Intraventricular morphine for control of pain in terminal cancer patients

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Satisfactory control of intractable pain has been achieved in 17 terminal cancer patients by injecting small doses of morphine into the lateral cerebral ventricle via an Ommaya reservoir. Pain relief together with a favorable behavioral response was obtained without interference with other sensory modalities, noticeable physical changes, or side effects annoying or severe enough for the patient to discontinue therapy. Eleven patients developed tolerance, but this phenomenon does not require withdrawal of treatment. Chronic intraventricular morphine administration can be safely performed on an outpatient basis, and results in control of midline, bilateral, and diffuse pain associated with orofacial and disseminated cancer. However, this experience is preliminary and further clinical trials are needed to determine the place of this method of therapy in the management of chronic pain.

KEY WORDS • pain relief • opiates • intraventricular morphine • cancer

A number of studies have identified opiate receptors in several central nervous system areas concerned with transmission and processing of pain. The question now arises as to whether parenteral and intrathecal opiates work on these sites to achieve analgesia. The experimental evidence that morphine reduces the ascending noiceptive information by exerting a direct effect in the substantia gelatinosa led clinical workers to assess the analgesic effectiveness of low-dose spinal opiates administered either epidurally or into the cerebrospinal fluid (CSF) circulation. Powerful and prolonged analgesia is obtained with much lower doses of morphine than are required to control pain if the drug is given intravenously. Feasibility of intraventricular morphine-induced analgesia is supported by laboratory experiments showing that microinjection of this agent into the central gray matter produces long-lasting naloxone-sensitive analgesia, which is thought to be mediated by activation of local interneurons, resulting in increasing activity of the descending spinopetal inhibitory pathways.

We have found, when producing chronic spinal opiate analgesia in our clinic, that low-dose morphine injected into the cisterna magna may suppress pain in any anatomical location without producing concomitant respiratory depression. This observation persuaded us to initiate chronic intraventricular morphine in patients with intractable pain caused by orofacial and disseminated cancer. We have also administered intraventricular morphine therapy to patients with malignancies elsewhere.

Clinical Material and Methods

The nature and location of cancer, the distribution, duration, and rhythm of pain, and the previous therapies employed in our 17 patients before resorting to intraventricular morphine are reflected in Table 1. Parenteral analgesics, including opiates, resulted in unsatisfactory control of pain in all cases. Hypophysectomy, bilateral cordotomy, and dorsal column stimulation produced transient and incomplete pain relief in four patients. Eleven of 14 patients treated with epidural morphine administration via externalized catheters achieved good to excellent analgesia for periods ranging from 1 to 6 months (Table 1). Seven of the responders developed tolerance to morphine, but in most cases failure of spinal analgesia was due to technical problems such as displacement of the catheters and epidural scarring or infection.

Prior to implanting the Ommaya reservoir, patients giving informed consent for intraventricular therapy received a morphine bolus into the cisterna magna (11 cases: 0.5 to 0.75 mg total dose) or the lumbar theca.
TABLE 1
Origin and characteristics of pain and previous therapies used in 17 patients receiving intraventricular morphine

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Etiology of Pain: Site of Cancer</th>
<th>Distribution &amp; Duration of Pain</th>
<th>Previous Treatment</th>
<th>Epidural Morphine</th>
<th>Route &amp; Dose</th>
<th>Response &amp; Follow-Up (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75, F</td>
<td>tongue, local invasion</td>
<td>orofacial, neck, midline, 4 mos continuous</td>
<td>local resection</td>
<td>cervical, 2 mg/24 hrs</td>
<td>good, 3 mos</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>60, F</td>
<td>maxillary, local invasion</td>
<td>orofacial, neck, bilateral, 9 mos continuous</td>
<td>local resection</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>59, M</td>
<td>larynx, local invasion</td>
<td>rt side of neck, midline, 3 mos continuous</td>
<td>laryngectomy, radiotherapy</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>51, M</td>
<td>maxillary, local invasion</td>
<td>orofacial, neck, bilateral, 4 mos continuous</td>
<td>local resection, radiotherapy</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>51, M</td>
<td>esophagus</td>
<td>rt side of neck, midline, 3 mos continuous</td>
<td>biopsy</td>
<td>cervical, 2 mg/24 hrs</td>
<td>good, 1 mo</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>68, M</td>
<td>prostate, skull &amp; rib metastases</td>
<td>generalized, 18 mos continuous</td>
<td>transurethral resection, estrogens, hypophysectomy</td>
<td>lumbar, 2 mg/6 hrs</td>
<td>poor, 1 mo</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>50, M</td>
<td>colon, chest wall, diaphragm invasion</td>
<td>thoracic; upper abdomen, 5 mos continuous</td>
<td>local resection, pneumonectomy, colostomy, chemotherapy</td>
<td>lumbar, 2 mg/8 hrs</td>
<td>fair, 4 mos</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>17, M</td>
<td>acute lymphocytic leukemia, bone infiltration</td>
<td>inferior limbs, pelvis, 24 mos intermittent</td>
<td>radiotherapy, chemotherapy</td>
<td>lumbar, 2 mg/12 hrs (tolerance 3 mg/6 hrs)</td>
<td>excellent, 5 mos</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>77, M</td>
<td>prostate, spine, pelvic, femur metastases</td>
<td>lower limbs, pelvis, 12 mos continuous</td>
<td>transurethral resection, orchidectomy</td>
<td>lumbar, 2 mg/24 hrs (tolerance 2 mg/8 hrs)</td>
<td>fair, 4 mos</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>67, M</td>
<td>prostate, bone &amp; lung metastases</td>
<td>generalized, 6 mos continuous</td>
<td>transurethral resection, orchidectomy</td>
<td>lumbar, 2 mg/24 hrs</td>
<td>good, 2 mos</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>73, M</td>
<td>prostate, local invasion</td>
<td>perineal, anal, lower limbs, 10 mos continuous</td>
<td>transurethral resection, colostomy</td>
<td>lumbar, 2 mg/24 hrs</td>
<td>good, 1/2 mos</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>62, M</td>
<td>pancreas, liver metastases</td>
<td>abdominal, bilateral, 1 mos continuous</td>
<td>biopsy, celiac block</td>
<td>lumbar, 2.5 mg/12 hrs</td>
<td>fair, 1 mo</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>47, F</td>
<td>breast, local relapse, bone metastases</td>
<td>It upper limb, neck, 8 mos continuous</td>
<td>mastectomy, radiotherapy</td>
<td>cervical, 2 mg/12 hrs (tolerance 2 mg/6 hrs)</td>
<td>good, 6 mos</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>71, M</td>
<td>rectum, local invasion</td>
<td>perineal, anal, midline, sciatic bilateral, 6 mos continuous</td>
<td>colostomy, bilateral cordotomy</td>
<td>lumbar, 2 mg/24 hrs (tolerance 2 mg/4 hrs)</td>
<td>excellent, 4 mos</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>62, M</td>
<td>chordoma in sacrum</td>
<td>pelvis, lower limbs, 48 mos continuous</td>
<td>laminectomy, dorsal column stimulation, bilateral cordotomy</td>
<td>lumbar, 1 mg/12 hrs</td>
<td>excellent, 2 1/2 mos</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>46, M</td>
<td>lung, chest wall invasion</td>
<td>chest wall, rt shoulder, midline, 6.5 mos continuous</td>
<td>transbronchial biopsy</td>
<td>cervical, 2 mg/12 hrs (tolerance 2 mg/8 hrs)</td>
<td>excellent, 6 mos</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>59, M</td>
<td>lung</td>
<td>It side of chest, midline, 4 mos continuous</td>
<td>thoracotomy</td>
<td>cervical, 2 mg/24 hrs (tolerance 3 mg/8 hrs)</td>
<td>excellent, 3 1/2 mos</td>
<td></td>
</tr>
</tbody>
</table>

(three cases: 0.5 to 1 mg total dose) to assess the analgesic effect and the possible risks of subarachnoid morphine (Table 2). Pain relief ranging from good to excellent and lasting for 6 to 48 hours was recorded in all cases without serious accompanying side effects (Table 2).

The reservoirs were inserted under local anesthesia, with the catheter tip in the frontal horn of the right lateral ventricle at the level of the foramen of Monro. On the day of surgery, and with the patient under intensive care, 0.2 to 1 mg of preservative-free sterile morphine chloride dissolved in saline solution (0.5 to 1 cc total volume) was given through the reservoir. The onset, quality, and duration of analgesia were noted, and vital signs, respiratory and cardiovascular parameters, and neurological function were evaluated repeatedly. The person responsible for home treatment was taught the technique of aseptic injection, which consists in Betadine skin preparation followed by reservoir tapping by means of a tuberculin syringe with a No. 25 needle. To prevent fibrosis of the skin over the reservoir, we recommended moving the site of injection from day to day. It has been our policy to reduce to a minimum the amount of oral and parenteral narcotics given prior to initiating intraventricular therapy, and then to discontinue these agents. Because of previous depression, insomnia, and anxiety, many patients were given amitryptiline and levomepromazine during the ventricular trial. Patients' relatives were given simple charts to record morphine doses delivered at home, and patients...
Pain relief with intraventricular morphine

### TABLE 2
Results of subarachnoid and intraventricular morphine in 17 patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Route &amp; Pain Relief</th>
<th>Dose (mg) &amp; Duration (hrs)</th>
<th>Initial Dose (mg/hrs)</th>
<th>Course (mos)</th>
<th>Final Dose (mg/hrs)</th>
<th>Onset (min)</th>
<th>Quality</th>
<th>Physical Changes</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>--</td>
<td>--</td>
<td>0.25/12</td>
<td>2.5</td>
<td>0.5/24</td>
<td>5–30</td>
<td>excellent</td>
<td>miosis</td>
<td>none</td>
</tr>
<tr>
<td>2</td>
<td>cisternal good</td>
<td>0.25/24</td>
<td>3.5</td>
<td>1/12</td>
<td>5–10</td>
<td>10–15</td>
<td>excellent</td>
<td>--</td>
<td>disorientation, visual hallucinations</td>
</tr>
<tr>
<td>3</td>
<td>cisternal excellent</td>
<td>0.25/12</td>
<td>1.2</td>
<td>0.25/12</td>
<td>5–10</td>
<td>2–10</td>
<td>good</td>
<td>--</td>
<td>none</td>
</tr>
<tr>
<td>4</td>
<td>cisternal good</td>
<td>0.25/12</td>
<td>1.2*</td>
<td>0.5/8</td>
<td>8–20</td>
<td>5–15</td>
<td>excellent</td>
<td>miosis</td>
<td>somnolence, dizziness</td>
</tr>
<tr>
<td>5</td>
<td>cisternal excellent</td>
<td>0.25/12</td>
<td>0.5*</td>
<td>0.5/24</td>
<td>8–20</td>
<td>5–15</td>
<td>good</td>
<td>--</td>
<td>somnolence, itching</td>
</tr>
<tr>
<td>6</td>
<td>cisternal excellent</td>
<td>1/12</td>
<td>1.5</td>
<td>2/3</td>
<td>5–15</td>
<td>10–15</td>
<td>excellent</td>
<td>--</td>
<td>disorientation, confusion</td>
</tr>
<tr>
<td>7</td>
<td>--</td>
<td>2/4</td>
<td>0.5/24</td>
<td>1.5</td>
<td>5–15</td>
<td>2–12</td>
<td>good</td>
<td>--</td>
<td>somnolence, nystagmic jerks</td>
</tr>
<tr>
<td>8</td>
<td>lumbar excellent</td>
<td>0.25/12</td>
<td>0.5/24</td>
<td>3.5*</td>
<td>5–10</td>
<td>10–20</td>
<td>excellent</td>
<td>miosis</td>
<td>none</td>
</tr>
<tr>
<td>9</td>
<td>lumbar excellent</td>
<td>0.25/12</td>
<td>0.5/24</td>
<td>5–15</td>
<td>12</td>
<td>5–15</td>
<td>excellent</td>
<td>--</td>
<td>delayed respiratory depression, itching</td>
</tr>
<tr>
<td>10</td>
<td>--</td>
<td>0.25/48</td>
<td>0.8</td>
<td>0.25/48</td>
<td>5–15</td>
<td>5–15</td>
<td>excellent</td>
<td>--</td>
<td>delayed disorientation</td>
</tr>
<tr>
<td>11</td>
<td>cisternal excellent</td>
<td>0.75/24</td>
<td>1.4*</td>
<td>2/6</td>
<td>10–20</td>
<td>5–10</td>
<td>good</td>
<td>miosis</td>
<td>none</td>
</tr>
<tr>
<td>12</td>
<td>cisternal excellent</td>
<td>0.75/24</td>
<td>1.4*</td>
<td>2/6</td>
<td>10–20</td>
<td>5–10</td>
<td>good</td>
<td>miosis</td>
<td>none</td>
</tr>
<tr>
<td>13</td>
<td>cisternal good</td>
<td>0.75/12</td>
<td>1.4*</td>
<td>2/6</td>
<td>10–20</td>
<td>5–10</td>
<td>good</td>
<td>miosis</td>
<td>none</td>
</tr>
<tr>
<td>14</td>
<td>cisternal good</td>
<td>0.75/24</td>
<td>1.4*</td>
<td>2/6</td>
<td>10–20</td>
<td>5–10</td>
<td>good</td>
<td>miosis</td>
<td>none</td>
</tr>
<tr>
<td>15</td>
<td>cisternal excellent</td>
<td>0.75/12</td>
<td>1.4*</td>
<td>2/6</td>
<td>10–20</td>
<td>5–10</td>
<td>good</td>
<td>miosis</td>
<td>none</td>
</tr>
<tr>
<td>16</td>
<td>cisternal excellent</td>
<td>0.75/12</td>
<td>1.4*</td>
<td>2/6</td>
<td>10–20</td>
<td>5–10</td>
<td>good</td>
<td>miosis</td>
<td>none</td>
</tr>
<tr>
<td>17</td>
<td>cisternal excellent</td>
<td>0.75/24</td>
<td>1.4*</td>
<td>2/6</td>
<td>10–20</td>
<td>5–10</td>
<td>good</td>
<td>miosis</td>
<td>none</td>
</tr>
</tbody>
</table>

* Still alive at the time of manuscript submission.
† Relief of pain evoked by movement of parts of the body invaded by tumor.

were reviewed periodically during the period of treatment.

Pain relief was conventionally graded as excellent (80% to 100% reduction), good (40% to 80%), fair (20% to 40%), and poor (less than 20%).

### Results

The initial and final morphine dose, the duration of treatment, the onset and quality of analgesia, the physical changes, and the side effects observed in this series are summarized in Table 2.

### Pain Relief and Development of Tolerance

Since most patients were elderly, we used low morphine doses initially. Good to excellent analgesia lasting for 12 to 52 hours was achieved with morphine doses ranging from 0.25 to 1 mg. The onset of analgesia occurred within 2 to 30 minutes of drug instillation. Apart from pain relief, most patients reported decreased anxiety and a feeling of overall well-being derived from the absence of chronic pain. Duration of treatment ranged from 2 weeks to 4 months at the time of manuscript submission, at which time seven patients were still alive.

Some degree of tolerance to morphine occurred in 11 patients with the passage of time. Tolerance was more marked and appeared more rapidly in the three patients who received large amounts of parenteral opiates before initiating intraventricular treatment (Cases 6, 7, and 15). During the last week of his life, one...
patient (Case 6) received 16 mg of morphine to maintain an adequate level of analgesia. Six patients did not develop tolerance after treatment periods ranging from 1 to $3\frac{1}{2}$ months.

**Physical Changes**

Seven patients were noted to present miosis soon after morphine administration, but obvious changes in temperature, blood pressure, and heart or respiratory rates were not recorded. Sensory performance and motor power were unaltered in all cases. One patient had spontaneous nystagmic jerks after receiving the first morphine dose.

**Side Effects**

Immediately after initiation of therapy, three patients complained of facial or generalized pruritus, and another developed urinary retention lasting for 2 to 3 days. Three patients were disoriented as to space and time during the first 2 days of treatment, and two of them also exhibited confusion and complex visual hallucinations during this period. These changes, like transient somnolence which occurred in four more patients, subsided spontaneously without discontinuation of therapy.

After receiving morphine for 1 month (1 mg daily dose) without presenting noticeable side effects, one patient with breast cancer (Case 13) developed temporal and spatial disorientation. Computerized tomography scan excluded intracranial pathology that would account for the neurological change. It is interesting that discontinuation of morphine did not result in recurrence of pain, nor in mental improvement. A similar intriguing "permanent" analgesia occurred in Case 11. This man enjoyed complete pain relief until therapy had to be discontinued because he developed an aseptic CSF reaction that could be controlled without removing the reservoir. Surprisingly, pain relief persisted and the patient remains free of pain 2 months after cessation of therapy.

One patient (Case 10) developed respiratory depression 4 hours after the first ventricular injection (1 mg); he had not been exposed to subarachnoid morphine prior to implantation of the reservoir. Naloxone (0.4 mg in an intravenous bolus, followed by continuous infusion of 2 mg during 19 hours) restored respiratory function without reversing analgesia. Subsequent very low doses of morphine (0.25 to 0.5 mg/24 hours) achieved excellent analgesia without causing respiratory depression.

One patient (Case 16) developed infection of the implanted reservoir with headache, fever, and meningeal signs; CSF culture was negative, and the symptoms disappeared 5 days after the reservoir was removed. The patient refused a second implantation and we performed stereotaxic mesencephalotomy. Two lesions, 4 and 8 mm from the midline and 5 mm posterior and inferior to the posterior commissure, were made with a Radionics electrode. Unequivocal analgesia involving the right side was accompanied by complete pain relief. Despite definite pinprick analgesia, pain recurred 6 weeks after the operation, together with a local burning sensation. A second trial of ventricular morphine resulted in almost complete control of pain (Table 2).

**Discussion**

We have shown that intractable pain in terminal cancer patients is relieved by injecting small doses of morphine into the lateral cerebral ventricle. Analgesia, which appears within a few minutes of injection irrespective of the anatomical location of pain, together with a favorable behavioral response, can be maintained for several months without resorting to additional medical or surgical therapies. The side effects of treatment are short-lasting, and the most dreaded sequela (respiratory depression) occurred in only one instance and was easily reversed by naloxone therapy. The fact that this agent did not reverse analgesia in our patient supports the suggestion that opiate analgesia is mediated by a subpopulation of receptors that are probably located on neurons different from those regulating respiratory depression.

It has been found that opiate iontophoresis excites some central gray matter neurons and inhibits others, but only inhibition is reversible by naloxone. Naloxone has also failed in reversing intraventricular morphine-induced analgesia in the laboratory, and stimulation-induced analgesia in man, and it should be borne in mind that opiates may achieve pain relief by activating non-opiate analgesic systems.

It is doubtful that persistent disorientation occurring in our patient (Case 13), who also developed "permanent" analgesia, can be attributed to morphine therapy. Disorientation as an isolated symptom does not occur with chronic morphine administered by other routes, and the lack of improvement after cessation of treatment argues against a pharmacological origin. However, much caution is necessary because the possibility that ventricular morphine may result in lasting neurological changes does exist. Temporal and spatial disorientation linked to complete pain relief lasting for a month has also been observed after short-term intraventricular morphine in a woman with breast cancer (F San Emeterio, et al., personal communication, 1982). The fact that analgesia outlasted morphine administration is difficult to explain but, taking into account the complex and widespread influence of opiates upon hypothalamic function and pituitary hormones, an unclear mechanism akin to that following hypophysectomy might have been involved in the above-mentioned cases and in another patient (our Case 11) who also had a hormone-dependent cancer and developed "permanent" analgesia without accompanying neurological changes. Development of tolerance was not a serious problem in the present series, presumably because of
the small doses of morphine employed. A low-level receptor
activation may explain why repeated morphine
microdoses did not result in the rapid and marked
tolerance seen with high-dose oral or parenteral opi-
ates. Since cross-tolerance seems to occur between
systemic and intraventricular morphine, it is advisable
to reduce or discontinue parenteral administration prior
to initiating ventricular therapy.

The interaction of exogenously given opiates and the
endogenous transmitter modulator system is poorly
understood at the present time. Extensive laboratory
work suggests that opiates may directly inactivate some
neural components throughout the ascending pain
transmission pathways, or may result in activation of
the endogenous centrifugal inhibitory system, or
both. Most probably, intraventricularly administered morphine acts at a supraspinal
level, and the short latency of the analgesia observed
in our patients, irrespective of the cranial or distal location
of pain, is consistent with this hypothesis. It seems
logical that for intraventricular morphine to elicit
the complex anti-nociceptive behavioral response observed
in our patients in such a short time, rapid diffusion of
the drug from the ventricular lumen to the neurons
must be acted upon is required, and the location of the central
gray matter along the ventricular lumen favors this
possibility.

We did not measure cisternal or lumbar morphine
levels but, taking into account the low biotransforma-
tion rate into the CSF circulation, it is possible that
diffusion of the drug to more caudal levels in a concen-
tration high enough to result in a direct spinal action
could occur in such a manner that the analgesia elicited
at the brain level is continued or reinforced by spinal
analgesia. The fact that the rapid-onset analgesia we
observed is exerted supraspinally is also supported by
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Pain relief with intraventricular morphine

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could occur in such a manner that the analgesia elicited
at the brain level is continued or reinforced by spinal
analgesia. The fact that the rapid-onset analgesia we
observed is exerted supraspinally is also supported by
the fact that pain relief achieved in patients with pelvic
malignancies occurred more rapidly following intraven-
tricular injection than when morphine had been given
into the lumbar theca. Furthermore, the mental changes
produced by ventricular morphine were never seen after
analgesic-effective cisternal injections, suggesting that
they result from opiate interaction at supramedullary
level. Provided this is true, it does not mean that
intraventricular-elicited analgesia is necessarily operat-
ing at the same sites. A recent study suggests that
intraventricularly injected morphine achieves analgesia
at a spinal level, and we observed that morphine
injected into the cisterna magna failed to alleviate pain
in one of our patients with a cervical spine sarcoma
causing complete subarachnoid block. Thus, it may be
necessary for the drug to gain the dorsal horn of the
medullary segment involved in pain processing for an-
algesia to result. Experimental studies using radiola-
beled opiates are necessary to determine the diffusion
patterns of these agents into the CSF circulation.

According to the present results and those obtained
by Leavens, et al. Roquefeuil, et al. and San Emene-
teno, et al. (personal communication, 1982), chronic
intraventricular morphine is a feasible and effective
method of pain therapy. Like stimulation-induced an-
algesia, intraventricular morphine achieves pain
relief without interfering with other sensory modalities,
and in our hands it has been more effective than the
former technique for the management of diffuse and
bilateral pain caused by orofacial, neck, and disseminated
cancer which so frequently evades neurosurgical ablative procedures. The surgical risk of reservoir im-
plantation is low and the hazard of infection and the
short-lasting pharmacological side effects occasionally
seen at initiation of therapy are counterweighed by the
potential dangers and the neurological deficits linked to
major ablative procedures.

Our experience with ventricular morphine is prelim-
nary, and subsequent controlled trials are needed to
evaluate this form of therapy and determine its place
in the management of chronic pain. The occurrence of
unpredictable mental changes, even in a small propor-
tion of patients, would entail a serious limitation. By
contrast, development of tolerance is not an obstacle,
and the availability of new drugs liable to retain the
analgesic effects while eliminating the unwanted ones
by activating specific receptor populations administered in continuous or alternating regimes by
means of implantable devices will probably cir-
cumvent tolerance and decrease the risk of infection
linked to multiple injections.

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Manuscript received December 30, 1982.  
Accepted in final form May 4, 1983.

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