Effect on parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation

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Summary

In monkeys rendered parkinsonian, lesions and electrical stimulation of the subthalamic nucleus reduce all major motor disturbances. The effect of electrical stimulation of the subthalamic nucleus was assessed in three patients with disabling akinetic-rigid Parkinson's disease and severe motor fluctuations.

Quadripolar electrodes connected to a pulse generator were implanted in the subthalamic nuclei on both sides. Patients were evaluated with the unified Parkinson's disease rating scale and timed motor tests. 3 months after surgery, activities of daily living scores had improved by 58–88% and motor scores by 42–84%. This improvement was maintained for up to 8 months in the first patient operated upon. One patient was confused for 2 weeks after surgery, and another developed neuropsychological impairment related to a thalamic infarction which improved over 3 months. In one patient, stimulation could induce ballism that was stopped by reduction of stimulation.

This is the first demonstration in human beings of the part played by the subthalamic nuclei in the pathophysiology of Parkinson's disease.

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Introduction

Overactivity of the excitatory neurons from the subthalamic nucleus to internal pallidum has been shown in monkeys with parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).[1] Lesions[2-4] or high-frequency stimulation[5] of, the subthalamic nucleus in this animal model decrease tremor, rigidity, and akinesia mainly in the contralateral limbs, but sometimes a lesser, ipsilateral improvement is also noted. Involuntary movements were induced in some monkeys.

In human beings, long-term thalamic high-frequency electrical stimulation has been used for several years to treat parkinsonian and essential tremor.[6-10] The reversibility of this stimulation permits control of side-effects and thus makes this technique preferable to a destructive tissue lesion. We have applied the same technical procedure to the subthalamic nucleus of three patients with the aim of improving severe Parkinson's disease.

Patients and methods

Patients

Three patients suffering from akinetic-rigid Parkinson's disease were operated upon (table 1). After initial sustained benefit from levodopa, they had progressively developed sudden and unpredictable fluctuations in motor performance. During off-periods, they needed assistance with walking and daily living (table 2, figure 1); and patients 1 and 3 also had painful dystonia. During on-periods, they were mildly disabled but experienced levodopa-induced involuntary movements of variable severity. They had no dementia and no systemic disease. They remained severely handicapped despite all available pharmacological treatment. This study was approved by the Grenoble University Hospital ethics committee and patients gave their informed written consent.

Surgical procedures

Electrode implantations in each subthalamic nucleus were done under local anaesthesia in two operating sessions in two patients (separated by 3 months in patient 1 and by 1 month in patient 2) and in a single session in patient 3 (table 1). Medication was stopped 6 h before surgery. The subthalamic nucleus was seen on magnetic resonance imaging (MRI) as a well delineated hypointense signal on a T2-weighted coronal view. This image, when drawn on the subthalamic nucleus Talairach diagram,[11] derived from coronal and lateral contrast ventriculography, corresponded in location to the subthalamic nucleus area in atlases.[11,12]

Electrode trajectories were aimed at the centre of the subthalamic nucleus area. A microdrive allowed five simultaneous trajectories, with four trajectories each 2 mm apart from a central one. An Ohye's semi-microelectrode (Unique Medical Co Ltd, Tokyo, Japan) 450 μm diameter, electrical resistance about 100 kΩ, was introduced into each trajectory for multiunit activity recording and electrical stimulation

Patient	Age (years)	Sex	Years' duration of Parkinson's disease	Levodopa dose (mg per day)	Oral dopaminergic agonist (mg per day)	Subcutaneous apomorphine	Surgery date right side/left side
1	55	M	15	1800	Bromocriptine (20)	Yes	Jul 93/Oct 93 2
2	54	M	20	150	Lisuride (2)	No	Jan 94/Feb 94
3	47	M	8	1500	Bromocriptine (30)	Yes	Feb 94

Table 1: **Characteristics of patients**

(monopolar, cathode, 130 Hz, 60 μs pulse width, 0–10 mA) with an external stimulator (WPI, model A310+A365R+A362, World Precision Instrument Inc, New Haven, CT, USA).

Stimulation and recording began 5–10 mm from the target, in steps of 1 mm. At each step, the 5 electrodes were connected successively. The location of the electrodes was checked by teleradiography. Intraoperative clinical assessment was by passive movements of the wrist for evaluation of rigidity corresponding to item 22 of the unified Parkinson's disease rating scale[13] (UPDRS) scored from 0 (normal) to 4 (maximum disability); and timed test for akinesia (20 successive oppositions of the thumb to the index finger.) Tests were done at least three times with the patient and the evaluator unaware of the conditions of stimulation. The criterion for final location of the electrode was alleviation of parkinsonian symptoms synchronous with electrical stimulation. An electrode for chronic stimulation was inserted into the trajectory of the electrophysiological electrode where the beneficial clinical effect was obtained. This electrode was the DBS 3387 electrode (Medtronic, Minneapolis, MN, USA), 1·3 mm diameter, with 4 contacts (contact 0 distal to contact 3 proximal), each measuring 1·5 mm in length, separated by 1·5 mm. Programmable pulse generators (Itrell II, Medtronic) were implanted in the subclavicular region ipsilateral to the electrode and connected to the electrodes about 3 weeks after surgery.

Postoperative testing

We evaluated the relation between motor effects and electrical variables for 3 months after surgery, with the external stimulator during the initial postoperative period, and implanted pulse generator afterwards. To assess the effects of the electrical variables we used the UPDRS item for rigidity of the limbs[13] and a hand-tapping test (the patient had to tap 2 manual counters, fixed 20 cm apart, alternately with both hands, the score being the sum of 2 trials of 30 s). During procedures, the patient remained unaware of all conditions of stimulation applied. Frequencies from 2 to 185 Hz (maximum frequency) were studied with implanted stimulators, in a double-blind randomised manner, with a constant intensity (4 V) and pulse width (60 μs), with monopolar cathodic stimulation on contact 0 (figure 2) for 4 subthalamic nuclei in three patients.

Clinical assessment

General motor assessments, with video recordings, were carried out during off-periods after overnight withdrawal of medication and during on-periods, 2 to 4 times during the 2 months before surgery, and monthly thereafter. They were UPDRS parts I to VI;[13] an involuntary movement scale (scored from 0 [absent] to 4 [severe] in the limbs, face, and trunk); timed tests including the hand-tapping test, a pronation-supination test, and a stand-walk-sit test (the score being the mean of 2 trials).[14] Continuous stimulation was used for the on-stimulation conditions (table 3). The rigidity score for each side was the sum of item 22 of the UPDRS motor score[13] for the upper and for the lower limb. The akinesia score for a side was the sum of items 23–26 of the UPDRS motor score.[13] Levodopa tests (200 or 300 mg of levodopa, plus benserazide) were done to evaluate latency and duration of on-periods. Neuropsychological tests were a frontal battery adapted from Pillon et al,[16] which examines verbal fluency; the Wisconsin card-sorting test;[16] and motor sequencing; maximum score on this battery is 50. These tests were done before, and 1 and 3 months after surgery.

Results

During surgery

Acute intraoperative electrical stimulation through only 1 or 2 of the 5 electrophysiological semi-microelectrodes induced a beneficial effect generally from 3 to 5 mm below the bicommissural (AC-PC) line along the electrode trajectory. Rigidity was alleviated bilaterally in all patients by stimulation of 0·5–3·0 mA. Finger akinesia was improved contralaterally in 2 patients. In the other cases, the patients were too tired during the procedure to perform timed voluntary repetitive movements. Multiunit activity recordings did not show patterns sufficiently characteristic to assist in the determination of the target.

After surgery

Improvement in rigidity and in akinesia occurred at 30 Hz, plateauing above 50 Hz (figure 2). In patient 1, frequencies up to 2000 Hz were studied during the post-operative period, with the external stimulator: results remained approximately stable over 100 Hz (data not shown). Contact 0, presumed to be located in the subthalamic nucleus, always gave the most beneficial effects. For chronic stimulation, a cyclical mode was

Patient/state	1/A		1/B	1/C	1/D	2/A		2/C	3/A		3/C
Drug	off	on	off	off	off	off	on	off	off	on	off
Stimulation	..	..	off/R-on	off/on	off/on	..	..	off/on	..	..	off/on
Test											
L rigidity (/8)	5·5	2·5	5·2/3·2	4·5/1·5	7·0/2·0	5·0	0·7	5·0/2·0	6·2	1·3	6·0/3·0
R rigidity (/8)	5·5	2·0	5·9/5·7	4·0/1 5	5·0/2·0	5·7	0·7	4·0/1·0	6·2	2·3	6·0/3·0
L akinesia (/16)	11 5	1·0	13·0/6·2	13·5/1·5	13·0/4·5	10·2	0·7	8·0/2·0	12·0	1·8	11·7/8·5
R akinesia (/16)	10·0	0	12·2/12·1	11·0/1·5	13·5/4·5	7·8	0·7	6·0/3·0	10·0	0	9·0/6·5
L tapping counts/min	46	85	43/66	32/87	42/86	82	101	110/189	26	77	51/67
R tapping counts/min	62	113	55/58	55/95	63/99	101	127	148/215	33	84	67/78
L PS-test (s)	67·7	19·3	59·4/17·7	210·6/18·3	120·2/19·5	39·0	14·4	33·5/20·5	np	23·0	np/65·6
R PS test (s)	25·9	16·7	35·0/22·7	34·5/16·1	31·0/18·4	33·0	14·8	24·5/21·2	np	22·4	np/41·0
S-W-T test (s)	np	13 1	28·6/14·6	46·4/15·4	24·2/14·4	130·0	11·8	12·8/11·2	np	15·7	49·1/20·3
AIMS (/24)	0	4	0/0	0/5	0/2	0	22	0/5	0	9	0/0
UPDRS II	32	13	na/23	na/4	na/7	25	3	na/3	31	4	na/13
Hoehn & Yahr[13]	5	2	na/4	na/2	na/2	4	2	na/2	5	2	na/2·5
n	2	2	4/4	2/2	1/1	3	3	1/1	4	3	2/2

np=not possible, na=not applicable, L=left, R=right, PS-test=pronosupination test, S-W-T=stand-walk-sit test.

Table 2: **Motor scores of patients before (A) and 3 months after bilateral surgery (C) and also for patient 1 after unilateral surgery (B) and 6 months after bilateral surgery (D)**

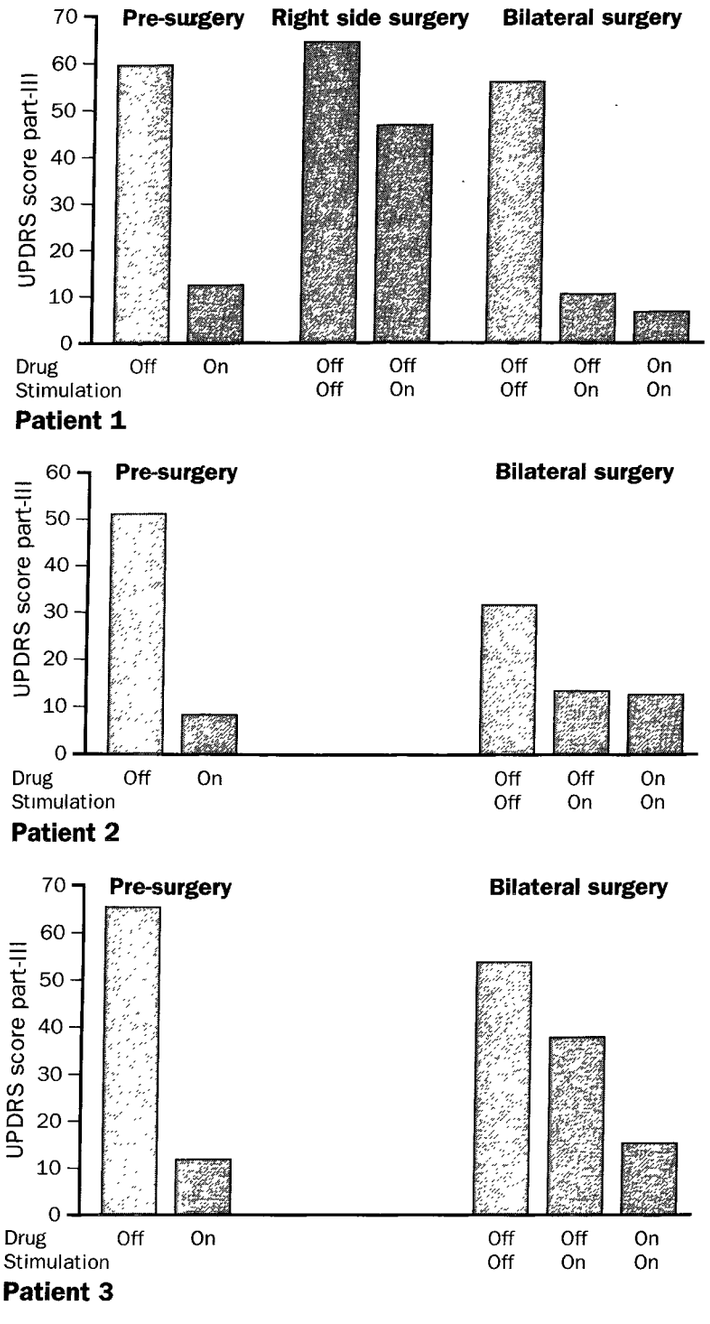

Figure 1: **Global motor scoring (UPDRS part III) before and 3 months after surgery, according to drug and stimulation conditions**

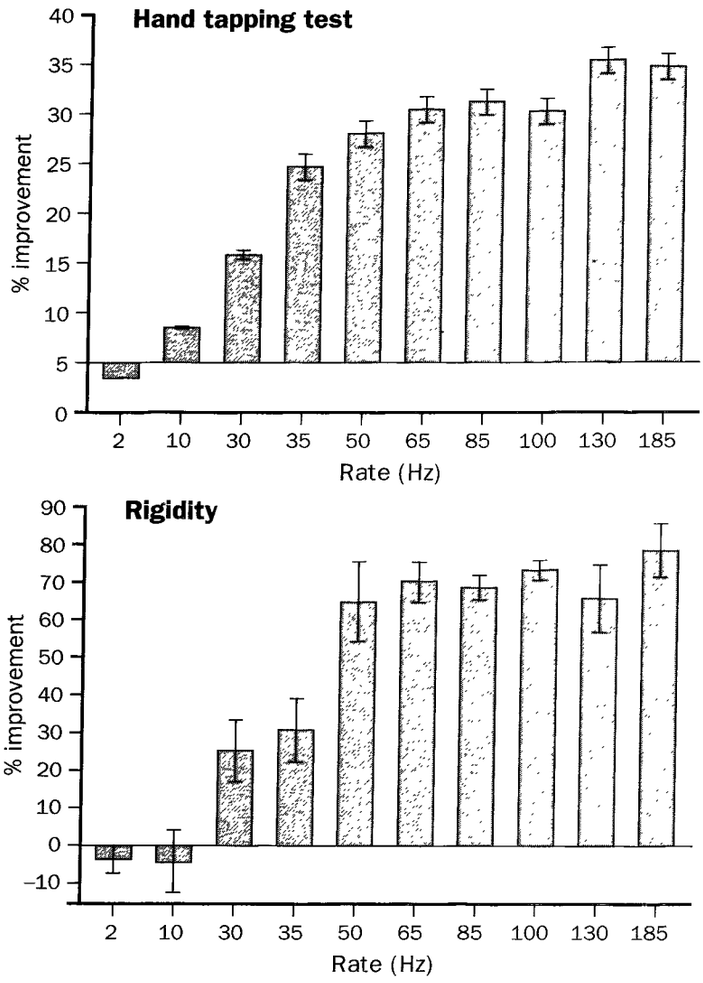

Figure 2: **Effect of stimulation frequency on tapping test and rigidity scores**
Mean and standard SE derived from studying 4 subthalamic electrodes in three patients.

selected in order to avoid possible tolerance. Patients remained unaware of the repetitive short duration arrest of stimulation, which alternated from one side to the other. Monopolar stimulation was used in patients 1 and 3, and bipolar stimulation, between contact 0 (cathode) and contact 1 (anode), in patient 2.

After surgery, without medication or stimulation, off-period dystonia almost completely disappeared, the UPDRS motor subscore had improved by 7% (patient 1), 38% (patient 2), and 18% (patient 3) at 3 months follow-up, and the stand-walk-sit test became feasible. When unilateral subthalamic nucleus stimulation was switched on, improvement appeared mostly in contralateral rigidity and akinesia (table 2). With bilateral stimulation (table 3), the UPDRS motor subscore decreased by 84% in patient 1, 75% in patient 2, and 42% in patient 3 in comparison with the presurgical score at 3 months follow-up (figure 1). In patient 3, the improvement reached 55% with 4 V, but this voltage could not be applied for long because it induced involuntary movements. In this patient, contralateral hemiballism appeared within minutes to hours of stimulation; and in all patients, slight choreodystonic movements resembling those induced by levodopa appeared within seconds or minutes of stimulation. All types of involuntary movements were suppressed after the intensity was lowered or the stimulator switched off. Activity of daily living scores (UPDRS part II) in the off-medication state were improved at 3 months follow-up by 87% in patient 1, 88% in patient 2, and 58% in patient 3 (table 2); corresponding to a global subjective improvement, as assessed by patients on a visual analogue scale, of 90, 85, and 69% respectively. Levodopa dosage was maintained unchanged for 1 month after surgery, but was then decreased by 50% in patient 1 and by 40% in patient 3,

	Patient 1		Patient 2		Patient 3	
	R	L	R	L	R	L
Contact (cathode)	0	0	0	0	0	0
Coordinates						
X	3·5	3·3	6·0	5·5	4·7	4·8
Y	13·6	12·0	8 9	7·8	12 0	9·8
Z	14·1	12·3	11·5	11·5	11·3	10·8
Voltage (V)	2·4	3·0	3·0	3·0	1·3	1·1
Pulse width (μs)	60	60	60	60	60	60
Frequency (Hz)	130	130	130	130	130	130
Time on/off (s)	300/60	300/60	240/60	240/60	240/30	240/30

X=dorso-ventral direction, below AC-PC line; Y=rostro-caudal direction, anterior to PC; Z=lateral from the midline). R: right, L: left.

Table 3: **Electrical stimulation (at 3 month follow-up) and coordinates (mm) at tip of contact 0 of electrodes**

and the drug was withdrawn in patient 2. All patients continued to receive their original doses of oral dopaminergic agonist drugs, but subcutaneous apomorphine injections were stopped in patients 1 and 3.

No other adverse effects were directly related to stimulation. Patient 1 became slightly confused and hallucinated for 2 weeks after the second implantation. In patient 2, postoperative magnetic resonance imaging showed an 18 mm diameter hyperintense signal in T2-weighted images in the region of the upper thalamus and the anterior limb of the internal capsule, suggesting an infarction. His score on the frontal test battery, off-medication, was 35 before surgery and 8 at 2 weeks after surgery but improved to 29 at 3 months.

Discussion

In this study, bilateral subthalamic nucleus stimulation improved akinesia and rigidity in three patients with Parkinson's disease. This is in agreement with the results obtained in monkeys with MPTP-induced parkinsonism by lesions or stimulation of the subthalamic nucleus.[2-5] Unilateral stimulation influenced contralateral and axial, but not ipsilateral, signs, contrary to the results obtained in some MPTP-treated monkeys. Improvement in daily living activities occurred only after bilateral stimulation. During intraoperative tests, improvement in rigidity, synchronous to the onset of stimulation, has been easier to detect than improvement in akinesia. Slight improvement after the insertion of the electrodes could be ascribed to a subthalamotomy-like effect.

All patients had involuntary movements induced by subthalamic nucleus stimulation, close to those they had experienced on levodopa. Stimulation, by altering striatal output, reproduces this phenomenon presumed to be triggered by dopaminergic-receptor hypersensitivity within the striatum. Hemiballism was not induced by mechanical distortion of the tissue around the electrode, but could be triggered by stimulation in 1 patient. Hemiballism has also been induced in some monkeys with MPTP-induced parkinsonism with contralateral lesions in the subthalamic nucleus.[2-4] The inconstant occurrence in human beings and in monkeys after lesions or stimulation of the subthalamic nucleus area remains unexplained—the size of the lesion may not necessarily be related to the occurrence of hemiballism.[17] The reversibility and adaptability of the chronic stimulation procedure allows the control of induced involuntary movements, effectively making this the only technique suitable for subthalamic nucleus surgery in human beings.

The effectiveness of subthalamic nucleus stimulation depends on optimal electrode placement, which seems to be within about 3 mm. Within the 4 mm diameter cylinder explored by the 5 electrode approach, only 1 or 2 electrode settings gave beneficial results. In comparison with thalamic surgery, determination of the target is more difficult because of the lack of a known specific behaviour induced by stimulation of this area. Moreover the size, shape, and orientation of the subthalamic nuclei are highly variable, according to atlases.[11,12] This underlines the importance of locating the subthalamic nucleus on magnetic resonance imaging and of exploring several trajectories. The oblong hyposignal shown on magnetic resonance imaging coronal views seems to be the subthalamic nucleus because of the similarity with stereotaxic atlases[11,12] in the same plane, orthogonal to the AC-PC line.

The mechanism of action of chronic electrical stimulation is unknown. Since the effects are similar to those induced by a lesion,[2-4] an inhibitory mechanism is possible: electrical stimulation can trigger hemiballism, which is known to be provoked by a spontaneous lesion of the subthalamic nucleus or its connections.[18] Subthalamic nucleus inhibition by high-frequency stimulation could be related to induction of depolarising blockade of the subthalamic nucleus neurons, since this effect is frequency dependent. The maximum effect occurs over 50 Hz, and remains stable up to 2000 Hz. However the threshold rate to obtain an antiparkinsonian effect is about 30 Hz, which is lower than that necessary to arrest tremor in the thalamic ventral intermediate nucleus,[6] and is close to the spontaneous firing rate of primate subthalamic nucleus neurons.[19] Thus an alternative activation mechanism is also possible, through back-firing towards the external pallidum which in turn will inhibit the internal pallidum.[20,21]

We conclude that the effect of subthalamic nucleus stimulation in Parkinson's disease supports the hypothesis of the key role of the subthalamic nucleus in the basal ganglia circuitry and the importance of its overactivity in causing parkinsonian symptoms.[1-5,20,21] The long-term effects of this procedure need to be evaluated in a large number of patients and compared with other neurosurgical treatments especially internal pallidum surgery[22] and striatal grafts.[23-25] However, this experimental and technically demanding neurosurgical procedure should currently be restricted to severely disabled Parkinson's disease patients, and only performed in centres with the necessary neurosurgical, imaging, neurological, and neurophysiological expertise.

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Look-back study of infectivity of anti-HCV ELISA-positive blood components

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The infectivity of blood components from donors who were later found to be anti-HCV ELISA-positive was investigated in recipients who were enrolled in a look-back programme. Recipients received ELISA-positive blood components from donors who were PCR-positive and/or RIBA-2-positive (n=22, group A) or PCR-negative and indeterminate or negative on RIBA-2 (n=105, group B). 26 of 32 (81%) recipients of group A donors and none of 140 of group B were HCV-infected. All stored serum samples of previous donations (n=172) of group A donors were anti-HCV-positive in RIBA-3, indicating a chronic carrier state of HCV in these donors.

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The tracking and testing of recipients of blood components from donors who are later found to be infected with HIV is standard procedure in blood banking (look-back).[1] Look-back for recipients of blood components infected with hepatitis C virus (HCV) is controversial.[2] Dutch guidelines for blood banks required that all anti-HCV ELISA-positive blood products be discarded and the donors be deferred, irrespective of results of recombinant immunoblot assay (RIBA). Further, blood banks have to inform doctors when a patient has received blood components from a donor later found to be HCV infected. The blood bank must then be notified about the recipient's test results. In this study we assessed the infectivity of blood components donated before an anti-HCV ELISA-positive donation in two groups of donors with accurate ascertainment of HCV status.

From May, 1990, to January, 1992, 139 138 whole-blood donations were tested for anti-HCV antibodies (ELISA-1/2, Ortho). ELISA-positive (repeatedly reactive) donations were confirmed by RIBA-2 (Ortho) and PCR.[3] 32 (0·02%) donors were confirmed positive. Of these, 10 (31%) were first-time donors and 22 (69%) were repeat donors.

All hospitals were notified of blood components previously released from 22 donors later found to be HCV-infected—ie, PCR-positive and/or RIBA-2-positive (group A). As a research project, one academic hospital was informed about previously released blood components from 105 donors later found to be ELISA-positive, PCR-negative, and negative or indeterminate on RIBA-2 (group B). The general practitioner was asked to notify the recipient, and then a physician of the blood bank visited the patient at home. After informed consent, standardised interviews were done, including risk factors for HCV infection.[4] Blood samples were collected for anti-HCV and PCR testing.[3] All serum samples were tested in 1994 with a third-generation ELISA (ELISA-3, Ortho). ELISA-positive samples were confirmed by third-generation RIBA (RIBA-3, Ortho) and PCR.[3]

Stored serum specimens from previous donations (1986–92) from group A and B donors were tested in 1992 with ELISA-2. In addition the first and last serum sample of each group A donor was tested with RIBA-3 in 1994. Because of the costs, this was omitted in the group B donors. The χ^2 test with Yates' correction was used for comparison.

From 22 group A donors, 270 blood components were delivered to various hospitals (table). Information was received from the hospitals about 127 of 270 (47%) cases: 57 of 127 recipients (45%) had died, 31 (24%) could not be traced, and 39 (31%) were available for testing. Of these 39, 7 (18%) had an independent risk-factor for HCV infection (multi-transfusion) and were excluded. From the remaining 32 patients, 26 (81%) were HCV-infected (ELISA-3/RIBA-3/PCR-positive); 1 was ELISA-3-positive, RIBA-3-indeterminate (C100 only), and PCR-negative; and 5 (16%) were negative in all tests. Information from the other 143 (53%) cases is pending.

Of 26 HCV-infected recipients of blood products from group A donors, 17 (65%) received red-cell concentrates, 2 (8%) platelets, and 7 (27%) fresh frozen plasma. Of the 6 non-HCV-infected recipients, 5 (83%) received red-cell concentrates, and 1 fresh frozen plasma (not significant). Of 17 HCV-infected recipients of red-cell concentrates from group A donors, the age of the products (the time between donation and transfusion) was 8·2 (range 1–17) days and of 5 non-infected recipients 9·2 (1–14) days (not significant).