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IDIOPATHIC ORTHOSTATIC HYPOTENSION:
RECENT DATA (ELEVEN CASES) AND REVIEW OF THE LITERATURE

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16. Abstract The report covers a physiological and biochemical study of 8 cases of Shy-Drager syndrome and 3 of Bradbury-Eggleston idiopathic orthostatic hypotension. In all cases examination of circulatory reflexes showed major dysfunction of the sympathetic vasoconstrictor system. Anomalies in the vagal cardiomodulator system were less constant. Normal urinary elimination of catecholamines daily. Characteristically, no elevation of blood or urine norepinephrine levels in orthostatism. Insulin hypoglycemia normally raised urinary adrenalin elimination in 3 of 10 patients. Plasma DBH activity was normal. Renin-angiotensin-aldosterone system showed variable activity at basal state but usually rose during orthostatism. On average, very low homovanillic acid levels in cerebrospinal fluid before and after probenecid; hydroxyindolacetic acid normal. Cerebral autoregulation had deteriorated in 2 of 4 cases. Physiopathologically 2 clinical types indistinguishable with or without central neurological signs.			
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IDIOPATHIC ORTHOSTATIC HYPOTENSION:
RECENT DATA (ELEVEN CASES) AND REVIEW OF THE LITERATURE

J. Ninet , G. Annat , D. Boisson , L. Holznapfel , M. Vincent , L. Peyrin , D. Michel , B. Schott , M. Devic , R. Levrat , F. Deyrieux , J. Blum , M. Tartulier , J. Beaune and B. Renaud

Primary orthostatic hypotension with steady pulse was described/12* clinically by Bradbury and Eggleston (1925) [12]. In 1944 Pont [59] on the basis of animal experiments thought he was able to localize the responsible lesions at the bulbar and/or medullary level. He hypothesized a degenerative affection, more or less extensive but affecting in particular the autonomic nervous system (lateral chronic poliomyelitis or inferior polioencephalitis of the autonomic nuclei). In 1960 Shy and Drager [66] observed 2 patients for whom postural hypotension was accompanied by complex neurological signs that showed themselves progressively. The autopsy of one of these patients confirmed Pont's conclusions by indicating diffuse central lesions and lesions responsible for dysautonomy at the level of the dorsal vagal nucleus, the tractus intermediolateralis (TIL) and the sympathetic ganglia. Since then about fifty anatomical verifications have been reported in the literature but the nosological limits and the classification of the disease remain under discussion.

The major form comprises the Shy-Drager syndrome with central neurological signs, either purely extrapyramidal (Type I) or multiple (Type II) [3]. Mass involvement of the autonomic nervous system is the unifying factor and distinguishes it from idiopathic Parkinson's disease on the one hand and on the other from olivopontocerebellar or striatonigric atrophy. Anatomical data justify ascription of postural inadaptation to an interruption of the baroreflex arc, basically at the central and efferent preganglionic level, since cell loss steadily affects the vagal dorsal nucleus (parasympathetic system) and the TIL (first sympathetic neuron). A secondary role seems

* Numbers in the margin indicate pagination in the foreign text.

to be played by possible associated afferent or efferent peripheral lesions (irregular affection of sympathetic ganglia).

The Bradbury and Eggleston type of idiopathic orthostatic hypotension, defined by the presence of the dysautonomic syndrome alone, is sometimes a limited variant that corresponds to an early stage of the same disease and in other patients is a distinct entity. Localization of lesions along the reflex arc appears to be identical on the basis of the only two anatomoclinical observations in the literature that are complete [37, 61]. However, for some authors [40, 73] the chief role would be played by the predominant or even exclusive affection of the second postganglionic neuron.

Recent histochemical data [7, 56] tend to prove the unity of the disease. Histological lesions of the TIL are irregular. But in all cases there is an affection of the sympathetic ganglia with a breakdown at that level of DOPA-beta hydroxylase activity, a factor that appears to limit the activity of the postsynaptic noradrenergic neurons (normal activity of tyrosine hydroxylase and ACh transferase). Thus, the noradrenergic malfunctioning may be explained either by a primarily presynaptic affection of the TIL with transsynaptic anterograde degeneration or by a postsynaptic retrograde ganglionic degeneration in the direction of the TIL.

The aim of the present study is an attempt to define precisely by means of physiological and biological data the physiopathology of the postural disorder and of cerebral autoregulation and to find out whether it is possible to differentiate the two main clinical types of primary orthostatic hypotension.

Material and Methods

1. Clinical Characteristics

This study has to do with 11 patients suffering from an apparently primary orthostatic type of hypotension, who were hospitalized in a neurological department (7 cases), a cardiological de-

partment (2 cases) and a department of internal medicine (2 cases).

Group I, comprising 8 patients, 2 male and 3 female, presented symptoms of dysautonomy associated with neurological symptoms (Shy-Drager syndrome). The first symptoms appeared on the average 3 yr prior to hospitalization at average age 60 (ages 43-85) in the form, in 5 cases, of a dysautonomic syndrome of the orthostatic syncope type (Nos. 3, 8, 10) or of urinary incontinence (Nos. 2, 5) and, in 3 cases, of atypical cerebellar spasmodic neurological manifestations (Nos. 7, 9) or of polyneuritis (No. 1). The picture was completed within from 2 to 5 yr by the involvement of 3, 4 or 5 of the 7 systems (6 dysautonomic and 1 neurological) described in Table I.

TABLE I. CLINICAL CHARACTERISTICS OF 11 PATIENTS STUDIED

CAS n°	1	2	3	4	5	6	7	8	9	10	11
SEXE	M	M	M	F	F	F	M	M	F	F	F
AGE	72	60	71	77	50	63	69	59	56	87	48
ANCIENNETE DES TROUBLES	7	7	8	1	7	12	4	6	2	2	2
SIGNES NEUROLOGIQUES											
EXTRAPYR.	++	++	+		++		++	+			
MYO.	+										
CEREBEL.									++		
EMG	++	+			+						
PSY.	+										
S, DYSAUTONOMIQUES											
HYPOT. ORTHOST.	+	+	++	++	++	++	+	++	+	++	++
IMPUISSANCE			+					+			
INCONT. URIN.		++	+					+			
ANHYDROSE	+	+	+	+	+						
ANISOCORIE											
DYSF. ANO RECT.											
DIAGNOSTIC CLINIQUE	SD, SQ	SD, BE	SD, BE	SQ, BE	SQ, BE	SQ, SQ	SQ, SQ	SQ, SQ	SQ, BE		

Remarks: Length of disorders indicated in years

Clinical syndrome: ++ severe
+ overt
+ discrete

BE: Bradbury-Eggleston

SDI: Shy-Drager Type I, "Parkinson syndrome"

SDII: Shy-Drager Type II, "Plurisystematic atrophy"

Key: a. case number e. impotence
b. sex f. anhydrosis
c. length of disorders g. anisocoria
c' neurological signs h. clinical diagnosis
d. dysautonomic signs

Only the orthostatic hypotension is constant and the Parkinson syndrome is absent in only a single case (No. 9).

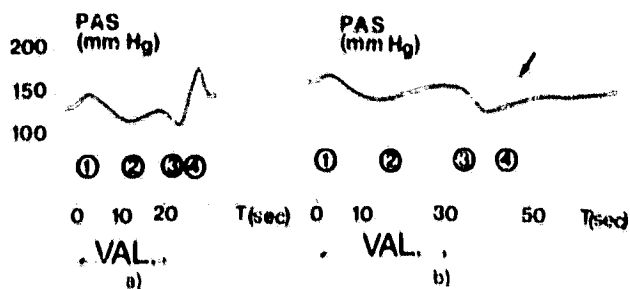


Fig. 1. Tensional changes observed during Valsalva test (VAL). a) Normal subject - Phase I: hypertensive peak with elevated intrathoracic pressure; Phase II: hypotension with depleted venous return followed by tensional correction (and tachycardia) on activation of baroreflex; Phase III: hypotension on violent reduction of hyperpressure in thoracic region at end of test; Phase IV: hypertensive rebound (and reflex brachycardia) on arteriolar vasoconstriction and restoration of venous return; b) subject with Shy-Drager syndrome (No. 9) - absence of hypertensive rebound in Phase IV (→)

a practically normal life.

In Group II, 3 female patients, the dysautonomic affection showed no particular features as compared with Group I. There was domination by the postural syndrome that constantly revealed the disease but was unaccompanied by any central neurological symptom (idiopathic orthostatic hypotension of Bradbury and Eggleston). In 2 cases the intermittent orthostatic complaints became syncopal over 2 and 10 years respectively of development and showed a secondary improvement because of the elastic containment of lower abdominal members, which was isolated [6] or associated with indomethacin [11]. In the latter case [4] the picture that presents itself as acute ictal becomes progressively worse, the patient is permanently bedridden and dies six months following first loss of orthostatic perception.

Four of the 6 patients who presented plurisystematic atrophy died, after from 2 to 7 yr disease development and 2 yr following appearance of the Parkinson syndrome, which was directly responsible for their invalid condition in 3 cases (except No. 10). The last 2 patients, presently under observation for 3 and 7 yr respectively, are greatly handicapped in the tensional and neurological areas. Two patients, now 6 and 8 yr respectively after 13 appearance of the clinical condition, show an isolated and moderate Parkinson. Their orthostatic hypotension, initially syncopal, has been attenuated by treatment that combines IMAO and DOPA [9] and they lead

2. Methods for Exploring Circulatory Reflexes

For all patients we recorded changes in BP and cardiac rate during a battery of tests that more or less selectively explored the baroreflex arc [35]. Cardiac rate was read on a continuous EKG and humeral BP measured with a cuff connected to a Hg manometer or recorded by bleeding.

The orthostatic test comprises measurements taken decubally following a night's rest, then every minute for at least 2 min in an immobile orthostatic position or in a seated position, if the patient's inability to stand has been established.

In the Valsalva test (Fig. 1) which also explores the integrity of the entire reflex arc, measurements are taken simultaneously before, during and immediately after a deep inspiration followed by an attempted expiration with glottis closed and of an intensity and duration not quantified in our record. For the Bannister [4] the hypertensive rebound, about 30 mm Hg in phase IV, evidences vaso-

constrictive sympathetic activity, and the tachycardia in phase II proceeds from the reflex suppression of the vagal tonus. Cardiac acceleration is normal above 21/min, insufficient at 11-20, insignificant or nonexistent below 10.

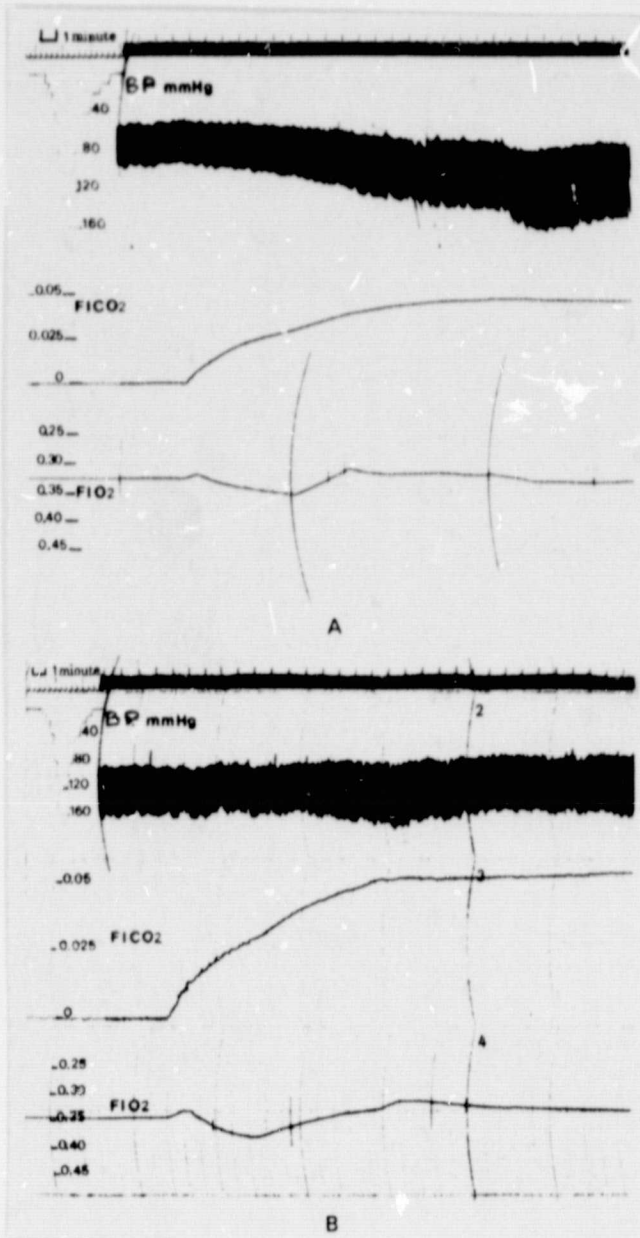


Fig. 2. Effect of paCO_2 increase due to inhalation of a CO_2 enriched gaseous mixture. Normal subject (upper record A); subject with Bradbury-Eggleston syndrome (No. 11) (lower B). FiCO_2 = fraction of CO_2 in inhaled gas; FiO_2 = fraction of O_2 in inhaled gas (kept constant)

Reactivity of the bulbar vasomotor centers was assessed by the hypercapnia test (Fig. 2A) using inhalation of a CO₂ enriched gaseous mixture (3-4% FiCO₂, FiO₂ constant). The increase in paCO₂ has a stimulating effect on the central vasomotor structures, inducing a general increase in sympathetic tonus which is a factor in elevated BP. As against this central effect, hypercapnia induces peripheral vasodilatation, but this is negligible and inadequate to counter elevated BP in the normal subject.

The stress response (sudden noise, mental arithmetic) and especially the cold test explore the integrity of the efferent sympathetic fibers intended for the arterioles. If the patient's hand is plunged for at least 60 sec in a basin of ice water, the normal reaction is an increase in tension which, starting with the first minute, reaches 16-20 mm Hg systolic and 12-15 diastolic [27].

The integrity of the cardiomodulator vagal fibers is judged by the response to operations of ocular and sinocarotid compression that are physiologically accompanied by cardiac retardation of 6-12 beats/min [59]. The effect of atropine is assayed prior to and each 2 min following an IV of 0.01-0.02 mg/kg up to minute 30. Heimbach [32] noted under the same conditions an average and maximal cardiac acceleration of 38±5 beats/min, dosage required for eliciting this response never being in excess of 0.03 mg/kg.

Finally, arteriolar and vagal reactivity were tested by an IV perfusion of norepinephrine (Levophed, registered trademark) in a dose of 1 microgram/kg/min [54].

These tests were complemented by a study of other functions of the autonomic nervous system, sudation and pupillomotor capability. The sudorimotor response of the adrenergic receptor was tested with pilocarpine (100 mg IM) and thermography used to evaluate adrenergic thermoregulatory vasomotor capability. Instillation of various col-14lyria made it possible to assess the functioning of the ocular receptors and the basal sympathetic or parasympathetic tonus.

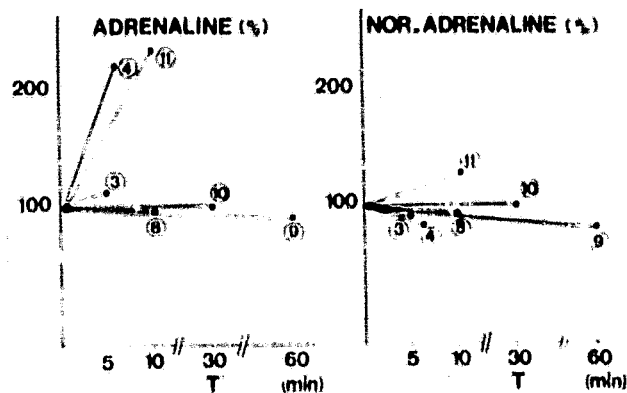


Fig. 3. Development, as a function of length of orthostatism, of concentration of plasma adrenalin and norepinephrine in subjects 3,4,8,9,10, 11. Results expressed in % of values observed following 12 hr decubitus.

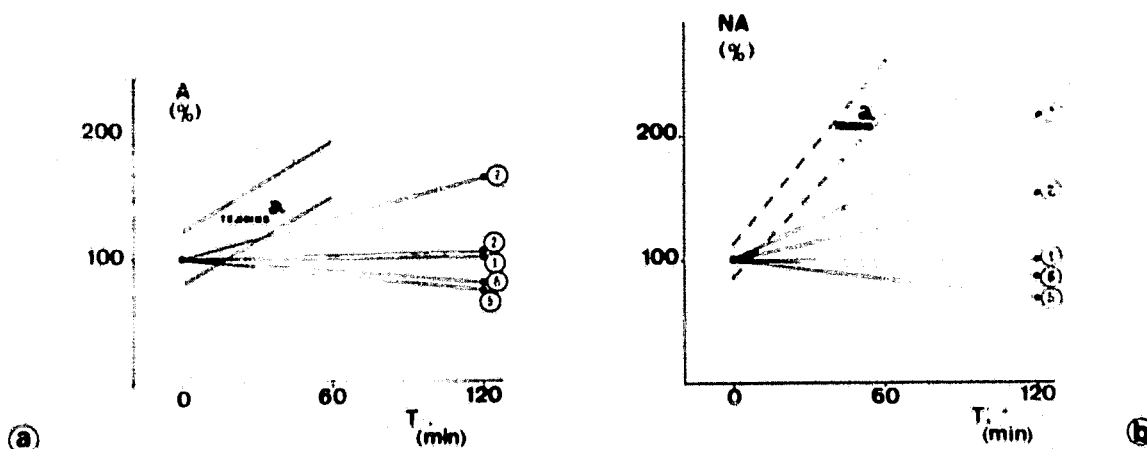


Fig. 4. Development, as a function of length of orthostatism, of urinary elimination output of adrenalin (A) and norepinephrine (NA) in subjects 1,2,5,6,7. Results expressed in % of values observed after 2 hr decubitus. Control values obtained under the same conditions by J. Juchmes [38] are shown.

Key: a. in all Figures "temoins" = controls

3. Biological Studies

For all patients tests were run under conditions of a normal sodium regime (ca 100 mM Na/day) in the absence of medication.

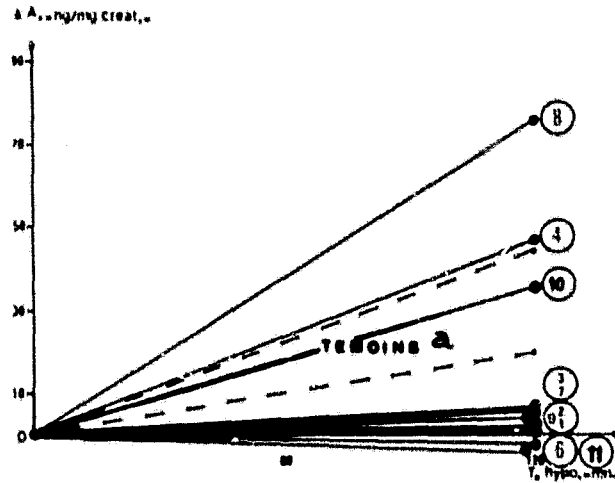


Fig. 5. Variation in urinary output of adrenaline in hypoglycemia. Y axis - increment in adrenalinuria expressed in ng/mg urinary creatinine; X axis - length of insulin hypoglycemia in minutes

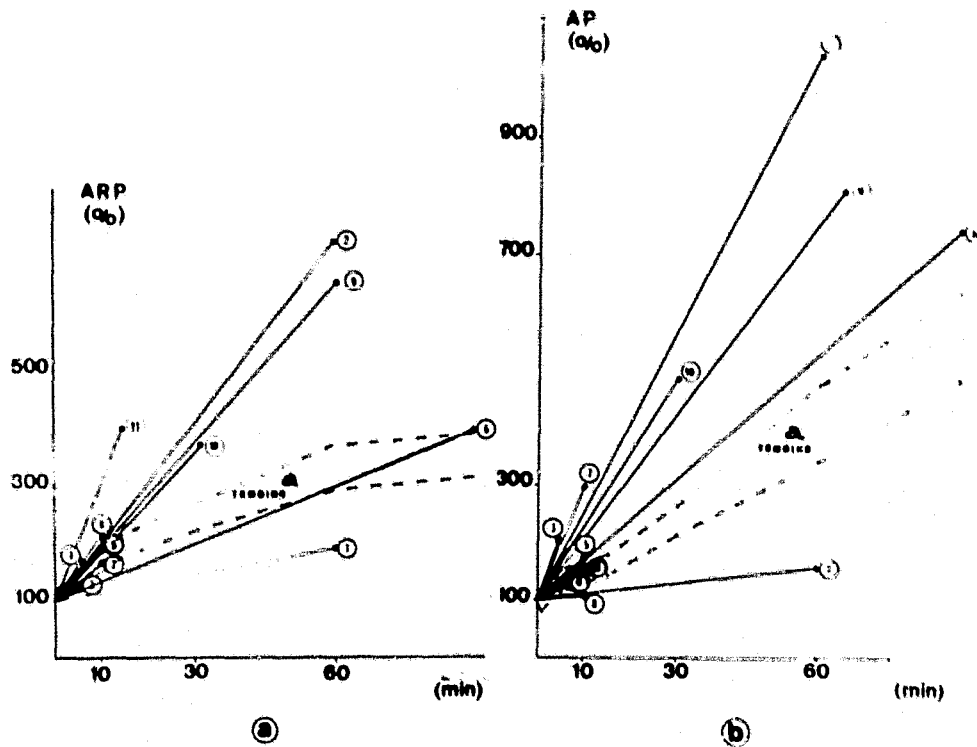


Fig. 6. Development, as a function of length of orthostatism, of plasma renin activity (ARP - a) and plasma aldosterone activity (AP - b). Results expressed in % of values observed after 1 hr decubitus. Test values obtained by Sassard [62] with normal subjects are shown.

TABLE II. RESPONSES OF 11 PATIENTS TO CIRCULATORY REFLEX TESTS

CAS n°	1	2	3	4	5	6	7	8	9	10	11
ORTHOST. (5min)											
PAS	50	45	56	55	70	70	55	65	45	55	115
PAD	20	25	26	25	60	30	25	?	10	?	34
F	16	20	6	10	10	24	21	15	6	0	0
VALSALVA											
PA (V)	0	0	0	0	0	0	0	0	0	0	0
F (H)	0	0	0	0	0	0	0	0	0	0	0
b FROID	0	0	0	0	+	+	0	0	+	0	0
STRESS	0	0	0	0	0	0	0	0	0	0	0
COMP. OCULARRE ^c	0	0	0	0	0	0	0	0	0	0	0
COMP. SINOC.	+	0	0	0	+	+	0	0	0	+	0
ATROPINE	0	±	-	0	0	+	±	±	0	0	0
NORADRENALINE											
PA	++	++	+	+	+	+	+	+	++	+	++
F	0	0	0	0	0	+	±	0	0	0	0

Response: ++ exaggerated PA = arterial pressure
 + normal PAS = systolic BP
 ± insufficient PAD = diastolic BP
 0 insignificant or zero F = cardiac rate
 - no test

Key: a. case b. cold c. ocular

MEANING OF ABBREVIATIONS

- A = adrenalin
- NA = norepinephrine
- MetaA = metadrenalin
- MetNA = normetanephrine
- MHPG = methoxy hydroxy phenyl glycol
- VMA = vanillyl mandelic acid
- HVA = homovanillic acid
- 5HIAA = 5-hydroxy indolacetic acid
- ARP = plasma renin activity
- AP = plasma aldosterone
- DBH = dopamine-beta-hydroxylase activity
- SB = cerebral blood flow (white matter)
- SG = cerebral blood flow (gray matter)

a) Urine Samples

Daily urinary elimination of catecholamines was dosed by the fluorometric method in respect to 1 or 3 consecutive diureses in 24 hr. Normal values \pm SEM (n = 22) [58]

A = 16 ± 3.4 mcg/24 hr; NA = 83 ± 10 mcg/24 hr; MetaA = 157 ± 20 mcg/24 hr; Met NA = 167 ± 19 mcg/24 hr.

VMA = 6.3 ± 4.2 mg/24 hr; HVA = 4 ± 1 mg/24 hr; MGPG = 0.93 ± 27 mg/24 hr.

Urinary output of adrenalin and norepinephrine were calculated on 2 hr diureses induced by a water load of 250 ml.

The decubital basal output, following a full night's rest, was compared with orthostatic yields (2 hr walking) and the hypoglycemic yield (ordinary insulin IV, 1 U/10 kg). Results are expressed in ng/mg creatinine (\pm SEM) and this makes it possible to ignore the low yield of renal filtration provoked by orthostatic hypotension.

Normal laboratory values:

- Decubitus [17]

- males (n = 4)

A = 27.8 ± 7.1 ng/mg creat.

NA = 121 ± 27 ng/mg creat.

- females (n = 4)

A = 17.4 ± 2.5 ng/mg creat.

NA = 89 ± 8 ng/mg creat.

- Hypoglycemia [50] (n = 10)

Δ adrenalin = $+ 31.9 (\pm 12.5)$ ng/mg creat.

Δ norepinephrine = $+ 55.6 (\pm 8)$ ng/mg creat.

- Orthostatism: in the absence of any concomitant study of healthy samples we compared our results with those of Juchmes [38] expressed during the first hr of walking in % basal value (n = 18: 10 men, 8 women): A - $171 \pm 21.4\%$, NA = $238 \pm 21.5\%$.

b) Blood Samples

Patients sampled were kept strictly in bed since the eve

and 20 ml were taken with a catheter from a vein in the forearm. The sample was kept at 4°C, then centrifuged and a measurement made of basal catecholamine values, plasma renin activity (PRA), aldosterone activity (PA) and dopamine-beta-hydroxylase (DBH). The same kind of sampling was done orthostatically after 5 and 90 min seated or standing and/or walking, depending upon clinical tolerance. PRA and DPH were measured also before and after insulin hypoglycemia. Finally, in the case of 3 patients there was a repetition of the renin and aldosterone dosage and an orthostatic test after 48 hr nonsodium regime and diuretic treatment (Diteriam, registered trademark, 2 cp/day).

Adrenalin and norepinephrine were separated on a CG 50 amberlite column and then dosed microfluorometrically.

Normal decubital values pg/ml \pm SEM [57]

- males: A = 47 \pm 9; NA = 190 \pm 56

- females: A = 25 \pm 7; NA = 89 \pm 16

Normal values following 1 hr seated pg/ml \pm SEM [54bis]

- males (n = 5): A = 83 \pm 18; NA = 375 \pm 45

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Plasma renin activity was determined by radioimmunological dosage of angiotensin I released [70].

Normal values ng/l/min \pm SEM:

decubitus 10 hr = 23.5 \pm 3.1

hypoglycemia (n = 9) 0 = 28.5 \pm 5.1 60 min = 61.9 \pm 9.5

orthostatism [62] (n = 12):

(results expressed in % decubital values for each patient at 100%)

0 = 100%; 5 min = 142 \pm 16.5%; 60 min = 329 \pm 38%;

90 min = 350 \pm 37%

Plasma aldosterone concentration was dosed by the solid phase radioimmunological method [6].

Normal values pg/ml \pm SEM:

decubitus 10 hr - 35 ± 4

orthostatism: 0 = 100%; 5 min = $132.2 \pm 17.6\%$;

60 min = $408.6 \pm 67.8\%$; 90 min = $558.9 \pm 77.1\%$

Plasma DBH activity was determined spectrophotometrically [52].

Normal value (IU \pm SD) decubitally = 24.1 ± 13.6

c) Central Neuromediator Metabolites

The analysis of the central neuromediator metabolites in the LCR was done with an IV probenecid test, associated in the case of 4 patients with a polygraph sleep recording. Two lumbar taps, from 1 to 3 days apart, were done at the same hour following 8 hr decubitus.

The first tap made it possible to define the basal metabolite count in the LCR.

Normal values (ng/ml \pm SEM) (5 samples) [60]:

HVA = 47 ± 8

5HIAA - 21 ± 3

The second, which followed 5 hr probenecid perfusion (75 mg/kg) gave an idea of the amount of metabolite regeneration in the LCR.

Normal values \pm SEM (5 samples) [60]:

HVA - 172 ± 30 ng/ml Δ HVA = 125 ± 28 ng/ml

5HIAA = 114 ± 19 ng/ml Δ 5HIAA = 93 ± 20 ng/ml

Probenecid = 18.3 ± 4 mcg/ml

4) Measurement of Cerebral Blood Flow

This was done by Xenon¹³³ inhalation and subtraction of 80 Kev - 30 Kev [47]. Recording was done at approximately the level of the same frontotemporal zones, first decubitally and then seated, 10 min following passage. The lavage curves trace a bi-exponential function corresponding to average blood flow in gray matter (steep) and white (shallow).

Normal values decubally (ml/min/100 g \pm SEM):

Gray matter = 60 \pm 5; white matter = 15 \pm 2

In a sitting position there was an average 4% drop in 3 samples for the gray matter and it was 17% for the white.

Results

1) Cardiovascular Responses (Table II)

From the first minute of orthostatism systolic and diastolic BP dropped on the average 61.9 and 28.3 mm Hg and cardiac rate accelerated 11.6 b/min. Seven patients presented an average basal rate of 85/min and insignificant or insufficient orthostatic tachycardia (less than 15/min). The other 4 patients showed a lower decubital rate (67/min) but it rose more than 15/min when they stood. /16

Response to the Valsalva was abnormal in all cases studied, with absence of tachycardia Phase II and/or hypertensive rebound Phase IV (Fig. 1).

When the paCO_2 was augmented, the single subject studied (No. 11) showed perceptible and abnormal lowering of BP (Fig. 2B).

Cold response was normal for 3 of the 10 cases studied, but not a single patient responded to stress.

Average tachycardia produced by atropine was insignificant (5.9/min). Only 1 of the 9 patients studied responded physiologically, while 3 others were the only patients sensitive to sinocarotid compression.

In all patients norepinephrine perfusion resulted in a major elevation of systolic and diastolic BP averaging 83 and 45.5 mm Hg. Reflex bradycardia was noted in only 2 of 11 cases and on the average remained negligible (2/min).

2) Biological Dosage

a) Catecholamines

For individuals daily urinary elimination of catecholamines varied greatly but was not notably different from normal subjects (10 patients studied):

VMA = 5.0 ± 0.6 mg/24 hr; A = 27.1 ± 5.6 mcg/24 hr; NA = 139 ± 29.4 mcg/24hr; MetA = 174.5 ± 42.1 mcg/24 hr; MetNA = 115.4 ± 23.2 mcg/24 hr; HVA = 2.2 mg/24 hr.

Elimination of methoxy-hydroxy phenyl glycol, likewise normal on average, 0.99 ± 0.2 mg/24 hr, nevertheless dropped in 3 of 7 patients studied (Nos. 2, 5, 7).

Decubital urinary output of adrenalin and norepinephrine as recorded for the 11 patients showed individual divergencies but on the average was normal both for women (A = 34.4 ± 8.4 ng/mg creat; NA = 124 ± 29.8 ng/mg creat) and for men (A = 26.5 ± 8.9 ng/mg creat; NA = 102 ± 33.5 ng/mg creat).

Decubital plasma amounts of adrenaline and norepinephrine showed a normal average in 6 patients (men: A = 72.5 ± 7.5 pg/ml; NA = 117 ± 3.5 pg/ml; women: A = 59.2 ± 40.8 pg/ml; NA = 259 ± 198 pg/ml). Individually the amounts were normal in 4 cases (Nos. 3, 4, 8, 11), down in one (No. 10) and up in one (No. 9).

In the orthostatic test (Figures 3 and 4) adrenalin or urinary adrenalin output increased for only 2 of 11 patients and there was never a satisfactory increase in noradrenalinemia or urinary norepinephrine output.

In hypoglycemia (Fig. 5) urinary output of adrenalin and nor- 17
epinephrine rose normally for only 3 of 10 patients studied.

b) Decubitally ARP (plasma renin activity) and AP (plasma aldosterone activity) vary greatly: normal in 5 cases, lower in 4, in-

creased in 1 case and in 1 case divergent. But on the average they are normal (ARP = 27.6 ± 10.2 ng/l/min; AP = 41.2 ± 7.9 pg/ml) and are connected by the following significant ratio (p less than 0.05):

$$\text{AP decubital} = 0.45 \text{ ARP decubital} + 28.8 \quad (n = 11; r = 0.58).$$

Orthostatically (Fig. 6) APP and AP rise in 10 of 11 patients (No. 1 excepted) in a synergic and normal way in 3 cases, in a synergic and explosive way in 3, and preferentially in 2 cases for the AP and in 2 cases for the ARP. The following equation is likewise significant (p less than 0.01):

$$\text{AP orthostatic} = 0.96 \text{ ARP orthostatic} + 41.3 \quad (n = 11; r = 0.80).$$

When 9 patients were subjected to hypoglycemia ARP was stimulated only in those presenting a normal adrenalinuria response. ARP went from 8.7 to 26.4 ng/l/min for No. 4 and from 16.3 to 39.8 ng/l/min for No. 8.

In Na depletion ARP decubital increased 82%, 523% and 19% in 3 patients studied (3, 4, 8) and AP increased 99%, 215% and 142%. Orthostatic additional rise is normal or explosive.

c) Plasma DBH

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Decubitally normal on the average (14.9 ± 1.7 IU) and in 7 of 9 cases studied. It went down moderately in 2 cases (No. 2, 6).

Orthostatically is it slightly high in 3 of these same patients (No. 7, 8, 10).

In hypoglycemia there is no variation in the 6 cases studied (No. 1, 2, 6, 7, 9, 10).

d) Probenecid Test

The test, given to 9 patients (not No. 6 or 10), was limited to the first time for 3 cases (No. 1, 5, 7) and the second time for 4 cases (4, 8, 9, 11). Only two patients (2, 3) were tested both times.

The basal amount of HVA (homovanillic acid) dropped on the average (22.7 ± 7.7 ng/ml) in 5 patients examined and individually in 3 of them (No. 2, 3, 7). Following probenecid, the HVA reading for 6 patients also dropped on the average (87.5 ± 26.4 ng/ml) and individually for 3 of them (2, 4, 9). Between times HVA increase is normal for No. 3 (Δ HVA = 106 ng/ml) and reduced for No. 2 (Δ HVA = 54 ng/ml).

The basal amount of 5HIAA (5-hydroxy indolacetic acid) assayed for 5 patients was individually low in one case (No. 3) but normal on average (17.2 ± 15.9 ng/ml) but this reduction was not distinct in 4 cases (distinct only for No. 4, 9). The increase in 5HIAA between the two tests is clearly down in case No. 2 (Δ 5HIAA = 59 ng/ml) and normal in case No. 3 (Δ 5HIAA = 76 ng/ml).

Finally, the amounts of probenecid measured the second time for 6 patients was normal both individually and on average (16.7 ± 2 mcg/ml).

3. Cerebral Regional Blood Flow

Blood flow for gray matter, measured decubally for 4 patients (No. 1, 2, 6, 7) was lower on the average (47.72 ± 5.63 ml/min/100 g) and in 3 of the 4 cases studied (except No. 2). In two cases (1, 2) it dropped in the sitting position.

Blood flow for white matter, calculated for 3 of these same patients (except No. 1) decubally was normal on the average (12.2 ± 1.4 ml/min/100 g) and lower in one case (No. 7). However in the seated position it never went down.

Comments

1) Results of our physiological and pharmacological tests confirm the profound change in the two neural mechanisms that reflexively control cardiac flow (rate times systolic ejection volume) and peripheral resistance and therefore arterial pressure.

Affection of the sympathetic vasoconstrictive system was established in our 11 cases, just as in the totality of the literature cases, by the existence of postural hypotension that was immediate, major and systolodiastolic, without tachycardiac reaction of the adaptive type, and likewise by the absence of hypertensive rebound in Phase IV of the Valsalva test.

The plethysmographic [2] and hemodynamic [10, 15, 35, 43, 44] studies lend objectivity, in orthostasis, to the drop in arteriolar resistance and reduction of cardiac flow due to a decrease on the one hand of venoconstriction and thus of venous return and on the other hand of myocardiac contractility.

However, it is very difficult to localize the sympathetic lesion. At times the physiological tests are negative in the normal subject and are not completely specific in their manner of exploration, since they depend upon somatic afference or centers.

With these reservations, the efferent pathway is intact in 3 patients who respond normally to cold (No. 5, 6, 9) and interrupted in the 8 others. Sensitivity of arteriolar receptors to catecholamines is maintained and likewise the norepinephrine perfusion which raises arterial pressure in all cases. The hypercapnia test does not give grounds for asserting a secondary central involvement for the single patient tested (No. 11). In the absence of appropriate testing it is impossible to objectify the integrity of the afferent pathway. Thus, the information we do have for our 11 patients, as in similar series found in the literature [4, 36], is an efferent affection (exclusive or associated with a central and/or afferent ? involvement) in 8 cases and a central affection (isolated or associated with an afferent affection ?) in 3 cases. This, then, agrees with the anatomical data but does not make it possible to differentiate the two clinical types with or without neurological signs nor classify them respectively as exclusively pre- or post-ganglionic. For some authors [14, 21, 40, 73] the Levophed test is discriminatory. Hypersensitivity to direct alpha stimulants would be noted only in Bradbury and Eggleston hypotension and would be e-

physiologically to atropine. Finally, patient No. 1 tends to show a set pulse in the course of development, as Pont [59] has already indicated.

However, these tests do not make it possible to individualize the forms with or without neurological signs nor to fix the central location and extent of parasympathetic lesions. Ocular compression that explores centers and efference is not very sensitive. Exaggerated tachycardia with isoproterenol [19] and the absence of response to atropine in 8 of our 9 patients studied makes it possible merely to affirm cardiac denervation. Therefore, whatever the type of primary orthostatic hypotension, only efferent degeneration can be explored physiologically. However, it may be anterograde and simply secondary to central involvement of the vagal dorsal nucleus, an anatomical constant that cannot be studied in isolation.

2) Static doses of norepinephrine, both urinary and plasmic, seem to us incapable of interpretation and different authors' results are also contradictory. Thus, diurnal urinary elimination may be normal, as in our observations [1, 15, 22, 29, 39, 42, 49, 63, 69] or reduced [18, 21, 24, 31, 53]. Decubitally the urinary output, which is very variable in our study, is reduced in Hedeland's work [31]. Above all, the plasmic amount in the forms with neurological signs is normal [19, 73] or low [4]. It is also normal [1, 19] or low [73] for the forms without neurological signs. Perhaps the variations observed relate to the fact that the dosages involve only released norepinephrine moving into circulation and therefore are merely an indirect proof of the activity of sympathetic neural terminals. Consequently it seems to us Ziegler's classification [73], which separates the two types of primary orthostatic hypotension according to the value of basal norepinephrine in decubitus, cannot be adopted.

In orthostatism, on the contrary, our 11 patients present, as happens in all the literature observations, no increase in plasma norepinephrine content [1, 4, 19, 53, 73] and no urinary output of norepinephrine [11, 31] proportional to the value of noradrenalinaemia.

vidence of the destruction of postganglionic sympathetic neurons incapable of capturing perfused exogenous norepinephrine or of releasing it with indirect sympathomimetics (Tyramine). We consider this hypothesis open to criticism, since it is based solely on the hypersensitivity of a more or less denervated alpha receptor. It does not take into account the absence of an antagonistic baroreflex reaction which sufficiently explains exaggerated reactions, whether they are hypersensitive and observed aside from any direct stimulation of alpha receptors when circulation volume is increasing [33, 71] or of angiotensin perfusion [15, 42, 46, 49], or are hyposensitive with arteriolar beta stimulants [18, 46] or venodilatators. These latter authors also note in the Shy-Drager syndromes and in the case of tetraplegics a hypersensitivity to norepinephrine and a hyporeactivity to Tyramine [20] which do not therefore seem to be specific to postganglionic lesions alone. Moreover, we obtain an exaggerated response in 3 cases of Shy-Drager and a single case of Bradbury-Eggleston.

Affection of the vagal cardiomodulator system is proved by the absence of bradycardia with sinocarotid compression (8 cases) and especially with hypertension induced by exogenous norepinephrine (10 cases) but likewise by the insufficiency of tachycardia in Phase II of the Valsalva and of orthostasis. Many authors [4, 31, 33, 35, 46, 53] admit in effect cardiac acceleration which is moderate but completely unadapted to the depth of the drop in pressure during swing-19ing or exercise in primary orthostatic hypotension. This tachycardia, which refutes the dogma of the absolutely fixed nature of the pulse, is only linked to the release of a vagal residual tonus, since Nanda [53] no longer observes it with atropine. Thus we are dealing with orthostatic asympathicotonic hypotension which is, however, more or less parasympathicotonic depending upon the stage of degeneration. Seven patients present basal tachycardia via debraking that is probably close to an autonomous sinus rhythm [59] and insignificant orthostatic acceleration. Four patients retain residual vagal tonus with cardiac rhythm that is slower in decubitus and postural acceleration in excess of 15/min. Among these patient No. 6 presents the most marked orthostatic tachycardia and is the only one who responds

Quantitative reduction in norepinephrine synthesis, due to a reduction in the number of functional sympathetic units, is the mechanism generally invoked ever since the isotopic studies of Goodall [24, 25]. A functional anomaly of its release seems exceptional [53]. We never note any aberration in its exogenous (catabolism) or endogenous (recapture) metabolism nor any enzymatic deficit (MAO and COMT). Thus, Bannister [4] thinks that the response to swinging represents the best and simplest method for estimating the number of intact efferent sympathetic pathways. This would give these dosages major importance as a tracking method that would make it possible to detect at an early stage any autonomous failure in patients with no postural hypotension but with isolated signs of Parkinson or with impotence and vesical disorders. But they do not make it possible to individualize the two clinical forms nor to define the lesion level. Actually it is impossible to separate instances of stimulation absence by involvement of the first neuron and absence of response by predominant destruction of the second neuron.

3) Basal adrenalin values do not seem to us to be more homogeneous than those of norepinephrine. Although the majority of authors find diurnal elimination and plasmatic amounts normal [1, 19, 24, 29, 53, 63], others note a drop in urinary output [21, 31].

On the other hand, no augmentation of adrenalinuria with hypoglycemia is ordinary for the two types of primary orthostatic hypotension, since we find it to be the case in 7 of 10 cases and it also appears to be constant in the literature [1, 11, 31]. This means extensive sympathetic degeneration involving, in the tractus intermediolateralis, the efferent fibers intended for the medullosuprenal area or possibly the gland itself [11]. Thus hypoglycemia is a good test to find out if the lesion responsible for postural hypotension strikes the centers or efferent sympathetic pathways [1], but it is of no value either in fixing the exact level. Finally, this affection is less constant than that of the fibers intended for the vessels and the physiological responses observed in hypoglycemia in 3 of our patients and in orthostasis by us and other authors [19, 53] seem to mean that these pathways are, at least in part, respected.

4) DBH is an enzyme electively localized in the granules of the sympathetic terminals where it makes possible the transformation of dopamine into norepinephrine. Its soluble fraction is released by neural stimulation at the same time as the catecholamines and this fraction has a longer halflife by far. Thus its plasma activity ought to be a proper reflection of sympathetic neural activity. In fact, however, our results are deceptive. In decubitus this activity does not reflect the constant drop in ganglionic DBH evidenced by histochemical studies [7, 56], since our values and those of various authors [4, 39] are very scattered and their mean is not different from that of the samples. Only Ziegler [73] finds amounts significantly low, as in two of our observations, one with and the other without neurological signs. Nor does this activity make it possible to judge the short term variations of plasma activity; it increases little, if at all, in orthostatism for patients and for controls [4, 72] and shows no variation in hypoglycemia, in our study.

5) The drop in the urinary elimination of MHPG (methoxy-hydroxy phenyl glycol) in 3 of the 6 cases studied, with central neurological signs, seems to reflect the quantitative deficit in catecholamine synthesis and its extent, both central and peripheral. Unfortunately this information cannot be interpreted with certitude, inasmuch as there is not available an elective metabolite for each compartment, for it is impossible at this time to assign precisely their relative importance in the formation of MHPG. Nonetheless, degeneration of the central noradrenergic neurons appears likely: /20

- Actually, in the animal the A6 cellular group, that corresponds anatomically to the locus coeruleus, contains most of the enzymes responsible for norepinephrine synthesis in the central sympathetic terminals. In the Shy-Drager syndrome degeneration here is steady and Black and Petito [56] find here a constant DBH activity that is normal but a drop in TH (tyrosine hydroxylase) activity, the enzyme that regulates the entire sequence of catecholamine synthesis.

- Moreover, sleep tracing anomalies argue cerebral depletion of predominant norepinephrine in respect to the dopamine deficiency [55]. Thus, we have observed in one patient (No. 8) with a discrete Parkinson syndrome and normal amounts of HVA and 5HIAA in the LCR a hypoexcitation of the cortex in polygraphic recording. Experimentally Mouret [5] finds the same irregularities in the animal on destruction of the noradrenergic ascending dorsal fascicle issuing from the locus coeruleus and normally inhibiting the intermediary and anterior serotonergic raphe nuclei in slow sleep. In the other two patients (No. 2, 3) the qualitative abnormalities observed (retention of muscular force and delta waves during paradoxal sleep, blepharospasm and nictitation) would be linked with the destruction of the posterior two thirds of the locus coeruleus.

- Finally, if probable degeneration of the central noradrenergic neurons is extensive, it may likewise play a role in cardiovascular dysautonomy; the noradrenergic neurons issuing from the lateral pressive area (A1 nucleus) actually control, through a descending bulbospinal fascicle, the activity of the preganglionic sympathetic neuron and, through ascending fascicles, dorsal and ventral, the activity of the depressive areas (nucleus of the solitary tract, vagal nucleus) and of the hypothalamus.

On the other hand the central serotonergic neurons seem to be usually intact, since amounts of 5HIAA in the LCR (before and/or after probenecid) are normal in 6 of our cases as in that of Nanda [53] and depleted in only 3 cases, 2 with and the other without neurological signs. The vasodepressive serotonergic area (B), located in the raphe nuclei of the median portion of the cerebral trunk and its bulbospinal projections onto the preganglionic sympathetic neuron are therefore usually respected by the degeneration process. The ratio which Schober [63] sets up between the degree of reduction in the basal amount of 5HIAA and the importance of the TIL cellular loss appears to us therefore open to question.

The central dopaminergic neurons are essentially localized at the nigrostriatal level that presents steady anatomical degeneration

and a drop in TH activity [7, 56] in the Shy-Drager disease. Like other authors [63, 64], we actually find, in 4 of the 7 patients with neurological signs, a reduction in the basal amount and/or following probenecid of HVA (homovanillic acid) correlated in 2 of them with a quantitative reduction in paradoxal sleep. In one of our 3 cases showing no neurological signs and in that of Nanda [53] we cannot, on the other hand, explain the drop in the amount of HVA following probenecid without concurrent irregularity in the sleep pattern.

6) The study of the RAAS (renin-angiotensin system) during orthostatic hypotension of the primary type is important for two reasons.

First of all, we know that this system can play an important role in blood pressure control because of the vasoconstrictive property of angiotensin II and sodium retention induced by aldosterone. In the case of orthostatic hypotension one would anticipate RAAS hyperactivity allowing the organism to compensate for the failure of the sympathetic system and to attempt to maintain suitable BP. Actually the plasma renin activity measured under basal conditions (decubitus, normal sodium regime) is on the average normal with major individual variations. It was found to be really augmented in only a single case (No. 3) and will be brought back to normal parallel with the pressure figures with a treatment that combines IMAO and L-DOPA. These findings are in agreement with the 34 observations in the literature (1, 4, 8, 11, 15, 18, 21, 31, 39, 46, 48, 64) where basal plasma renin activity was found to be normal (or in rare cases slightly high) in 20 cases and low in 14.

Next, it has been clearly established that the adrenergic system is an important mechanism for triggering renin secretion, especially because of the contingent of sympathetic fibers intended for the kidneys [72]. It seems to play a decisive role in the rapid increase of renin secretion induced by orthostasis [28, 41, 72]. Yet, despite the serious autonomic dysfunctioning observed in our patients, response to postural stimulus dropped in only a single case (No. 1) among the 11 studied. Among the 27 postural tests run by the authors cited above only 9 showed abnormally low renin secretion.

In order to explain the usually normal character of this response to orthostatism the following two hypotheses may be proposed:

- maintenance of integrity of sympathetic fibers intended for the kidneys. This hypothesis is not very likely;

- intervention of one of the two intrarenal mechanisms for triggering renin secretion: barosensitivity of granular cells of the /21 afferent arteriole stimulated by the great drop in pressure observed when the orthostatic position is assumed. This hypothesis is favored by the good correlation found by Bannister [4] in his Shy-Drager patients between the degree of orthostatic pressure reduction and the rise in plasma renin activity. In 3 of the 11 patients studied postural stimulation of renin secretion may be considered above normal. Although this reaction evokes an attempt to make up for the adrenergic deficit through the RAS, it should be emphasized that it is still quite inadequate to challenge the pressure drop induced by orthostasis.

When sodium was depleted the PRA of our patients went up normally. This response probably indicates the macula densa's integrity in regard to chemosensitivity to sodium, the second intrarenal mechanism for renin secretion control. We should likewise note that insulin hypoglycemia produces augmented PRA only when the medullosuprarenal response to this stimulus is normal: the renin producing cells have then retained normal sensitivity to circulating catecholamines.

Finally, Love [42] and later Bannister [4] have tried to localize the efferent sympathetic lesion on the basis of the level and reactivity of renin secretion. Finding normal or hyperstimulable PRA would mean a lesion limited to the central or preganglionic region, whereas a decreased amount and absence of reactivity to orthostatism would signify transsynaptic degeneration that extended to the postganglionic neuron.

Actually, we find no difference between the two clinical types in our study. Christlieb [16] and Campbell [13] in particular show

that reactivity may be retained when the postganglionic neuron is affected. The absence of reactivity in their diabetics, with identical sympathetic lesions, is observed only in cases of nephropathy with direct involvement of renin producing cells.

7) Results of aldosterone dosing are fairly uniform in different publications and in both clinical types.

Decubitably and with normal sodium diet PA (plasma aldosterone) concentration varies greatly individually but on the average is either normal, as in our study [30, 38], or low [4, 46]. The ASR (aldosterone secretion rate) and sodium retention remain normal [8, 15, 21, 31]. In orthostatism the PA goes up normally [46] or more than normally [4], as in 10 of our patients. Finally, sodium depletion results in physiological augmentation either of PA in our series or of the ASR and reduced natriuresis [8, 15, 21, 39]. Sodium overload has inverse effects [8, 21]. The urinary elimination dosage for aldosterone, on the other hand, seems inexact, since it is highly variable in decubitus [49] and does not go up much with sodium depletion [45].

The basic stimulus for aldosterone secretion at the glomerule level is, as in the healthy subject, the RAAS, since we have found a good correlation between plasma content for renin and aldosterone, both decubitably and orthostatically. The same correlations are noted on the one hand between PRA and PA decubitably and during swinging with a normal sodium diet [4 46] and on the other hand between PRA and ASR with a normal and sodium-free diet [21, 31]. Intervention of other regulatory factors appears to be accessory. It seems they can perpetualize the response induced by the RAAS in prolonged orthostatism, but the part they play in the extremely early and supranormal rise in aldosterone, as observed, is at times more open to question. Thus, increased kalemia, which can directly stimulate the glomerules [31], appears only at minute 15 of active orthostatism and is linked to a muscular release [62]. This phenomenon, which is absent in passive swinging [46], does not seem to intervene in the case of our patients who are hyperreactive and whose PA

rises before minute 10. Finally, the PA and its urinary excretion are at one and the same time a reflection of aldosterone production by the suprarenal cortex and of its essentially hepatic metabolic purification. In orthostatism a reduction in hepatic blood flow may then, in our patients, reduce the metabolic clearing of aldosterone, prolong its physiological halflife (30 min) and therefore increase its plasmic quantity.

8) Cerebral circulation is provided with autoregulation, i. e. a capacity for maintaining constant flow despite variable perfusion pressure, through an active change in vascular diameter. However this should be pictured within pressure limits usually et at 60-160 mm Hg for average BP. There is still a great deal of controversy about the participation of the vasoconstrictive sympathetic nervous system in this phenomenon. Thus, the study of postural variations in cerebral blood flow is of special interest in the case of our patients, whose autonomic nervous system has broken down, in order to find out exactly whether, on the one hand, there is really any loss of cerebral autoregulation and whether it can be connected with an exclusive neurogenic factor that may possibly be localized and, on the other hand, whether there is a parallel between the loss of autoregulation and the rate of orthostatic syncope or whether the latter occur only when the adaptation mechanism is surpassed.

- Among the 16 literature observations we have collected (14, 23, 26, 30, 49, 65, 67, 68) autoregulation is actually deficient in 11 cases (10 SD, 1 BE) and normal in 5 (3 SD, 1 BE). This division is identical with that in our study and 2 of the 4 patients examined, one with and the other without neurological signs, show an abnormal reduction in CBF (cerebral blood flow) of the regional type sitting.

- Most authors attribute the failure of autoregulation to sympathetic degeneration, since chemical control remains functional and discretely compensatory. Thus, reactivity of cerebral vessels to changes in $p\text{CO}_2$ is retained for the entire hemisphere and exceptionally diminished in some zones [30]. The reactivity index, defined as

the variation in hemispheric flow per mm Hg of pCO₂ variation, is always normal, even above normal [65]. When regional CBF is measured, the deficiency in autoregulation is not found everywhere in the hemisphere. Thus, the autonomic denervation responsible does not affect all cerebral vessels in identical fashion [30], but it is illusory to pretend to limit it to the postganglionic fibers alone [14]. Finally, cerebral autoregulation may change from one day to the next and may not start to fail until development has begun [65]. We discovered that our 2 patients with deficient autoregulation likewise presented central neurological affections that were the most disabling and had the longest history. On the other hand, Shinohara [65] finds no relationship with the intensity of orthostatic hypotension and other dysautonomic signs. /22

In our observations the frequency of syncope runs parallel not with failure of cerebral autoregulation but the average orthostatic pressure level. Thus, the occurrence of orthostatic loss of consciousness seems to be basically connected with a rapid and deep drop in pressure below the threshold of autoregulation, whether the latter has been maintained or not, this threshold being possibly higher in the latter condition.

Conclusion

In the light of our findings it seems impossible to separate the two clinical types of primary orthostatic hypotension at the physiological level. A study of circulatory reflexes and hormonal adaptations continues to be deceptive in respect to the exact localization of sympathetic lesions and the respective importance of pre- and postganglionic involvement. Only very accurate anatomical and histochemical studies will enable us to answer these questions and to find out whether we are dealing with variants, perhaps succeeding each other in time, of a single degenerative disease or with two distinct entities.

Despite these physiological and biological uncertainties, the therapeutic results are encouraging, since two of our patients, who present a Shy-Drager syndrome, have undergone improvement in pressure

and functioning that is noteworthy after several years (3 and 5) due to a treatment that combines IMAO and L-DOPA and one of our Bradbury-Eggleston patients has been able to resume activities with the help of indomethacin.

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