CONGENITALE DOPAMINE BETA-HYDROXYLASE DEFICIENTIE;

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Een nieuw orthostatisch syndroom

CONGENITAL DOPAMINE BETA-HYDROXYLASE DEFICIENCY;

A novel orthostatic syndrome

PROEFSCHRIFT
TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
AAN DE ERASMUS UNIVERSITEIT ROTTERDAM
OP GEZAG VAN DE RECTOR MAGNIFICUS PROF.DR. A.H.G. RINNOOY KAN
EN VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN.
DE OPENBARE VERDEDIGING ZAL PLAATSVINDEN
OP WOENSDAG 11 MEI 1988 OM 15.45 UUR PRECIES.

door
Arie Jacob Man in 't Veld
geboren te Rotterdam.

PROMOTIECOMMISSIE:

Promotor:	Prof.dr. M.A.D.H. Schalekamp
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Over promovendi:

"Onweerstaanbaar is de rustelooze begeerte tot onderzoek, doch groot de misleiding der zinnen, voorbarig en bedriegelijk het oordeel en vlijend de eigenliefde. Spoedig wordt het eenvoudige door de verbeelding en de zonderlingste verbindingen, waardoor men verlangt tot enig inzigt en begrip te zullen komen, zoodanig ingekleed, opgesierd en scheef voorgesteld, dat het later voor de wetenschap hoogst moeijelijk, ja vrij onmogelijk is de eenvoudige waarheid op te delven, of aan te tonen, hoe en langs welke wegen, door welke bijkomende omstandigheden men eene zinnelijk waargenomen zaak zoo zeer heeft kunnen verduisteren en toch algemeen geloof doen vinden."

Uit: Geschiedenis van de vroegere Geneeskunde en van hare Beoefenaren in Nederland door J. Banga, Leeuwarden 1868, W. Eekhoff, p. 15.

INHOUD

HOOFDSTUK 1

INLEIDING

Historie

Sinds decennia wordt chronische autonome dysfunctie herkend als een belangrijk klinisch probleem hoewel het relatief zeldzaam is. Bradbury en Eggleston beschreven in 1925 het sindsdien naar hen genoemde syndroom als "primary postural hypotension", ook bekend als "idiopathische orthostatische hypotensie" en "idiopathische autonome dysfunctie" (1). Sindsdien zijn medici zich bewust van het feit, dat een groot aantal medicamenten en systeemziekten het door Bradbury en Eggleston beschreven syndroom kunnen nabootsen. De combinatie van orthostatische hypotensie, hypohydrosis, een relatief gefixeerde polsfrequentie, impotentie en dysfunctie van de urinewegen en het maagdarmkanaal is een complex van symptomen, dat gemakkelijk herkend wordt als dysfunctie van het autonome zenuwstelsel.

Klinische symptomen bij autonome dysfunctie

Bij sommige patiënten met autonome dysfunctie gaan de autonome afwijkingen gepaard met extra-pyramidale verschijnselen, cerebellaire dysfunctie of andere neurologische afwijkingen, zoals o.a. beschreven door Shy en Drager (2). Bij andere patiënten is de autonome dysfunctie beperkt tot de baroreflex, terwijl overige sympathische en parasympathische functies onaangetast blijven. Bij de meeste patiënten met autonome dysfunctie is ernstige, invalide-

rende orthostatische hypotensie de voornaamste handicap. De klinische kenmerken van orthostatische hypotensie zijn moeheid, duizelingen, de neiging om flauw te vallen bij gaan staan of geringe inspanning en wazig zien. Soms is de orthostatische bloeddrukdaling zo groot, dat de patiënt het bewustzijn verliest binnen 15 tot 30 seconden na gaan staan. Sommige patiënten zijn hierdoor met name in de ochtenduren volledig aan het bed gekluisterd. In vroege stadia van de ziekte klaagt de patiënt soms alleen over een licht gevoel in het hoofd na langere periodes van staan of inspanning. Bij het lichamelijk onderzoek wordt bij patiënten met autonome dysfunctie altijd een orthostatische bloeddrukdaling van minstens 25/15 mm Hg gevonden. De compensatoire toename van de hartfrequentie is meestal gering of geheel afwezig.

Oorzaken van orthostatische hypotensie

Orthostatische hypotensie kan door een groot spectrum van aandoeningen veroorzaakt worden (3, Tabel).

Onderscheid dient gemaakt te worden tussen vormen van orthostatische hypotensie waarbij de baroreflex wel (A, B, soms C) en niet (soms C, D) intakt is. Dit onderscheid is relatief simpel te maken, hoewel daarvoor intra-arteriële bloeddrukregistratie noodzakelijk is. Waar de baroreflexboog ook onderbroken mag zijn, afferent, centraal of efferent, de zogenaamde Valsalva-respons is afwijkend. Tijdens verhogen van de intrathoracale druk, door middel van persen met open glottis, daalt het hartminuutvolume en treedt baroreflex-gemedieerde vasoconstrictie op. Na de Valsalva manoeuvre, als het hartminuutvolume terugkeert

TABEL: OORZAKEN VAN ORTHOSTATISCHE HYPOTENSIE

A. **Hypovolaemie**
- iatrogeen (bv. diuretica).
- post-haemorragisch.
- diarree, braken.
- bijnierinsufficiëntie (Morbus Addison).
- phaeochromocytoom.
- varicosis cruris.

B. **Pathologische vasodilatatie**
- hyperbradykinisme (Syndroom van Streeten, dumping syndroom).
- postprandiaal.

C. **Medicamenteus**
- diuretica.
- prazosine.
- clonidine, guanfacine.
- alpha-methyldopa.
- adrenerge neuronblokkers.
- ganglionblokkers.
- fenothiazines, barbituraten.
- antidepressiva.
- L-DOPA.
- atropine.
- narcotische analgetica.

D. **Baroreflex-dysfunctie**

- AFFERENT
  - arteriosclerose.
  - luetische aortitis.
  - chirurgisch (na hoofd-hals dissecties).

- CENTRAAL
  - tumor cerebri (bv. craniopharyngioma).
  - Syndroom van Shy-Drager.
  - Syndroom van Holms-Adie.
  - Morbus Parkinson.
  - syringobulbie.

- EFFERENT
  - Syndroom van Bradbury-Eggleston.
  - Syndroom van Riley-Day.
  - amyotrofische lateraal sclerose.
  - syringomyelie.
  - hoge dwarslaesie.
  - post-sympathectomie.
  - infectieus (tabes dorsalis, Morbus Chagas, acute pandysautonomie).
  - polyneuropathie
    - uraemie
    - diabetes mellitus
    - amyloidose
    - hypothyreoidie
    - porphyrie
    - paraneoplastisch
    - M. Guillain-Barré
    - rheumatoide arthritis
    - botulisme
    - aethanol
  - congenitale dopamine beta-hydroxylase deficiëntie.

tot de uitgangswaarde, stijgt de bloeddruk tot boven het niveau van voor de manoeuvre. Deze bloeddruk "overshoot" is afwezig als de baroreflexboog is onderbroken. Bij hypovolaemie of pathologische vasodilatatie en een intacte baroreflex is deze reactie vaak juist meer uitgesproken dan normaal.

Behandeling van orthostatische hypotensie

De behandeling van orthostatische hypotensie is vaak niet effectief of wordt overschaduwd door gevaarlijke neveneffecten. De grote variëteit aan therapeutische mogelijkheden, die voor orthostatische hypotensie beschreven is, getuigt hiervan. Een onvolledige lijst van therapieën omvat o.a. pogingen het circulerende volume te vergroten (4-7), sympathicomimetische amines (8-10), vasoconstrictoren (11, 12), beta-blokkers (13-20), prostaglandine synthese remmers (21, 22), antihistaminica (23), serotonine antagonisten (24) en dopamine antagonisten (25, 26). Sommige van deze therapeutica zijn van nut bij de minder ernstige vormen van orthostatische hypotensie, doch falen bij de ernstiger vormen. De hoeksteen van de therapie is steeds een aantal fysische maatregelen: elastische kousen gedurende de dag om veneuze stase in de benen tegen te gaan, en gedurende de nacht slapen met het hoofdeinde van het bed 10 tot 20 cm boven het niveau van het voeteneinde. Door deze maatregelen vermindert de bij deze patiënten optredende nachtelijke druk-natriurese (27), zoals reeds beschreven in 1925 door Bradbury en Eggleston (1). Dientengevolge zal de hypovolaemie in de ochtenduren minder ernstig zijn, hetgeen een gunstig effect heeft op de orthostatische hypotensie. Verhoging van de keukenzout inname met

het dieet versterkt dit gunstige effect. Tenslotte dienen de patiënten, hoe paradoxaal dit ook lijken mag, overdag zoveel mogelijk geactiveerd te worden, waardoor de locale autoregulatie van de hersendoorstroming wordt bevorderd en een optimale adaptatie aan lage perfusiedrukken wordt bewerkstelligd.

Congenitale dopamine beta-hydroxylase deficiëntie

In dit proefschrift wordt een nieuw orthostatisch syndroom beschreven ten gevolge van congenitale dopamine beta-hydroxylase deficiëntie. Dopamine beta-hydroxylase is het enzym, dat verantwoordelijk is voor de omzetting van dopamine in de sympathische neurotransmitter noradrenaline (zie omslag). Dientengevolge treedt de door noradrenaline veroorzaakte vasoconstrictie bij gaan staan niet op en ontstaat orthostatische hypotensie. De therapie van dit nieuwe syndroom wordt eveneens beschreven: DL-threo-3,4-dihydroxyfenylserine, een niet-natuurlijk aminozuur dat door aromatisch L-aminozuur-decarboxylase kan worden omgezet in het bij dit syndroom ontbrekende noradrenaline, zodat het defect in de synthese kan worden omzeild.

Literatuur:

1. Bradbury S, Eggleston C. Postural hypotension. A report of 3 cases. *Am Heart J* 1925; 1: 73-86.
2. Shy GM, Drager GA. A neurological syndrome associated with orthostatic hypotension: a clinical-pathological study. *Arch Neurol* 1960; 2: 511-527.
3. Hines S, Houston M, Robertsen D. The clinical spectrum of autonomic dysfunction. *Am J Med* 1981; 70: 1091-1096.
4. Bannister R, Ardill L, Fentem P. An assessment of various methods of treatment of idiopathic orthostatic hypotension. *Q J Med* 1969; 38: 377-395.
5. Chobanian AV, Volicer L, Tifft CP, Gavras H, Liang SS, Faxon D. Mineralocorticoid-induced hypertension in patients with orthostatic hypotension. *N Engl J Med* 1979; 301: 68-73.

6. Man in 't Veld AJ, Wenting GJ, De Bruijn JHB, Schalekamp MADH. Age-related differences in the long-term responses of systemic flow and resistance to mineralocorticoid excess in man. *Prog Biochem Pharmacol* 1980; 17: 44-53.
7. Man in 't Veld AJ, Wenting GJ, Schalekamp MADH. Hemodynamics of early and sustained sodium-induced hypertension: consecutive measurements in man. In: *Hypertension in the Young and Old*, edited by G. Onesti and K.E. Kim, 1981; pp. 263-273. Grüne and Stratton, New York.
8. Barnett AJ. Idiopathic orthostatic hypotension: a pharmacological study of the action of sympathomimetic drugs. *Med J Aust* 1968; 1: 212-216.
9. Diamond MA, Murray RH, Schmidt PG. Idiopathic postural hypotension: physiologic observation and report of a new mode of therapy. *J Clin Invest* 1970; 49: 1341-1348.
10. Parks VJ, Sandison AG, Skinner SL, Wheeland RF. Sympathomimetic drugs in orthostatic hypotension. *Lancet* 1961; 1: 1133-1136.
11. Nordenfelt I, Mellander S. Central hemodynamic effects of dihydroergotamine in patients with orthostatic hypotension. *Acta Med Scand* 1972; 191: 115-120.
12. Robertsen D, Goldberg MR, Hollister AS, Robertsen RM. Clonidine raises blood pressure in severe idiopathic orthostatic hypotension. *Am J Med* 1983; 74: 193-200.
13. Boesen F, Andersen EB, Kanstrup Hansen IL, Hesse B, Christensen NJ. Behandling af invaliderende ortostatisk hypotension med pindolol ved diabetish autonom neuropati. *Vidensk. Praksis* 1982; August: 2335-2338.
14. Brevetti G, Chiariello M, Lavecchia G, Rengo F. Effects of propranolol in a case of orthostatic hypotension. *Br Heart J* 1979; 41: 245-248.
15. Chobanian AV, Volicer L, Liang CS, Kershaw G, Tifft C. Use of propranolol in the treatment of idiopathic orthostatic hypotension. *Trans Assoc Am Physicians* 1977; 90: 324-334.
16. Frewinn DB, Leonello PP, Penhall RK, Harding PE. Pindolol in orthostatic hypotension. Possible therapy? *Med J Aust* 1980; 1: 128.
17. Man in 't Veld AJ, Boomsma F, Schalekamp MADH. Effects of beta-adrenoceptor agonist and antagonists in patients with peripheral autonomic neuropathy. *Br J Clin Pharmacol* 1982; 13: 367S-374S.
18. Man in 't Veld AJ, Schalekamp MADH. Pindolol acts as beta-adrenoceptor agonist in orthostatic hypotension: therapeutic implications. *Br Med J* 1981; 282: 929-931.
19. Man in 't Veld AJ, Boomsma F, Schalekamp MADH. Regulation of alpha- and beta-adrenoceptor responsiveness. Studies in patients with chronic autonomic failure. *Br J Clin Pharmacol.* 1983; 15: 507S-519S.
20. Robson D. Pindolol in postural hypotension. *Lancet* 1981; 2: 1280.

21. Crook JE, Robertsen D, Whorton AR. Prostaglandin suppression: inability to correct severe idiopathic orthostatic hypotension. *South Med J* 1981; 731: 1318-1320.
22. Kocher MSj, Itskovitz HD. Treatment of idiopathic orthostatic hypotension (Shy-Drager syndrome) with indomethacin. *Lancet* 1978; 1: 1011-1014.
23. Stacpoole P, Robertsen D. Combination of H1 and H2 receptor antagonist therapy in diabetic autonomic failure. *South Med J* 1982; 75: 634-635.
24. Mahondeau D, Singer B, Gilbert JC, Goulon M, Gajados PA. A propos d'un cas de maladie de Shy et Drager: études hémodynamiques et pharmacodynamique: intéret de la cyproheptadine. *Revé Neurol* (Paris) 1971; 126: 402-414.
25. Kuchel O, Buu NT, Hamet P, et al. Orthostatic hypotension: a posture-induced hyperdopaminergic state. *Am J Med Sci* 1985; 289: 3-11.
26. Kuchel O, Debinski W, Larochelle P. Isolated failure of autonomic noradrenergic neurotransmission. *N Engl J Med* 1987; 317: 1415-1416.
27. Schalekamp MADH, Man in 't Veld AJ, Wenting GJ. "What regulates whole body autoregulation ?" *J Hypertension* 1985; 3-2: 97-108.

HOOFDSTUK 2

DOEL VAN HET ONDERZOEK

In 1976 werd een 21-jarige vrouw naar ons ziekenhuis verwezen (dr. R. Pilaar) wegens orthostatische hypotensie, die bleek te berusten op autonome dysfunctie. Het plasma noradrenaline gehalte, gemeten volgens Henry et al (1), bleek niet aantoonbaar (< 25 pg/ml). Het zou toen nog 5 jaar duren voordat ons laboratorium overging op bepaling van alle catecholamines (dus ook dopamine en adrenaline) volgens Peuler en Johnson (2). Toen bleek, dat ook adrenaline niet aantoonbaar was, en dat het plasma dopamine gehalte sterk verhoogd was. Achteraf gezien waren er een aantal opmerkelijke aspecten en verschijnselen bij de vorm van autonome dysfunctie die onze patiënte had:

1. patiënte leek niet aan één van de bekende oorzaken van autonome dysfunctie te lijden,
2. bovendien was ze opmerkelijk jong voor de meeste vormen van chronische autonome dysfunctie en zij bleek bij nader doorvragen al ziekteverschijnselen te hebben sinds de geboorte,
3. de stijging van de polsfrequentie bij gaan staan was normaal aanwezig, pleitend voor intacte baroreflex afferenten en efferente parasympathische cardiale innervatie en
4. bij de meeste vormen van autonome dysfunctie is het plasma noradrenaline weliswaar verlaagd en stijgt het niet bij gaan staan, maar het is meestal wel aantoonbaar.

Het doel van ons onderzoek was dit syndroom nader pathofysiologisch te karakteriseren en de oorzaak ervan vast te

stellen, zodat daarna eventueel een passende behandeling kon worden ingesteld en geëvalueerd. Dit alles nam meer dan 5 jaar in beslag.

Literatuur:

1. Henry DP, Starman BJ, Johnson DG, Williams RH. A sensitive radioenzymatic assay for norepinephrine in tissues and plasma. *Life Sci.* 1975; 16: 375-384.
2. Peuler JD, Johnson GA. Simultaneous single isotope radioenzymatic assay of plasma norepinephrine, epinephrine and dopamine. *Life Sci* 1977; 21: 625-636.

CONGENITAL DOPAMINE-BETA-HYDROXYLASE DEFICIENCY*
A Novel Orthostatic Syndrome

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Summary A woman was referred with severe orthostatic hypotension at the age of 21. Ptosis, skeletal muscle hypotonia, and recurrent hypoglycaemia had been noticed in early childhood. There was noradrenergic denervation and adrenomedullary failure but baroreflex afferents, cholinergic innervation, and adrenocortical function were intact. Noradrenaline and adrenaline were undetectable in plasma, urine, and cerebrospinal fluid (CSF), but dopamine was 7-fold to 12-fold normal in plasma, 4-fold normal in urine, and 20-fold normal in CSF. Measurements of catecholamine metabolites showed further evidence for impairment of noradrenaline and adrenaline biosynthesis due to deficient dopamine-beta-hydroxylation. Dopamine-beta-hydroxylase was undetectable in plasma and CSF. Physiological and pharmacological stimuli of sympathetic neurotransmitter release caused increases in plasma dopamine rather than plasma noradrenaline.

* THE LANCET, JANUARY 24, 1987

Introduction

WITH progression of chronic autonomic failure, whatever its aetiology, the symptoms usually reflect loss of both noradrenergic and cholinergic function. Here we describe a patient with severe orthostatic hypotension due to virtually complete loss of noradrenergic innervation but with intact cholinergic function. This syndrome seemed to be caused by congenital dopamine-beta-hydroxylase deficiency.

Case-report

The patient (A) was born in 1955. She was the first child of unrelated parents. Her brother and sister are in good health. Before she was born her mother had two spontaneous abortions at 12 and 14 weeks' gestation and one stillborn child at 38 weeks. Immediately after an uneventful delivery the patient was cyanotic and hypotonic but she recovered quickly. In her first year of life unexplained vomiting led to four hospital admissions because of dehydration, cyanosis, coma, and hypothermia (29–32°C). On each occasion hypoglycaemia was found (glucose 0·7–1·5 mmol/l). After intravenous fluid and glucose, recovery was always quick and uneventful. At that time it was noted that she had mild ptosis of both eyelids and slightly hypotonic skeletal muscles. Mental and physical development in childhood were normal, although she was said to be apathetic and to avoid physical exercise. Sexual maturation was normal and menarche was at the age of 14. Since then she has had regular menstrual periods. From the age of 15 she had episodes of blurred vision, dizziness, faintness, and occasionally syncope. Orthostatic hypotension was diagnosed 6 years later and she was referred to our hospital. There was no family history of a similar disease.

On physical examination she had mild ptosis of both eyelids, a nasal voice, a high palate, and hyperflexible joints. Supine blood pressure was 105/65 mm Hg and heart rate was 72–80/min. When

she was upright the systolic blood pressure fell to 60 mm Hg, and diastolic pressure could not be measured before the patient fainted. Heart rate rose to 96 on standing. There was weakness of the facial musculature and deep tendon reflexes were sluggish. No sensory or other motor abnormalities were observed. Although small (3 mm in diameter) the pupils reacted normally to light and accommodation. Smell and taste were normal and she was able to cry tears. Routine clinical and laboratory investigations, including a chest X-ray, echocardiogram, computed tomographic scan of the head, nerve conduction studies, electromyogram, and rectal biopsy, were all normal; the electrocardiogram showed sinus rhythm with normal sinus arrhythmia, but T waves in precordial leads were negative or flat. On routine cytogenetic analysis the karyotype was a normal 46,XX.

Physiological and Pharmacological Tests

For these tests the patient was investigated under basal conditions in the supine position. Arterial pressure was measured directly. Tests were conducted only when the patient had been untreated for at least a week and were done on separate occasions over 3 years.

Biochemical Measurements

Catecholamines in plasma from arterial blood and in cerebrospinal fluid (CSF) obtained by lumbar puncture after 12 hours' bedrest were extracted[1] and then measured by the radioenzymatic procedure of Peuler and Johnson.[2] Detection limits are 10 pmol/l for noradrenaline and adrenaline and 50 pmol/l for dopamine. Results in our patient were compared with those in 12 other patients with chronic autonomic failure (table 1) and 56 patients with borderline hypertension, who all appeared to be normotensive after three days in the hospital. Results were validated on a high performance liquid chromatography (HPLC) system with electrochemical detection.

TABLE I—PATIENTS WITH CHRONIC AUTONOMIC FAILURE

Patient	Sex	Age	Diagnosis	Onset of symptoms
A	F	30	DBH-deficiency	1955
2	F	78	Idiopathic OH	1976
3	F	58	Idiopathic OH	1970
4	F	58	Idiopathic OH	1972
5	M	36	Hereditary amyloidosis	1976
6	M	43	Hereditary amyloidosis	1970
7	F	34	Hereditary amyloidosis	1975
8	M	74	Amyloidosis and multiple myeloma	1979
9	F	62	Primary amyloidosis	1973
10	M	63	Shy-Drager syndrome	1972
11	M	76	Parkinsonism	1980
12	M	75	Parkinsonism	1981
13	F	42	Diabetic neuropathy	1982

DBH = dopamine-beta-hydroxylase; OH = orthostatic hypotension.

L-dopa was measured by conversion to dopamine and quantification of the dopamine by HPLC. Complete conversion of L-dopa was obtained by incubation for 30 min of 500 µl plasma, 200 µl 0·7 mol/l phosphate buffer containing 0·7 mmol/l ethylenediaminetetra-acetic acid and 19·4 mmol/l dithiothreitol (pH 7·0), 50 µl of 0·245 mmol/l pyridoxal-5-phosphate, and 50 µl of a crude pig kidney extract. Aromatic-L-aminoacid decarboxylase (EC 4.1.1.28) was measured as described previously.[3]

Dopamine-beta-hydroxylase (EC 1.14.17.1) in plasma and CSF was measured by its ability to convert tyramine into octopamine.[4] Limit of detection is 0·1 U/l. Assays were done in the presence of the co-factor ascorbic acid in the incubation mixture in large excess (12 × Km). Results in our patient were compared with those in 12 other patients with chronic autonomic failure and in 76 outpatients without cardiovascular disease.

Free catecholamines in urine were determined on an HPLC system after extraction.[1] Metabolites of catecholamines

(normetanephrine, metanephrine, and 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) and free vanilmandelic acid, homovanillic acid, and 3-methoxytyramine) were determined as described before.[5-7] Results were compared with those in 9 other patients with chronic autonomic failure. Normal values were obtained from 20 healthy sedentary hospital employees. Two 24 h urine collections were used to calculate the average excretion of catecholamines and their metabolites in μmol/mol creatinine. Free homovanillic acid and MHPG in CSF were determined as in urine after deproteination of CSF with perchloric acid.

All subjects gave informed consent to participate in the studies, which were approved by the hospital ethical review committee.

Results

Physiological and Pharmacological Tests

All patients with chronic autonomic failure had severe orthostatic hypotension. Disruption of the integrity of the baroreflex arc was demonstrated by the absence of a systolic pressure overshoot in phase IV of the Valsalva manoeuvre. However, in contrast to the other patients with autonomic failure, patient A showed an increase in heart rate from 73 to 102/min during phase III of the Valsalva response. She also showed normal sinus arrhythmia and normal heart rate responses to changes in mean arterial pressure (table II). Thus, her baroreflex afferents were intact. However, during hyperventilation, the cold-pressor test, isometric handgrip, and mental arithmetic, mean arterial pressure and heart rate did not change. This evidence of sympathetic failure was confirmed by the absence of any haemodynamic response to alpha and beta adrenoceptor antagonists. She was strikingly sensitive to beta-adrenoceptor agonists and the alpha-1-adrenoceptor agonist phenylephrine. A pressor response to the alpha-2-adrenoceptor agonist clonidine illustrated the

TABLE II—PHYSIOLOGICAL AND PHARMACOLOGICAL TESTING IN PATIENT A

Tests*	Type of drug	Dose	Changes in: MAP	Changes in: HR
Head-up tilt	—	60°, 5 min	−48	+58
Head-down tilt	—	30°, 5 min	+23	−19
Hyperventilation	—	1 min	±5	±3
Cold-pressor test	—	1 min hand in ice-water	±4	±4
Isometric handgrip	—	50% of max for 1 min	±4	±3
Mental arithmetic	—	1 min	±3	±2
Propranolol	$Beta_{1,2}$ antagonist	1–16 mg	±2	±2
Metoprolol	$Beta_1$ antagonist	0·5–8 mg	±3	±3
Isoprenaline	$Beta_{1,2}$ agonist	1–20 ng/kg per min	−34	+63
Prenalterol	$Beta_1$ agonist	0·05–5 mg	+16	+33
Salbutamol	$Beta_2$ agonist	10–200 ng kg per min	−30	+62
Phentolamine	$Alpha_{1,2}$ antagonist	5–30 mg	±3	±3
Yohimbine	$Alpha_2$ antagonist	1–5 mg	±3	±2
Phenylephrine	$Alpha_1$ agonist	5–50 μg	+41	−23
Clonidine	$Alpha_2$ agonist	10–250 μg	+55	−31
Tyramine	$Alpha_1$ agonist (indirect)	1–12 mg	−6	+6
Atropine	Acetylcholine-M-antagonist	0·5–2 mg	+24	+61
Edrophonium	Acetylcholin-esterase inhibitor	5–20 mg	−15	±3
Metoclopramide	$DA_{1,2}$ antagonist	5–20 mg	+19	−6
Domperidone	DA_2 antagonist	5–20 mg	+25	−5
Insulin		0·05 U/kg per min for 90 min	−32	±4

*All tests were done with the patient supine. Drugs were given as slow bolus injections in incremental doses every 5 min, unless dose/min is indicated, in which case a continuous infusion was given with incremental dose steps every 10 min. Changes in mean arterial pressure and heart rate are those at the highest dose.

MAP = mean arterial pressure (mm Hg); HR = heart rate per min; DA = dopamine.

severity of her sympathetic denervation.[8,9] The indirectly acting sympathomimetic agent tyramine caused a slight fall instead of an increase in mean arterial pressure, confirming the absence of noradrenaline in sympathetic nerve endings. Integrity of cardiac vagal efferents was demonstrated by a pronounced rise in mean arterial pressure and heart rate after atropine. The acetylcholinesterase inhibitor edrophonium, which causes ganglionic stimulation, induced a fall in mean arterial pressure but heart rate did not rise: these findings suggest that parasympathetic stimulation was not associated with increased sympathetic activity. During hypotension induced by insulin infusion (a potent sympathetic and parasympathetic stimulus) again there was no change in heart rate. Metoclopramide and domperidone raised mean arterial pressure and lowered heart rate. The flat or negative T-waves in the precordial leads of the electrocardiogram disappeared after beta-1 stimulation by prenalterol.

After body heating with radiant heat a normal sweating pattern (observed by use of quinizarin staining powder) proved that sympathetic cholinergic innervation of eccrine sweat glands was intact. Absence of change in pupil size after conjunctival instillation of 2% methacholine, 5% homatropine, or 1% hydroxyamphetamine indicated that parasympathetic innervation was intact and sympathetic innervation was deficient.[10] During infusion of insulin (0·05 U/kg per min) a fall in gastric pH from 5·0 to 1·5 confirmed that vagal gastric parietal cell innervation was intact; and when hypoglycaemic the patient sweated profusely—further evidence of the integrity of sympathetic cholinergic innervation.

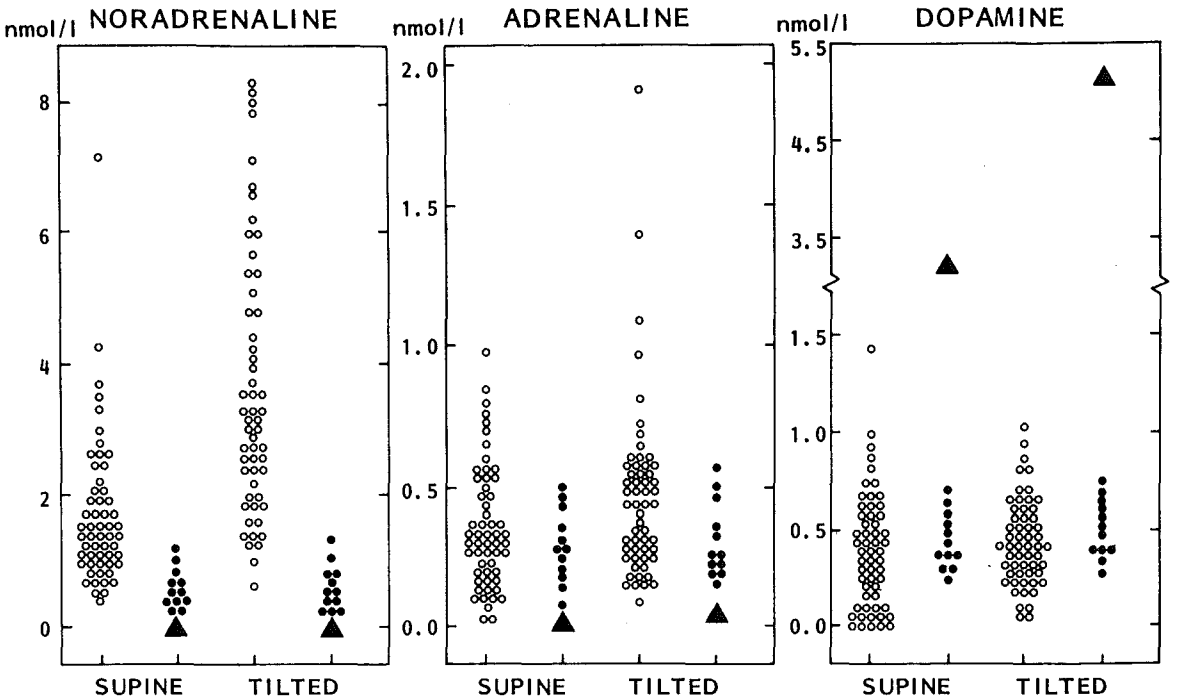

Fig 1—Basal and stimulated (5 min 60° head-up tilt) concentrations of plasma catecholamines.

● = patients with chronic autonomic failure; ○ = age and sex matched controls; ▲ = patient A.

Biochemical Measurements

In patients with chronic autonomic failure plasma noradrenaline was abnormally low and did not rise after 60° head-up tilting (fig 1); plasma adrenaline and dopamine were normal. In patient A, however, noradrenaline and adrenaline were undetectable, whereas basal dopamine was 7 times normal (3·4 nmol/l) and increased to 5·3 nmol/l after tilting. L-dopa in plasma was also raised (mean of six determinations 21·0 SD 3·8 nmol/l; normal 10·6 SD 2·8 nmol/l, n = 40). In the other patients with chronic autonomic failure it was normal (9·0 SD 3·4 nmol/l, n = 9).

All catecholamines and their metabolites were abnormally low in patients with chronic autonomic failure. In patient A noradrenaline and adrenaline were less than 0·5 μmol/mol creatinine, normetanephrine and metanephrine were less than 5 μmol/mol, and vanilmandelic acid and MHPG were undetectable (less than 20 μmol/mol); these findings were in striking contrast to the raised excretion of dopamine, homovanillic acid, and 3-methoxytyramine (fig 2). Aromatic-L-aminoacid-decarboxylase activity in the patient's plasma was normal (30·7 SD 3·0 mU/l, 6 tests; normal 34·6 SD 12·1, n = 40).

Plasma dopamine-beta-hydroxylase was normal in 12 patients with chronic autonomic failure but below the limit of detection in patient A (fig 3). Recovery of dopamine-beta-hydroxylase activity added to the patient's plasma was complete. Addition of extra amounts of N-ethylmaleimide, copper sulphate, or catalase had no effect.

Noradrenaline, adrenaline, and dopamine-beta-hydroxylase were not detectable in patient A's CSF. Dopamine was strikingly high at 1·84 nmol/l. MHPG was about 70% below normal and homovanillic acid was three

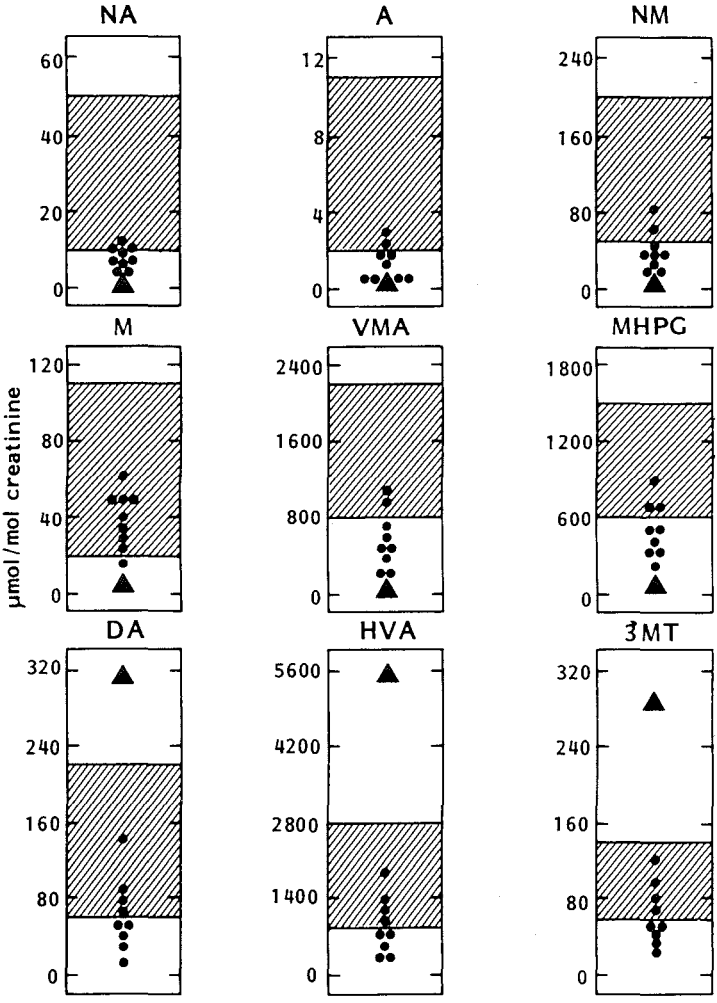

Fig 2—Excretion of catecholamines and their degradation products in urine.

● = patients with chronic autonomic failure; ▲ = patient A. Hatched areas indicate 95% confidence interval in 20 healthy sedentary hospital employees.

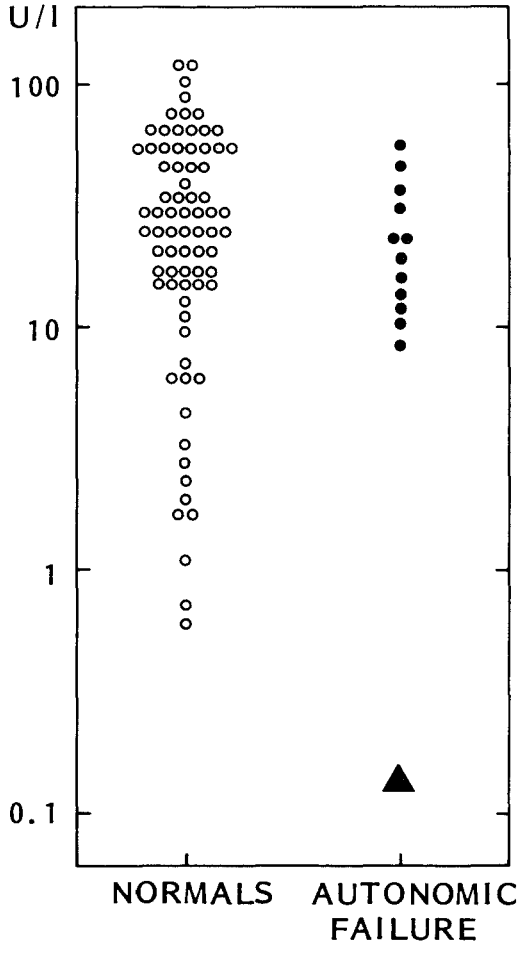

Fig 3—Basal levels of plasma dopamine-beta-hydroxylase activity.

○ = controls; ● = patients with chronic autonomic failure; ▲ = patient A.

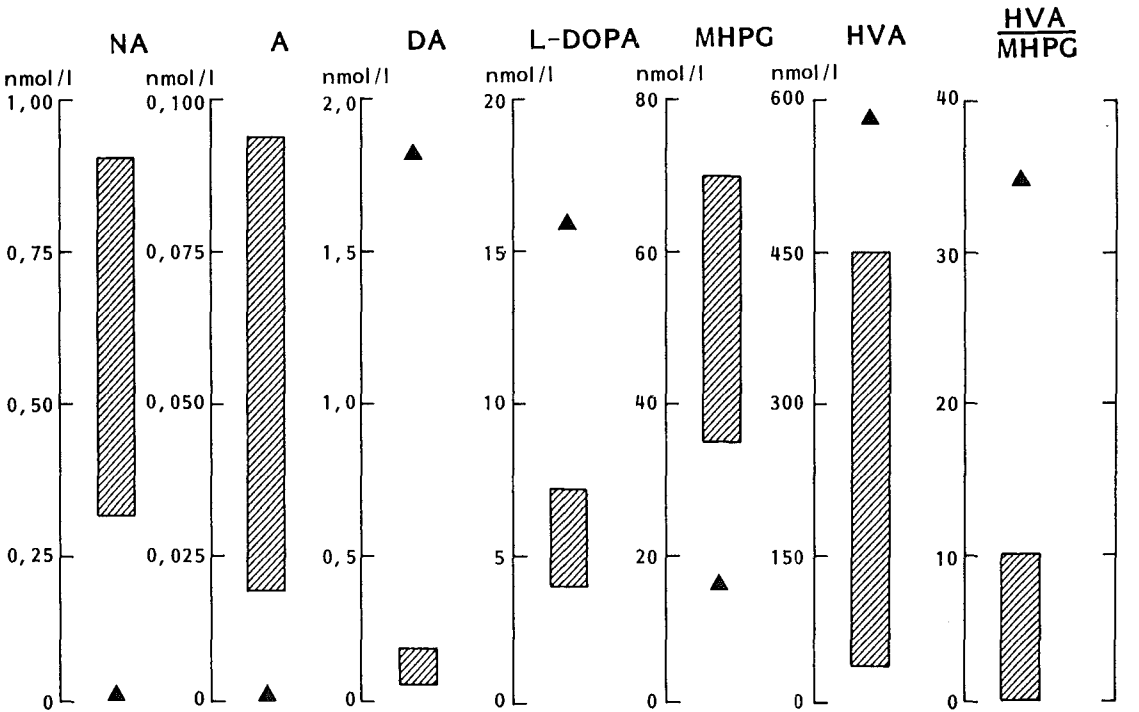

Fig 4—Catecholamine concentrations and HVA/MHPG ratios in CSF.

Hatched area, normals with 95% confidence intervals; ▲ = patient A. NA = noradrenaline; A = adrenaline; DA = dopamine; HVA = homovanillic acid.

times normal, so that the HVA/MHPG ratio was increased 10-fold (fig 4). L-dopa in CSF (single measurement) was greatly raised at 16·3 nmol/l (normal 5·2 SD 1·3 nmol/l, n = 12).

After 500 μg of corticotropin (1–24), plasma cortisol rose from 0·56 to 2·86 μmol/l and plasma aldosterone from 0·22 to 1·66 nmol/l, proving that adrenocortical function was intact. During a low-dose infusion of insulin (0·05 U kg/min for 90 min) glucose fell from 6·5 to 1·9 mmol/l and plasma cortisol rose from 0·35 to 1·00 μmol/l. Despite this potent sympathoadrenal stimulus, noradrenaline and adrenaline were undetectable—ie, the adrenal medulla was not secreting.

Manipulation of Plasma Dopamine

Hypoglycaemia, ganglionic stimulation, standing, tyramine, yohimbine, and head-up tilting were all tried as methods of increasing sympathetic activity but plasma noradrenaline and adrenaline remained undetectable. Surprisingly, plasma dopamine rose considerably after these stimuli, and the initially high value was depressed by head-down tilting and by clonidine (fig 5). These results suggest that central, preganglionic, and postganglionic modulation of sympathetic activity was intact but that the major catecholamine released from sympathetic nerves was dopamine rather than noradrenaline.

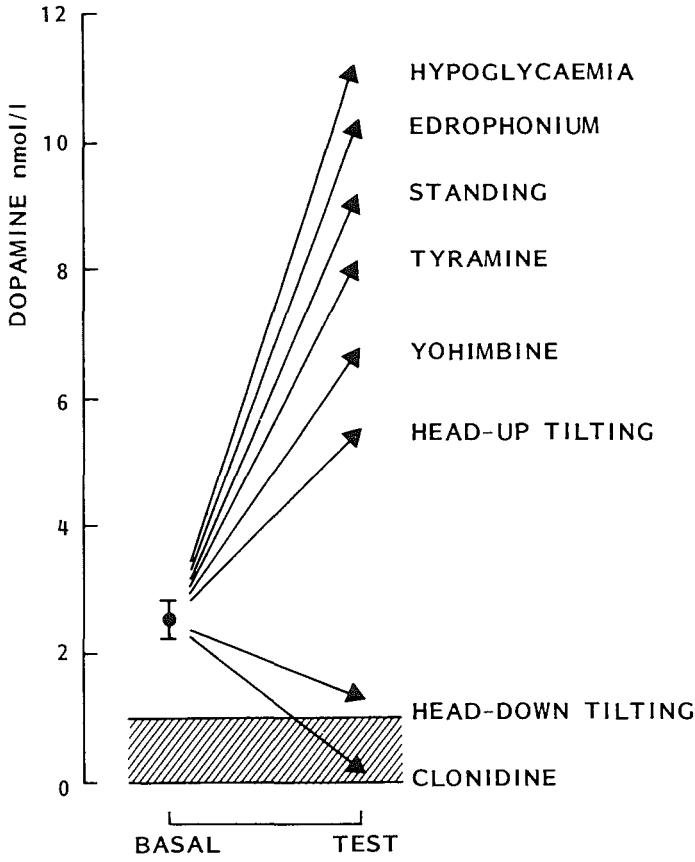

Fig 5—Changes in dopamine concentrations in patient A after various manoeuvres to manipulate plasma noradrenaline and adrenaline concentrations.

Hatched area indicates 95% confidence interval in 56 control subjects. The basal dopamine level in the patient is the mean value (with SEM) of 14 determinations. For dosages of drugs see table II. Arterial blood was sampled 90 min after the start of insulin infusion, when blood glucose had fallen from 6·5 to 1·9 mmol/l; 5 min after the highest doses of edrophonium, tyramine, yohimbine, or clonidine; and 5 min after standing up or tilting.

Discussion

The following are our conclusions about patient A:

1. She had severe noradrenergic denervation of the heart, blood vessels, and pupils together with adrenomedullary failure. Baroreflex afferents and parasympathetic innervation of the heart, gastric mucosa, and pupils were intact as was sympathetic cholinergic innervation. The negative or flat T-waves on the electrocardiogram, which disappeared after beta-1 stimulation with prenalterol, the congenital ptosis, and the weakness of the facial musculature may be also related to the failure of noradrenergic control. Spontaneous hypoglycaemia and supersensitivity to exogenous insulin suggest diminished insulin antagonism, which may be due to adrenomedullary failure.

2. Plasma noradrenaline and adrenaline were undetectable and dopamine was greatly increased. Central, preganglionic, and postganglionic stimulation of sympathetic neurotransmitter release caused plasma dopamine to rise whereas noradrenaline and adrenaline remained undetectable.

3. Urinary noradrenaline, adrenaline, and their degradation productions were not detectable, whereas dopamine and its degradation products were increased.

4. CSF did not contain noradrenaline or adrenaline, and MHPG was reduced, in contrast to a 20-fold increase in dopamine, a 3-fold increase in its degradation product homovanillic acid, and a 10-fold increase in the HVA/MHPG ratio.

5. Dopamine-beta-hydroxylase activity could not be demonstrated in plasma and CSF. Immunohistochemistry of skin biopsy material was negative for dopamine-beta-hydroxylase and noradrenaline but positive for dopamine (unpublished).

The relevance of three diagnostic criteria has to be discussed in more detail. First, variations in plasma dopamine-beta-hydroxylase in a randomly selected population are genetically determined. Very low amounts, measured enzymatically or immunologically, are found in

3–4% of the population and this trait in apparently healthy individuals is inherited as an autosomal recessive.[15] Thus, plasma measurements of dopamine-beta-hydroxylase cannot be used as a key diagnostic criterion for the syndrome in patient A. Second, severe orthostatic hypotension with intact cardiac vagal innervation has been described in two patients before.[16-18] Neither resembled patient A: one had autonomic neuropathy of acute onset and Hodgkin's disease;[16] the other had normal plasma concentrations of noradrenaline and adrenaline.[17] Robertson et al[18] have described a patient with orthostatic hypotension and noradrenergic failure but intact cholinergic function. Plasma dopamine was raised but the patient differed from ours in having detectable plasma and urinary noradrenaline and normal plasma and urinary adrenaline concentrations; also the arterial pressure did not rise when dopamine was antagonised with metoclopramide. Robertson and co-workers proposed impairment of dopamine-beta-hydroxylation as an explanation for their biochemical findings but the normal vanilmandelic acid values in urine argue strongly against this explanation. Third, a congenital form of orthostatic hypotension occurs in patients with familial dysautonomia, but these patients have combined sympathetic-parasympathetic failure.[19] Moreover, plasma dopamine-beta-hydroxylase is normal[20] or slightly subnormal[21] in these cases.

There is good evidence for the existence of either a single gene or linked genes for tyrosine hydroxylase, dopamine-beta-hydroxylase, and phenylethanolamine-N-methyltransferase.[22] If the dopamine-beta-hydroxylase deficiency in our patient is due to deletion of part of the chromosome, it is possible that this deficiency is not isolated.

Our data suggest that tyrosine hydroxylase is not deficient, since L-dopa in plasma and CSF was raised. Immunohistochemically the presence of tyrosine hydroxylase was also confirmed (unpublished). Since this is the rate-limiting enzyme in the catecholamine synthesis cascade, the raised L-dopa might indicate induction of tyrosine hydroxylase activity through loss of negative feedback by noradrenaline. Aromatic-L-aminoacid decarboxylase activity was also normal. We have as yet no information on phenylethanolamine-N-methyltransferase. Routine cytogenetic analysis revealed no abnormalities; specifically, the short arm of chromosome 11, to which the human tyrosine hydroxylase gene has been assigned,[23] showed no gross abnormality. The evidence, taken together, strongly suggests that our patient has isolated congenital dopamine-beta-hydroxylase deficiency.

We thank Dr A. F. Lever, MRC Blood Pressure Unit, Glasgow, for helpful comments; Dr H. W. M. Steinbusch, Department of Pharmacology, Free University of Amsterdam, for doing the immunohistochemistry; and Dr J. O. van Hemel, Department of Clinical Genetics, Erasmus University Rotterdam, for doing the cytogenetic analysis.

REFERENCES

1. Smedes F, Kraak JC, Poppe H. Simple and fast solvent extraction system for selective and quantitative isolation of adrenaline, noradrenaline and dopamine from plasma and urine. *J Chromatogr* 1982; **231:** 25–39.
2. Peuler JD, Johnson GA. Simultaneous single isotope radioenzymatic assay of plasma norepinephrine, epinephrine and dopamine. *Life Sci* 1977; **21:** 625–36.
3. Boomsma F, Van der Hoorn FA, Schalekamp MADH. Determination of aromatic-L-amino acid decarboxylase in human plasma. *Clin Chim Acta* 1986; **159:** 173–83.
4. Kato T, Kuzuya H, Nagatsu T. A simple and sensitive assay for dopamine-beta-hydroxylase activity by dual-wavelength spectrophotometry. *Biochem Med* 1974; **10:** 320–28.
5. Moleman P, Borstrok JJM. Analysis of urinary 3-methoxy-4-hydroxy-phenyl-glycol by high-performance liquid chromatography and electrochemical detection. *J Chromatogr* 1982; **227:** 391–405.

6. Moleman P, Borstrok JJM. Determination of urinary vanillymandelic acid by liquid chromatography with electrochemical detection. *Clin Chem* 1983; **29:** 878–81.
7. Moleman P, Borstrok JJM. Analysis of urinary catecholamines and metabolites with high performance liquid chromatography and electrochemical detection. *Biogenic Amines* 1985; **3:** 33–71.
8. Man in 't Veld AJ, Boomsma F, Schalekamp MADH. Regulation of alpha- and beta-adrenoceptor responsiveness. Studies in patients with chronic autonomic failure. *Br J Clin Pharmacol* 1983; **15** (suppl 4): 507S–20S.
9. Robertson D, Goldberg MR, Hollister AS, Robertson RM. Clonidine raises blood pressure in severe idiopathic orthostatic hypotension. *Am J Med* 1983; **74:** 193–200.
10. Johnson RH. Autonomic failure and the eyes. In: Bannister R, ed. Autonomic failure. Oxford: Oxford University Press, 1983: 508–52.
11. Sternberg DE, Van Kammen DP, Lake CR, Ballenger JC, Mander SR, Bunney WE. The effect of pimoside on CSF norepinephrine in schizophrenia. *Am J Psychiatry* 1981; **138:** 1045–51.
12. Post RM, Jimerson DC, Ballenger JC, Lake CR, Uhde TW, Goodwin FK. CSF norepinephrine and its metabolites in manic-depressive illness. In: Post RM, Ballenger JC, eds. Frontiers of chemical neuroscience, vol 1: Neurobiology of mood disorders. Baltimore: Williams and Wilkins, 1984: 539–53.
13. Sharpless NS, Tyce GM, Thal LJ, Waltz JM, Tabaddor K, Wolfson LI. Free and conjugated dopamine in human ventricular fluid. *Brain Res* 1981; **217:** 107–18.
14. Asberg M, Bertilsson L, Martensson B, Scalia-Tomba GP, Thoren P, Traskman-Bendz L. CSF monoamine metabolites in melancholia. *Acta Psychiatr Scand* 1984; **69:** 201–19.
15. Dunnette J, Weinshilboum RM. Inheritance of low immunoreactive human plasma dopamine hydroxylase. *J Clin Invest* 1977; **60:** 1080–87.
16. Lieshout JJ, Wieling W, Montfrans GA van, Settels JJ, Speelman JD, Endert E, Karemaker JM. Acute dysautonomia associated with Hodgkin's disease. *J Neurol Neurosurg Psychiatry* 1986; **49:** 830–32.
17. Nanda RN, Boyle FC, Gillespie JS, Johnson RH, Keogh HJ. Idiopathic orthostatic hypotension from failure of noradrenaline release in a patient with vasomotor innervation. *J Neurol Neurosurg Psychiatry* 1977; **40:** 11–19.
18. Robertson D, Goldberg MR, Onrot J, et al. Isolated failure of autonomic noradrenergic neurotransmission. *N Engl J Med* 1986; **314:** 1494–97.
19. Dancis J. Familial dysautonomia (Riley-Day syndrome). In: Bannister R, ed. Autonomic failure. Oxford: Oxford University Press, 1983: 615–41.
20. Freedman LS, Ebstein RP, Goldstein M, Axelrod FB, Dancis J. Serum dopamine beta-hydroxylase in familial dysautonomia. *J Lab Clin Med* 1975; **85:** 1008–12.
21. Weinshilboum RM, Axelrod J. Reduced plasma dopamine-beta-hydroxylase activity in familial dysautonomia. *N Engl J Med* 1971; **285:** 938–42.
22. Joh TH, Beatge EE, Reis DJ. Molecular biology of catecholamine neurons. Similar gene hypothesis. *Hypertension* 1984; II-1-II-6.
23. Powell JF, Boni C, Lamoroux A, Craig IW, Mallet J. Assignment of the human tyrosine hydroxylase gene to chromosome 11. *FEBS Lett* 1984; **175:** 37–40.

CONGENITAL DOPAMINE BETA-HYDROXYLASE DEFICIENCY *

SIR,—The suggestion that the impaired β-hydroxylation of dopamine in our patient could be due to reduced availability of copper, the co-factor for dopamine-β-hydroxylase (EC 1.14.17.1), as in Menkes' disease[1] or in Ehlers-Danlos syndrome type IX, is interesting. In Menkes' syndrome and in some X-linked forms of Ehlers-Danlos syndrome plasma copper and caeruloplasmin are decreased while urinary copper excretion is increased.[1,2] Our patient's plasma caeruloplasmin (0·39 g/l; normal 0·36–0·40) and copper (21·3 μmol/l; normal 10·2–26·0) levels were normal, and 24 h urinary copper excretion (below 100 μg) was not increased.

Furthermore, in the functional assay for plasma dopamine-β-hydroxylase[3] cupric sulphate was added in the incubation mixture in a final concentraion of 1 μmol/l to achieve optimum enzyme activity. Recovery of dopamine-β-hydroxylase activity in the patient's plasma was always complete. Addition of extra amounts of N-ethylmaleimide, cupric sulphate, or catalase had no effect.

In copper-deficient mottled mouse mutants, a reduced level of brain noradrenaline arising from a depressed in vivo conversion of dopamine to noradrenaline has been reported.[4,5] In contrast, the in vitro activity of brain and adrenal dopamine-β-hydroxylase activity, after addition of the missing co-factor copper, is increased and not decreased.[6,7] Neither in vitro (functionally) nor in vivo (immunohistochemically) were we able to demonstrate the dopamine-β-hydroxylase in our patient.

Monoamine oxidase also requires copper for optimum activity.[8] The increased excretion of homovanillic acid in our patient suggests that monoamine oxidase activity was not impaired.

* THE LANCET, MARCH 21, 1987

Our patient has some clinical findings in common with patients with Menkes' disease or Ehlers-Danlos type IX syndrome—ie, vomiting, hypothermia, hyperflexible joints, and syncopal episodes. Growth and intellectual development were normal in our patient. In Menkes' disease most patients die before the age of 3, because of degenerative brain disease, whereas our patient is 31 years old. She has no abnormal (steely) hair, no depigmentation, no cutis laxa, no scorbutic bone change, and no evidence of arterial disease, as seen in Menkes' syndrome.

We do not think that the syndrome of congenital dopamine-β-hydroxylase deficiency is causally related to either Menkes' disease or Ehlers-Danlos type IX syndrome.

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1. Horn N. Copper metabolism in Menkes' disease. In: Rennert OM, Chan WY, eds. Metabolism of trace metals in man: Vol II. Boca Raton, Florida: CRC Press, 1984: 25–52.
2. Danks DM, Camakaris J. Mutations affecting trace elements in humans and animals. *Adv Hum Genet* 1983; **13:** 149–216.
3. Kato T, Kusuya H, Nagatsu T, Nagatsu T. A simple and sensitive assay for dopamine-beta-hydroxylase activity by dual-wavelength spectrofotometry. *Biochem Med* 1974; **10:** 320–28.
4. Hunt DM, Johnson DR. Aromatic amino acid metabolism in brindled (Mo^{br}) and viable-brindled (Mo^{vbr}), two alleles at the mottled locus in the mouse. *Biochem Genet* 1972; **6:** 31–40.
5. Hunt DM, Johnson DR. An inherited deficiency in noradreneline biosynthesis in the brindled mouse. *J Neurochem* 1972; **19:** 2811–19.
6. Hunt DM. Primary defect in copper transport underlies mottled mutants in the mouse. *Nature* 1974; **249:** 852–54.
7. Hunt DM. Catecholamine biosynthesis and the activity of a number of copper-dependent enzymes in the copper deficient mottled mouse. *Comp Biochem Physiol* 1977; **57C:** 79–83.
8. Yamada H, Yasunobu KT. Monoamine oxidase II: Copper, one of the prosthetic groups of plasma monoamine oxidase. *J Biol Chem* 1962; **237:** 3077–82.

EFFECT OF UNNATURAL NORADRENALINE PRECURSOR ON SYMPATHETIC CONTROL AND ORTHOSTATIC HYPOTENSION IN DOPAMINE-BETA-HYDROXYLASE DEFICIENCY *

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Summary A patient with severe orthostatic hypotension due to dopamine-beta-hydroxylase deficiency was treated with the unnatural aminoacid D,L-threo-3, 4-dihydroxyphenylserine (DOPS) in the hope that it would serve as a substrate of aromatic-L-aminoacid decarboxylase to produce (−)-noradrenaline. With a dose of 500 mg twice daily by mouth, blood pressure rose gradually from 100/55 to 145/85 mm Hg, and orthostatic hypotension disappeared. After 4 months' treatment the patient is free of symptoms and able to live a normal life. DOPS switched on the production of noradrenaline and reduced the excessive production of dopamine. During treatment plasma noradrenaline rose normally after standing and after infusion of tyramine, a biogenic amine that liberates stored neurotransmitter from sympathetic nerve terminals.

* THE LANCET, NOVEMBER 21, 1987

These data demonstrate that in congenital dopamine-beta-hydroxylase deficiency dopamine instead of noradrenaline is released as the sympathetic neurotransmitter but that the integrity of the sympathetic neuron is otherwise intact.

Introduction

EARLY this year we described a novel orthostatic syndrome, apparently caused by congenital dopamine-beta-hydroxylase (EC 1.14.17.1, DBH) deficiency.[1] We hypothesised that the functional integrity of the sympathetic neuron was essentially intact in this syndrome but that, owing to DBH-deficiency, dopamine instead of noradrenaline was released as the neurotransmitter. If this hypothesis is correct, administration of the noradrenaline precursor D,L-threo-3, 4-dihydroxyphenylserine (DOPS) may cure this orthostatic syndrome. L-threo-DOPS, an unnatural aminoacid devoid of direct pressor activity, is converted into (−)-noradrenaline through a single decarboxylation step by aromatic-L-aminoacid decarboxylase (EC 4.1.1.28, ALAAD).[2] ALAAD is present in the cytoplasm of most tissues including the stomach, liver, brain, and kidney as well as in sympathetic nerves. Restoration of sympathetic function in our patient with DBH-deficiency by DOPS was tested by subjecting her to gravitational stress and by infusion of tyramine, a biogenic amine that liberates stored noradrenaline from sympathetic nerve terminals.

Methods

The patient did not use any drugs for three weeks before the study. After 3 days of placebo twice daily she was switched to D,L-threo-DOPS (Sigma Chemical Co, St Louis, USA) at 10 am and 10 pm by mouth. Blood pressure measurements, blood sampling, and sympathetic function tests were performed between 10 am and noon, after 1 h of supine rest. Arterial pressure was measured directly in a radial artery, the pressure transducer being fixed at the level of the heart. The electrocardiogram was recorded continuously. Arterial blood was sampled with the patient supine and after 5 min of standing at both 10 am and noon. During placebo and after 7 days of treatment tyramine HCl was given as iv bolus injections in incremental doses of 1, 2, 4, and 8 mg, into a femoral vein. The injections were given 10 min apart, 2 h after DOPS administration. 2 min after each injection arterial and venous blood samples were taken simultaneously. Throughout the study 24 h urine specimens were collected. The protocol was approved by the hospital ethical review committee and the patient gave written informed consent.

For measurement in plasma and urine, catecholamines and DL-threo-DOPS were extracted.[3] Catecholamines were quantitated by high performance liquid chromatography (HPLC) with electrochemical detection—3 μm 'Cp Microspher C-18' column; 30°C; 0·6 V; mobile phase 0·23 mol/l acetic acid and 0·05 mol/l sodium acetate containing 100 mg/l of ethylenediaminetetraacetic acid (EDTA) and sodium dodecylsulphate (SDS) each, and 25% of methanol. Addition of DOPS to plasma before or after extraction of catecholamines does not interfere with measurements of noradrenaline or dopamine. Tyramine, likewise, does not interfere with measurements of DOPS and catecholamines. The final concentration step for measurement of DOPS was performed in 0·4 mol/l instead of 0·08 mol/l acetic acid. Quantitation was done by HPLC with electrochemical detection (3 μm Cp microspher C-18 column; 35°C; 0·8 V; mobile phase 0·025 mol/l sodium

phosphate containing 100 mg/l of EDTA and SDS each, and 10% methanol, pH adjusted to 2·1 with phosphoric acid).

Results

Blood Pressure and Plasma Catecholamines

After the first 500 mg of D,L-threo-DOPS both supine and standing blood pressure increased, noradrenaline became detectable in plasma, and there was a decrease in the raised plasma dopamine concentration. During the next 2 weeks supine blood pressure rose gradually from 100/55 to 145/85 mm Hg and the orthostatic fall in blood pressure disappeared almost completely. Noradrenaline concentrations 12 h after dosing stabilised between 50 and 100 pg/ml and rose upon standing to 140–210 pg/ml. 2 h after dosing these concentrations were 100–190 pg/ml when the patient was supine and 300–500 pg/ml when she was standing. Basal and stimulated dopamine levels fell, but the rise in dopamine from 80–150 to 300–550 pg/ml after standing remained abnormal: in normal subjects basal dopamine values do not exceed 125 pg/ml and do not change after standing.[1] Concentrations of D,L-threo-DOPS 2 h after dosing were between 4 and 6·5 μg/ml and trough values were between 0·5 and 1 μg/ml; there was no evidence of drug accumulation. The fact that not only noradrenaline but also D,L-threo-DOPS rose after standing (by 5–35%) is evidence for release of the precursor after neuronal stimulation.

After 7 days of treatment the patient was completely free of symptoms. All orthostatic symptoms—tiredness, dizziness, faintness, and dimming of vision on standing or physical exertion—had completely disappeared. The patient reported that she felt better than ever before, slept well, and

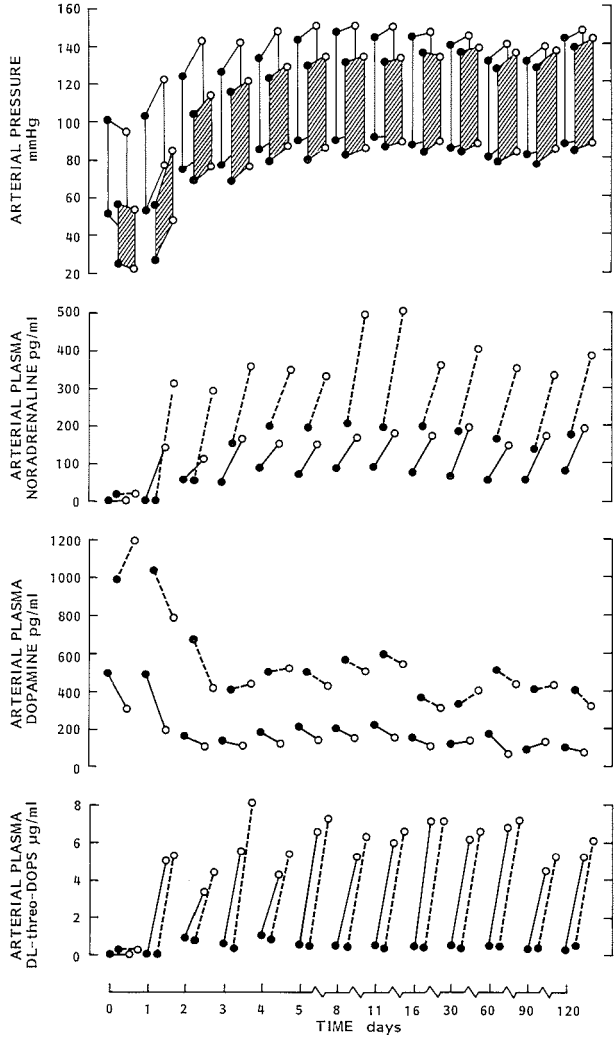

Fig 1—Effects of DL-threo-3, 4-dihydroxyphenylserine (DOPS)

Open columns and solid lines patient supine; hatched columns and broken lines, patient standing. ● = 12 h after dosing; ○ = 2 h after dosing.

did not experience her usual feeling of generalised weakness. Even early in the morning she was able to rise from her bed quickly, which contrasted with the distressing syncopal episodes that occurred regularly in the morning hours before treatment. She was able to cycle, climb stairs, and sit in the sun without feeling light-headed or faint. She did not report any side-effects or adverse reactions. Routine monitoring of haematological indices, blood chemistry, urine, and electrocardiogram did not reveal any significant changes. After 4 months of treatment the patient is still free of symptoms and lives a normal life.

Urinary Excretion of Catecholamines and DOPS

During placebo administration noradrenaline was not detectable in urine, whereas dopamine excretion was above normal (0·58–0·66 mg/24 h; normal 0·27 SD 0·06 mg/24 h, n = 40) (fig 2). After DOPS, noradrenaline excretion gradually rose to 1·0–2·1 mg/24 h, which is much higher than normal (11·4 SD 3·1 μg/24 h). As in plasma, dopamine fell to normal values. About 20% of the orally administered dose of D,L-threo-DOPS appeared unchanged in the urine.

Neuronal Release of Catecholamines and DOPS

Before treatment with DOPS tyramine hardly exerted any haemodynamic effect and did not cause plasma noradrenaline to rise to a detectable level (fig 3). Plasma dopamine and the venous/arterial (V/A) dopamine ratio, however, rose in a dose-dependent manner. This is evidence for excessive peripheral production of dopamine and its increased release in response to tyramine. During treatment with DOPS, tyramine caused a rise in plasma noradrenaline.

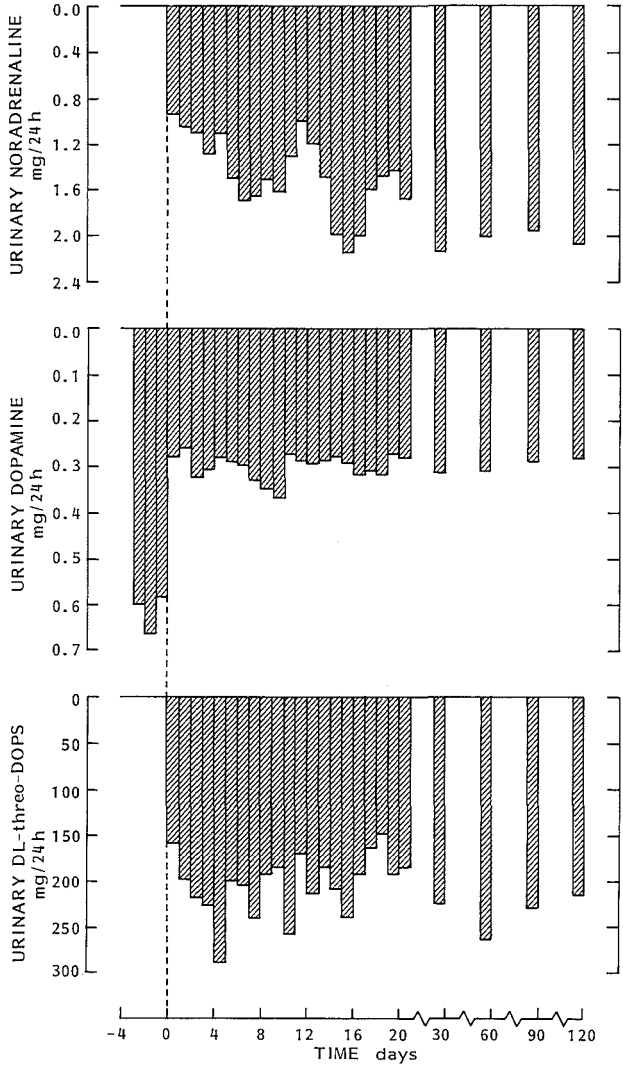

Fig 2—Effects of DOPS (see legend to fig 1) on urinary excretion or noradrenaline, dopamine, and DOPS.

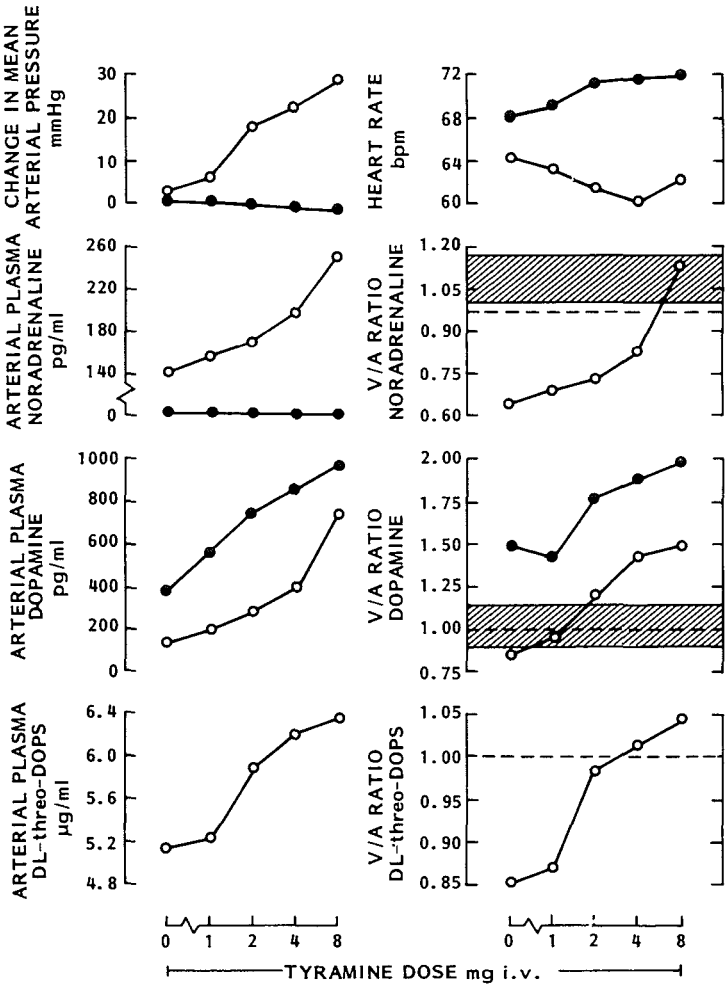

Fig 3—Effects of tyramine before (●) and after (○) treatment with DOPS (see legend to fig 1).

V/A = venous/arterial. Hatched areas indicate 95% confidence interval of V/A ratios for noradrenaline and dopamine for 30 untreated patients with borderline hypertension under basal conditions.

Net peripheral extraction of noradrenaline (V/A ratio 0·63) changed into net peripheral production (V/A ratio 1·12), after tyramine. Peripheral production of dopamine was strikingly reduced by DOPS; its V/A ratio decreased from 1·50 to 0·86. Although attenuated, the responses of dopamine and its V/A ratio to tyramine were still abnormal during treatment. Apparently, despite neuronal substitution of noradrenaline, large stores of dopamine were still available for displacement by tyramine. Further evidence for neuronal uptake of DOPS and for its subsequent release was obtained from measurements of DOPS in plasma after tyramine infusion. After tyramine, plasma DOPS rose in a dose-dependent manner and net peripheral extraction (V/A ratio 0·86) changed into net peripheral production (V/A ratio 1·05).

Discussion

These observations confirm the hypothesis that the sympathetic neuron in our patient with congenital DBH-deficiency was essentially intact but that dopamine instead of noradrenaline was released as the neurotransmitter. During treatment with D,L-threo-DOPS the production of noradrenaline was switched on and the excessive release of dopamine was switched off. Neuronal release of noradrenaline, which was absent before treatment, could be demonstrated after treatment by subjecting the patient to gravitational stress and by infusion of tyramine. More importantly, treatment resulted in almost complete disappearance of orthostatic hypotension and the patient became free of orthostatic symptoms. No unwanted side-effects were noted.

Noradrenaline could have been produced intraneuronally or extraneuronally before uptake and storage in sympathetic nerve terminals. Our observation that DOPS was released into the circulation by sympathetic stimulation and infusion of tyramine is evidence for intraneuronal production. Thus, it appears that DOPS is taken up by sympathetic nerves where it is exposed to neuronal ALAAD.

Production of noradrenaline from DOPS has been reported in patients with autonomic failure due to familial amyloid polyneuropathy.[4,5] However, in these patients the orthostatic fall in blood pressure could not be prevented and evidence for neuronal production and release of noradrenaline was not obtained. This suggests that in autonomic neuropathy, accompanied by loss of nerve fibres, noradrenaline is produced extraneuronally from DOPS, thereby escaping physiological control by the baroreflex.

Our in-vivo observations with D,L-threo-DOPS are at variance with experiments in vitro, which have shown that with respect to ALAAD D-threo-DOPS is a competitive inhibitor of decarboxylation of L-threo-DOPS below equimolar concentrations, and a noncompetitive inhibitor above equimolar concentrations.[6] Probably in vivo it is L-DOPS that is selectively exposed to ALAAD. Separate measurements of D- and L-DOPS in plasma and urine will be required to answer the question of how these stereo-isomers are handled in the body.

Neuronal production of noradrenaline after DOPS did not completely turn off the excessive production of dopamine under conditions of stimulation. It could be argued that noradrenaline should inhibit tyrosine hydroxylase, the rate-limiting enzyme in the biosynthetic cascade, and reduce the production and abnormal storage of dopamine. However,

endogenous L-DOPA is a competitive inhibitor of L-DOPS on ALAAD.[6] More importantly, L-DOPA is a better substrate for ALAAD than DOPS, particularly at physiological pH. The optimum pH for the formation of dopamine from L-DOPA is 7·0,[7] whereas the optimum pH for the formation of noradrenaline from DOPS is 8·6.[6] When pH was increased from 7·0 to 8·6 the rate of formation of noradrenaline from DOPS increased six fold. Thus, our finding that dopamine production did not entirely return to normal is not unexpected.

In conclusion, DBH deficiency is one of those experiments of nature that allow the clinican to collect crucial information on the physiological role of the different catecholamines. Noradrenergic neurotransmission was restored and excessive dopamine production was suppressed by the oral adminstration of an alternative substrate that bypasses the enzyme defect.

REFERENCES

1. Man in't Veld AJ, Boomsma F, Moleman P, Schalekamp MADH. Congenital dopamine beta-hydroxylase deficiency: a novel orthostatic syndrome. *Lancet* 1987; i: 183–87.
2. Reches A, Jackson-Lewis V, Fahn S. DL-threo-DOPS as a precursor of noradrenaline. *Naunyn-Schmiedeberg's Arch Pharmacol* 1985; **331**: 202–08.
3. Smedes F, Kraak JC, Poppe H. Simple and fast solvent extraction system for selective and quantitative isolation of adrenaline, noradrenaline and dopamine from plasma and urine. *J Chromatogr* 1982; **231**: 25–39.
4. Suzuki T, Higa S, Sakoda S, et al. Effect of infused L-threo-3, 4-dihydroxyphenylserine on adrenergic activity in patients with familial amyloid polyneuropathy. *Eur J Pharmacol* 1980; **17**: 429–35.
5. Suzuki T, Higa S, Sakoda S, et al. Orthostatic hypotension in familial amyloid polyneuropathy: treatment with DL-threo-3, 4-dihydroxyphenylserine. *Neurology* 1981; **31**: 1323–26.
6. Inagaki C, Tanaka C. Characteristics of enzymatic decarboxylation of L-threo-3, 4-dihydroxyphenylserine using hog renal L-aromatic aminoacid decarboxylase. *Biochem Pharmacol* 1978; **27**: 1081–86.
7. Boomsma F, Van der Hoorn FA, Schalekamp MADH. Determination of aromatic L-aminoacid decarboxylase in human plasma. *Clin Chim Acta* 1986; **159**: 173–83.

HOOFDSTUK 6

SAMENVATTING

Orthostatische hypotensie kan worden veroorzaakt door een groot scala van aandoeningen, waaronder verschillende vormen van dysfunctie van het autonome zenuwstelsel. Dit proefschrift beschrijft een ziektebeeld met ernstige orthostatische hypotensie tengevolge van een nieuwe vorm van autonome dysfunctie.

Diagnose

Een vrouw van 21 jaar werd wegens ernstige orthostatische hypotensie naar ons verwezen. In het eerste levensjaar waren ptosis van het bovenooglid en hypotonie van de skeletspieren reeds opgevallen en traden recidiverende hypoglycaemieën op. De orthostatische hypotensie bleek te berusten op autonome dysfunctie. Deze werd gekarakteriseerd door selectieve noradrenerge denervatie, terwijl de baroreflex afferenten en de cholinerge innervatie intact waren. Er bleek eveneens een bijniermerginsufficiëntie te bestaan, terwijl de bijnierschorsfunctie intact was.
Noradrenaline en adrenaline waren niet aantoonbaar in plasma, urine en liquor cerebrospinalis. Dopamine was echter 7- tot 12-voudig verhoogd in plasma, 4-voudig verhoogd in urine en 20-voudig in de liquor. Meting van catecholamine metabolieten leverde verdere steun voor de veronderstelling, dat de omzetting van dopamine in noradrenaline gestoord was. Inderdaad bleek dopamine beta-hydroxylase activiteit afwezig in plasma en liquor. Dit enzym is

verantwoordelijk voor de omzetting van dopamine in noradrenaline.
Een aantal fysiologische en farmacologische manoeuvres om sympathische activiteit te stimuleren veroorzaakte toename van dopamine in plasma, terwijl noradrenaline ook dan niet aantoonbaar was. Deze gegevens brachten ons tot de conclusie dat we hier te maken hadden met een nieuwe oorzaak van autonome dysfunctie, namelijk congenitale dopamine beta-hydroxylase deficiëntie. De waarnemingen suggereerden, dat de functionele integriteit van het sympathisch neuron intact was maar dat, in plaats van noradrenaline, dopamine als neurotransmitter werd vrijgemaakt.

Kopermetabolisme

De gestoorde omzetting van dopamine in noradrenaline bleek niet te berusten op deficiëntie van de voor dopamine beta-hydroxylase activiteit noodzakelijke co-factor koper. Het plasma en urine koper gehalte was normaal, evenals het ceruloplasmine gehalte van plasma.

Behandeling

De patiënte werd behandeld met het niet-natuurlijke aminozuur D,L-threo-3,4-dihydroxyfenylserine (DOPS). DOPS, vroeger ook wel carboxylnoradrenaline genoemd, kan *in vitro* door aromatisch L-aminozuur decarboxylase worden omgezet in noradrenaline via één enkele decarboxyleringsstap. Metingen van aromatisch L-aminozuur decarboxylase in plasma en liquor wezen erop, dat de activiteit van dit enzym bij patiënte normaal was.
Bij een dosering van 2 maal daags 500 mg DL-threo-DOPS

steeg de liggende bloeddruk geleidelijk van 100/55 tot 145/85 mm Hg in enkele dagen. De orthostatische hypotensie verdween. Na 4 maanden behandeling was patiënte geheel klachtenvrij en leidde zij een normaal leven. Na behandeling met DOPS verscheen noradrenaline in plasma en verminderde de excessieve produktie van dopamine. Na orthostatische stimulatie steeg het noradrenaline in plasma normaal evenals na infusie van tyramine, een biogeen amine dat opgeslagen noradrenaline vrijmaakt uit sympathische zenuwuiteinden.

Deze gegevens bevestigden onze hypothese, dat de functionele integriteit van het sympathisch neuron intact is bij deze ziekte, doch dat dopamine in plaats van noradrenaline wordt vrijgemaakt.

SUMMARY

Diagnosis

A woman was referred with severe orthostatic hypotension at the age of 21. Ptosis, skeletal muscle hypotonia and recurrent hypoglycaemia had been noticed in early childhood. There was noradrenergic denervation and adrenomedullary failure but baroreflex afferents, cholinergic innervation and adrenocortical function were intact. Noradrenaline and adrenaline were undetectable in plasma, urine and cerebrospinal fluid, but dopamine was 7-fold to 12-fold normal in plasma, 4-fold normal in urine and 20-fold normal in cerebrospinal fluid. Measurements of catecholamine metabolites showed further evidence for impairment of noradrenaline and adrenaline biosynthesis due to deficient dopamine beta-hydroxylation. Dopamine beta-hydroxylase was undetectable in plasma and cerebrospinal fluid. Physiological and pharmacological stimuli of sympathetic neurotransmitter release caused increases in plasma dopamine rather than plasma noradrenaline.

Copper metabolism

Lack of dopamine beta-hydroxylase activity could not be explained by deficiency of its co-factor copper. Plasma copper concentrations were normal, urinary copper excretion was not increased and plasma caeruloplasmin was also normal.

Treatment

The patient was treated with the unnatural aminoacid D,L-threo-3,4-dihydroxyphenylserine (DOPS) in the hope that it would serve as a substrate of aromatic-L-aminoacid decarboxylase to produce (–)-noradrenaline. With a dose of 500 mg twice daily by mouth, blood pressure rose gradually from 100/55 to 145/85 mm Hg, and orthostatic hypotension disappeared. After 4 months' treatment the patient was free of symptoms and able to live a normal life. DOPS switched on the production of noradrenaline and reduced the excessive production of dopamine. During treatment plasma noradrenaline rose normally after standing and after infusion of tyramine, a biogenic amine that liberates stored neurotransmitter from sympathetic nerve terminals. These data demonstrate that in congenital dopamine beta-hydroxylase deficiency dopamine instead of noradrenaline is released as the sympathetic neurotransmitter but that the integrity of the sympathetic neuron is otherwise intact.

TOEKOMSTIG ONDERZOEK

Inmiddels hebben wij een tweede patiënte met deze ziekte in Nederland gevonden (1), (Drs. J. Lenders en Th. Thien). Patiënten met dopamine beta-hydroxylase deficiëntie bieden een unieke mogelijkheid om de functie van dopamine bij de mens te bestuderen. Dopamine wordt o.a. van belang geacht bij de regulatie van de prolactine secretie, de slaap en de natriumexcretie door de nier. De in hoofdstuk 5 beschreven resultaten van de behandeling van onze patiënte met DL-threo-DOPS wijzen erop dat dit middel wordt opgenomen in de sympathische zenuweinden. Door metingen van L- en D-threo-DOPS kan meer inzicht verkregen worden in dit proces. Nu het ziektebeeld van de dopamine beta-hydroxylase deficiëntie is gedefinieerd kan getracht worden het genetisch defect te karakteriseren. Tenslotte kan de invloed van dopamine op de dopamine receptordichtheid worden onderzocht, daar behandeling met DOPS de dopamine produktie vermindert. De volgende studies zijn voltooid, in bewerking of in een gevorderd stadium:

1. Karakterisering van het genetisch defect (dr. J. Mallet, Parijs en dr. B. Oostra, Rotterdam).
2. In vivo-meting van dopamine receptoren met behulp van Positronen Emissie Tomografie (dr. W. Rutgers, Groningen).
3. Effecten van behandeling met dopamine antagonisten en DOPS op prolactine suppressie (Prof.dr. S.W.J. Lamberts, Rotterdam).

4. Effecten van behandeling met dopamine antagonisten en DOPS op de slaap en verschillende slaapstadia (drs. J. Tulen, Rotterdam).
5. Farmacokinetische en farmacodynamische interactie tussen D- en L-threo-DOPS (dr. F. Boomsma, Rotterdam, 2).
6. Catecholamine metabolisme voor en na het starten en stoppen van behandeling met DOPS (dr. C. Julien, Lyon, dr. P. Moleman, Rotterdam).
7. Effecten van dopamine antagonisten en DOPS op de druknatriurese.

Literatuur:

1. Man in 't Veld AJ, Boomsma F, Lenders J, Julien C, Lamberts S, Moleman P, Tulen J, Thien T, Schalekamp MADH. "Patients with dopamine beta-hydroxylase deficiency: a lesson in catecholamine physiology. *Am J Hypertension* 1988, in press.
2. Boomsma F, Van der Hoorn FAJ, Man in 't Veld AJ, Schalekamp MADH. Determination of DL-threo-dihydroxyphenylserine and the D- and L-enantiomers in plasma and urine. *J Chromatography* 1988, in press.

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LIJST VAN PUBLICATIES

1. Man in 't Veld AJ, Zeedijk H. "De invloed van ozon op belastbaarheid van sportlieden". *Tijdschrift voor Sociale Geneeskunde* 1972; 12: 441-446.
2. Schalekamp MADH, Kolsters G, Verhoeven RP, Man in 't Veld AJ, Birkenhager WH, Lever AF. "Possible role of the kidney in essential hypertension". In: *Advances in Nephrology*. Eds.: Giovannetti, Bonomini and Amico. Karger, Basel 1975; 327-333.
3. Derkx FHM, Van Gool JM, Wenting GJ, Man in 't Veld AJ, Schalekamp MADH. "Measurements of active and inactive renin precursor during stimulation of renin release". In: *Interference with mechanisms in hypertension* Ed. Birkenhager and Vandongen, Excerpta Medica, Amsterdam, 1976; 23-33.
4. Derkx FHM, Van Gool JMG, Wenting GJ, Verhoeven RP, Man in 't Veld AJ, Schalekamp MADH. "Inactive renin in human plasma". *Lancet* 1976; II: 496-500.
5. Wenting GJ, Man in 't Veld AJ, Verhoeven RP, Derkx FHM, Schalekamp MADH. "Volume-pressure relationships during development of mineralocorticoid hypertension in man". *Circulation Research* 1977; 40 suppl. 1: 163-170.
6. Schalekamp MADH, Man in 't Veld AJ, Verhoeven RP, Wenting GJ, De Bruyn JHB. "Hypertensive emergencies". *Netherlands Journal of Medicine* 1977; 20: 192-196.
7. Schalekamp MADH, Wenting GJ, Man in 't Veld AJ, Verhoeven RP, Derkx FHM. "Vasodilating drugs as a tool for pathophysiological studies in hypertension". In: *Hypertension, pathophysiological aspects* Ed. Birkenhager, Excerpta Medica, Amsterdam, 1977; 3-10.
8. Man in 't Veld AJ, Wenting GJ, Verhoeven RP, Schalekamp MADH. "Quantitative radiocardiography by single-probe counting using 99m-technetium albumin". *Netherlands Journal of Medicine* 1978; 21: 166-175.
9. Man in 't Veld AJ, Wenting GJ, Verhoeven RP, Schalekamp MADH. "Sympathetic and parasympathetic components of reflex cardiostimulation during vasodilator treatment of hypertension". *Clinical Science and Molecular Medicine* 1978; 55: 329s-332s.
10. Man in 't Veld AJ, Van Maanen JH, Schicht IM. "Stimulated sweating in chronic renal failure''. *British Medical Journal* 1978; 2: 172-173.
11. Schalekamp MADH, De Bruyn JHB, Derkx FHM, Wenting GJ, Man in 't Veld AJ. "The nature of low-renin hypertension". In: *Aldosterone antagonists in clinical medicine*. Excerpta Medica, Amsterdam, 1978; 442-448.

12. Derkx FHM, Wenting GJ, Man in 't Veld AJ, Verhoeven RP, Schalekamp MADH. "Control of enzymatically inactive renin in man under various pathological conditions: implications for the interpretation of renin measurements in peripheral and renal venous plasma". *Clinical Science and Molecular Medicine* 1978; 54: 529-538.
13. Derkx FHM, Verhoeven RP, Wenting GJ, Man in 't Veld AJ, Schalekamp MADH. "Renal release of active and inactive renin in essential and renovascular hypertension". *Clinical Science and Molecular Medicine* 1978; 55: 129s-132s.
14. Wenting GJ, Man in 't Veld AJ, Derkx FHM, Brummelen P van, Schalekamp MADH. "ACTH-dependent aldosterone excess due to adrenocortical adenoma: a variant of primary aldosteronism". *Journal of Clinical Endocrinology and Metabolism* 1978; 46: 326-335.
15. Derkx FHM, Verhoeven RP, Wenting GJ, Man in 't Veld AJ, Schalekamp MADH. "Renal Secretion of Inactive Renin". In: *Contributions to Nephrology* Eds. Berlyne and Brooklyn. Karger, Basel. 1978; 11: 160-163.
16. Man in 't Veld AJ, Wenting GJ, Schalekamp MADH. "Time course of haemodynamic changes induced by renal sodium retention in man; analogies to essential hypertension". In: *The kidney in arterial hypertension* Bunge Scientific Publishers, Utrecht 1979; 31-34.
17. Man in 't Veld AJ, Wenting GJ, Schalekamp MADH. "Does Captopril lower blood pressure in anephric patients ?" *British Medical Journal* 1979; 2: 1110.
18. Van Brummelen P, Man in 't Veld AJ, Schalekamp MADH. "Haemodynamics during long-term thiazide treatment in essential hypertension: differences between responders and nonresponders". *Clinical Science* 1979; 57: 359s-362s.
19. Schalekamp MADH, De Bruyn JHB, Derkx FHM, Wenting GJ, Man in 't Veld AJ. "Kenmerken van hypertensie met lage reninewaarden". In: *Hypertensie*. Excerpta Medica Amsterdam-Oxford, 1979; 37-43.
20. Derkx FHM, Wenting GJ, Man in 't Veld AJ, Verhoeven RP, Schalekamp MADH. "Evidence for activation of circulating inactive renin by the human kidney". *Clinical Science* 1979; 56: 115-120.
21. Derkx FHM, Tan-Tjiong HL, Man in 't Veld AJ, Schalekamp MPA, Schalekamp MADH. "Activation of inactive plasma renin by tissue kallikrein". *Journal of Clinical Endocrinology and Metabolism* 1979; 49: 765-769.
22. Derkx FHM, Tan-Tjiong HL, Man in 't Veld AJ, Schalekamp MPA, Schalekamp MADH. "Activation of inactive plasma renin by plasma and tissue kallikrein". *Clinical Science* 1979; 57: 351-357.
23. Derkx FHM, Man in 't Veld AJ, Schalekamp MADH. "Prekallikrein (Fletcher-factor)-dependent pathway for activating renin". *IRCS Medical Sciences* 1979; 7: 135.

24. Man in 't Veld AJ, Schicht IM, Derkx FHM, De Bruyn JHB, Schalekamp MADH. "Effects of an angiotensin converting enzyme inhibitor (Captopril) on blood pressure in anephric subjects". *British Medical Journal* 1980; 40: 288-290.
25. Man in 't Veld AJ, Wenting GJ, Boomsma F, Verhoeven RP, Schalekamp MADH. "Sympathetic and parasympathetic components of reflex cardiostimulation during vasodilator treatment of hypertension". *British Journal of Clinical Pharmacology* 1980; 9: 547-551.
26. Man in 't Veld AJ, Schalekamp MADH. "Haemodynamics of renoprival hypertension in man: studies during graded fluid withdrawal". *Clinical Science* 1980; 59: 165s-167s.
27. Man in 't Veld AJ, Wenting GJ, De Bruyn JHB, Schalekamp MADH. "Age-related differences in the long-term responses of systemic flow and resistance to mineralocorticoid excess in man". In: *Progress in Biochemical Pharmacology* 1980; 17: 44-53. Karger, Basel.
28. Van Brummelen P, Man in 't Veld AJ, Schalekamp MADH. "Haemodynamic changes during long-term thiazide treatment of essential hypertension in responders and nonresponders". *Clinical Pharmacology and Therapeutics* 1980; 27: 328-336.
29. De Graaf P, Man in 't Veld AJ, Schicht IM, Souveryn JHM. "Changes in the activity of S.G.O.T. and other enzymes after haemodialyses. Evidence of haemoconcentration as major cause". *Netherlands Journal of Medicine* 1980; 23: 14-17.
30. De Bruyn JHB, Wenting GJ, Man in 't Veld AJ, Derkx FHM, Schalekamp MADH. "Captopril affects blood pressure equally in renovascular and essential hypertension and in the fluid depleted anephric state". *Clinical Science* 1980; 59: 83s-86s.
31. Derkx FHM, Bouma BN, Tan-Tjiong HL, Man in 't Veld AJ, De Bruyn JHB, Wenting GJ, Schalekamp MADH. "The Plasma Kallikrein-Renin Connection". *Archives Internationales de Pharmacodynamie et Thérapie* 1980; 16: 165-177.
32. Schalekamp MADH, De Bruyn JHB, Wenting GJ, Man in 't Veld AJ, Derkx FHM. "Een nieuw aangrijpingspunt voor de behandeling van hypertensie: Captopril, een oraal werkzame remmer van de enzymatische omzetting van angiotensine I in angiotensine II". *Nederlands Tijdschrift voor Geneeskunde* 1980; 124: 1996-2003.
33. Derkx FHM, Bouma BN, Tan-Tjiong HL, Man in 't Veld AJ, De Bruyn JHB, Wenting GJ, Schalekamp MADH. "Plasma Kallikrein as an activator of inactive renin (prorenin). Studies in-vitro and in-vivo". In: *Hypertension: mechanisms and management* Ed. Philipp and Distler, Springer-Verlag. Berlin-Heidelberg-New York, 1980; 149-163.

34. Derkx FHM, Bouma BN, Tan-Tjiong HL, Man in 't Veld AJ, De Bruyn JHB, Wenting GJ, Schalekamp MADH. "Role of plasma kallikrein in the proteolytic activation of the renin angiotensin system". *Clinical and Experimental Hypertension* 1980; 2: 557-592.
35. Man in 't Veld AJ, Schalekamp MADH. "Pindolol acts as beta-adrenoceptor agonist in orthostatic hypotension: therapeutic implications". *British Medical Journal* 1981; 282: 929-931.
36. Man in 't Veld AJ, Wenting GJ, Schalekamp MADH. "Haemodynamics of early and sustained sodium-induced hypertension: consecutive measurements in man". In: *Hypertension in the young and old* Eds. Onesti and Kim. Grune and Stratton, New York 1981; 263-273.
37. Man in 't Veld AJ, Schalekamp MADH. "De invloed van intrinsieke sympathicomimetische activiteit (ISA) op de haemodynamische effecten van de beta-adrenoceptor blokkerende middelen bij de behandeling van hypertensie". *Sandorama* 1981; III-1-10.
38. Man in 't Veld AJ, Schalekamp MADH. "De invloed van intrinsieke sympaticomimetische activiteit (ISA) op de haemodynamische effecten van beta-adrenoceptor blokkerende middelen bij de behandeling van hypertensie". In: *Beta-blokkade met ISA. De klinische relevantie van blokkade met of zonder intrinsieke sympathicomimetische activiteit.* Ed. Van Zwieten. Stafleu's Wetenschappelijke Uitgeversmaatschappij BV, Alphen aan den Rijn, 1981; 37-55.
39. Man in 't Veld AJ, Schalekamp MADH. "Behandeling van orthostatische hypotensie door autonome dysfunctie met pindolol". In: *Beta-blokkade met ISA. De klinische relevantie van blokkade met of zonder intrinsieke sympathicomimetische activiteit.* Ed. Van Zwieten. Stafleu's Wetenschappelijke Uitgeverijmaatschappij BV, Alphen aan den Rijn, 1981; 28-36.
40. Man in 't Veld AJ, Schalekamp MADH. "Pindolol in postural hypotension". *Lancet* 1981; ii: 1279-1280.
41. Man in 't Veld AJ, Schalekamp MADH. "Pindolol acts as beta-adrenoceptor agonist in orthostatic hypotension". *British Medical Journal* 1981; 283: 561.
42. De Bruyn JHB, Man in 't Veld AJ, Wenting GJ, Boomsma F, Derkx FHM, Schalekamp MADH. "Cardiovascular effects of Captopril monotherapy in low-renin versus high-renin hypertension". In: *Recent advances in hypertension therapy: Captopril* Excerpta Medica 1981; p41-49, Amsterdam-Oxford-Princeton.
43. De Bruyn JHB, Man in 't Veld AJ, Wenting GJ, Derkx FHM, Schalekamp MADH. "Haemodynamic profile of captopril treatment in various forms of hypertension". *European Journal of Clinical Pharmacology* 1981; 20: 163-168.
44. Wenting GJ, Man in 't Veld AJ, Schalekamp MADH. "Time course of vascular resistance changes in mineralocorticoid hypertension of man". *Clinical Science* 1981; 61: 97S-100S.

45. Man in 't Veld AJ, Schalekamp MADH. "How intrinsic sympathomimetic activity modulates the haemodynamic responses to beta-adrenoceptor effects of beta-adrenoceptor agonists in patients with peripheral autonomic neuropathy". *British Journal of Clinical Pharmacology* 1982; 13: 367S-374S.
46. Man in 't Veld AJ, Schalekamp MADH. "Effects of beta-adrenoceptor agonists in patients with peripheral autonomic neuropathy". *British Journal of Clinical Pharmacology* 1982; 13: 367S-374S.
47. Man in 't Veld AJ, Schalekamp MADH. "Endogenous and exogenous agonist regulation of responses to beta-adrenoceptor agonists". Studies in patients with chronic autonomic failure. *Clinical and Experimental Pharmacology and Physiology* 1982; 9: 271-275.
48. Man in 't Veld AJ, Vincent HH, Schalekamp MADH. "Preferential desensitisation to cardiovascular beta-2-adrenoceptor stimulation in patients with peripheral autonomic neuropathy after treatment with Pindolol". *Clinical Science* 1982; 63: 467S-470S.
49. Man in 't Veld AJ, Wenting GJ, Schalekamp MADH. "Farmacotherapie van hypertensie met vasodilatatoren. Relaties tussen vaatverwijdende mechanismen en circulatoire homeostase". In: *Moderne Toepassing van vaatverwijders*. Ed. Van Zwieten. Stafleu's Wetenschappelijke Uitgeverijmaatschappij BV, Alphen aan den Rijn 1982; 34-65.
50. Man in 't Veld AJ, Lubsen J. "Milde hypertensie: behandelen of niet"? *Post Universitair Vraag en Antwoord Journaal* Medical World Press, IMS Communication Services, Holland BV.
51. Man in 't Veld AJ, Boomsma F, Schalekamp MADH. "Effecte von Beta-Rezeptoren-Agonisten und -Antagonisten bei Patienten mit peripherer autonomer Neuropathie". In: *Die Beta Rezeptoren-blockade aus pathophysiologischer Sicht* .Ed. H. Roskamm, H. Holzgreve, F.K. Schattauer Verlag, Stuttgart 1982;133-146.
52. Man in 't Veld AJ, Schalekamp MADH. "Hogyan befolyasolja az intrinsic szimpatomimetikus aktivitás a béta-adrenerg receptor blokkolók hemodinamikai hatását a hypertonia hezelése során". *Sandoz Revue*, 1982;18-25.
53. Man in 't Veld AJ, Schalekamp MADH. "The influence of intrinsic sympathomimetic activity (ISA) on the haemodynamic effects of beta-adrenergic receptor blockers in the treatment of hypertension". *The physician's Panorama* 1982;II:28-34.
54. Man in 't Veld AJ, Schalekamp MADH. "Influence exercée par l'activité sympathomimétique intrinsèque (ASI) sur les effects hémodynamiques des bèta-bloquants dans le traitement de l'hypertension artérielle". *Sandorama, panorama médical.* 1982;1: 32-38.
55. Man in 't Veld AJ, Schalekamp MADH. "Der Einfluss der spezifische sympathomimetischen Aktivität (ISA) auf die hämodynamische Wirkungen von Beta-Adrenozeptoren-blockern bei den Behandlung der Hypertonie". *Sandorama, das ärzliche Panorama.* 1982;32-38.

56. Vincent HH, Man in 't Veld AJ, Boomsma F, Wenting GJ, Schalekamp MADH. "Elevated plasma noradrenaline in response to beta adrenoceptor stimulation in man". *British Journal of Clinical Pharmacology* 1982;13: 717-721.
57. Wenting GJ, Man in 't Veld AJ, Derkx FHM, Schalekamp MADH. "Recurrence of hypertension in primary aldosteronism after discontinuation of spironolactone". Time course of changes in cardiac output and body fluid volumes. *Clinical and Experimental Hypertension* 1982;1727-1748.
58. Wenting GJ, Man in 't Veld AJ, Woittiez AJ, Boomsma F, Schalekamp MADH. "Treatment of hypertension with ketanserin, a new selective 5-HT2 receptor antagonist". *British Medical Journal* 1982;284:537-539.
59. Schalekamp MADH, Wenting GJ, de Bruyn JHB, Man in 't Veld AJ, Derkx FHM. "Haemodynamic effects of Captopril in essential and renovascular hypertension. Correlations with plasma renin". *Cardiovascular Reviews and Reports* 1982;3:651-658.
60. Schalekamp MADH, Wenting GJ, Man in 't Veld AJ. "Pathogenesis of mineralocorticoid hypertension". In: *Clinics in Endocrinology and Metabolism.* Ed.Biglieri, Saunders, 1982;10-3:397-417.
61. Wenting GJ, Woittiez AJ, Boomsma F, Man in 't Veld AJ, Schalekamp MADH. "Serotonin (5-HT) and blood pressure". Treatment of hypertension with a highly selective 5-HT receptor antagonist. *Clinical Science* 1982; 63:435 S-438 S.
62. Wenting GJ, de Bruyn JHB, Man in 't Veld AJ, Woittiez AJJ, Derkx FHM, Schalekamp MADH. "Haemodynamic effects of Captopril in essential hypertension, in hypertension with renal artery stenosis and in cardiac failure. Correlations of short-term and long-term effects with plasma renin". *American Journal of Cardiology* 1982; 49: 1453-1459.
63. De Bruyn JHB, Man in 't Veld AJ, Wenting GJ, Derkx FHM, Schalekamp MADH. "Haemodynamisch profiel van behandeling met Captopril bij hypertensie". In: *Captopril, een nieuw principe bij de behandeling van hoge bloeddruk en hartfalen.* Excerpta Medica, Amsterdam 1982; 59-70.
64. Wenting GJ, Man in 't Veld AJ, Woittiez AJJ, Boomsma F, Laird-Meeter K, Simoons ML, Hugenholtz PG, Schalekamp MADH. "Behandeling van ernstige acute en chronische decompensatio cordis met Captopril". In: *Captopril, een nieuw principe bij de behandeling van hoge bloeddruk en hartfalen. Excerpta Medica, Amsterdam 1982; 119-129.*
65. Van Zwieten PA, Man in 't Veld AJ. "Moderne toepassingen van beta-blokkers". *Post Universitair Vraag en Antwoord Journaal.* Medical World Press, IMS Communication Services, Holland BV, 1982.
66. Man in 't Veld AJ, Boomsma F, Schalekamp MADH. "Regulation of alpha- and beta adrenoceptor responsiveness. Studies in patients with chronic autonomic failure". *British Journal of Clinical Pharmacology* 1983;15: 507 S-519 S.

67. Man in 't Veld AJ, Schalekamp MADH. "Effects of 10 different beta-adrenoceptor antagonists on haemodynamics, plasma renin activity and plasma norepinephrine in hypertension: the key role of vascular resistance changes in relation to partial agonist activity". *Journal of Cardiovascular Pharmacology* 1983;5:S30-S45.
68. Man in 't Veld AJ, Schalekamp MADH. "On the antihypertensive mechanism of beta-adrenoceptor antagonists in relation to intrinsic sympathomimetic activity, cardioselectivity and hydrophilicity". *Journal de Pharmacologie* 1983;14 suppl II:69-104.
69. Man in 't Veld AJ, Schalekamp MADH. "Haemodynamic consequences of intrinsic sympathomimetic activity in relation to changes in plasma renin activity and noradrenaline during beta-blocker therapy for hypertension". *Postgraduate Medical Journal* 1983; 59 suppl 13:140-158.
70. Man in 't Veld AJ, Schalekamp MADH. "Interaction of the calcium antagonist nifedipine with the pressor responses of alpha-adrenoceptor agonists in patients with chronic autonomic failure". *Progress in Pharmacology* 1983;5/2:59-69
71. Man in 't Veld AJ, Schalekamp MADH. " How beta-blockers lower blood pressure: divulgence of the non-essentiality of cardiodepression and renin-suppression by partial agonism and the key role of vascular resistance changes". *Vascular Medicine* 1983; 1: 159-218.
72. Man in 't Veld AJ, Wenting GJ, Schalekamp MADH. "Een (hemo) dynamische visie op de relatie zout en hypertensie". *Hart Bulletin* 1983;14:101-108.
73. Man in 't Veld AJ, Schalekamp MADH. "Haemodynamic consequences of intrinsic sympathomimetic activity and cardioselectivity in beta-blocker therapy for hypertension". *European Heart Journal* 1983; 4D:31-41.
74. Man in 't Veld AJ, Schalekamp MADH. "Ambulatory blood pressure monitoring during administration of atenolol, metoprolol, pindolol and slow release propranolol". *British Medical Journal* 1983; 286: 306.
75. Schalekamp MADH, Man in 't Veld AJ, Wenting GJ. "Behandeling van hypertensie. Een blik in de toekomst". In: *Cardiovasculair 2000* Ed. van Zwieten. Stafleu's Wetenschappelijke Uitgeversmaatschappij BV, Alphen aan de Rijn, 1983;84-103.
76. Derkx FHM, Man in 't Veld AJ, Jones R, Reid JL, Schalekamp MADH. "DDAVP (1-desamino-8-D-arginine vasopressin) antagonist of the pressor action of endogenous vasopressin"? *Journal of Hypertension* 1983; 1 suppl 2:58-61.
77. Vincent HH, Boomsma F, Man in 't Veld AJ, Schalekamp MADH. "Beta-receptor stimulation by adrenaline elevates plasma noradrenaline and enhances the pressor responses to cold exposure and isometric exercise". *Journal of Hypertension* 1983; 1:74-76.

78. Vincent HH, Man in 't Veld AJ, Boomsma F, Derkx FHM, Wenting GJ, Schalekamp MADH. "Cardioprotection by blockade of beta-2-adrenoceptors". *European Heart Journal* 1983; 4-D:109-115.
79. Wenting GJ, Man in 't Veld AJ, Woittiez AJ, Boomsma F, Laird-Meeter K, Simoons ML, Hugenholtz PG, Schalekamp MADH. "Effects of Captopril in acute and chronic heart failure. Correlations with plasma levels of noradrenaline, renin and aldosterone". *British Heart Journal* 1983;49:65-76.
80. Derkx FHM, Tan-Tjiong L, Wenting GJ, Boomsma F, Man in 't Veld AJ, Schalekamp MADH. "Asynchronous changes in prorenin and renin secretion after Captopril in patients with renal artery stenosis". *Hypertension* 1983;5:244-256.
81. Schalekamp MADH, Vincent HH, Man in 't Veld AJ. "Adrenaline, stress and hypertension". *Lancet* 1983;i:362. (letter)
82. Man in 't Veld AJ. "Het advies inzake hypertensie van de Gezondheidsraad". *Nederlands Tijdschrift voor Geneeskunde* 1983; 127:2145-2147.
83. Man in 't Veld AJ, Schalekamp MADH. "Haemodynamics of beta-blockers" In: *Beta-blockers in the treatment of cardiovascular disease.* Eds. Kostis J, De Félice EA, Frishman WH. Raven Press, New York, 1984,229-251.
84. Man in 't Veld AJ, Schalekamp MADH. "Effects of beta-blockers in autonomic failure". In: *Beta-blockers in the treatment of cardiovascular disease.* Eds. Kostis J, De Félice EA, Frishman WH. Raven Press, New York, 1984, 197-210.
85. Man in 't Veld AJ, Schalekamp MADH. "Beta-blockers in hypertension: mechanism of action". In: *Beta-blockers in the treatment of cardiovascular disease.* Eds. Kostis J, De Félice EA, Frishman WH. Raven Press, New York; 75-93.
86. Wenting GJ, Man in 't Veld AJ, Woittiez AJ, Derkx FHM, Schalekamp MADH. "Captopril in the treatment of severe acute and chronic heart failure". *Progress in Pharmacology* 1984;108-112.
87. Wenting GJ, Woittiez AJ, Man in 't Veld AJ, Schalekamp MADH. "5-HT, alpha-adrenoceptors and blood pressure. Effects of Ketanserin in essential hypertension and autonomic failure". *Hypertension* 1984; 6:100-109.
88. Vincent HH, Boomsma F, Man in 't Veld AJ, Derkx FHM, Wenting GJ, Schalekamp MADH. "Effects of selective and non-selective beta-agonists on plasma potassium and norepinephrine". *Journal of Cardiovascular Pharmacology* 1984; 6:107-114.
89. Vincent HH, Man in 't Veld AJ, Boomsma F, Derkx FHM, Schalekamp MADH. "Effects of beta-agonists and blockers on plasma noradrenaline and potassium concentration". In: *Hypertension and coronary heart disease.* Ed.E. Dorhout Mees, Astra, 1984. P.O.box 1, 2280 AA Rijswijk, 1984; 129-142.

90. Man in 't Veld AJ. "Moderne sympathicolitica". In: *Moderne farmacotherapie bij hypertensie.* Ed. van Zwieten, De Medicus, Leiden, 1984;24-43.
91. Man in 't veld AJ, Wenting GJ, Schalekamp MADH. "Distribution of extracellular fluid over the intra- and extravascular space in hypertensive patients". *Journal of Cardiovascular Pharmacology* 1984;6:S143-S150.
92. Man in 't Veld AJ, Schalekamp MADH. "Mechanism of action of beta-blockers in hypertension; vasodilatation through blockade of presynaptic beta-receptors". In: *Physiological receptor antagonism; an attempt at a perspective.* Ed. van Zwieten, Stafleu's Wetenschappelijke Uitgeversmaatschappij BV, Alphen aan de Rijn, 1984;50-68.
93. Van den Meiracker A, Man in 't Veld AJ, Schalekamp MADH. "Acute and long-term haemodynamic studies of pindolol in hypertension". In: *Physiological receptor antagonism; an attempt at a perspective.* Ed. van Zwieten, Stafleu's Wetenschappelijke Uitgeversmaatschappij BV, Alphen aan de Rijn, 1984;69-73.
94. Van den Meiracker A, Man in 't Veld AJ, Ritsema van Eck H, Wenting GJ, Schalekamp MADH. "Direct 24-hours haemodynamic monitoring during the onset of the antihypertensive action of beta-blockers. Studies with pindolol". *Journal of Hypertension* 1984;2:5560-5568.
95. Wenting GJ, Tan-Tjiong HL, Derkx FHM, De Bruyn JHB, Man in 't Veld AJ, Schalekamp MADH. "Split renal function after captopril in unilateral renal artery stenosis". *British Medical Journal* 1984;288: 886-890.
96. Schalekamp MADH, Man in 't Veld AJ. "Mono-aminergic receptors and blood pressure". *Netherlands Journal of Medicine* 1985; 28: 83-90.
97. Man in 't Veld AJ. "De plaats van angiotensine I converting enzyme remmers bij de behandeling van hypertensie". In: *Vorderingen en praktijk.* Boerhaave Commissie, R.U. Leiden: 1984: 103-109.
98. Woittiez AJJ, Wenting GJ, Man in 't Veld AJ, Boomsma F, Schalekamp MADH. "Ketanserin, a possible tool for studying the role of serotonin in hypertension". *Journal of Cardiovascular Pharmacology* 1985; 7:5130-5136.
99. Vincent HH, Man in 't Veld AJ, Schalekamp MADH. "The adrenergic system and potassium balance". In: *Adrenergic blood pressure regulation.* Ed. WH. Birkenhäger, Excerpta Medica,1985:26-34.
100. Schalekamp MADH, Man in 't Veld AJ, Wenting GJ. "What regulates whole body autoregulation"? *Journal of Hypertension* 1985; 3-2:97-108.
101. Derkx FHM, Tan-Tjiong HL, Wenting GJ, Man in 't Veld AJ, Schalekamp MADH. "Use of Captopril in the diagnostic work-up of renoprival hypertension. In: *Ambulatory monitoring in hypertension.* Ed. Mallion, 1985.
102. Wenting GJ, Man in 't Veld AJ, Boomsma F, Schalekamp MADH. "Oscillation of bloodpressure in a patient with a phaeochromocytoma". In: *Ambulatory monitoring in hypertension.* Ed. Mallion, 1985.

103. Man in 't Veld AJ. "Het hoge bloeddrukprobleem in de lage landen". *The Practitioner,* 1985;april:315-318.
104. Vincent HH, Boomsma F, Man in 't Veld AJ, Schalekamp MADH. "Compound ICI 118.551, a beta-2-adrenoceptor antagonist, lowers blood pressure". *Journal of Hypertension,* 1985;3 Suppl.3: S247-S249.
105. Wenting GJ, Man in 't Veld AJ, Boomsma F, Schalekamp MADH. "Cyclic bloodpressure changes in a patient with a phaeochromocytoma. Role of a central oscillator?". *Journal of Hypertension,* 1985;3 Suppl.3: S437-S349.
106. Derkx FHM, Tan Tjiong HL, Wenting GJ, Man in 't Veld AJ, Schalekamp MADH. "Use of Captopril in the diagnostic work-up of renovascular hypertension". *Journal of Hypertension,* 1985;3 Suppl.3:S287-S289.
107. Schalekamp MADH, Man in 't Veld AJ. "Mechanism of antihypertensive action of beta-blockers. Role of presynaptic beta-receptors". In: *Hochdruck-therapie : Mechanismen und Konzepte,* Ed. Palm, Schattauer Verlag, 1985.
108. Vincent HH, Man in 't Veld AJ, Schalekamp MADH. "Prevention of epinephrine-induced hypokalemia". *American Journal of Cardiology,* 1985;56:10-14.
109. Man in 't Veld AJ. "Beta-blokkers bij hypertensie". *Hartbulletin,* 1985;16:5-10.
110. Man in 't Veld AJ, Schalekamp MADH. "Beta-blockers and vascular resistance; correlates with plasma renin and noradrenaline". *Portugese Journal of Cardiology* 1986;5 suppl 2:15-24.
111. Man in 't Veld AJ, Van den Meiracker AH, Schalekamp MADH. "The effect of beta-blockers on total peripheral resistance". *Journal of Cardiovascular Pharmacology,* 1986; 8 suppl. 4: S49-60.
112. Vincent HH, Boomsma F, Man in 't Veld AJ, Schalekamp MADH. "Stress levels of adrenaline amplify the blood pressure response to sympathetic stimulation". *Journal of Hypertension,* 1986;4:225-260.
113. Man in 't Veld AJ, Van den Meiracker AH, Ritsema van Eck HJ, Wenting GJ, Schalekamp MADH. "Blood pressure variability during ambulation, bedrest and sensory deprivation in hypertension and autonomic failure". In: *Adrenergic physiology and pathophysiology.* Ed. Christensen, Munksgaard Int. Publ. Ltd. Copenhagen, 1986: 116-126.
114. Meiracker van den AH, Man in 't Veld AJ, Ritsema van Eck HJ, Schalekamp MADH. "Systemic and renal vasodilatation after beta-blockade with pindolol: a hemodynamic study on the onset and maintenance of its antihypertensive effect". *American Heart Journal,* 1986; 112:368-374.
115. Woittiez AJ, Wenting GJ, Van den Meiracker AH, Ritsema van Eck HJ, Man in 't Veld AJ, Zantvoort FA, Schalekamp MADH. "Chronic effect of ketanserin in mild to moderate hypertension". *Hypertension,* 1986; 8,2: 167-173.

116. Van den Meiracker AH, Man in 't Veld AJ, Schalekamp MADH. "Acute and long-term haemodynamic effects of bopindolol". *The position of bopindolol, a new beta-blocker,* Royal Society of Medicine Services 1986;35-41.
117. Man in 't Veld AJ. "Beta-blockers in hypertension". *The position of bopindolol, a new beta-blocker,* Royal Society of Medicine Services 1986; 21-33.
118. Blankestijn P, Man in 't Veld AJ. "Twee gevallen van Methanol-intoxicatie". *Nederlands Tijdschrift voor Geneeskunde,* 1986; 130:1364-1367.
119. Man in 't Veld AJ. "The effect of beta-blockers on vascular resistance in hypertension". *American Journal of Cardiology,* 1986;59:21F-25F.
120. Schalekamp MADH, Woittiez AJJ, Wenting GJ, Van den Meiracker AH, Man in 't Veld AJ. "Ketanserin: haemodynamic effects and mechanism of action". *Journal of Hypertension,* 1986; 4(suppl 1):S7-S12.
121. Derkx FHM, Tan Tjong HL, Wenting GJ, Man in 't Veld AJ, Van Seyen AJ, Schalekamp MADH. "Captopril test for diagnosis of renovascular hypertension". *Renovascular hypertension,* Glorioso N, Laragh JH, Rappelli A, eds, New York, Raven Press, 1986.
122. Van den Meiracker AH, Man in 't Veld AJ, Schalekamp MADH. "Comparison of the onset of the antihypertensive action of pindolol and propranolol. A 24 hour haemodynamic study". *British Journal of Clinical Pharmacology,* 1987; 24-1:39S-45S.
123. Derkx FHM, Tan Tjiong HL, Van Seyen AJ, Wenting GJ, Man in 't Veld AJ, Schalekamp MADH. "Renal vein immunoreactive renin in patients with renal artery stenosis or essential hypertension". *Clinical and Experimental Hypertension,* 1987; 9:1341-1352.
124. Vincent HH, Man in 't Veld AJ, Boomsma F, Derkx FHM, Schalekamp MADH. " Is beta-1-antagonism essential for the antihypertensive action of beta-blockers?". *Hypertension* 1987; 9: 198-203.
125. Wenting GJ, Blankestein P, Poldermans D, Van Geelen J, Derkx FHM, Man in 't Veld AJ, Schalekamp MADH. "Blood pressure response of nephrectomized subjects and patients with essential hypertension to ramipril (HOE 498): indirect evidence that inhibition of tissue angiotensin converting enzyme is important". *American Journal of Cardiology,* 1987; 59: 92D-97D.
126. Van den Meiracker AH, Man in 't Veld AJ, Molinoff PB, Fischberg DJ, Schalekamp MADH. "Effects of pindolol and propranolol on haemodynamics and lymphocyte beta-receptors in essential hypertension". *Journal of Cardiovascular Pharmacology,* 1987; 10-S4:S55-S61.
127. Van den Meiracker AH, Man in 't Veld AJ, Ritsema van Eck HJ, Boomsma F, Derkx FHM, Schalekamp MADH. "The clinical pharmacology of bopindolol, a new long-acting beta-adrenoceptor antagonist in hypertension". *Clinical Pharmacology and Therapeutics,* 1987; 42:411-419.

128. Brouwer RML, Wenting GJ, Man in 't Veld AJ, Schalekamp MADH. "Role of alpha-adrenergic blockade in the cardiovascular actions of ketanserin. Studies in patients with essential hypertension, autonomic insufficiency and Raynaud's phenomenon". *Journal of Cardiovascular Pharmacology,* 1987; 10-S3:S26-S31.
129. Wenting GJ, Van den Meiracker AH, Simoons ML, Bos E, Ritsema van Eck HJ, Man in 't Veld AJ, Weimar W, Schalekamp MADH. "Circadian variations of heart rate but not of blood pressure after heart transplantation". *Transplantation Proceedings*, 1987; 19: 2554-2555.
130. Wenting GJ, Van den Meiracker AH, Ritsema van Eck HJ, Simoons ML, Bos E, Weimar W, Man in 't Veld AJ, Schalekamp MADH. "Lack of variation of blood pressure after heart transplantation". *Journal of Hypertension,* 1987; in press.
131. Wenting GJ, Derkx FHM, Tan-Tjiong HL, Van Seyen AJ, Man in 't Veld AJ, Schalekamp MADH. "Risk of angiotensin converting enzyme inhibition in renal artery stenosis". *Kidney International,* 1987; 31: S180-S183.
132. Man in 't Veld AJ, Boomsma F, Moleman P, Schalekamp MADH. "Congenital dopamine beta-hydroxylase deficiency". *Lancet,* 1987; i:183-188.
133. Man in 't Veld AJ, Boomsma F, Van den Meiracker AH, Schalekamp MADH. "Effect of unnatural noradrenaline precursor on sympathetic control and orthostatic hypotension in dopamine beta-hydroxylase deficiency". *Lancet,* 1987;ii:1172-1175.
134. Van den Meiracker AH, Man in 't Veld AJ, Ritsema van Eck HJ, Wenting GJ, Schalekamp MADH. "Determinants of short-term blood pressure variability: effects of bedrest and sensory deprivation in essential hypertension". *American Journal of Hypertension,* 1988, in press.
135. Wenting GJ, Brouwer RML, Van den Meiracker AH, Man in 't Veld AJ, Schalekamp MADH. "Mechanism of action of ketanserin in hypertension and vasospastic disease. *Acta Cardiologica*, 1988, in press.
136. Man in 't Veld AJ, Van den Meiracker AH, Schalekamp MADH. "Do beta-blockers really increase peripheral vascular resistance? Review of the literature and new observations under basal conditions". *American Journal of Hypertension,* 1988, in press.
137. Man in 't Veld AJ, Boomsma F, Lenders J, Julien C, Lamberts S, Moleman P, Tulen J, Thien T, Schalekamp MADH. "Patients with dopamine beta-hydroxylase deficiency: a lesson in catecholamine physiology. *American Journal of Hypertension,* 1988, in press.
138. Blankestijn PJ, Man in 't Veld AJ. "Ernstige methanolintoxicatie". *Tijdschrift voor medische analysten.* 1987;42-11:251-253.
139. Man in 't Veld AJ, Boomsma F, Schalekamp MADH. "Congenital dopamine beta-hydroxylase deficiency". *Birth Defects Encyclopedia,* 1988; Alan R. Liss. Inc. New York, in press.

140. Man in 't Veld AJ, Boomsma F, Schalekamp MADH (letter). "Copper metabolism in dopamine beta-hydroxylase deficiency". *Lancet* 1987; i: 693.
141. Man in 't Veld AJ (book review). "Orthostatic disorders of the circulation". *Lancet,* 1987:1240.
142. Man in 't Veld AJ, Van den Meiracker AH, Schalekamp MADH. " Age-dependency of blood pressure reponse to beta-blockade". *Journal of Cardiovascular Pharmacology,* 1988, in press.
143. Man in 't Veld AJ, Van den Meiracker AH. "Pindolol". In: *Current cardiovascular therapy,* ed. Messerli FH. Saunders Company, London, 1988, in press.
144. Man in 't Veld AJ. "Effects of antihypertensive drugs on peripheral vascular-hemodynamics". In: *Hypertension : pathophysiology, diagnosis and management.* Eds. Laragh JH and Brenner B., Raven Press, New York, 1988, in press.
145. Van den Meiracker AH, Man in 't Veld AJ, Fischberg DJ, Ritsema van Eck HJ, Molinoff P, Schalekamp MADH. "Acute and long-term effects of acebutolol on systemic and renal hemodynamics, body fluid volumes, catecholamines, active renin, aldosterone and lymphocyte beta- adrenoceptors". *Journal of Cardiovascular Pharmacology,* 1988, in press.
146. Van den Meiracker AH, Man in 't Veld AJ, Schalekamp MADH. "Haemodynamic effects of bopindolol". *Journal of Hypertension,* 1988, in press.
147. Van den Meiracker AH, Man in 't Veld AJ, Ritsema van Eck HJ, Schalekamp MADH. "Determinants of blood pressure and heart rate variabilities in man". *Journal of Hypertension,* 1987; 5(suppl 5): S475-S477.
148. Man in 't Veld AJ, Van den Meiracker AH, Schalekamp MADH. "How beta-blockers lower blood pressure." In: *Beta-blokkade tegen angina pectoris en hypertensie; focus op bisoprolol.* Ed. W.H. Birkenhager, Excerpta Medica, Amsterdam 1988, in press.
149. Boomsma F, Van der Hoorn F, Man in 't Veld AJ, Schalekamp MADH. "Determination of DL-threo-dihydroxyphenylserine and the D and L enantiomers in plasma and urine. "*Journal of Chromatography* 1988, in press.
150. Man in 't Veld AJ, Boomsma F, Schalekamp MADH. "Dopamine beta-hydroxylase deficiëntie, een les in catecholamine fysiologie." *Endocrinologie Nascholingscursus*, Noordwijkerhout 1987, 62-85.

VERANTWOORDING

Sinds 1975 heeft de auteur het voorrecht om onder leiding van Maarten Schalekamp bijdragen te mogen leveren aan het in dit proefschrift genoemde werk. Dit kwam tot stand binnen de afdeling Inwendige Geneeskunde I van het Academisch Ziekenhuis Dijkzigt in samenwerking met: P. Blankestijn, F. Boomsma, R.M.L. Brouwer, P. van Brummelen, J.H.B. de Bruyn, F.H.M. Derkx, D.J. Fischberg, P. de Graaf, C. Julien, G. Kolsters, S. Lamberts, J. Lenders, J.H. van Maanen, A.H. van den Meiracker, P. Moleman, P.B. Molinoff, D. Poldermans, H. Ritsema van Eck, I.M. Schicht, H.L. Tan-Tjiong, J. Tulen, R.P. Verhoeven, H.H. Vincent, G.J. Wenting en A.J.J. Woittiez.

NAWOORD

In 1967 naar Rotterdam. Twintig jaar later de vraag wat je heeft gebonden. Mensen; symbiosen in microcosmossen, die mijn macrocosmos vormen. Namen noemen is soms overbodig. De meeste zijn al vaak in dit werkje afgedrukt. Blijven de niet gedrukte namen. Zij, die met en voor mij zorgen en met wie ik zorgen draag: de anatomische grenzen en het steunweefsel van de macrocosmos. Dank voor het vertrouwen, omdat falen mag. Ook voor de commissie, die de twijfel over de laatste stelling met mij wilde delen.

Over ontspanning:

"Tegen onmatigheid in den bijslaap waarschuwt hij (Laurentius Frisius), en verhaalt, dat te Parijs een jongeling bij eene goede dochter door uitputting stierf... De geleerden openden het hoofd en vonden bijna geene hersenen."

Uit: Geschiedenis van de vroegere Geneeskunde en van hare Beoefenaren in Nederland door J. Banga, Leeuwarden 1868, W. Eekhoff, p. 23.