

Comparison of the clinical pharmacology of (-)-NPA and levodopa in Parkinson's disease

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Abstract

Direct acting dopamine agonists are generally less effective than levodopa in relieving symptoms of Parkinson's disease. In an attempt to quantitate and explain this situation, the acute motor responses to intravenous injections of the dopamine agonist, (-)-N-n-propyl-norapomorphine hydrochloride (NPA), were compared with those of the dopamine precursor, levodopa. At optimum dose levels, the acute anti-Parkinsonian efficacy of NPA averaged only about 50% of maximum, while essentially total symptom suppression was obtained with levodopa in patients previously treated with the amine precursor. Dyskinesia severity, however, was similar with the two drugs. These differences in anti-Parkinsonian efficacy may reflect the fact that while NPA acts mainly on D-2 dopamine receptors, levodopa results in stimulation of both the D-1 and D-2 subsets of receptors at a more physiological ratio. Future efforts to develop dopamine agonists for the treatment of Parkinsonian symptoms may thus have to consider focusing on drugs having pharmacological profile more similar to that of dopamine.

Motor fluctuations and dyskinesias eventually complicate the management of most levodopa treated patients with Parkinson's disease.^{1,2} These adverse effects have prompted the search for effective anti-Parkinsonian agents with little or no potential for producing motor response complications. Over the years, many direct acting dopamine agonists have been tested clinically and several are now in general use.³⁻¹⁰ All, however, appear to possess less anti-Parkinsonian efficacy than the dopamine precursor, levodopa.^{3,6-8,10} The basis for this

relative lack of efficacy remains essentially speculative. To address this question and to quantitate these differences, the acute motor responses to a dopamine agonist, (-)-N-n-propyl-norapomorphine hydrochloride (NPA),¹¹⁻¹³ were compared with levodopa in patients at various stages of Parkinson's disease.

Methods

Fifty one patients with idiopathic Parkinson's disease participated in the study after full disclosure of its purposes, risks and potential benefits. Of these, 24 were studied with intravenous NPA, and 36 with intravenous levodopa; nine patients were studied twice, once with NPA and again with levodopa (table 1). Subjects were grouped according to their clinical response to optimally administered oral levodopa/carbidopa as determined by physicians' evaluations every 30 minutes for at least nine hours:¹⁴ 1) patients not previously treated with levodopa or other dopaminomimetics; 2) those having a stable motor response while receiving levodopa every four to six hours; 3) those who had only wearing-off phenomenon with motor fluctuations related to the timing of levodopa given every two to three hours; and 4) those with on-off phenomenon manifested as abrupt, unpredictable shifts between on and off states in no apparent relation to levodopa dosage or other identifiable exogenous factors. Other anti-Parkinsonian medications were maintained at stable dose levels throughout both parts of the study.

Levodopa dose-response studies were conducted as previously described.¹⁴ Intravenous NPA studies were carried out under double-blind, placebo-controlled conditions by injecting various drug doses or saline as isovolumic boluses (100 ml) over a period of 10 minutes. Each patient received a single daily injection

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Received 7 August 1990.
Accepted 24 September 1990

Table 1 Patient characteristics by levodopa response group*

	Never treated	Stable responders	Wearing-off	On-off
Number	11	9	17	14
Age	57 (3)	58 (4)	58 (3)	59 (2)
Symptom onset age	54 (3)	51 (4)	49 (2)	45 (3)
Symptom duration†	3.5 (0.61)	6.9 (0.70)	9.2 (0.90)	14 (1.1)
H and Y stage‡	1.7 (0.20)	2.7 (0.24)	2.9 (0.16)	4.4 (0.17)
Levodopa treatment duration§	0	4.0 (1.1)	7.1 (0.90)	12 (0.87)
Oral levodopa dose (mg/kg/hr)§	0	0.46 (0.08)	0.68 (0.05)	1.0 (0.08)

*Data are means (SEM).

†ANOVA $p < 0.0001$ for difference among all groups except between stable responders and wearing-off.

‡Hoehn and Yahr stage; $p < 0.05$ (by Kruskal-Wallis) for difference among all groups except between stable responders and wearing-off.

§ANOVA $p < 0.0001$ for the difference of levodopa treatment duration and its optimal oral maintenance dose among all four groups.

at 8.00 am, an hour after being premedicated with 20 mg of domperidone. All anti-Parkinsonian medications were withheld after 10.00 pm on the night before each study day. Patients received four to six different doses of NPA ranging from those which produced little or no motor changes to those which resulted in various degrees of abnormal involuntary movements among fluctuating patients and blood pressure changes or nausea among those who did not manifest dyskinesias.

Parkinsonian severity was rated by scoring rigidity, tremor and bradykinesia in all four extremities and axial muscles as well as gait difficulty each on a scale of 0 (absent) to 4 (severe), with a maximum score of 64. Similarly, dyskinesias were rated in all four extremities and axial muscles each on a scale of 0 (absent) to 4 (severe), with a maximum score of 20. Motor function was evaluated every 10 minutes following drug administration until returned to baseline. Patient's usual anti-Parkinsonian medications were then resumed for the rest of the day. Anti-Parkinsonian response to each dose was expressed as the improvement at peak action compared with baseline scores. For each patient, optimum dose requirements for both NPA and levodopa were defined as that which produced the greatest reduction in Parkinsonian signs with the least degree of peak-dose choreiform dyskinesias.

On another occasion, five of the subjects participated in studies addressing the possibility of tolerance to NPA within the context of the study design. Each of these subjects received their previously determined optimum dose repeatedly for four consecutive days. Another four patients were studied for the potential motor effects of domperidone. Each was treated with optimum dose levodopa infusion at steady-state for two consecutive days, and received 20 mg domperidone every three hours on one day and identically appearing placebo tablets on the other day in random order. Motor evaluations were performed every 20 minutes.

Data are reported as means (SEM). Oral levodopa dosages were calculated in mg/kg/hour for the waking hours. Statistical analysis employed the non-parametric tests Mann-Whitney U, Kruskal-Wallis and Friedman for motor scores, and analysis of variance followed by Fisher post hoc test for the other variables.

Table 2 Comparison of optimal dose requirements between NPA and levodopa*

	NPA† (µg/kg)	Levodopa‡ (mg/kg)
Never treated	0.25 (0.04) [5]	1.1 (0.2) [8]
Stable responders	0.39 (0.07) [5]	1.1 (0.2) [5]
Wearing-off	0.35 (0.04) [8]	1.0 (0.1) [12]
On-off	0.58 (0.06) [6]	0.9 (0.1) [11]

*Data are means (SEM) for the number of patients in square brackets. Optimum dose is defined as the dose, given as an intravenous bolus, at which best possible anti-Parkinsonian motor response could be achieved with the least degree of adverse effects, including dyskinesias.

†ANOVA $p < 0.003$ for difference between on-off group and all other groups.

‡Differences among the groups are not significant.

Results

Comparison of the pharmacological profiles of NPA and levodopa at their respective optimal doses showed both differences and similarities (table 2). Optimal dose requirements for NPA boluses were significantly higher in patients with on-off phenomenon compared with all other groups. On the other hand, intravenous levodopa doses that produced optimal therapeutic response were essentially equal in all groups (table 2).

Anti-Parkinsonian efficacy at this optimal dose was suboptimal for NPA in all patients groups, averaging about 50%, while that for levodopa was virtually complete, except in levodopa-naive patients (table 3 and fig 1). Differences in anti-Parkinsonian efficacy of the two drugs were significant for the two fluctuating groups ($p < 0.01$). In contrast, NPA and levodopa were equally effective in inducing abnormal involuntary movements, and progressively higher dyskinesia scores were found with worsening response groups; differences between the two drugs were not significant, except for the wearing-off group ($p < 0.01$). Similarly, the toxic to therapeutic ratio for NPA and levodopa, expressed here as the ratio of dyskinesia scores and per cent anti-Parkinsonian response at optimal doses were not significantly different, and had the same tendency to progressively worsen with the development and deterioration of motor fluctuations.

Comparison of the quantal dose-response curves for NPA between the four response groups revealed narrowing of the therapeutic window with the development of increasingly severe motor complications (fig 2). While none

Table 3 Comparison of motor responses at optimal doses between NPA and levodopa*

	Parkinsonian response NPA†	LD†	Dyskinesia severity NPA§	LD§	Toxic/therapeutic ratio NPA§	LD§
Never treated	44 (12)	50 (9.0)	0	0	0	0
Stable responders	51 (11)	74 (4.9)	0	0.60 (0.60)	0	0.007 (0.007)
Wearing-off	46 (2.8)	88 (3.0)	1.8 (0.46)	4.3 (0.67)	0.04 (0.01)	0.05 (0.008)
On-off	57 (12)	88 (4.3)	5.3 (1.1)	7.2 (1.1)	0.1 (0.02)	0.08 (0.01)

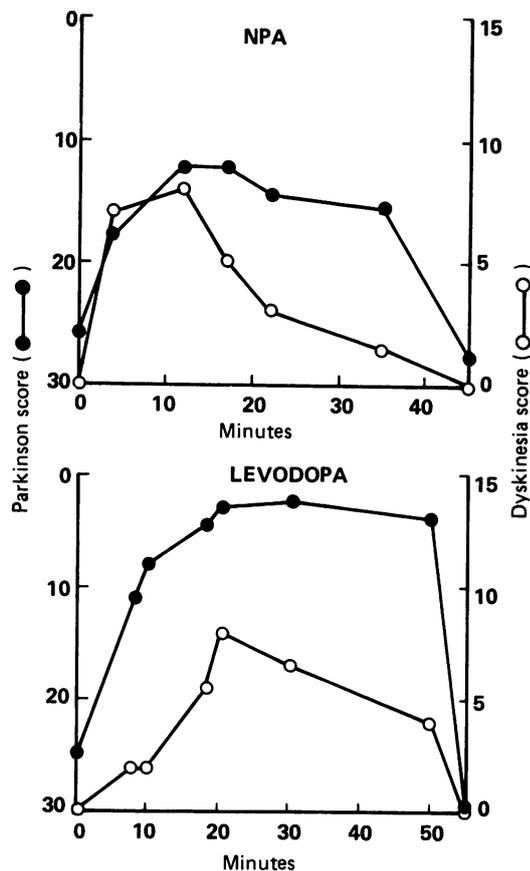
*Data are means (SEM). Number of subjects in each group is given in table 2. Optimum dose is defined in legend to table 2 and in methods. Parkinsonian response is the per cent improvement at peak action of optimal dose compared with baseline scores. Dyskinesia scores are the actual scores obtained at peak action of optimal dose. Toxic/therapeutic ratio is the ratio of dyskinesia scores and percentage Parkinsonian improvement.

†No significant difference among the four groups.

‡ $p < 0.05$ for difference between the two non-fluctuating groups and the two fluctuating ones.

§ $p < 0.05$ for difference among all groups except between never treated patients and stable responders.

Figure 1 Motor response to an optimal dose of NPA and levodopa in a representative patient. Anti-Parkinsonian score is on a scale of 0 (best) to 64 (worst), and dyskinesia score is on a scale of 0 (absent) to 20 (severe). Note that the anti-Parkinsonian response to NPA is partial compared to near complete abatement with levodopa. The degree and phenomenology of dyskinesias induced by both drugs are comparable.



of those in the levodopa-naïve and stable responder groups developed dyskinesias following NPA, despite administration of doses inducing peripheral dopaminomimetic side effects, all patients with motor fluctuations manifested abnormal involuntary movements. In fact, dyskinesias were encountered in patients with fluctuations, particularly those with on-off phenomenon, at doses lower than those needed for the anti-Parkinsonian effect. In addition, a tendency towards a shift to the right in the anti-Parkinsonian efficacy curve was found in the on-off group: 50% of patients

Figure 2 Quantal dose-response plots for NPA grouped according to patients' pattern of motor response to optimally adjusted oral levodopa. Data were obtained by calculating the percentage of patients in each group who manifested at least 30% improvement in Parkinsonian scores and any detectable degree of peak-dose dyskinesias. Number of subjects is given in table 2.

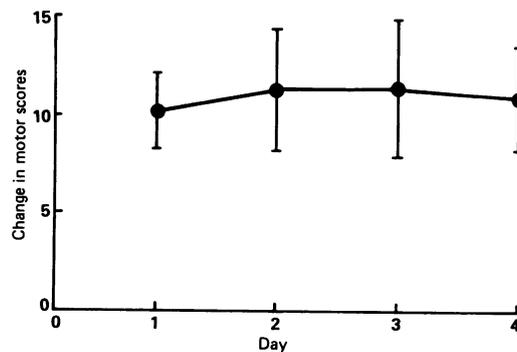
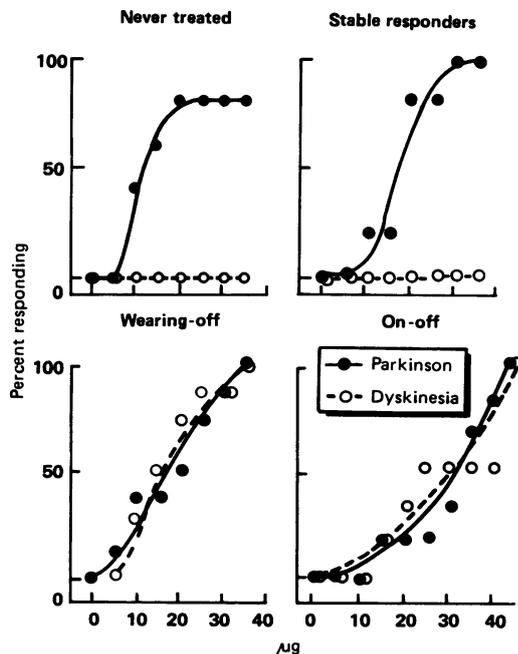


Figure 3 Improvement of Parkinsonian motor scores to repeated single daily injections of optimal dose NPA for four consecutive days. Each point is the mean (SEM) for five subjects. No evidence of tolerance was found ($p \geq 0.05$ by Friedman test).

in the latter group responded to NPA at about 30 µg, while 50% of those in the other categories responded at or below 20 µg.

No evidence of tolerance was found to single daily injections of optimal dose NPA given for four consecutive days (fig 3). The improvement in Parkinsonian scores at peak action compared with the baseline values for each day remained stable with repeated drug administration (Friedman test $p \gg 0.05$). Similarly, the duration of anti-Parkinsonian efficacy of NPA did not change significantly over the four day period; response (SEM) duration on day one was 80 (26) minutes, and on day four 65 (17) minutes (repeated measures ANOVA $p \gg 0.05$).

Domperidone had no effect on the anti-Parkinsonian action of levodopa. Mean (SEM) Parkinsonian scores with levodopa and placebo, 3.7 (1.7) were not significantly different than scores obtained with the combination of levodopa and domperidone, 4.4 (1.3); $p \gg 0.05$. Similarly, dyskinesia scores were not affected 3.9 (1.4) with placebo, 3.7 (0.9) with domperidone; $p \gg 0.05$.

Discussion

The anti-Parkinsonian efficacy of NPA, like several other direct acting dopamine agonists, appears substantially inferior to that of levodopa.^{3,8} The best motor response that could be achieved in response to NPA averaged only about 50% in Parkinsonian patients at any stage of their disease, compared with nearly total symptomatic relief with levodopa in all those previously exposed to the amine precursor. The suboptimal efficacy of dopamine agonists like bromocriptine, lisuride, pergolide and others is well recognised clinically, frequently necessitating co-administration of levodopa.^{6,7,10} Despite this discrepancy in anti-Parkinsonian efficacy between NPA and levodopa, their potential to generate peak-dose dyskinesias did not differ significantly. Indeed the therapeutic window for NPA (that is, the difference between doses that induce abnormal involuntary movements and those that ameliorate Parkinsonian signs) was dramatically narrowed in patients with motor fluctuations, a pharmacological profile reminis-

cent of that of levodopa.¹⁴ The foregoing observations are not influenced by the possibility of tolerance to NPA which has been reported in association with other dopamine agonists, such as apomorphine, when given every few hours.¹⁵ In this study, no evidence of tolerance was found when NPA was administered repeatedly as single daily injections. A critical time interval between repeated doses of dopaminomimetics appears necessary for tolerance to develop.¹⁶ Furthermore, the inferior anti-Parkinsonian efficacy of NPA compared with levodopa cannot be due to co-administration of domperidone, since the peripherally acting dopamine antagonist had no effect on the anti-Parkinsonian response to levodopa.¹⁷⁻¹⁹

Consideration of the pharmacological similarities and differences between NPA, a relatively selective D-2 dopamine agonist,¹¹⁻¹³ and levodopa, the prodrug for the D-1/D-2 equipotent dopamine, may help elucidate some of the central dopaminergic mechanisms relevant to Parkinson's disease and its therapy. The requirement of patients with on-off phenomenon for significantly more NPA compared with less advanced patients could suggest a state of decreased functional sensitivity of D-2 dopamine receptors in this group.²⁰ A more likely explanation, however, is the severe neuronal drop out in advanced cases which may drastically reduce the contribution of endogenous dopamine to provide some degree of D-1 receptor stimulation which appears necessary for a full motor response.^{11,13} The requirements of patients with advanced disease for higher doses of dopamine agonists, which are generally more selective at the D-2 receptor, is well recognised in clinical practice.²¹⁻²³ The apparent discrepancy between increased levodopa dose requirements with oral maintenance therapy, but not with intravenous boluses, is likely to reflect the widely disparate paradigms.

The superior anti-Parkinsonian efficacy of levodopa compared with NPA may be due to obligate simultaneous stimulation of both D-1 and D-2 dopamine receptors at a physiological ratio provided by the endogenous transmitter, dopamine.^{24,25} The partial D-1 agonism of NPA only at around 60% of that provided by dopamine¹³ appears inadequate to give a full anti-Parkinsonian response. Mechanisms for the suboptimal efficacy of levodopa in patients exposed to it for the first time, however, also a recognised clinical phenomenon, remains unclear.²⁶ The relatively equal anti-Parkinsonian response among patients in all four levodopa response categories to the direct acting, postsynaptic agonist, NPA, raises the possibility that the suboptimal response of levodopa-naive patients to levodopa may be at the level of presynaptic metabolic processing of levodopa, rather than altered sensitivity of the postsynaptic receptors. The induction of dyskinesias in response to NPA as well as CY 208-243, both partial D-1 agonists,^{13,27} suggests that even a small degree of D-1 activation may be sufficient to generate abnormal involuntary movements. In addition, other functionally

interactive transmitter systems within the basal ganglia may well contribute to the development of dopaminomimetic-induced chorea.²⁸⁻³⁰

The observations described earlier have direct therapeutic implications. Relatively selective D-2 agonists, while appearing to have no advantage over levodopa with respect to the induction of peak-dose dyskinesias, have much less anti-Parkinsonian efficacy. It would thus appear that the future development of anti-Parkinsonian agents should focus on dopamine agonists having more equal D-1/D-2 receptor potency in order to attain optimal clinical benefit. Alternatively, the more precise targeting of drugs on dopamine receptor subtypes defined molecularly would yield pharmacological agents with more clear profiles and improved functional efficacy.³¹

- Fahn S. "On-off" phenomenon with levodopa therapy in parkinsonism. Clinical and pharmacologic correlations and the effect of intramuscular pyridoxine. *Neurology* 1974;24:431-41.
- Marsden CD, Parkes JD. "On-off" effects in patients with Parkinson's disease on chronic levodopa therapy. *Lancet* 1976;i:292-6.
- Parkes JD, Debono AG, Marsden CD. Bromocriptine in parkinsonism: long-term treatment, dose response, and comparison with levodopa. *J Neurol Neurosurg Psychiatry* 1976;39:1101-8.
- Rascol A, Guiraud B, Montastruc JL, David J, Clanet M. Long-term treatment of Parkinson's disease with bromocriptine. *J Neurol Neurosurg Psychiatry* 1979;42:143-50.
- Lees AJ, Stern GM. Sustained bromocriptine therapy in previously untreated patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1981;44:1020-3.
- Lewitt PA, Ward CD, Larsen TA, et al. Comparison of pergolide and bromocriptine therapy in parkinsonism. *Neurology* 1983;33:1009-14.
- Obeso JA, Luquin MR, Martinez Lage JM. Intravenous lisuride corrects oscillations of motor performance in Parkinson's disease. *Ann Neurol* 1986;19:31-5.
- Lang AE. Update on dopamine agonists in Parkinson's disease: "beyond bromocriptine". *Can J Neurol Sci* 1987;14:474-82.
- Rinne UK. Early combination of bromocriptine and levodopa in the treatment of Parkinson's disease: a 5 year follow up. *Neurology* 1987;37:826-8.
- Stiibe CMH, Lees AJ, Kempster PA, Stern GM. Subcutaneous apomorphine in parkinsonian on-off oscillations. *Lancet* 1988;i:403-6.
- Menon MK, Clark WG, Neumeier JL. Comparison of the dopaminergic effects of apomorphine and (-)-N-n-propylnorapomorphine. *Eur J Pharmacol* 1978;52:1-9.
- Anderson PH. Comparison of the pharmacological characteristics of [³H]raclopride and [³H]SCH 23390 binding to dopamine receptors in vivo in mouse brain. *Eur J Pharmacol* 1988;146:113-20.
- Arnt J, Bogeso KP, Hyttel J, Meier E. Relative dopamine D1 and D2 receptor affinity and efficacy determine whether dopamine agonists induce hyperactivity or oral stereotypy in rats. *Pharmacol Toxicol* 1988;62:121-30.
- Mouradian MM, Juncos JL, Fabbri G, Schlegel J, Bartko JJ, Chase TN. Motor fluctuations in Parkinson's disease: central pathophysiological mechanisms, Part II. *Ann Neurol* 1988;24:372-8.
- Grandas F, Obeso JA. Motor response following repeated apomorphine administration is reduced in Parkinson's disease. *Clin Neuropharmacol* 1989;12:14-22.
- Grandas F, Obeso JA, Gancher S, et al. Response to apomorphine in Parkinson's disease depends on the time interval between doses. *Neurology* 1989;39 (Suppl):365.
- Critchly JM, Langdon N, Parkes JD, Quinn NP, Shindler JS, Marsden CD. Domperidone. *BMJ* 1985;290:788.
- Lake-Bakaar G, Cameron HA. Domperidone. *BMJ* 1985;290:241-2.
- Parkes JD. Domperidone and Parkinson's disease. *Clin Neuropharmacol* 1986;9:517-32.
- Reisine TD, Fields JZ, Yamamura HI, et al. Neurotransmitter receptor alterations in Parkinson's disease. *Life Sci* 1977;21:335-44.
- Larsen TA, Newman R, LeWitt P, Calne DB. Severity of Parkinson's disease and the dosage of bromocriptine. *Neurology* 1984;34:795-7.
- Jankovic J. Long-term study of pergolide in Parkinson's disease. *Neurology* 1985;35:296-9.
- Staal-Schreinemachers AL, Wesseling H, Kamphuis DJ, Burg W, Lakke JPWF. Low-dose bromocriptine therapy in Parkinson's disease: Double-blind, placebo-controlled study. *Neurology* 1986;36:291-3.
- Braun AR, Chase TN. Obligatory D-1/D-2 receptor interaction in the generation of dopamine agonist related

- behaviors. *Eur J Pharmacol* 1986;131:301-6.
- 25 Walters JR, Bergstrom DA, Carlson JH, Chase TN, Braun AR. D1 dopamine receptor activation required for post-synaptic expression of D2 agonist effects. *Science* 1987;236:719-22.
- 26 Marsden CD, Parkes JD. Success and problems of long-term levodopa therapy in Parkinson's disease. *Lancet* 1977;i:345-9.
- 27 Temlett JA, Quinn NP, Jenner PG, et al. Antiparkinsonian activity of CY 208-243, a partial D-1 dopamine receptor agonist, in MPTP-treated marmosets and patients with Parkinson's disease. *Movement Disorders* 1989;4:261-5.
- 28 Javoy-Agid F, Ruberg M, Taquer H, et al. Biochemical neuropathology of Parkinson's disease. *Adv Neurol* 1984;40:189-98.
- 29 Uhl GR, Hackney GO, Torchia M, et al. Parkinson's disease: nigral receptor changes support peptidergic role in nigrostriatal modulation. *Ann Neurol* 1986;20:194-203.
- 30 Crossman AR. A hypothesis on the pathophysiological mechanisms that underlie levodopa- or dopamine agonist-induced dyskinesia in Parkinson's disease: Implications for future strategies in treatment. *Movement Disorders* 1990;5:100-8.
- 31 Bunzow JR, Van Tol HHM, Grandy DK, et al. Cloning and expression of a rat D2 dopamine receptor cDNA. *Nature* 1988;336:783-7.