NALOXONE REVERSAL OF ISCHAEMIC NEUROLOGICAL DEFICITS IN MAN

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Summary Two patients with cerebral ischaemia and one patient with cerebral infarction received intravenous infusions of the opiate antagonist naloxone or saline in double-blind manner. Naloxone completely reversed neurological deficits in both patients with cerebral ischaemia, but did not in the patient with cerebral infarction. Naloxone administration produced no changes in blood pressure, pulse rate, respiratory rate, temperature, or arterial blood gases. Intravenous administration of morphine sulphate profoundly exacerbated hemiparesis in one patient without alteration of vital signs; hemiparesis was completely reversed by naloxone.

Introduction

SINCE the discovery of opiate receptors within the central nervous system (CNS)[1-3] it has become apparent that endogenous opiate ligands are concerned with CNS function in both health and disease. While the most accepted role for these substances is the modulation of the perception of painful stimuli, they have been implicated in pituitary function,[4] CNS heat adaptation,[5] seizure disorders,[6] and mental illness.[7,8] Endogenous opiate ligands have partially defined roles in endotoxic,[9-11] hypovolaemic,[12,13] and spinal shock.[14-16] In one report, hypotension and neurological recovery from induced spinal cord injury was improved in cats by administration of the opiate antagonist naloxone.[16] Brandt et al.[17] reported raised concentrations of endorphins in the cerebrospinal fluid (CSF) of a comatose patient with acute necrotising encephalomyelopathy; coma in this patient was at times reversed by naloxone administration. We report here the previously undescribed reversal, by intravenous administration of the opiate antagonist naloxone, of ischaemic deficits in man.

Case-reports

Patient 1

In March, 1980, a 72-year-old woman became suddenly unconscious and awoke after 5 min with a moderate left hemiparesis that resolved completely within a few hours. Vision in her right eye had been deteriorating progressively for 10 years, and when examined on July 2, 1980, she was blind in that eye; in the left eye, visual acuity and fields were normal. Computerised tomographic (CT) scans and cerebral angiograms showed a giant right internal carotid aneurysm and a second smaller aneurysm in the supraclinoid portion of the left internal carotid artery. On July 9, 1980, the right internal carotid artery was ligated at the level of the carotid bifurcation. The patient did well postoperatively, and a CT scan was consistent with postoperative thrombosis of the giant aneurysm on the right side.

In December, 1980, the patient complained of decreased vision in her left eye. This became worse over the next two months, and she was referred to our department on Feb. 6, 1981, for further evaluation. The blind right eye had a Marcus Gunn pupil (diminished reaction to light, normal consensual reaction). The left eye showed a temporal hemianopic scotoma with sharp margins, and there was a narrow band of optic nerve fibre atrophy corresponding to the field defect. Otherwise the neurological findings were normal.

A CT scan taken on Feb. 7 showed a large mass extending from the tuberculum sellae into the right side of the suprasellar cistern; the mass had a low-density centre and a contrast-enhancing rim (fig. 1a). Cerebral angiograms obtained on the same day showed an aneurysm of the supraclinoid portion of the left carotid artery and a large avascular mass in the right suprasellar region that elevated both proximal segments of the anterior cerebral arteries. There was rapid cross-filling of the right cerebral hemisphere from the left internal carotid circulation (fig. 1b). On Feb. 9, a right fronto-temporal craniotomy was performed. The wall of the aneurysm displaced the internal carotid bifurcation posteriorly and the right optic nerve superiorly. The aneurysm was trapped, the wall was incised, and intramural thrombi were removed.

The patient was awake and alert without focal weakness on the first postoperative day, with a Glasgow coma score (GCS) of 15. However, on the eighth postoperative day she became drowsy and disoriented and a severe monoparesis developed in the left arm (GCS of 11). The weakness was in a pyramidal distribution, with moderate proximal arm weakness and complete paralysis of the left hand.

She was mildly hyponatraemic. A CT scan showed only a small extra-axial collection of air and fluid (fig. 1c). After informed consent was obtained from the next-of-kin, a CSF sample was obtained by lateral cervical puncture, and 0·4 mg of naloxone HCl (Endo Laboratories) was administered intravenously. Within 4 min the patient was awake, alert, and oriented (GCS of 15), and her left-sided weakness had completely resolved. This effect lasted for 20 min and then quickly disappeared. A repeat naloxone infusion produced identical results. Over the next 24 h, six additional

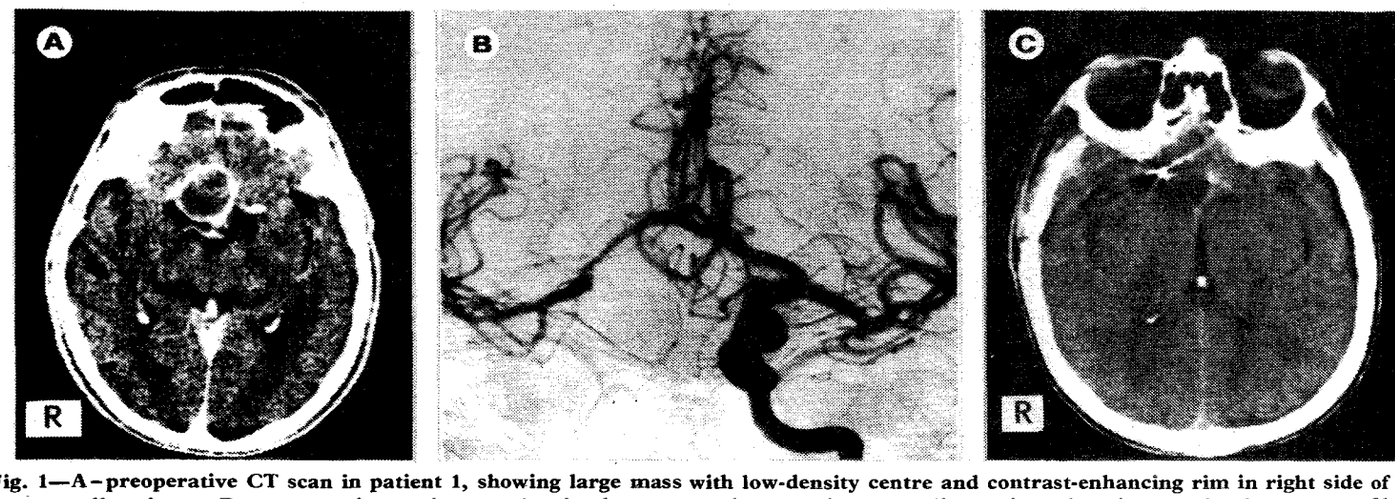

Fig. 1—A—preoperative CT scan in patient 1, showing large mass with low-density centre and contrast-enhancing rim in right side of the suprasellar cistern; B—preoperative angiogram showing large avascular mass in suprasellar region, elevating proximal segments of both anterior cerebral arteries; C—postoperative CT scan showing a small extra-axial collection of fluid and air and a low-density area at the site of the obliterated giant aneurysm.

infusions of either 0·4 mg of naloxone or 1 ml of saline were administered intravenously in a double-blind manner. Naloxone produced identical results on every occasion whereas saline had no effect. Blood pressure, pulse rate, repiratory rate, temperature, and arterial blood gases were measured continually before, during, and after the administration of naloxone; none changed. Cervical CSF was analysed for an immunoreactive β-endorphin-like substance (IrBE) and for leucine enkephalin by a technique previously described;[18] the IrBE level was 440 pg/ml (normal less than 200 pg/ml), and the leucine enkephalin level was 22 pg/ml (normal less than 25 pg/ml).

Fluids were restricted and the hyponatraemia resolved; mental status became normal, but the left-sided weakness improved only slightly. A lateral cervical puncture was done on the 12th postoperative day; the IrBE level was 300 pg/ml and the leucine enkephalin level was 52 pg/ml. A left cerebral arteriogram taken on the same day indicated slow cross-filling of the right middle cerebral artery territory. There was a single focal area of narrowing in a vessel at the region of the right middle cerebral artery take-off from the previously ligated and thrombosed right internal carotid artery.

After the angiographic procedure, the patient had severe pain at the left femoral puncture site. No haematoma was present and the groin and leg were normal on neurovascular examination. 5 mg of morphine sulphate was administered intravenously, and the pain abated within 5 min. During and after morphine administration there were no changes in blood pressure, pulse rate, respiratory rate, temperature, arterial blood gases, or mental status, but the patient's left hemiparesis became dramatically worse. 0·4 mg naloxone was administered intravenously and the hemiparesis completely resolved, again without any change in vital signs. Over the next week, the patient required intramuscular injections of morphine sulphate for pain control. After each injection the left hemiparesis was profoundly exacerbated without any accompanying changes in vital signs. Invariably hemiparesis could be reversed by intravenous infusion of 0·4 mg naloxone. Cervical CSF obtained on the fifteenth postoperative day had an IrBE level of 410 pg/ml and a leucine enkephalin level of 48 pg/ml.

The hemiparesis slowly improved, and the patient was discharged on the twenty-fourth postoperative day. 8 weeks later she was readmitted for further study. She still had a moderate hemiparesis of the distal musculature of the left hand that could be completely reversed by intravenous administration of 0·4 mg of naloxone without changes in vital signs. Cervical CSF IrBE and leucine enkephalin levels were 250 pg/ml and 34 pg/ml, respectively. As shown by a radionuclide technique,[19] cerebral blood flow was decreased in the right parietal area; naloxone infusion did not alter flow despite complete reversal of hemiparesis. A repeat cerebral angiogram showed no changes from the previous postoperative study (fig. 2). Angiograms made before and after naloxone administration showed no change in the appearance of cerebral vessels. While still in the angiography suite, with the Seldinger catheter in place, the patient again had severe left groin pain. 5 mg morphine sulphate was given intravenously and her left hemiparesis worsened considerably within 5 min without a change in vital signs or mental status. Because of this sudden neurological change, arteriography was repeated, but there was no change in the appearance of the cerebral vessels. For the next 3 days the patient needed intramuscular injections of morphine for pain in the left groin puncture site. After each injection her hemiparesis became worse, but this effect could be reversed by 0·4 mg intravenous naloxone (fig. 3).

The femoral pain resolved, and the patient was discharged to have intensive physiotherapy as an outpatient. During follow-up, intravenous naloxone continued to reverse her residual hemiparesis. Her hemiparesis has now resolved except for mild incoordination in the fingers of the left hand.

Patient 2

A woman of 28, who had a 14-year history of seizure disorders, was admitted on Jan. 5, 1981, with a story of episodes of nausea, vomiting, and vertigo that had begun 1 year before and had been getting more frequent and severe. An arteriogram taken in July, 1980, had revealed a large, low left parietal arteriovenous malformation with the primary arterial supply from branches of the middle cerebral artery.

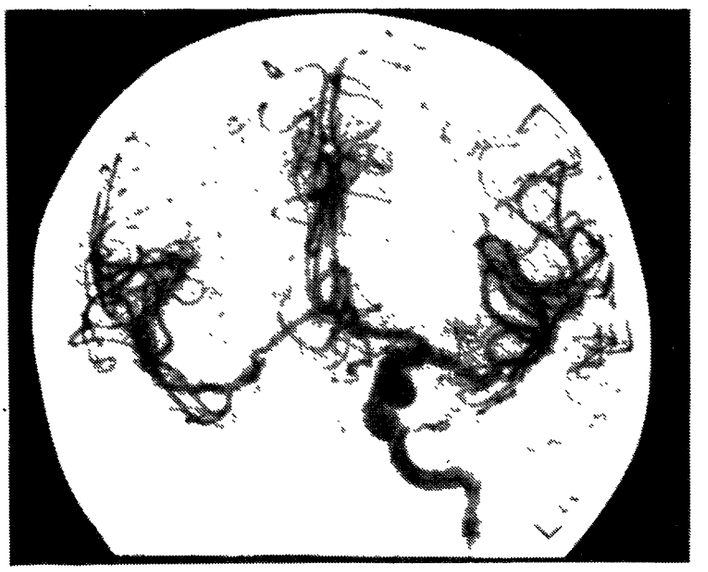

Fig. 2—Patient 1: postoperative cerebral angiogram showing focal narrowing of the vessel at the region of the right middle cerebral artery take-off from the previously ligated and thrombosed right internal carotid artery.

On admission she was neurologically normal. Angiographic embolisation reduced the size of the malformation by one-third and surgical excision was attempted the next day. Because of excessive intraoperative bleeding and severe cerebral oedema, excision was subtotal. On the first postoperative day, the patient showed signs of transtentorial herniation and an intracerebral haematoma was evacuated. Because of massive cerebral oedema, the bone flap was not replaced.

Barbiturate coma was induced for 72 h[20] and the patient awoke with a dense right hemiplegia, a partial left third nerve palsy, and a right homonymous hemianopia; she was aphasic, confused, and disoriented (GCS of 9). During a long and complex postoperative course her mental status improved, the left third nerve palsy resolved, but the right hemiplegia was unchanged (GCS of 13).

On Feb. 15, 1981, the patient had an operation for replacement of the bone flap. On awakening she had a new partial left third nerve palsy and her level of consciousness deteriorated rapidly (GCS 5). 0·4 mg of naloxone was given intravenously after informed consent had been obtained from the next-of-kin. Within 5 min the patient was awake, alert and responding to commands (GCS 12), and could move her previously plegic right arm and leg to order. The third nerve palsy was unchanged. The effect lasted 20 min, at which time the right hemiplegia returned and somnolence ensued (GCS 5). A repeat intravenous infusion of 0·4 mg naloxone produced identical results. Four additional infusions of either saline or 0·4 mg of naloxone were administered in a double-blind manner over the next 2 h; only naloxone reversed her hemiparesis. Blood pressure, pulse rate, respiratory rate, temperature, and arterial blood gases were monitored before, during, and after naloxone infusions, and no changes were noted.

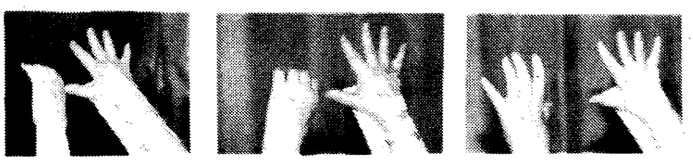

Fig. 3—Patient 1: effects of morphine and naloxone.

The photographs show a moderate hemiparesis of the extensors of the left hand (left) that is exacerbated by administration of 5 mg intravenous morphine sulphate (centre), and reversed by the 0·4 mg intravenous naloxone (right). There were no changes in vital signs after administration of morphine or naloxone.

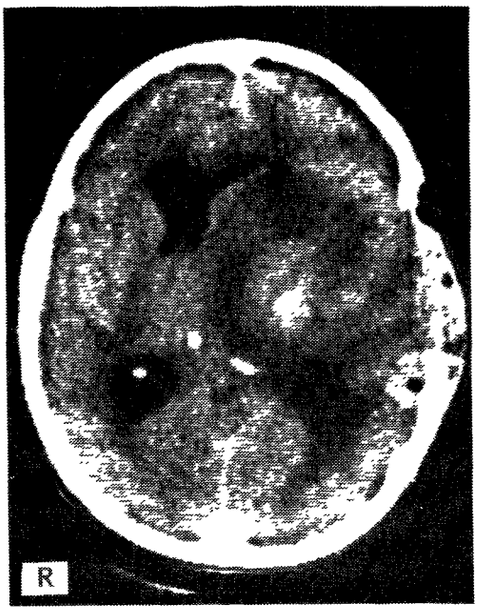

Fig. 4—Patient 2: CT scan at level of the temporal craniectomy after replacement of bone flap.

Massive cerebral oedema is present with a large shift of midline structures.

A CT scan showed cerebral oedema with a shift of midline structures (fig. 4). After operation for removal of the bone flap, she awoke from anaesthesia with a GCS of 13, although the right hemiplegia persisted. Two additional infusions of 0·4 mg of naloxone were given on the first and second postoperative days; each reversed the right hemiplegia for 20 min without changing vital signs. After a protracted hospital course, the patient has regained some use of the right arm and leg.

Patient 3

A 66-year-old woman was admitted to another hospital after the sudden onset of severe headache, nuchal rigidity, and lethargy. On lumbar puncture she had grossly bloody CSF and a CT scan showed evidence of subarachnoid haemorrhage with blood in the left Sylvian fissure. Cerebral angiography revealed a left middle cerebral trifurcation aneurysm, with spasm in the surrounding proximal segments of the anterior and middle cerebral arteries. Hydrocephalus developed one month later, and a ventriculoperitoneal shunt was inserted. Despite evidence that the shunt was properly placed and functioning normally, she became progressively less responsive and the hemiparesis worsened. On examination at our centre she was drowsy and able to follow only simple, one-step commands. She had a right central weakness of the face and a right hemiparesis, the face and arm being weaker than the leg. There was mild hypaesthesia (all sensory modalities) on the entire right side of the body. The deep tendon reflexes were hyperactive on the right, and the right plantar response was extensor. The GCS was 7. Blood count and serum biochemistry were normal. A CT scan showed low-density areas bilaterally in the regions of the internal capsules, the left being more affected than the right (fig. 5).

After informed consent was obtained from the next-of-kin, 0·4 mg of naloxone was administered intravenously; within 3 min, there was a striking increase in the tone in the entire right side of her body without an increase in strength. This lasted for 20 min and then rapidly disappeared. There were no changes in blood pressure, pulse rate, respiratory rate, temperature, or arterial blood gases before, during, or after the infusion. The infusion was repeated four times double-blind with either saline or 0·4 mg of naloxone; only naloxone had an effect.

The patient gradually improved over the next few weeks and then had an operation for her cerebral aneurysm. She did well postoperatively, and was discharged with only a mild right-sided weakness.

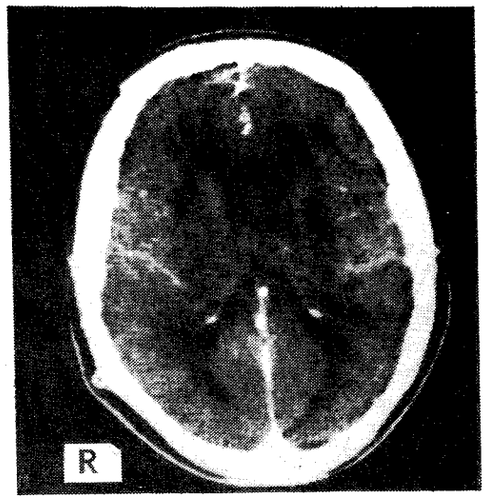

Fig. 5—Patient 3: CT scan showing bilateral internal-capsule low densities, with the left more affected than the right.

Discussion

Responses to naloxone implicate the endogenous opiate ligands in several disease states. Experimentally naloxone can prolong survival in rats,[10,12,14] cats,[14] and dogs[11,13] with hypovolaemic and endotoxic shock; it modifies the effects of electroconvulsive shock on blood pressure, heart rate, and respiratory rate in rats;[6] and it reverses the hypotension that accompanies partial spinal transection in rats and cats.[14-16] In man,[17] naloxone has reversed prolonged apnoea and unconsciousness in a patient with subacute necrotising encephalomyelopathy; the CSF and postmortem brain of the patient had raised concentrations of endorphins. Dunger[21] gave naloxone to a patient with a disorder of hypothalamic function including abnormal regulation of temperature, appetite, and thirst, hyperprolactinaemia, and inappropriate secretion of antidiuretic hormone. The patient was also insensitive to pain and had disturbances of sleep, respiration, and mentation. Naloxone reversed central analgesia, altered urine output and electrolyte excretion, modified the response to gonadotropin and thyroid releasing hormones, and improved auditory and visual reaction times.

The complete reversal of hemiparesis that we saw in the two patients with focal cerebral ischaemia is a novel observation. In contrast to the results of Faden et al.[16] in spinal injured cats, improvement in neurological function was not associated with a change in blood pressure or other vital signs. The ability of naloxone to reverse and morphine to induce hemiparesis in patient 1 persisted for several months after the original ischaemic event. The twofold increase in IrBE and leucine enkephalin levels found in the cervical CSF of patient 1 provides additional evidence for the role of endogenous opiate ligands in this effect.

Volavka et al.[22] gave 20 mg naloxone to normal volunteers and observed significant increases in peripheral blood concentrations of corticotropin, cortisol, and luteinising hormone. However, these effects began 25 min after injection of naloxone, whereas in our patients the response (to a dose 50 times lower) began within 3 to 5 min and disappeared within 20–25 min.

The observations in these 3 patients suggest that neurological deficits secondary to cerebral ischaemia can be reversed by a small dose of naloxone, though an area of brain with cell death and tissue loss cannot be expected to recover function. In patient 1, cerebral ischaemia was confirmed by radionuclide blood flow studies, and delayed flow was noted

during carotid angiography. In patient 2, cerebral oedema was seen on the CT scan, and the rapid improvement in neurological function after removal of the replaced bone flap supports the notion of an ischaemic aetiology related to cerebral oedema. In patient 3, naloxone did not restore voluntary control of the hemiparetic limb, although the tone increased. Cell death and tissue necrosis are undoubtedly present in some of the severely infarcted areas seen on the CT scan of this patient. The increase in tone in the hemiparetic limb in patient 3 is intriguing, and may represent modification of the influence of cerebral tissue adjacent to the area of cell death.

Lately in our laboratory we have demonstrated naloxone reversal of ischaemic neurological deficits produced in gerbils under controlled conditions (Hosobuchi Y, Baskin DS, Woo S, Loh HH, unpublished). Because of anomalies in the circle of Willis, homolateral ischaemic brain damage can be produced in 30–50% of Mongolian gerbils by unilateral common carotid artery ligation. The usual manifestation is contralateral hemiplegia, and 1 mg/kg naloxone administered intraperitoneally completely reversed hemiplegia in all gerbils tested. Furthermore, in gerbils that did not have a neurological deficit after unilateral carotid ligation, intraperitoneal injections of morphine produced hemiparesis contralateral to the side of carotid ligation; morphine-induced hemiparesis was reversed by naloxone. This effect is stereospecific; it can be produced by the stereoisomeric opiate agonist levorphanol but not by its inactive enantiomer dextrorphan. Subcutaneous implantation of a 10 mg pellet of naloxone into hemiparetic gerbils significantly extended survival (deficit-free for up to two weeks after ligation). Opiate receptor characteristics in the ischaemic and non-ischaemic hemispheres of 20 gerbils were compared in vitro by means of ^{3}H-naloxone and ^{3}H-dihydromorphine.[1] The animals were killed and hemispheres were dissected free of cerebellum and brain stem and separated. Crude synaptosomal fractions were isolated from each hemisphere, and a standard binding assay was performed. Scatchard analysis of the data indicated no significant differences between the ischaemic and the non-ischaemic hemispheres either in the kinetics of the individual binding sites or in the number of high and low affinity sites. On preliminary analysis in several gerbils with induced neurological deficits, the level of IrBE has been 40–80% higher on the stroke side than on the control side.

Naloxone reversal of ischaemic neurological deficits in human beings and gerbils is a novel observation with important therapeutic implications for patients with cerebrovascular disease.

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Requests for reprints should be addressed to D. S. B., c/o Editorial Office, Department of Neurological Surgery, 350 Parnassus Ave., Suite 807, San Francisco, California 94117, U.S.A.

REFERENCES

1 Pert CB, Snyder SH Opiate receptor: Demonstration in nervous tissue. *Science* 1973; **179:** 1011–14

2 Terenius L Characteristics of the "receptor" for narcotic analgesics in synaptic plasma membrane fraction from rat brain. *Acta Pharmacol Toxicol* 1973; **33:** 377–84.

3 Simon EJ, Hiller JM, Edelman I. Stereospecific binding of the potent narcotic analgesic (³H)etorphine to rat-brain homogenate. *Proc Natl Acad Sci USA* 1973; **70:** 1947–49

4 Van Vugt DA, Meites J Influence of endogenous opiates on anterior pituitary function. *Fed Proc* 1980; **39:** 2533–38.

5 Cowan A, Dettmar PW, Metcalf G. The effect of prototype opiate receptor agonists and opioid peptides on body temperature and behaviour after central administration to cats In: Way EL, ed Endogenous and exogenous opiate agonists and antagonists New York Pergamon Press, 1979: 475–78

References continued at foot of next column

FERTILITY IN MALES WITH SICKLE CELL DISEASE

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Summary Seminal fluid examination of 23 Nigerian men with sickle cell anaemia showed that their sperm density, motility, and morphology fell into the subfertile/infertile range. Moreover, many of them had sexual problems such as impotence, frequent priapism, and premature ejaculation, which would further reduce their fertility.

Introduction

UNTIL three decades ago, it was unusual for patients with sickle cell anaemia to survive until adulthood in Africa. Most patients died before the age of 5 years, from anaemia, infection, or heart-failure.[1] Today 10% of the sickle cell population attending our special clinic are adults. Children with homozygous sickle cell disease tend to be physically under-developed and may have delayed sexual and skeletal development.[2,3] Of serious importance is the reported tendency to lowered fertility in these patients. So far these reports have emanated from studies in females.[3,4] We have evaluated the fertility potential of men with sickle cell disease.

Patients and Methods

40 male patients aged 17 years and above and attending the routine sickle cell outpatient clinic at Lagos University Teaching

DR BASKIN AND DR HOSOBUCHI: REFERENCES—*continued*

6. Belenky GL, Holaday JW The opiate antagonist naloxone modifies the effect of electroconvulsive shock (ECS) on respiration, blood pressure and heart rate. *Brain Res* 1979; **177:** 414–17.
7. Lindström LH, Widerlöv E, Gunne L-M, Wahlström A, Terenius L. Endorphins in human cerebrospinal fluid: Clinical correlations to some psychotic states. *Acta Psychiat Scand* 1978; **57:** 153–64.
8. Lehmann HE, Cooper TH, Nair NPV, Kline NS Beta-endorphins and naloxone in psychiatric patients: Clinical and biological effects. In: Saletu B, Berner P, Hollister L, eds. Neuro-psychopharmacology (Proceedings of 11th congress of the Collegium Internationale Neuro-Psychopharmocologicum, Vienna, July 9–14, 1978). Oxford: Pergamon Press, 1979: 535–39.
9. Holaday JW, Belenky GL, Faden AI, Loh HH. Possible function of β-endorphin In: Saletu B, Bermer P, Hollister L, eds. Neuro-psychopharmacology (Proceedings of 11th congress of the Collegium Internationale Neuro-Psychopharmocologicum, Vienna, July 9–14, 1978). Oxford: Pergamon Press, 1979: 503–14.
10. Holaday JW, Faden AI. Naloxone improvement of shock pathophysiology: Evidence for opiate receptor involvement. In: Way EL, ed. Endogenous and exogenous opiate agonists and antagonists. New York: Pergamon Press, 1979· 479–86.
11. Reynolds DG, Gurll NJ, Vargish T, Lechner RB, Faden AI, Holaday JW. Blockage of opiate receptors with naloxone improves survival and cardiac performance in canine endotoxic shock *Circulatory Shock* 1980; **7:** 39–48.
12. Faden AI, Holaday JW. Opiate antagonists: A role in the treatment of hypovolemic shock. *Science* 1979; **205:** 317–18.
13. Vargish T, Reynolds DG, Gurll NJ, Lechner RB, Holaday JW, Faden AI. Naloxone reversal of hypovolemic shock in dogs. *Circulatory Shock* 1980; **7:** 31–38.
14. Faden AI, Jacobs TP, Holaday JW. Endorphin-parasympathetic interaction in spinal shock. *J Autonom Nerv Syst* 1980; **2:** 295–304.
15. Holaday JW, Faden AI. Naloxone acts at central opiate receptors to reverse hypotension, hypothermia and hypoventilation in spinal shock *Brain Res* 1980; **189:** 295–99.
16. Faden AI, Jacobs TP, Holaday JW. Opiate antagonists improves neurologic recovery after spinal injury. *Science* 1981; **211:** 493–94
17. Brandt NJ, Terenius L, Jacobsen BB, Klinken L, Nordius A, Brandt S, Blegvad K, Yssing M. Hyper-endorphin syndrome in a child with necrotizing encephalomyelopathy. *N Engl J Med* 1980; **303:** 914–16.
18. Guillemin R, Ling N, Vargo T. Radioimmunoassays for α-endorphin and β-endorphin. *Biochem Biophys Res Commun* 1977; **77:** 361–66.
19. Barnes BD, Rosenblum ML, Pitts LH, Winestock DP, Parker H, Nohr ML. Carotid-cavernous fistula. Demonstration of asymptomatic vascular "steal." *J Neurosurg* 1978; **49:** 49–55.
20. Hoff JT, Marshall L. Barbiturates in neurosurgery. *Clin Neurosurg* 1979; **29:** 637–42.
21. Dunger DB, Wolff OH, Leonard JV, Preece MA. Effect of naloxone in a previously undescribed hypothalamic syndrome. A disorder of the endogenous opioid peptide system? *Lancet* 1980; i: 1277–81.
22. Volavka J, Bauman J, Pevnick J, Reker D, James B, Cho D. Short-term hormonal effects of naloxone in man. *Psychoneuroendocrinology* 1980; **5:** 225–34.