In patients with chronic pain, whether cancer-related or non-malignant, may be offered intrathecal drug therapy ("the pump") or intraspinal narcotic analgesia (INA).

There are significant risks with this form of therapy, including the risk of causing or exacerbating arachnoiditis.

Initially designed to give superior analgesia to the terminally ill, avoiding intolerable side effects, the ?pump' is now used for chronic non-malignant pain.

This means that continued use over decades may be being proposed and as yet we are unable to say for certain how safe that may be.

A study on the neurotoxicity of intrathecal agents ([i]) suggests that complications may occur in patients after high doses of morphine.

These were related to one of its metabolites, morphine-3-glucuronide. High concentrations of intrathecal morphine produce an allodynia and hyper-reactivity that may be related to this metabolite. (Yaksh et al, 1986; Yaksh and Harty, 1988)

Yaksh, ([ii]) writing on the toxicology of intrathecal morphine, has noted

"Continuous intrathecal infusion of morphine is widely used in chronic pain management. In spite of, and perhaps because of, its long history of use, there have been no systematic

safety studies on the effects of continuously infused morphine sulfate. Now convergent preclinical and clinical observations suggest the consequences of this omission."

He also comments on the doses used. In general, patients may receive up to 20 mg/day with long pump refill intervals, so

" it is likely that patients routinely receive morphine at concentrations which exceed even that which is commercially available (e.g. 25 mg/mL), employing concentrations of morphine which are at or near the absolute solubility of morphine sulfate (e.g. 50-55 mg/mL). Market research indicates that approximately 80% of morphine used in implanted pumps is compounded (*K Hildebrand, Medtronic Corp. personal communication)*."

In humans, the doses of morphine associated with granulomas frequently exceeded 20-25 mg/day. However, Yaksh suggests a combination of causative factors: reaction to catheter or infusion, opiate receptor activation and morphine actions. Studies have shown that the granuloma is not an infectious process.

Studies have suggested that morphine may activate lymphocyte activity (Chuang et al, 1997) and can initiate the inflammatory mediator nitric oxide.

In vitro experiments have shown that prolonged exposure of immunocytes leads to an exaggerated response of monocytes to inflammatory stimulus. (Stefano, et al, 1995)

Yaksh therefore proposes that morphine may activate inflammatory mediators within meningeal vasculature and initiate an increase in local capillary permeability to activated cells.

Yaksh and Malkmus ([iii]) examined the effects of intrathecal morphine sulfate infused over 28 days in chronically catheterized dogs at a dose of 1 ml/day in concentrations from 1.5 to 12 mg/ml.

They found a time and concentration-dependent increase in the severity of motor dysfunction (manifesting as increased hind limb motor tone).

Histopathology revealed modest pericatheter reaction in all animals. At higher morphine concentrations, an inflammatory mass developed at the catheter tip producing a local compression of the spinal cord.

This mass consisted of multifocal accumulations of neutrophils, monocytes, macrophages and plasma cells.

At concentrations / doses of 12 mg/mL/day, all dogs displayed granuloma formation.

There have been several clinical case reports describing patients receiving chronic morphine infusion who present with a motor or sensory dysfunction secondary to a local compressive lesion. ([iv] ; [v] ; [vi] ; [vii] ; [viii] ; [ix] ; [x] ; [xi] ;).

Note that Sabbe et al ([xii]) in 1994, found that the synthetic opioid sufentanil administered spinally in dogs, resulted in

"an inflammatory reaction secondary to the catheter was found in all animals." This localised irritation may well give rise to more chronic inflammation in susceptible individuals.

Coffey and Burchiel ([xiii]) have looked at 41 cases of inflammatory mass lesions associated with intrathecal drug infusion catheters.

They suggested a variety of hypotheses to account for this phenomenon, including: drug related mechanisms, infection, pyrogens, silicone hypersensitivity, and surgical trauma. Of these

possibilities, they felt that the

"use of relatively high-concentration, high-dose, or unlabeled analgesic drugs and admixtures is a plausible aetiology."

They further suggested that delivery of these drugs may stimulate a chronic immune response around the catheter tip.

The onset of the neurological symptoms in 23 patients was characterized as sudden in 6 patients, sudden with prodromal symptoms in 2 and slowly progressing in 15.

Kamran and Wright ([xiv]), writing about the complications of intrathecal drug delivery systems, fail, as do the majority of authors, to adequately address the issues of long-term adverse effects.

They refer to incidences of reduced libido and impotence of 6.1%, constipation 16.5% and peripheral oedema 5.1%; they also mention granuloma, seroma and infection.

However, they do not discuss the longer term sequelae to these problems, of which arachnoiditis may be one.

Jones et al. ([xv]) reported on an outbreak of serious neurological complications associated with the inadvertent administration of morphine preparation, which also contained methadone, or, in one case, traces of ethanol.

8 patients out of a practice of 61, (and out of 13 who were on morphine pump rather than other drugs) during one 4-week period developed complications such as sterile abscesses, and were left with new neurological deficit including paralysis. The authors attributed this outbreak to

"Medical errors in an outpatient pharmacy."

As explained earlier, there are a variety of adverse effects that can arise from the intrathecal delivery of narcotics, as with any drug. (Note: only preservative free solutions are licensed by the FDA).

In 1999, Brown et al ([xvi]) looked at the outcomes of using the pump for a variety of conditions. The authors reported:

"Intrathecal opioid treatment provides some benefit although substantial physical impairment continues to cause debilitation in the patient population."

They conclude: "Generally, patients after 3 years or more of intrathecal opioid treatment can be characterised as having substantially impaired physical functioning with a high prevalence of side effects."

These ongoing side effects include:

- reduced libido
- pruritus (itching)
- hyperalgesia (paradoxical increase in pain)
- myoclonus (involuntary jerks)
- urinary retention
- amenorrhoea (discontinued periods)
- uncommonly: raised antidiuretic hormone causing oedema in the lower limb
- constipation

The use of adjuvants in the pump, such as clonidine, is becoming more widespread, despite a warning by the manufacturer of Duraclon stating clearly that it does not recommend intrathecal administration ([xvii]).

Epidural clonidine has been found to be helpful in combating neuropathic pain and was initially used in terminally ill patients. It is preservative free. Clonidine acts at a spinal level to produce analgesia.

It was first used clinically for this purpose in 1984.

Gordh ([xviii]) from Sweden, in reviewing 15 years of what he terms

" long term medication of the spinal cord"

noted that its use for post-operative pain might be limited if it were used as a single agent, as doses sufficient to provide adequate analgesia also produce

"troublesome side effects"

including hypotension and bradycardia. He expressed doubt as to clonidine's useful role in post-operative pain management.

However, he did cite its use in treating neuropathic cancer pain.

In conclusion, Gordh remarked

"It may also be useful in chronic non-malignant pain, but large scale use in this field can hardly be recommended before results from controlled long term studies are available."

The UK based Development and Evaluation Committee Report ([xix]) No.55 (June 1996) suggested that 30-50% of patients report ?excellent' pain relief. However, there is a warning:

"There are significant risks and complications with these devices."

See below, under Treatment for further information on INA adverse effects.

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[xvii] Data from Clinical Pharmacology 2000 Website.

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