transarterial chemoembolisation (TACE) to reduce the symptoms. Or he/she may have selective internal radiotherapy (SIRT).

Treating symptoms of insulinoma - some cancerous (malignant) insulinomas are diagnosed when they are already advanced. And some come back after treatment. The most common place for malignant insulinoma to spread to is the liver.

Not everyone with a non-cancerous (benign) insulinoma can have surgery. This may be because of other medical conditions or the position of the tumour. If surgery is not possible, the patient will have treatment to control the amount of insulin the tumours are producing.

The aim of treatment for insulinomas that cannot be completely removed is to control any symptoms the patient has rather than cure it. Treatments may include:

- Surgery
- Drugs and diet to control blood sugar
- Chemotherapy

Radiofrequency ablation – This procedure uses heat made by radio waves to kill cancer cells.

Cryotherapy – This procedure uses a cold probe to destroy cells and tissue by freezing.

Transcatheter arterial chemoembolisation (it is also sometimes referred to as transarterial chemoembolisation or TACE) - is a minimally invasive procedure performed in interventional radiology to restrict a tumour's blood supply. Small embolic particles coated with chemotherapeutic agents are injected selectively into an artery directly supplying a tumour. The substance may also be a gel or tiny plastic beads and helps to keep the chemotherapy around the tumour.

Selective internal radiation therapy (SIRT) - is a form of radiation therapy used in interventional radiology to treat cancer. It is generally for selected patients with unresectable cancers, those that cannot be treated surgically, especially hepatic cell carcinoma or metastasis to the liver. SIRT - is when microscopic beads that are coated with a radioactive substance called Yttrium-90 and is a type of targeted radiotherapy.

Drugs and diet to control blood sugar - the symptoms of an insulinoma can be difficult to cope with. To help to control blood sugar, the patient may need to have a high glucose diet. Being aware of the symptoms of a low blood sugar will help the patient correct it quickly by eating something that contains glucose.

The drug diazoxide helps to control blood sugar by reducing the amount of insulin the patient makes. It is taken as a tablet. The possible side effects include feeling or being sick, loss of appetite, and fluid build-up in the legs or other parts of the body.

Other drug treatments that help control blood sugar are verapamil, diphenylhydantoin and steroids. Some tumours have somatostatin receptors and then somatostatin analogue drugs such as octreotide and lanreotide can also reduce the amount of insulin in the body.

Chemotherapy - can also help to control symptoms of a malignant insulinoma that cannot be removed with surgery. The drugs used may include doxorubicin and streptozocin.
(Cancer Research UK).

About Clinical Trials

Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the

development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials

Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different “phase” in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects.

Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or “trial arms”: (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new

intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.
In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or “control” interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.

- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

Medical Disclaimer

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