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THE HUMAN LOCUS COERULEUS IN NEUROLOGY AND PSYCHIATRY

(Parkinson's, Lewy body, Hallervorden–Spatz, Alzheimer's and Korsakoff's disease, (pre)senile dementia, schizophrenia, affective disorders, psychosis)

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Contents

A preliminary version of this paper has appeared in Van Dongen (1980b).

Abbreviations

ACh	acetylcholine
AMP	adenosine monophosphate
CA	catecholamine
ChAT	choline-acetyltransferase
CNS	central nervous system
COMT	catechol-O-methyltransferase
CSF	cerebrospinal fluid
DA	dopamine
DBH	dopamine-β-hydroxylase
DMI	desmethylimipramine
E	epinephrine
ECT	electroconvulsive treatment
GABA	γ-aminobutyric acid
Glu	glutamate
5-HIAA	5-hydroxyindole-acetic acid
5-HT	5-hydroxytryptamine
IMI	imipramine
LC	locus coeruleus
MAO	monoamine oxidase
MHPG	3-methoxy-4-hydroxyphenylethylene glycol
Mot X	nucleus motorius nervi vagi
NE	norepinephrine
PHF	paired helical filament
SF	straight filament
SN	substantia nigra
TH	tyrosine hydroxylase

1. Introduction

Research on the locus coeruleus. In the floor of the fourth ventricle, a blue streak is visible in primates; this region is called "locus coeruleus" (LC). Neuropathologists have been interested for many years in this small nucleus, which appears to be depigmented in the brains of patients of idiopathic Parkinson's disease (Hassler, 1938). In 1964, it was discovered that the LC consists of norepinephrine-(NE)-containing cells, and that its cell number is by far the largest of all NE cell groups in the CNS (Dahlström and Fuxe, 1964; Swanson and Hartman, 1975). Since this discovery, investigations into the LC have become a hot-spot in science, resulting in 8 reviews during the last years (Amaral and Sinnamon, 1977; Clark, 1979, Ramm, 1979; Mason, 1979a; Moore and Bloom, 1979; McNaughton and Mason, 1980; Van Dongen, 1980b, 1981). The social relevance of LC research is closely connected with knowledge of diseases in which the LC is involved, and with knowledge of the treatment of these diseases. But apart from the few remarks of McNaughton and Mason (1980), no survey has been presented to my knowledge, on the LC in neurology and psychiatry; therefore these data will be reviewed here.

Diagnostic criteria. For the evaluation of brain changes in various diseases, one needs definitions both of the brain changes (Section 1.3.) and of the diseases. A diagnosis is a hypothesis concerning which disease the patient "really" has: in the past decade, systems of criteria have been developed for diagnosis in psychiatry, and these criteria have been used by increasing numbers of investigators (Feighner *et al.*, 1972, Spitzer *et al.*, 1975b, DSM-III, 1980). A short comment on the interrater agreement ("reliability") of settling a diagnosis will be given in the description of the various diseases. The use of standarized diagnostic criteria has undoubtedly increased the symptomatological homogeneity within a group of patients whose disease is given the same name, but this by no means guaran-

tees that we deal with an etiologically homogeneous group: "high (diagnostic) reliability is no guarantee of validity and there is no independent "test" of most of the diagnostic conditions" (Spitzer *et al.*, 1978). For some diseases, the validity of a diagnosis can be assessed from biochemical data, drug response or post-mortem examination. The validity of the diagnosis of the various forms of Parkinsonism and dementia can be determined, while the validity of the diagnoses schizophrenia and depression cannot be determined as long as there is no independent "test" of these diseases. Recent diagnostic criteria (often DSM-III, 1980) will be mentioned for each disease, but also the data obtained from patients subjected to routine diagnosis or to other diagnostic systems will be mentioned in this paper.

1.1. THE LOCUS COERULEUS

Noradrenergic cells of the LC. The LC of all mammals investigated consist of catecholamine-containing cells (CA cells), and in man, cat and rat, this catecholamine has been demonstrated to be NE (Farley and Hornykiewicz, 1977, Jones *et al.*, 1977; Amaral and Sinnamon, 1977). Under the conventional criteria for neurotransmitters, NE is a synaptic and nonsynaptic neurotransmitter of the LC, and possibly a neurohormone (review Van Dongen, 1981). In this paper, "LC" is used as a collective term for the NE cells in the dorsolateral pontine tegmentum of mammals. General statements on a brain region are only meaningful when this region is a single entity (or a "functional system", cf. Van Dongen and Van den Bercken, 1981). Under the above mentioned definition, the LC seems to be an entity, and a further subdivision of the LC (cf. Van Dongen, 1980b, p. 22) need not to be made in this paper, because no attempts to further subdivide the LC have been made in the literature on the LC in neurology and psychiatry. The LC of young adult humans contains some 18,000 cells, the number being slightly larger in women than in men (Brody, 1976; Vijayashankar and Brody, 1979; Wree *et al.*, 1980, Tomlinson *et al.*, 1981).

Projections and terminals of the LC. In the rat and cat, almost all central NE fibers in the cerebral cortex, hippocampus, septum, thalamus, cerebellum and spinal cord originate from dorsal and ventral parts of the LC, and other CNS parts also receive a LC innervation (Levitt and Moore, 1979, Van Dongen, 1980b, pp. 44–57). No other single CNS region is known to innervate that many regions in the CNS. A great variety of LC terminals has been described: symmetrical and asymmetrical synapses on other neurons, free endings without synaptical specializations, and terminals close to the ventricle, glia cells, cerebral capillaries and neurosecretory cells. The dorsal part of the LC seems to project mainly to sensory and integrative CNS regions, and the ventral parts to hormonal and motor regions (cf. Levitt and Moore, 1979; Van Dongen, 1980b); apart from this global generalization, however, no further generalizations can be made at the moment on the regions receiving either a dense LC innervation, or no LC fibers. Circumstantial evidence has been presented for a difference between man and rodents: the homologue of the dopaminergic area ventralis tegmenti in rodents (with its projections to the nucleus accumbens and other regions) is probably noradrenergic in man: the nucleus paranigralis and the nucleus pigmentosus (cf. Farley and Hornykiewicz, 1976, 1977).

Pigmentation. The blue color of the LC is due to the pigment neuromelanin (Moses *et al.*, 1966, Maeda and Wegman, 1969, German and Bowden, 1975). Both neuromelanin and NE are present only in the medium-sized cells in the LC region and not in the small ones (Forno and Alvord, 1974, Swanson, 1976, Shimizu *et al.*, 1979). Neuromelanin consists (among others) of chains of non-enzymatically oxidized CAs (Hirosawa, 1968; Barden, 1969; Rodgers and Curson, 1975; Craham, 1978, 1979); it is different from the enzymatically (tyrosinase) formed skin pigment melanin (see Barden, 1969). Neuromelanin is present in the brains of albino animals and man (Foley and Baxter, 1958; Kastin *et al.*, 1976). It is present in the LC and in other CA neurons; the association between CA and neuromelanin is so strong that an atlas of human CA cells could be made with neuromelanin as a natural marker (Bazelon *et al.*, 1967, Bogerts *et al.*, 1981).

1.2. COMPENSATORY ACTIONS IN THE CENTRAL NE TRANSMISSION

Introduction. The LC fibers and the central adrenoceptors appear to be very flexible. The LC fibers regenerate after damage, and the central adrenoceptors adapt to the presence of both low and high concentrations of adrenoceptor agonists. These processes are extensively investigated in the rat, while data from human material are not available on this subject. The data from the rat will be mentioned here, because they seem to have relevance for the interpretation of malfunctions of the human LC and their treatments.

Regeneration. The LC fibers regenerate after damage, in contrast to most other CNS fibers (Fig. 1; review Björklung and Stenevi, 1979). After damage, the intact part of the fiber shows sprouting and regrowth, and the regrown LC fibers contain and accumulate NE (Jonsson *et al.*, 1974; Sachs and Jonsson, 1975; Björklund *et al.*, 1975; Chiba *et al.*, 1979; Björklund and Lindvall, 1979; Schmidt *et al.*, 1980; Levitt and Moore, 1980). The regrowth of LC fibers is age- and region-dependent. The various LC terminal regions have different critical periods for regrowth: it depends on the age of the animal whether the various regions are (partly) denervated, innervated to the same degree as controls, or hyperinnervated (Konkol *et al.*, 1978; Schmidt *et al.*, 1980). Hyperinnervation of the cerebellum after administration of 6-hydroxydopamine (6-OHDA) in neonatal rats is extensively investigated and generally accepted. The regrowth is limited in aged rats (Scheff *et al.*, 1978). The original connections are often accurately restored, but sometimes hyperinnervation or deviating trajectories are found (Björklund and Lindvall, 1979; Björklung *et al.*, 1979; Levitt and Moore, 1980). There is some evidence that the regrown fibers are indeed functioning (Nygren and Olson, 1977). After cell death, a LC cell is definitively lost. It is however uncertain whether other LC cells re-innervate the NE-denervated terminal region of the lost LC cell (cf. Fig. 1); it has been demonstrated that fibers from the LC and other central NE groups each re-innervate their original target regions (Levitt and Moore, 1980).

Central adrenoceptors. Four subtypes of central adrenoceptors have been described, similar to the peripheral adrenoceptors: α_1, α_2, β_1 and β_2. (For simplicity, "adrenergic binding sites" are called "adrenoceptors".) The adrenoceptors most often found on LC target cells are of the β type (review Van Dongen, 1981); interaction of adrenoceptor agonists with these β-adrenoceptors causes the synthesis of c-AMP and suppression of these target cells. Some LC target elements have β_1-adrenoceptors, while it is still uncertain whether the β_2-adrenoceptors are target sites of NE from the LC or from the blood (Minneman *et al.*, 1979; U'Prichard *et al.*, 1980b). The most investigated adrenoceptors on LC terminals are of the α_2-subtype, influencing the amount of NE released (Langer, 1980). Only a small proportion of the central α_2-adrenoceptors, however, are located on NE terminals (U'Prichard *et al.*, 1979, 1980a; Jonsson *et al.*, 1979; Morris *et al.*, 1981).

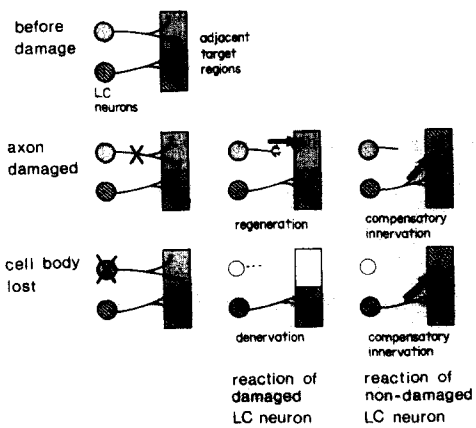

FIG. 1. Compensatory innervation after damage of the axon or the cell body of LC neurons; comments see the text.

The best investigated example of α_2-adrenoceptors on LC target cells are on the LC cells themselves (collateral NE-induced suppression, Van Dongen, 1980, pp. 42–43). It is an open question whether the other α_2-adrenoceptors are mainly located on neurons, or on non-neuronal elements (glia cells or cerebral blood vessels). Indirect evidence is present that α_1-adrenoceptors are target sites of the LC terminals (U'Prichard *et al.*, 1979, 1980a; Morris *et al.*, 1981). The only other electrophysiologically well documented example of α-adrenoceptors (not further subdivided) on LC target cells are those in the lateral geniculate body (Rogawsky and Aghajanian, 1980).

Adrenoceptor changes after lesions. The LC target cells compensate for a change in LC/NE terminals with a change in the number of adrenoceptors: when the number of LC terminals in a region is decreased by a lesion, the number of adrenoceptors increases (reviews Schwartz *et al.*, 1978; Lefkowitz, 1978). Such compensatory actions have been most extensively investigated for the central β-adrenoceptors; concomittant with the change in the number of β-adrenoceptors, the effects of β-adrenoceptor agonists change (Wolfe *et al.*, 1978; Wagner and Davies, 1979; Manier *et al.*, 1980). (Such effects of lesions are generally called "supersensitivity" or "hypersensitivity"; here they will be called simply "increase in the number of adrenoceptors".) The β_1-adrenoceptors show such compensatory changes, while it is still uncertain whether they also occur in the β_2-adrenoceptors (Minneman *et al.*, 1979; U'Prichard *et al.*, 1980b). Compensatory changes have also been described for α_1-adrenoceptors (Jonsson *et al.*, 1979; U'Prichard *et al.*, 1979, 1980a; Morris, 1981). The effects of lesions of LC fibers on the α_2-adrenoceptors on LC target cells are less straightforward to determine since α_2-adrenoceptors are located both on LC terminals and on other elements. Yet similar compensatory changes seem to be present for α_2-adrenoceptors (U'Prichard *et al.*, 1979, 1980a; Morris *et al.*, 1981).

Drug-induced adrenoceptor changes. Some drugs influencing the amount of NE near the adrenoceptors, have similar effects on the number of adrenoceptors as lesion-induced denervation or hyperinnervation (reviews Schwartz *et al.*, 1978; Sulser *et al.*, 1978). Chronic administration of clinically effective antidepressant drugs diminishes the effectiveness of the central NE transmission either by a decrease in the central adrenoceptors (tricyclic antidepressants and MAO inhibitors), or by other effects on the NE-stimulated cyclic AMP-generating system (mianserine, zimilidine; Banerjee *et al.*, 1977; Wolfe *et al.*, 1978, Clements-Jewery, 1978; U'Prichard and Enna, 1979; Bergstrom and Kellar, 1979; Sellinger-Barnette *et al.*, 1980; Paul and Crews, 1980; Mishra *et al.*, 1980; Tang *et al.*, 1981). An antidepressant-induced decrease in the number of β-adrenoceptors has been demonstrated neurochemically, and is also reflected in a decrease in the isoprenaline-induced accumulation of c-AMP (Wolfe *et al.*, 1978), and in the NE-induced suppression of cingulate cortical cells (Olpe and Schellenberg, 1980). The number of β_1-adrenoceptors is reduced, while the number of β_2-adrenoceptors is reported as being unaffected (Minneman *et al.*, 1979). The effects of chronic antidepressant treatment on α-adrenoceptors are less clear (Bergstrom and Kellar, 1979; Rehavi *et al.*, 1980; Tang *et al.*, 1981). Electrophysiological evidence is present for an antidepressant-induced decrease in the number of α_2-adrenoceptors on the LC cells (Svensson and Usdin, 1978; McMillen *et al.*, 1980), and behavioral evidence is present as well for a decrease in the number of central α_2-adrenoceptors (rat, Spyraki and Fibiger, 1980; man, Checkley *et al.*, 1981). It has been suggested that antidepressant drugs have their therapeutic action by decreasing the number of central (β_1 and α_2 ?) adrenoceptors (Sulser *et al.*, 1978; Clements-Jewery, 1978; Sellinger-Barnette *et al.*, 1980, see Section 9.3.).

1.3. HISTOLOGICAL SIGNS OF DECAY OF LC NEURONS

Lewy bodies. Lewy (1912) was the first to describe spherical hyaline inclusion bodies in brain nerve cells of Parkinsonian patients. These bodies are now generally called "Lewy bodies". Lewy bodies vary in size from 5 to 25 μm; they have an eosinophilic core and a pale outer zone or halo (Greenfield and Bosanquet, 1953; Duffy and Tennyson, 1965).

(For a survey of staining reactions and histochemical criteria to identify Lewy bodies see Greenfield and Bosanquet (1953) and Den Hartog Jager (1969).) Lewy bodies have been found in the central CA cells, sympathetic ganglia, the spinal sympathetic columns and the cerebral cortex. Various forms of Lewy bodies with intermediate forms have been described; different forms have been found in a single patient (Forno and Norville, 1976; Forno *et al.*, 1978). The cortical Lewy bodies are more homogeneous than the Lewy bodies in the CA cells (Kosaka, 1978; Kosaka and Mehraein, 1979; Ikeda *et al.*, 1978, 1980; Yagishita *et al.*, 1980a). The most frequent type of Lewy body in CA cells is the "filamentous Lewy body", consisting of filaments with diameters ranging from 7.5 to 20 nm, which are closely packed in the core and radiate in the periphery (Duffy and Tennyson, 1965; Roy and Wolman, 1969; Forno, 1969; Forno and Norville, 1976; Forno *et al.*, 1978). Filamentous Lewy bodies are surrounded by neuromelanin granules, and the filaments extend into the zone of these granules. (In Parkinsonian patients these neuromelanin granules have often lost part of their neuromalanin, leaving a lipofuscin matrix behind, Forno and Alvord, 1974.) The chemical composition of Lewy bodies is still uncertain: on the basis of histochemistry either proteins (Lipkin, 1959; Issidorides, *et al.*, 1978) or sphyngomyelin (Den Hartog Jager, 1969) has been proposed. It is also uncertain whether neuromelanin (see above), dense core vesicles (Watanabe *et al.*, 1977) or protein vesicles (Issidorides *et al.*, 1978) contribute to the formation of Lewy bodies.

Neurofibril tangles. Alzheimer (1907) described tangles of degenerated neurofibril in the brains of patients with presenile dementia; these tangles are now called "Alzheimer's neurofibrillary tangles" (review Wisniewski and Iqbal, 1980). "Alzheimer's neurofibrillary tangles" also occur in the brains of individuals without neurological symptoms, and with other diseases than Alzheimer's disease (cf. Section 4; Wisniewski *et al.*, 1979). Two different types of neurofibrillary tangles have been described: paired helical filaments (PHFs) and straight filaments (SFs) (Tomonaga, 1977a, b, 1981; Bugiani *et al.*, 1979; Yagishita *et al.*, 1979, 1980b; Ghatak *et al.*, 1980): both types may occur in one patient, but only incidentally in one cell (Yagishita *et al.*, 1979). PHFs are by far the most frequent type of neurofibrillary tangles: the most common type of neuronal decay leads to PHF-formation. The PHFs are related to neurofilament proteins, and subunits of them are present in the brains of asymptomatical young adults (Kidd, 1962; Wisniewski *et al.*, 1970, 1976, 1978; Wisniewski and Iqbal, 1980). The distribution of the neurofibrillary tangles is similar in the brains of controls and patients: they are predominantly found in the hippocampus and neocortex and in monoaminergic neurons (Hirano and Zimmerman, 1962; Ishii, 1966; Meyers *et al.*, 1974; Tomonaga 1977a; Wisniewski *et al.*, 1978, 1979).

Depigmentation. On macroscopic inspection of the brain, the pigmented brain stem regions (especially the substantia nigra (SN) and the LC) sometimes look paler than they normally do: i.e. depigmentation. On closer examination, displacement of neuromelanin in abnormal neurons, clumping of neuromelanin, and extracellular neuromelanin is observed (Duffy and Tennyson, 1965; Forno and Alvord, 1974; Mann and Yates, 1974, 1979; Graham, 1979). It is still uncertain whether the depigmentation is due to cell loss, or to loss of neuromelanin in the still living neurons (Forno and Alvord, 1974).

2. The LC in Development and Aging

Introduction. Knowledge of the brain in development and aging of individuals without neurological and psychiatric symptoms is necessary for evaluating brain changes in various diseases. For a survey of the biochemistry, morphology and physiology of the brain of elderly people see Alvord *et al.* (1974), Domino *et al.* (1979), Carlsson (1979) and Tomlinson (1980). Prominent findings are that although the weight, cell count and content of various compounds decrease with age in a number of brain regions, other regions show minimal changes.

2.1. MORPHOLOGY OF THE LC IN THE DEVELOPING AND AGING BRAIN

Neuromelanin. The neuromelanin content of the LC increases lineary with age between birth and middle age (Mann and Yates, 1974, 1979; Graham, 1979); this neuromelanin is contained in granules within the LC cell bodies. In the LC of individuals aged 60 or more, extracellular or clumped neuromelanin has been found, together with atrophy and death of the LC cells. Since the increase in the neuromelanin content precedes death of these cells, it has been suggested that this cell death is caused by a high (toxic) level of neuromelanin in individuals more than 60 years old (Mann and Yates, 1974, 1979; Graham, 1979). Neuromelanin is also the pigment of some other pigmentated brain nuclei like the SN and the nucleus dorsalis motorius nervi vagi (Mox X); a similar atrophy and cell death have been found in the other neuromelanin–containing nuclei.

Neurofibril tangles. From the age of 30 years, an increase in the occurrence of neurofibril tangles of the PHF type in the LC has been found (Alvord *et al.*, 1974, Tomonaga, 1977a, 1980). PHFs have been found in many other brain regions, but the LC is especially vulnerable to neuronal decay leading to PHF formation: no brain region has been described where the onset of PHF formation is as early as in the LC (Hirano and Zimmerman, 1962; Alvord *et al.*, 1974; Tomonaga, 1977a). The incidence of PHFs in aged people is highest in the LC and the hippocampus, while other regions (including the SN) are less frequently affected (Tomonaga 1977a).

Lewy bodies. In the LC of individuals aged more than 60, Lewy bodies have been found. Different pathological changes cause the formation of either Lewy bodies or PHFs: the combined occurrence of Lewy bodies and PHFs will be discussed in Section 3.2.

Cell loss. The number of human LC cells decreases with age (Alvord *et al.*, 1974; Brody, 1976; Mann and Yates, 1976, 1979; Vijayashankar and Brody, 1979; Wree *et al.*, 1980; Tomlinson *et al.*, 1981). A monotone reduction of LC cell numbers has been described in men already from age 20, and in women from age 40: in the eighth decade the mean LC number is reduced to about 50% (Brody, 1976; Vijayashankar and Brody, 1979; Wree *et al.*, 1980). Cell loss has also been found in the cerebral cortex, SN, cerebellum and spinal cord, but not in most other brainstem nuclei (Brody, 1976, 1978; Tomlinson, 1980). Cell loss in the LC is more severe than in the SN (Alvord *et al.*, 1974; Mann and Yates, 1976, 1979).

2.2. BIOCHEMISTRY OF THE CENTRAL NE TRANSMISSION IN AGING

Not only LC cell loss with age has been described, but also changes in the levels of compounds in the brain related to the central NE transmission: reductions of NE levels (Robinson, 1975; Carlsson, 1979; Pradhan, 1980; Gottfries, 1980), of the tyrosine hydroxylase activity (TH; McGeer and McGeer, 1976; McGeer, 1978; Pradhan, 1980), and of β-adrenoceptor binding (Maggi *et al.*, 1979; Pradhan, 1980; in the cerebellum, but not in other regions. The 3-methoxy-4-hydroxyphenyl-ethylene glycol (MHPG) content, monoamine oxidase (MAO) activity and, unexpectedly (cf. Van Dongen 1980b, p. 174–175), the CSF dopamine-β-hydroxylase (DBH) content have been reported as increasing with age (Robinson, 1975; Adolfsson *et al.*, 1978, Lerner *et al.*, 1978; Carlsson, 1979; Pradhan, 1980). The data on NE levels and adrenoceptor binding indicate that compensatory changes (sprouting, regeneration, adaptation of the number of adrenoceptors) are limited in the aging brain.

3. Parkinsonism; Motor Impairements

3.1. DEFINITION, DIAGNOSIS AND CLASSIFICATION

"*Parkinsonism*". The classical motor symptoms of patients with Parkinson's disease are

(1) akinesia, (2) rigidity and (3) tremor at rest (reviews Hornykiewicz, 1975; Barbeau, 1978). It was however recognized long ago that:

1. Parkinsonian motor symptoms can have various causes: they are symptoms of different diseases,
2. all of these diseases can be accompanied by other symptoms,
3. and all of these diseases (especially the early phases) can occur without Parkinsonian motor symptoms.

Differential diagnosis. The various diseases with Parkinsonian motor symptoms cannot be distinguished from their symptoms only. When the patient has a history of encephalitis lethargica, his disease is called "post-encephalitic Parkinsonism". When there is evidence of cerebrovascular insufficiency or intoxication that could cause the Parkinsonian motor symptoms, the diagnoses "vascular Parkinsonism" or "drug-induced Parkinsonism" are made. In the absence of such presumed causes, the disease is called "idiopathic Parkinson's disease".

Classification. At post-mortem inspection of the brains of Parkinsonian patients, various forms of brain damage have been found that could cause the Parkinson motor symptoms. It is assumed here, that these various forms of brain damage reflect the different "real" diseases: the classification of Parkinsonian diseases is therefore mainly based on the morphology of the brains of the patients (cf. Beheim–Schwarzbach, 1952; Stadlan *et al.*, 1966; Bannister and Oppenheimer, 1972; Alvord *et al.*, 1974, Sung *et al.*, 1979).

1. "Lewy body disease": at autopsies of these cases, Lewy bodies are found in the pigmented brain nuclei (Woodard, 1962; Forno, 1969; Hakim and Mathieson, 1979). (It is somewhat erroneous to call this state a "disease", since many people with Lewy bodies in their brains are asymptomatical.) Parkinsonian motor symptoms have been found in 26–56% of the cases of Lewy body disease: then the disease is called "idiopathic Parkinson's disease".
2. "Postencephalitic Parkinsonism": The patient has a history of encephalitis lethargica, and Parkinsonian motor symptoms; PHFs are present in the brain, but no Lewy bodies.
3. "Striato-nigral atrophy" and/or "olivo-ponto-cerebellar atrophy" or "multiple system atrophy": degenerative brain diseases without the presence of Lewy bodies.
4. "Vascular Parkinsonism": Parkinsonian motor symptoms that can be ascribed to arteriosclerosis of infarction of the brain (Pollock and Hornabrook, 1966; Bannister and Oppenheimer, 1972; De Reuck *et al.*, 1980).
5. "Drug-induced Parkinsonism": patients have motor symptoms resembling those of Parkinsonian patients that can be ascribed to the use of drugs such as phenothiazines, reserpine or butyrophenones (Pollock and Hornobrook, 1966; Robinson *et al.*, 1979), and the above mentioned brain damage is absent.

Reliability and validity. In well-advanced cases of Parkinson's disease, the diagnosis can be made without difficulty; a percentage of misdiagnosis as low as 10% has been mentioned (Pollock and Hornabrook, 1966). A remarkable agreement between the clinical diagnosis and the type of brain damage has been mentioned for idiopathic and postencephalitic Parkinson's disease (Beheim-Schwarzbach, 1952; Greenfield and Bosanquet, 1953; Bannister and Oppenheimer, 1972; Alvord *et al.*, 1974; Sung *et al.*, 1979): the validity of these clinical diagnoses is high. The names of the various forms of Parkinson's disease are defined here on the basis of brain damage, such that it can be determined with certainty only post-mortem which form was present. The validity of the clinical diagnosis however is high; in this paper, the restrictive adjectives "idiopathic", "post-encephalitic" etc. will therefore be used also for non-autopsied cases.

3.2. THE LC AND LEWY BODY DISEASE

Occurrence of Lewy bodies. The findings of some authors (Greenfield and Bosanquet, 1953; Bethlem and Den Hartog Jager, 1960) seemed to indicate that Lewy bodies occurred exclusively in the brains of idiopathic Parkinsonian patients. But studies in which hundreds of brains were investigated, have clearly shown Lewy bodies to occur also in non-Parkinsonian individuals (Woodard, 1962; Forno, 1969; Alvord *et al.*, 1974; Hakim and Mathieson, 1979): in 10% of the brains of individuals aged more than 60, Lewy bodies have been found, while only about 30% of these Lewy body containing cases were Parkinsonian patients.

Distribution of Lewy bodies. When Lewy bodies were found in a brain, they were always present in the LC, and in only 66% of the cases in the SN and Mot X also (Forno, 1969). Lewy bodies have been found almost exclusively in the brains of individuals aged more than 60 (with the exception of cases of Hallervorden-Spatz disease (Section 3.4.), and the case described by Ikeda *et al.*, 1980). Lewy bodies were mainly found in central and peripheral CA cell bodies, but also in regions without CA cell bodies, such as the neocortex; in all cases of cortical Lewy bodies there were Lewy bodies in CA neurons also (Forno, 1969). The brain regions containing Lewy bodies are similar whether or not Parkinsonian motor symptoms occur but the amount of Lewy bodies in the various regions differs (Forno, 1969; Ohama and Ikuta, 1976). In brains of cases with Lewy body disease, the cell loss is generally more severe in the LC than in the SN.

Pathological changes of Alzheimer's and Lewy body disease. Most cases of Lewy body disease (Parkinson's disease) also had cortical cell loss, plaques and neurofibrillary tangles, which are the defining characteristics of Alzheimer's disease (Section 4.1.; Alvord *et al.*, 1974; Forno *et al.*, 1978; Hakim and Mathieson, 1979; Kosaka and Mehraein, 1979; Rosenblum and Ghatak, 1979; Yagishita, 1980a; Forno and Norville, 1981; Tomonaga, 1981). Forno *et al.* (1978) speculated that the pathological state causing Lewy body disease, accelerates or predisposes to Alzheimer's disease, and *vice versa.* Much evidence has been presented in favour of such overall association between the pathological changes of Lewy body and Alzheimer's disease, but in most patients the pathological changes of just one of these diseases is dominant. Moreover, the association of the pathological changes of both diseases in one neuron seems to be by chance (Tomonaga, 1981).

Lewy bodies and symptoms. In a proportion of individuals with Lewy bodies in their brains, Parkinsonian motor symptoms are found (26% Woodard, 1962; 30% Forno, 1969; 56% Hakim and Mathieson, 1979); these individuals had a more severe cell loss than non-Parkinsonian cases of Lewy body disease, especially in the SN. Intellectual deterioration or "dementia" (56–64%, Forno, 1969; Hakim and Mathieson, 1979; Rosenblum and Ghatak, 1979), and vegetative disorders are found in many cases of Lewy body disease. It seems that a single disease causes the decay of predominantly CA cells as well as the formation of Lewy bodies, and that at a later stage of its course, Parkinsonian motor symptoms or other symptoms associated with this disease arise (cf. Forno, 1969). This idea is supported by the finding of Lewy bodies in an operatively removed sympathetic ganglion of a patient, 3 years before the diagnosis of "Parkinson's disease" was settled (Stadlan *et al.*, 1966). In the brains of patients with psychosis or intellectual deficiency, the presence of Lewy bodies is associated with paranoid states and "dementia" (Woodard, 1962).

3.3. THE LC AND CENTRAL NE IN IDIOPATHIC PARKINSON'S DISEASE

3.3.1. *The brains of idiopathic Parkinsonian patients*

Morphology of the Parkinsonian brains. At macroscopic inspection, depigmentation of the SN and LC is prominent in the brains of individuals diagnosed as idiopathic Parkinsonians. Some cortical atrophy, plaques and neurofibrillary tangles have been found in these brains (Selby, 1968; Alvord, *et al.*, 1974; Forno and Norville, 1981). Lewy bodies

have been found in almost all the brains and sympathetic ganglia of patients diagnosed as "idiopathic Parkinsonian patients", independently from drug-treatment (Beheim-Schwarzbach, 1952; Greenfield and Bosanquet, 1953; Bethlem and Den Hartog Jager, 1960; Duffy and Tennyson, 1965; Stadlan *et al.*, 1966; Den Hartog Jager, 1969; Bannister and Oppenheimer, 1972; Alvord *et al.*, 1974; Ohama and Ikuta, 1976). Lewy bodies are found together with cell loss and depigmentation in the LC, SN, Mot X, the spinal intermediolateral column, the sympathetic ganglia and the adrenal medulla. In the LC also a loss of small spherical intracellular protein-rich bodies has been described (Issidorides *et al.*, 1978).

Neurochemistry of the Parkinsonian brains. Concomitant with cell loss in the SN and LC in idiopathic Parkinson's disease, a number of biochemical changes have been found. A considerable decrease in the content of dopamine (DA) in the SN and basal ganglia is well documented (cf. Ehringer and Hornykiewicz, 1960; Birkmayer *et al.*, 1977; Carlsson, 1979). In a number of studies, a decrease in the NE content too has been mentioned (Ehringer and Hornykiewicz, 1960; Sano, 1960a, b (cited by Ohama and Ikuta, 1976), Fahn *et al.*, 1971; Teychenne *et al.*, 1977). The largest decrease in NE levels was found in the *n. paranigralis* and *n. pigmentosus* and their projection regions, while in the LC and its projection regions the decrease was present but moderate (amygdala, raphe and gyrus cinguli; Birkmayer *et al.*, 1974, 1977; Farley and Hornykiewicz, 1976). Moreover, in cases with idiopathic Parkinson's disease, the TH and DBH activity in the LC and its terminal regions is reported as being decreased (McGeer and McGeer, 1976; Riederer *et al.*, 1979; Nagatsu *et al.*, 1979).

3.3.2. *Symptoms in idiopathic Parkinson's disease*

Attention has to be paid to the various symptoms of Parkinson's disease, when we want to relate the symptoms to brain damage. Idiopathic Parkinson's disease is a progressive disorder: the severity and the incidence of the various symptoms increase with the duration of the illness, just as the brain changes do. By definition, idiopathic Parkinsonian patients have Parkinsonian motor symptoms. Also intellectual deterioration and "dementia" (Section 4.4.) and depression (Section 8.5.) are often encountered. Vegetative disorders, of which idiopathic orthostatic hypotension (Shy–Drager syndrome) is the most noteworthy, are frequently found in idiopathic Parkinson's disease (Vanderhaegen *et al.*, 1970; Appenzeller and Goss, 1971; Bannister and Oppenheimer, 1972; Rajput and Rozdilsky, 1976; Sung *et al.*, 1979). These vegetative disorders have been related to Lewy bodies and cell loss in the spinal intermediolateral column, the sympathetic ganglia and in the adrenal medulla (Den Hartog Jager, 1970; Thapedi *et al.*, 1971; Schober *et al.*, 1975; Rajput and Rozdilsky, 1976; Vuia, 1976; Castaigne *et al.*, 1977; Sung *et al.*, 1979).

3.3.3. *l-Dopa: influence on DA and NE in Parkinson's disease*

l-Dopa is a precursor of the endogenous catecholamines DA, NE and epinephrine (E): l-dopa increases the turnover and/or levels of DA and NE (Bartolini and Pletscher, 1968; Andén and Fuxe, 1971; Fahn *et al.*, 1971; Chalmers *et al.*, 1971; Keller *et al.*, 1974). Being a precursor of the active substances DA, NE and E, l-dopa can be therapeutically effective only when sufficient CA cells are still present to synthetize DA, NE or E. l-Dopa appears to be very effective in the treatment of idiopathic Parkinson's disease: in most patients, akinesia and rigidity declined, survival time increased, and the quality of life of most of the sufferers greatly improved (Barbeau, 1969, 1978; Yahr, 1969; Cotzias *et al.*, 1969; Birkmayer, 1976). l-Dopa therapy "can be regarded as a specific, though probably symptomatic, treatment of the main extrapyramidal symptoms in Parkinson's disease" (Bernheimer *et al.*, 1973); "l-dopa's principal therapeutic effects ... are consistent with its transformation to DA in the striatum" (Lloyd *et al.*, 1975). The effects of l-dopa on intellectual performance and mood in Parkinsonian patients will be mentioned elsewhere (Sections 4.4. and 8.5.). The idiopathic orthostatic hypotension in Parkinsonian patients has been reported as being reduced by l-dopa (Schober, 1975; Vuia, 1976).

3.4. HALLERVORDEN–SPATZ DISEASE

Hallervorden–Spatz disease is a hereditary disease, characterized by an early onset (about 10 years of age) with the symptoms rigidity and emotional and intellectual impairements. The name "Hallervorden–Spatz disease" seems to be used for two different diseases. (1) A type of Lewy body disease with early onset; in these cases, Lewy bodies, cell loss, depigmentation and extracellular neuromelanin are present in the pigmented brainstem nuclei (SN and LC), while the cerebral cortex is relatively intact (Bornstein *et al.*, 1964; Rozdilsky *et al.*, 1971; Defendini *et al.*, 1973; Dooling *et al.*, 1974). (2) Cases with degeneration of the cerebral cortex, without Lewy bodies in the pigmented nuclei (Rozdilsky *et al.*, 1968; Defendini *et al.*, 1973). The similarities and differences in the etiology of the Lewy body cases of Hallervorden–Spatz disease and Parkinson's disease are unclear. The intellectual deterioration in Hallervorden–Spatz disease is further mentioned in Section 4.4.

3.5. NON-IDIOPATHIC PARKINSON'S DISEASE

Brain changes in non-idiopathic Parkinsonism. The brains of patients with postencephalitic Parkinson's disease are characterized by cell loss, depigmentation and PHFs in the same brain regions as in idiopathic Parkinson's disease including the SN and LC (Beheim-Schwarzbach, 1952; Greenfield and Bosanquet, 1953; Duffy and Tennyson, 1965; Ishii, 1966; Ohama and Ikuta, 1976). Another form of "symptomatical Parkinsonism", striatonigral atrophy, is often accompanied by degeneration in other CNS regions (ponto-olivo-cerebellar atrophy, or "multiple system atrophy") but there are also relatively pure cases of striato-nigral atrophy, in which brain regions other than the SN and the basal ganglia are mostly spared (cf. Adams *et al.*, 1964; Stadlan *et al.*, 1966; Izumi *et al.*, 1971; Bannister and Oppenheimer, 1972; Sharpe *et al.*, 1973; Schober, 1975; Sung *et al.*, 1979).

Symptoms of postencephalitic and vascular Parkinsonism. Postencephalitic and vascular Parkinsonian patients often have intellectual impairment, "dementia", depression and psychotic disturbances apart from the Parkinsonian motor symptoms; in these patients the latter symptoms are more severe than in idiopathic Parkinsonian patients (Celestia and Wanamaker, 1972; Brown and Wilson, 1972; Martilla and Rinne, 1976).

Symptoms of striato-nigral and related degenerations. Since patients with striato-nigral degeneration show akinesia and rigidity, but much less or no tremor than idiopathic or postencephalitic Parkinsonians, this disease is also called "akinetic Parkinsonism" (Stadlan *et al.*, 1966; Jellinger and Danielzcyk, 1968; Gray and Rewcastle, 1967; Izumi *et al.*, 1971). Vegetative disturbances occur which could be ascribed to cell loss in the intermediolateral column and/or sympathetic ganglia (Sung *et al.*, 1979). Unfortunately, the data available on symptoms and brain changes are too limited to reliably ascribe other particular symptoms to a circumscribed brain deficit (see Sections 3.6. and 4.6.).

3.6. THE SN AND THE BASAL GANGLIA; PARKINSONIAN MOTOR SYMPTOMS

A number of reasons will be presented now for the theory that each of the following states in the CNS is a cause* of Parkinsonian-like akinesia and rigidity: (1) cell loss or lesions of the SN, (2) lesions of the basal ganglia, and (3) a decrease in the effects of DA in the basal ganglia.

1. A correlation is present between morphologically demonstrated changes in the dopaminergic SN and/or its main terminal region, the basal ganglia on the one hand,

* A specified brain change (*C*) is called a cause of a specified symptom (*E*), when the following statements are confirmed experimentally: (1) *C* is positively correlated with *E*, (2) *C* precedes *E*, and (3) manipulations increasing or decreasing *C* increase of decrease respectively *E*. *C* is said to be part of the causal explanation of *E*, if a more general theory is present from which it could be predicted that *C* is a cause of *E*.

Note that this does not imply that *C* is THE (only) cause of *E*: often *E* occurs if *C and* other events occur; and in many cases, *E* also occurs when some set of events, not including *C*, is present. In its turn, *C* is an effect of another event *B*, so either *B* or *C* can be called a cause of *E* (cf. Van Dongen 1980b, pp. 181–183).

and akinesia and rigidity on the other hand. (1) In cases of idiopathic Parkinson's disease, a simple relationship between SN cell loss and the severity of Parkinsonian motor symptoms has been described (Alvord *et al.*, 1974). Parkinsonian motor symptoms have been reported as being absent in cases of Lewy body disease in which the SN was relatively spared (Alvord *et al.*, 1974; Black and Petito, 1976; Yagishita *et al.*, 1980; Ikeda *et al.*, 1980). (2) In a number of cases of non-idiopathic Parkinsonism, the degree of SN cell loss correlated with the degree of Parkinsonian motor symptoms (Alvord *et al.*, 1974). (3) Cases of striato-nigral degeneration show Parkinsonian motor symptoms, whether or not other brain regions (including the LC) are affected (Adams *et al.*, 1964). (4) The Parkinsonian motor symptoms in cases of vascular Parkinsonism could be ascribed to destruction of the SN and/or the basal ganglia (Oppenheimer, 1967; Fahn *et al.*, 1971; De Reuck *et al.*, 1980).

2. Circumstantial evidence is present that changes in the SN and basal ganglia precede the Parkinsonian motor symptoms. (1) Lewy body disease seems to precede Parkinson's disease (Stadlan *et al.*, 1966; Forno, 1969). (2) In cases with Parkinsonian symptoms concomitant with infarct in the SN or basal ganglia, one is inclined to accept the infarct as preceding the motor symptoms.
3. Manipulations of the DA transmission have effects on Parkinsonian motor symptoms which are in line with the hypothesis that a decrease in the effects of DA is a cause of Parkinsonian motor symptoms. (1) The l-dopa therapy of Parkinsonian motor symptoms can be ascribed to a l-dopa-induced restoration of striatal DA (Lloyd *et al.*, 1975; Birkmayer, 1976; Hefti and Melamed, 1980). (2) Drug-induced "extra-pyramidal symptoms" ("Parkinsonian side-effects" of neuroleptics) are related to the action of these drugs as DA receptor antagonist (Van Rossum, 1967; Robinson *et al.*, 1979); a subgroup of DA receptors might be involved (Cools en Van Rossum, 1980; Kebabian and Calne, 1979).

The conclusion of many of the above mentioned authors is that dysfunction or cell loss in the SN and/or basal ganglia is a cause of akinesia and rigidity. Arguments have also been presented above that other regions that are affected in these diseases, are not, or to a much less extent, a cause of these symptoms. An implication of this conclusion is relevant for this whole paper: decay of LC cells is not a cause of akinesia and rigidity.

4. The Dementias; Intellectual and Memory Impairements

4.1. Definition, Diagnosis and Classification

"Dementia" and "normal aging". "The normal process of aging has been associated in a number of studies with certain decrements in intellectual functioning" (DSM-III, 1980, p. 125). "The diagnosis of Dementia is warranted only if intellectual deterioration is of sufficient severity to interfere with social or occupational functioning" (DSM-III, 1980, p. 110). In aged people, dementia seems to develop quite unpredictably within a few years; early stages of dementia cannot yet be reliably identified (Roth, 1978). (For recent reviews on the dementias see De Boni *et al.*, 1980; Gottfries, 1980 and Wisniewski and Iqbal, 1980.)

Diagnostic criteria for "dementia". The DSM-III (1980) criteria for "dementia" are summarized as follows.

A. A loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning,
B. memory impairement,
C. at least one of the following:
   1. impairment of abstract thinking,
   2. impaired judgement,
   3. aphasia, apraxia, agnosia or "constructional difficulty",
   4. personality change,

D. no indications for delirium or intoxication,
E. some indications for brain damage as a cause for these impairments.

Differential diagnosis

1. "Primary degenerative dementia" is defined as dementia with insidious onset and uniformly progressive deterioration, while a number of other diseases are excluded (DSM-III, 1980); this disease comprises the diseases generally called "Alzheimer's disease", "(pre)senile dementia" or "senile dementia of the Alzheimer's type" by other authors.
2. "Multi-infarct dementia" is defined as dementia with a step-wise deterioration, and other evidence for a cerebro-vascular disease (DSM-III, 1980).
3. "Subcortical dementia" is a hypothetical syndrome characterized by forgetfulness, slowing of thought processes, emotional or personality changes (depression or apathy) and an impaired ability to manipulate acquired knowledge, while aphasia, apraxia and agnosia are absent (Albert *et al.*, 1974; Albert, 1978). "Subcortical dementia" is intended to be a generalization of the intellectual deterioration in a number of diseases with subcortical damage, while the cortex is relatively spared; comments on this concept will be given in Section 4.6.

Further surveys on the differential diagnosis of the dementias are given by Todorov *et al.* (1975), Roth (1978) and Ingvar *et al.* (1978).

Classification. It is assumed in this paper that the histopathological pattern in the brain reflects the "real" different forms of intellectual deterioration: the classification of them is therefore mainly based on the type of brain damage (cf. Todorov *et al.*, 1975; Jellinger, 1976; Constantinidis, 1978; Blessed, 1980). The classification below is far from complete: only forms of intellectual deterioration are mentioned in which changes in the LC and/or the central NE transmission have been described (for a comprehensive list see Slaby and Wyatt, 1974).

1. Alzheimer's disease: dementia in a patient with severe cortical atrophy, plaques and neurofibril tangles of the PHF type, while some other diseases are excluded (cf. Tomlinson, 1980). These cortical changes are not specific for Alzheimer's disease, but "Alzheimer's disease" is said to be present, when these changes fulfill some criterion of severity (cf. Tomlinson *et al.*, 1970). In this paper, the presenile Alzheimer's disease and the senile dementia of the Alzheimer's type are treated as a single disease (for a discussion on this subject see Todorov *et al.*, 1975; Katzman *et al.*, 1978; Pro *et al.*, 1980; Tomlinson, 1980).
2. Vascular dementia: dementia in a patient with histopathological evidence of arteriosclerosis or multiple infarcts of a sufficient severity to cause the symptoms of dementia (for a survey see Jellinger, 1976).
3. Intellectual deterioration in Parkinson's/Lewy body disease.
4. Intellectual deterioration in progressive supranuclear palsy: in subcortical regions many neurofibrillary tangles are present, while the cortex is relatively spared (Steele *et al.*, 1964; Albert *et al.*, 1974).
5. Many other dementias such as Pick's and Jakob–Creutzfeldt diseases, and Huntington's chorea.

Senile dementia is commonly, but incorrectly, attributed to cerebrovascular insufficiency: the vast majority (50–70%) of the patients with senile dementia have Alzheimer's disease, and only a minority (10–30%) have vascular dementia (Tomlinson *et al.*, 1970; Marsden and Harrison, 1972; Todorov *et al.*, 1975; Katzman, 1976; Constantinidis, 1978; Blessed, 1980; Tomlinson, 1980). In most cases, one of the above mentioned types of cerebral degeneration is dominant, such that the intellectual deterioration can be ascribed to that type of degeneration, and the disease can be given one of the above mentioned names. Most demonstrated cases of Alzheimer's disease show however some cerebrovascular abnormalities, and most cases of vascular dementia show some cortical atrophy, plaques and tangles (Jellinger, 1976). Cortical atrophy, plaques and tangles on the one hand, and arteriosclerosis or multiple infarct on the other of a comparable severity are present in

10–30% of the cases of senile dementia (Tomlinson *et al.*, 1970; Jellinger, 1976; Blessed, 1980). Some association has also been described between the occurrence of Lewy bodies (characteristic for Parkinson's/Lewy body disease) and cortical atrophy, plaques and tangles (characteristic for Alzheimer's disease; cf. Section 3.2.).

Diagnostic reliability and validity. To my knowledge, the reliability (simultaneous inter-rater agreement) of the different diagnoses of dementia has not been investigated. The initially settled diagnosis of presenile dementia had to be revised relatively frequently (31–57%; Nott and Fleminger, 1975; Ron *et al.*, 1979); a diagnosis of (pre)senile dementia had to be revised into "depression" in 8–14% of the cases (Marsden and Harrison, 1972; Nott and Fleminger, 1975; Ron *et al.*, 1979). The correlation between the clinical diagnosis and brain pathology (i.e. validity) has been determined by a number of authors (Marsden and Harrison, 1972; Todorov *et al.*, 1975; Jellinger, 1976; Constantinidis, 1978; Blessed, 1980). A limited proportion (55–77%) of patients diagnosed as "presenile dementia", "senile dementia of the Alzheimer type" and "non-vascular senile dementia" appeared to suffer from Alzheimer's disease. Some demonstrated cases of Alzheimer's disease had received another diagnosis, and 3–5% of them were not demented. Only 31–42% of the cases diagnosed as multiple-infarct dementia actually had vascular dementia. Many cases regarded as patients with non-multiple-infarct dementia showed infarcts in their tomographs, and the tomographically demonstrated cortical atrophy of demented and non-demented cases showed considerable overlap (Jacoby and Levy, 1980). In order to deal with this limited diagnostic validity, the disease of non-autopsied cases is called "(pre)senile dementia", while the name "Alzheimer's disease" will be reserved for autopsied cases. Because of the preponderance of Alzheimer's disease in cases with (pre)senile dementia, some conclusion on (pre)-senile dementia will be generalized to Alzheimer's disease.

DSM-III versus common-sense "dementia". The common-sense concept "dementia" includes a number of nosologically and symptomatologically different diseases, all of them characterized by severe intellectual deterioration. Only in part of them, the symptoms seem to fulfill the DSM-III-criteria for "dementia" (e.g. Alzheimer's and Pick's disease), while in others the main symptoms seem to be different from the DSM-III criteria (e.g. in Parkinson's and Korsakoff's disease and in progressive supranuclear palsy). For instance, the main and most often cited symptoms of "Parkinsonian dementia" are confusions, delusions and hallucinations (Section 4.3.); these symptoms are characteristic for schizophrenia rather than for DSM-III-dementia, but the diagnosis "schizophrenia" is not warranted by the diagnostic criteria of age of onset (40 or 45 years) and the absence of preexisting neurological diseases (cf. DSM-III, 1980). The common-sense concept of "dementia" covers a very heterogeneous collection of symptoms. The introduction of the concepts "cortical" and "subcortical dementia" does not solve this problem (Section 4.6.). In this paper, intellectual deterioration (such as in Alzheimer's disease) which apparently fulfills DSM-III is called "dementia", while other forms of intellectual impairments (such as in Parkinson's disease) are called "(severe) intellectual deterioration", and they will be characterized by their main symptoms.

4.2. (Pre)Senile Dementia and Alzheimer's Disease

Brain changes in Alzheimer's disease. In Alzheimer's disease the neocortex and hippocampus are (by definition) severely affected: cortical atrophy, cell loss, dendritic plaques and neurofibril degeneration (PHFs) are present (Blessed *et al.*, 1968; Tomlinson *et al.*, 1970; Tomlinson, 1980; Wisniewski and Iqbal, 1980). The brain changes are not limited to the cortex: some subcortical brain regions are also affected and others are not (Wisniewski *et al.*, 1978). Subcortical regions often affected are the hypothalamus, SN, LC, reticular formation and other regions; particularly vulnerable are the monoaminergic neurons (Hirano and Zimmerman, 1962; Ishii, 1966; Wisniewski *et al.*, 1978). Changes in the transmission of acetylcholine (ACh), DA, NE and 5-hydroxytryptamine (serotonin, 5-HT) have been described (Carlsson, 1979; Gottfries, 1980; Bowen, 1980).

The LC and central NE in Alzheimer's disease. Atrophied cells, PHFs, extracellular neuromelanin and a severe cell loss have been found in the LC of cases of senile dementia: in 40% of these cases the LC cell number was less than 25% of the number of LC cells in intellectually well preserved aged people (Mann *et al.*, 1980; Tomlinson *et al.*, 1981). Such reduction in the LC cell number has been confirmed in case of Alzheimer's disease (Forno and Norville, 1981). The LC cell loss is positively correlated with the density of cortical senile plaques (Tomlinson *et al.*, 1981). A similar reduction in the number of cortical LC/NE fibers has been found in biopsies of patients of Alzheimer's disease (Berger *et al.*, 1980). The loss of LC cells and fibers is also reflected in the brain NE levels, which are reduced, in some cases even to 10% of control values or less (Adolfsson *et al.*, 1978, 1979; Mann *et al.*, 1980; Berger *et al.*, 1980; Gottfries, 1980). In conclusion, in Alzheimer's disease there is a loss of LC cells of unknown cause, which could result in some symptoms of dementia (Mann *et al.*, 1980; cf. Section 4.7 and 10.). Attempts to treat (pre)senile dementia, however, by administration of l-dopa to restore the central NE transmission have yielded poor results (Kristensen *et al.*, 1977; Adolfsson *et al.*, 1978; Gottfries, 1980).

Brain damage and symptoms of dementia. The severity of the dementia in Alzheimer's disease correlates with NE levels, cortical changes and the activity of choline-acetyltransferase (ChAT, the enzyme for the synthesis of ACh). The reduction of the NE levels in a number of LC terminal regions (frontal, cingulate and hippocampal cortex, and hippocampus, but not the thalamus) is positively correlated with the intellectual and emotional impairement; such correlation was not found for DA (Adolfsson *et al.*, 1978). Tomlinson *et al.* (1981) did not find, however, a correlation between LC cell loss and the score on a simple psychological test. In cases of Alzheimer's disease and senile dementia, the localization and severity of the cortical damage correlates with amnesia, aphasia, apraxia and agnosia (Blessed *et al.*, 1968; Alvord *et al.*, 1974; Farmer *et al.*, 1976; Brun and Gustafson, 1976; Constantinidis, 1978); the regional activity of brain ChAT also correlates with intellectual abilities (Perry *et al.*, 1978).

4.3. INTELLECTUAL DETERIORATION IN PARKINSON'S/LEWY BODY DISEASE

Introduction. Lewy body disease is a progressive disease in which both the severity of the various symptoms on the one hand, and the localization and severity of the brain damage on the other varies between the individual patients. For instance, intellectual impairments can precede the motor symptoms and *vice versa.* A limited proportion of patients diagnosed as suffering from "presenile dementia" appeared to be Parkinsonian patients (Ron *et al.*, 1979). About 30% of the Parkinsonian patients show clear intellectual impairments (Mindham, 1970).

Early stages of intellectual deterioration in Parkinsonism. The intellectual performance of many Parkinsonian patients is impaired (review Boller, 1980). The various intellectual activities are affected to a differing degree "with orientation, constructions and memory particularly affected, while social behavior, language, praxis and, to some extent, manipulation of old information were relatively less impaired" (Boller, 1980, cf. Celestia and Wanamaker, 1972; Martilla and Rinne, 1976). Such impairements have also been demonstrated by using IQ (WAIS) tests: even when depressed and "demented" Parkinsonian patients were excluded, the remaining group showed intellectual impairments (Loranger *et al.*, 1972a). It is noteworthy that the intra-individual variation in the various WAIS-scores was larger than in age-matched controls: the performance IQ was much lower than the verbal IQ. The most severely affected WAIS-factor was that on "perceptual organization" (Meier and Martin, 1970; Loranger *et al.*, 1972a). The intellectual impairments could not be attributed to the age of the patients, and only a part could be attributed to motor impairments. "It seems that the Parkinsonians' greatest difficulty is in comprehending and analyzing novel or unfamiliar stimuli. His immediate memory span is also impaired, but to a less extent" (Loranger *et al.*, 1972a). In Parkinsonian

patients, the WAIS-scores "verbal" and "verbal comprehension" were normal (Loranger *et al.*, 1972a).

More severe intellectual deterioration. As Parkinson's disease progresses, the intellectual impairments become more severe, and the symptoms disorientation, personality change, confusions, hallucinations and delusions arise (Pollock and Hornabrook, 1966; Mindham, 1970; Celestia and Wanamaker, 1972; Martilla and Rinne, 1976; Hakim and Mathieson, 1979; Lieberman *et al.*, 1979). The incidence of intellectual deterioration in Parkinson's disease is a tenfold higher than in an age-matched group of non-Parkinsonians (Lieberman *et al.*, 1979; cf. Martilla and Rinne, 1976). These intellectual symptoms are part of the natural history of Parkinson's disease: they also occur in non-drug-treated Parkinsonians (Pollock and Hornabrook, 1966; Celestia and Wanamaker, 1972; Martilla and Rinne, 1976), while they can also be caused by l-dopa administration (Section 8.2.). The symptoms of intellectual deterioration are similar in the various forms of Parkinsonism, but they are more severe in the postencephalitic and arteriosclerotic forms (Loranger *et al.*, 1972a; Brown and Wilson, 1972). It should be remarked that impairments of the so-called "higher cortical functions" aphasia, apraxia and agnosia are rare in Parkinsonian patients.

Cerebral degeneration and intellectual deterioration. In most patients with Parkinson's or Lewy body disease, cortical atrophy, plaques and neurofibrillary tangles have been found; these cortical changes are more severe in cases of Parkinson's and Lewy body disease than in an age-matched control group (Alvord *et al.*, 1974; Hakim and Mathieson, 1979; Yagishita *et al.*, 1980a; Ikeda *et al.*, 1980). Such cortical degeneration is found independently from l-dopa treatment. In most cases of Parkinson's disease, the cortical degeneration is not severe enough to permit also the diagnosis "Alzheimer's disease" (cf. Tomlinson *et al.*, 1970); only the diagnosis "idiopathic Parkinson's disease" is justified. Only in a small proportion of Parkinsonian patients, the simultaneous presence of Parkinsonian motor symptoms, Lewy bodies in CA neurons, and cortical atrophy, plaques and neurofibrillary tangles is of sufficient severity to permit the simultaneous diagnoses "idiopathic Parkinson's disease" and "Alzheimer's disease" (Kosaka and Mehraein, 1979). This is paralleled by the occurrence of symptoms: aphasia, apraxia and agnosia, which are outstanding characteristics for cortical damage, are rare in Parkinson's disease. In Parkinsonian patients, a more severe intellectual impairment has been found than in a coupled group of non-Parkinsonians with comparable cortical degeneration (Alvord *et al.*, 1974), so it is obvious to conclude that subcortical cell loss in Parkinson's disease contributes to the intellectual deterioration.

l-Dopa and intellectual impairments in Parkinson's disease. The intellectual impairments of Parkinsonian patients in their early stages can be effectively treated by l-dopa, which improvements cannot be accounted for only by its relief of akinesia and rigidity (Cotzias *et al.*, 1969; Meier and Martin, 1970; Loranger *et al.*, 1972a, b). l-Dopa restores the central DA and NE transmission, so the l-dopa-induced improvement of intellectual capacities can be regarded as a support for the hypothesis that dysfunctions in the LC and/or SN are a cause of intellectual deterioration in Parkinson's disease. In further progressed stages of Parkinson's disease, neither the intellectual, nor the motor impairments can be effectively treated by l-dopa (Markham, 1974; Martilla and Rinne, 1976): most probably the cell loss in the LC and/or SN has progressed too far for beneficial action of l-dopa. Part of the smaller success of l-dopa in relieving intellectual deterioration in Parkinsonian patients can also be ascribed to l-dopa-induced psychotic symptoms (Section 8.2.).

4.4. Intellectual Deterioration in Hallervorden–Spatz Disease

For the present subject only the Lewy body cases of Hallervorden–Spatz disease are relevant (cf. Section 3.4.). These cases show "mental retardation", memory impairments, aphasia and apraxia (cf. Bornstein *et al.*, 1966; Rozdilsky *et al.*, 1971; Defendini *et al.*, 1973; Dooling *et al.*, 1974). In these cases, Lewy bodies, cell loss and depigmentation in

the LC has been found. It is plausible that cell loss in the LC is a cause of intellectual deterioration in Hallervorden–Spatz disease (cf. Section 10.), but no data are available to directly corroborate this suggestion.

4.5. INTELLECTUAL DETERIORATION IN PROGRESSIVE SUPRANUCLEAR PALSY

Progressive supranuclear palsy is a disease characterized by motor impairments of which a loss of vertical eye movements is most prominent (Steele *et al.*, 1964; Ishino and Otsuki, 1975; Bugiani *et al.*, 1979; Ghatak *et al.*, 1980). In cases of progressive supranuclear palsy, cell loss and neurofibrillary tangles are present in subcortical brain regions, while the cerebral cortex is relatively spared; predominantly affected are the basal ganglia, and the mesencephalic and pontine tegmentum, while the LC is affected in about half of the cases (Steele *et al.*, 1964; Bugiani *et al.*, 1979). Two different types of neurofibrillary tangles have been found: straight filaments (SFs) and paired helical filaments (PHFs). Cases of progressive supranuclear palsy have been described with exclusively SFs, exclusively PHFs, and mixed cases; it is still an open question whether the different types of neurofibril degeneration are manifestation of different diseases, or different stages of one disease (cf. Tomonaga 1977b; Yagishita *et al.*, 1979). Some patients with progressive supranuclear palsy are intellectually impaired: they show disorders of memory and abstract thinking, and severe cases require help in feeding and dressing. In the data available, no systematic relationship can be discovered between intellectual deterioration and cell loss and tangles in the LC (cf. tables of Steele *et al.*, 1964 and Bugiani *et al.*, 1979; cf. also Tomonaga, 1977b; Queiroz *et al.*, 1977).

4.6. "CORTICAL" VERSUS "SUBCORTICAL DEMENTIA"

Albert *et al.* (1974) introduced the concepts "cortical" versus "subcortical dementia" in an attempt to relate different symptoms of intellectual deterioration in various diseases on the one hand, to damage in various brain regions on the other.

1. "Cortical dementia" is a concept intended to generalize the intellectual symptoms in Alzheimer's disease, Pick's disease and other forms of senile dementia; the most conspicious symptoms are impairments of language-dependent activities and perceptual and perceptual-motor skills (asphasia, apraxia, agnosia).
2. "Subcortical dementia" is a concept intended to generalize the intellectual impairments in Parkinson's and Korsakoff's disease, Huntington's chorea and progressive supranuclear palsy; the most conspicuous symptoms are forgetfulness, slowing of thought processes, emotional or personality changes and an impaired ability to manipulate acquired knowledge, while aphasia, apraxia and agnosia are absent.

Aphasia, apraxia and agnosia are indeed the outstanding characteristics of cortical damage. On closer inspection of the data available, however, exceptions on this differentiation are found: emotional or personality changes after frontal cortical damage on the one hand, and symptoms of aphasia and apraxia in Lewy body cases of Hallervorden–Spatz disease on the other. Moreover, the types and localizations of subcortical damage in Parkinson's and Korsakoff's disease, Huntington's chorea and progressive supranuclear palsy are different, as are the concomitant intellectual symptoms in these diseases (cf. Sections 3.2., 3.3., 4.3., 4.5. and 5.). In my opinion, the generalizations of these different subcortical lesions to one concept "subcortical damage", and of the different intellectual symptoms to one concept "subcortical dementia" are too global to gain further insight in brain and behavior. After a more detailed analysis of the various symptoms of intellectual deterioration, and of the brain regions affected, one might be able to formulate some new brain-and-behavior relationships, and to formulate the "behavioral functions" of some brain regions.

4.7. THE PRESUMED INTELLECTUAL EFFECTS OF THE LC'S DYSFUNCTION

Introduction. Cell loss in the LC has been found in a number of diseases with intellectual deterioration. In a symptom-oriented approach (Van Dongen, 1980b, pp. 306–307), it will now be examined which symptoms of intellectual deterioration are related to the LC's dysfunction. The conclusions will mainly be derived from cases of Parkinson's and Alzheimer's disease, from which many data are available, and less from cases of Hallervorden–Spatz disease and progressive supranuclear palsy.

Intellectual deterioration in Alzheimer's disease. The symptoms of aphasia, apraxia and agnosia in Alzheimer's disease are most probably NOT due to LC dysfunction, because (1) these symptoms are related to cortical atrophy and tangles in Alzheimer's disease, (2) these symptoms arise also after really selective cortical damage, and (3) these symptoms are rare in Parkinson's disease, in which a severe LC cell loss and a less severe cortical atrophy is present. Some circumstantial evidence is present that cell loss in the LC in Alzheimer's disease is a cause of some other symptoms of intellectual deterioration, such as impairment of memory and personality changes, and maybe the impairments of abstract thinking and judgement.

1. LC cell changes and changes in the central NE transmission correlate with intellectual impairments. (1) The temporal pattern of occurrence of PHF inclusions in the LC, and the development of intellectual deterioration is similar (Alvord *et al.*, 1974); unfortunately, from the data presented it is not clear whether this concerns the same individuals. Such association was not found for the SN. (2) In a number of cases of senile dementia, severe cell loss in the LC, and an intact SN has been found (Mann *et al.*, 1980). (3) The NE content of a number of LC terminal regions in Alzheimer's disease correlates with intellectual performance, while such association was not found for DA (Adolfsson *et al.*, 1978).
2. No direct evidence is present that cell changes and cell loss in the LC precedes the symptoms of Alzheimer's disease.
3. l-Dopa is not effective in the treatment of presentile dementia (Kristensen *et al.*, 1977) like in progressed intellectual deterioration in Parkinson's disease (Section 4.3.); this does not invalidate the LC/NE-intellectual deterioration hypothesis, because (1) the LC cell loss in Alzheimer's disease might be progressed too far for beneficial action of l-dopa, or (2) the limited success might be due to l-dopa-induced psychotic manifestations.

Intellectual deterioration in Parkinson's disease. Some evidence is present that cell loss in the LC is a cause of intellectual deterioration in Parkinson's disease: impairment of perceptual organization and memory, disorientation, confusions, delusions and hallucinations.

1. Although the relationship between LC cell loss and intellectual impairments has not yet been directly investigated, these processes might correlate. (1) In an intellectually impaired case of Lewy body disease, moderate LC cell loss and only mild SN cell loss has been described (Ikeda *et al.*, 1980). (2) In cases with striato-nigral degeneration, amnesia and disorientation are associated with severe LC cell loss (Adams *et al.*, 1964).
2. No direct evidence is present that cell loss in the LC in Parkinson's disease precedes the intellectual impairments.
3. Manipulations of the central NE transmission have effects on intellectual capacities which are in line with the hypothesis that cell loss in the LC and/or impairment of the central NE transmission is a cause of intellectual deterioration like in Parkinson's disease. (1) l-Dopa causes improvement of the intellectual capacities in some Parkinsonian patients. (2) States of confusion are induced by administration of inhibitors of DBH (fusaric acid, disulfiram; Liddon and Sartran, 1967; Hotson and Langston, 1976; Cross *et al.*, 1978; Hartman and Keller-Teschke, 1979). (3) Amphetamines and l-dopa cause psychotic manifestations (Section 8.2.).

Is LC cell loss a cause of mental deterioration? In the brains of some patients without

intellectual deterioration, cell loss in the LC has been described: in Parkinson's/Lewy body disease (Forno, 1969; Kosaka and Mehraein, 1979), multiple system atrophy (Reznik *et al.*, 1980) and in progressive supranuclear palsy (Steele *et al.*, 1964; Tomonaga, 1977b; Queiroz *et al.*, 1977; Bugiani *et al.*, 1979). The severity of the LC cell loss is however poorly quantified in these cases. Both in man and in animals, the effects of cell loss in a part of the brain are difficult to relate to its "normal function"; the hypothesis that the LC's dysfunction is a cause of intellectual impairments is in line with conclusions from animal studies on the LC's "function" (Section 10.). (The concept "function" in this paper is identical to the concept "I/O-function" as defined by Van Dongen and Van den Bercken, 1981.)

5. Korsakoff's Disease; Memory

"*Korsakoff's disease*". Korsakoff's disease is a disease in which impairments of the short-term- and long-term-memory are the predominant features, while other intellectual abilities are less affected ("amnestic syndrom", DSM-III, 1980). The diagnosis "Korsakoff's disease" is warranted only if evidence is present for the amnestic syndrome following, and probably due to, excessive alcohol ingestion (DSM-III, 1980). Other intellectual abilities that are much less, but still to some degree, impaired are attention, concentration, ability to change mental set, visual and verbal abstraction, while also confabulations often occur (Victor and Banker, 1978). Symmetrical paraventricular lesions over the whole brainstem are the histopathological evidence of Korsakoff's disease (Victor and Banker, 1978).

The LC and NE in Korsakoff's disease. One group of investigators suggested that impairment in the central NE transmission from the LC is a cause of amnesia in Korsakoff's disease (McEntee and Mair, 1980).

1. The level of CSF MHPG is positvely correlated with memory abilities (McEntee and Mair, 1978). The lesions in Korsakoff's disease overlap more or less with the NE pathways (McEntee and Mair, 1980). Discussion continues, however, on the correlation between the occurrence of Korsakoff's amnesia and the localization of brain damage (hippocampus, mammilary bodies, medial dorsal thalamic nuclei or ascending LC fibers; cf. Victor and Banker, 1978).
2. No data are available whether or not changes in the central NE transmission precede Korsakoff's amnesia.
3. The memory of patients with Korsakoff's disease is reported as being improved by the α_2-adrenoceptor agonist clonidine (McEntee and Mair, 1980).

A specific memory hypothesis of the LC's action is, however, not supported by other experimental evidence on the LC's "function" (cf. Amaral and Sinnamon, 1977; Clark, 1979; McNaughton and Mason, 1980; Van Dongen, 1980b). Interestingly, the less conspicuous symptoms of Korsakoff's disease (attention, concentration, visual and verbal abstraction) are more in line with hypotheses on the LC's "function" (cf. Section 10).

6. Epilepsy, Convulsions and Electroconvulsive Treatment

NE, epilepsy and convulsions. The generally confirmed conclusion from animal studies is that central NE reduces susceptibility to seizure, probably via α_2-adrenoceptors; at least part of these effects are due to NE from LC terminals (review Maynert *et al.*, 1975; Libet *et al.*, 1977; Browning and Maynert, 1978; Jobe *et al.*, 1978; London and Buterbaugh, 1978; Quatrone *et al.*, 1978; McNamara, 1978; Mason and Corcoran 1979a, b, c, d; Ioseliani *et al.*, 1979; Corcoran and Mason, 1980; Horton *et al.*, 1980; apart from post-decapitation convulsions). Other putative neurotransmitters are also involved: ACh, GABA, glutamate (Glu) (Maynert *et al.*, 1975). The above mentioned agreement in the conclusions from animal studies contrasts with the results in epileptic

patients. Manipulations to increase the NE concentration at the central adrenoceptors both increased (tricyclic antidepressants) and decreased (amphetamines) susceptibility to seizure, while manipulations designed to diminish the effects of central NE increased the susceptibility (cf. Maynert *et al.*, 1975). Moreover, the CSF MHPG content was normal in epileptic patients (Peters, 1979; Laxer *et al.*, 1979). Some authors maintain that clinically effective anticonvulsants (diphenylhydantoin, carbamazepine, barbiturates) act through the central NE transmission, but there are many contradictory results (for references see Quatrone *et al.*, 1978). In any case, these anticonvulsants do not act selectively, let alone exclusively, via the central NE transmission.

Electroconvulsive treatment: therapeutical action and central NE. The view that epilepsy and a variety of psychotic manifestations ("dementia praecox") are mutually exclusive, or antagonistic, the so-called "antagonism theory", has been popular for some time (reviews Flor-Henry, 1969, 1972). Some patients show indeed an alternation of convulsive and psychotic manifestations but "the antagonism theory in its original and general formulation was clearly shown to be incorrect" (Flor-Henry, 1969). The antagonism theory was a theoretical basis for electroconvulsive treatment (ECT) of psychotic manifestations. Whatever the value of the antagonism theory may be, ECT is reported as being rather effective in the treatment of psychosis in endogenous depression (Kalinowsky, 1975). In animal studies, acute as well as chronic ECT increased the turnover of NE leaving DA and 5-HT unaffected (Kety *et al.*, 1967; Schildkraut, 1975; Modigh, 1976); moreover, the number of β-adrenoceptors, and the NE-induced accumulation of cyclic AMP is decreased (Pandey *et al.*, 1979; Gillespie *et al.*, 1979). In man, however, ECT diminished lumbal CSF MHPG (Härnryd *et al.*, 1979), which indicates a decrease in NE turnover and activity of the LC cells. Evidently, the relationship in man between epilepsy and ECT on the one hand, and the central NE transmission on the other hand is unclear.

7. Anxiety

7.1. Introduction

"Normal" and "pathological" anxiety. Klein *et al.* (1978) define "anxiety" as a state of being "uneasy, apprehensive, or worried about what may happen". A distinction is made between "normal" (situational) anxiety for which some good reason is present (stressor, disease, or justifiable anxious expectancy), and "pathological" anxiety ("phobic" and "anxiety disorders"; cf. Feighner *et al.*, 1972; Klein *et al.*, 1978; McNair and Fisher, 1978, DSM-III, 1980).

7.2. The "LC-anxiety" Hypothesis

The "LC-anxiety" hypothesis. Redmond has postulated the "LC-anxiety" hypothesis: "brain NE systems, such as the LC, are involved in the production of fear or anxiety" (Redmond and Huang, 1979; Redmond *et al.*, 1976; Redmond, 1977; for a critical discussion see Mason and Fibiger 1979b and Redmond and Huang, 1979). Judging from other remarks by Redmond and his colleagues, the intended meaning of the remark quoted above appears to be (in terms of Van Dongen and Van den Bercken, 1981): "activity of central NE neurons, such as the LC neurons, is an effect of threatening stimuli, and a cause of flight or defense behavior", which relates the "function" of the LC to situational ("normal") anxiety.

Experiments: flight and defense, and the LC. Experimental manipulations in the LC regions of the stump-tailed monkey elicits defense behavior; the "LC-anxiety" hypothesis was based on these results (Redmond *et al.*, 1976; Redmond, 1977; Redmond and Huang, 1979). Electrical stimulation of this region in man (without precise localization however) is reported to cause feelings of fear (Nashold, 1974). Destruction or electrical stimulation of the LC region in the rat, however, did not confirm the "LC-anxiety" hypothesis (Crow

et al., 1972; Simon *et al.*, 1975; Mason *et al.*, 1978; Mason and Fibiger, 1979a, b; File *et al.*, 1979). Similar anxiety reactions as in the stump-tailed monkey could be elicited by intracerebral injection of the cholinergic agonist carbachol in the cat (Van Dongen, 1980a); the effective region in this respect was not the LC, but the rostral pontine reticular formation. With intracerebral injections, cell bodies are affected more selectively, while by electrical stimulation of nerve tissue, the threshold current is generally lower for myelinated fibers than for cell bodies (Ranck, 1975). The data in the cat, and the data of Redmond's group in the stump-tailed monkey are in agreement, if one assumes that the changes in flight and defense behavior described by Redmond's group were actually due to stimulation or interruption of the afferent or efferent fibers of the rostral pontine reticular formation.

7.3. DRUG-TREATMENT OF ANXIETY

Introduction. Drug-treatment of situational and pathological anxiety is different: situational anxiety is generally treated with minor tranquilizers like benzodiazepines (mainly diazepam, valium), or β-adrenoceptor blocking agents (mainly propranolol), while the NE-reuptake blocking tricyclic antidepressants are used to treat pathological anxiety (Klein *et al.*, 1978). In the latter cases, β-blockers are ineffective (Floru, 1977; Greenblatt and Shader, 1978; Bernadt *et al.*, 1980).

Benzodiazepines, anxiety and the LC. The drugs most often used in the treatment of situational anxiety are the benzodiazepines (review Haefely 1978). The benzodiazepines enhance the amount of GABA released, thereby enhancing the effects of activity of GABAergic neurons. GABA and the benzodiazepines suppress the LC cells' activity (Cedarbaum and Aghajanian 1977; Guyenet and Aghajanian, 1979; Grant *et al.*, 1980). These data have been considered as supporting the LC-anxiety hypothesis (Redmond, 1977; Redmond and Huang, 1979), but the benzodiazepine-induced effect on the NE turnover showed tolerance, while the anti-anxiety action of the benzodiazepines showed sensitization rather than tolerance (Haefely, 1978). Consequently, the anti-anxiety action of the benzodiazepines is probably not caused via the LC cells, and the action of the benzodiazepines on the LC cells does not support the LC-anxiety hypothesis.

β-Andrenoceptor blocking agents, anxiety and the LC. β-Adrenoceptor blocking agents are used in the treatment of situational anxiety (review Floru, 1977; Greenblatt and Shader, 1978). This anti-anxiety action has been considered as supporting the LC-anxiety hypothesis (Redmond, 1977; Redmond and Huang, 1979). The majority of investigations, however, indicate that β-adrenoceptor blocking agents reduce the somatic rather than the psychic effects of threatening stimuli: their anti-anxiety action is mainly, but not exclusively, due to blockade of peripheral β-adrenoceptors (Floru, 1977; Greenblatt and Shader, 1978; Bernadt *et al.*, 1980). So the anti-anxiety action of β-adrenoceptor antagonists is at best a weak support of the LC-anxiety hypothesis.

7.4. CONCLUSIONS

According to the LC-anxiety hypothesis, the LC cells are supposed to say (in terms of Van Dongen and Van den Bercken, 1981): "there is a threatening stimulus; flee or defend". From the data published in the literature, the LC cells appear to be activated not only by threat, but also by much milder, non-threatening stimuli (Foote *et al.*, 1980); the behavioral response to these non-threatening stimuli would also be "flee or defend", if the LC-anxiety hypothesis were generally valid. Moreover, other authors do not confirm that flight or defense is an effect of the LC's activity. In patients with a disturbed LC or a disturbed NE transmission, "phobic" or "anxiety disorders" are not a prominent feature. The LC-anxiety hypothesis could still be saved by making extra assumptions, but for the time being I prefer another and simpler suggestion on the "function" of the LC (Section 10., cf. Van Dongen, 1980b).

8. Schizophrenia; Psychotic Manifestations

8.1. SCHIZOPHRENIA

8.1.1. *Definition and diagnosis*

"*Schizophrenia*". "Schizophrenia" is the name of a family of complex disorders "characterized by a withdrawal in a private fantasy world, which is maintained throughout the use of personal beliefs, idiosyncratic thought patterns, and percepts that are not culturally shared" (Bemporad and Pinsker, 1974). "An especially important aspect is the splitting, or disintegration, of the so-called psychological functions: thought, affect, impulses, and so forth are disassociated from one another and within their own constitutive elements" (Arana, 1978). (For an extensive description of symptoms of schizophrenia, and of the meanings of the words to describe them see Arana (1978) and DSM-III (1980).)

Diagnostic criteria. The DSM-III (1980) diagnostic criteria for "schizophrenia" are summarized as follows:

A. at least one of the following: (1) delusions, (2) hallucinations, or (3) incoherence,
B. deterioration from a previous level of functioning in work, social relations and self-care,
C. onset before age 45,
D. other organic mental disorders, mental deterioration, depression or mania must be excluded.

Differential diagnosis. The following symptomatical subtypes of schizophrenia are generally distinguished (DSM-III, 1980; see also Bemporad and Pinsker, 1974; Arana, 1978; these authors also review further classifications).

1. Disorganized type: characterized by often occurring incoherence, the absence of systematized delusions, and the presence of an inappropriate affect.
2. Catatonic type: characterized by a marked psychomotor disturbance called "catatonia".
3. Paranoid type: dominated by either persecutory or grandiose delusions, delusional jealousy, or persecutory or grandiose hallucinations.
4. Undifferentiated type which does not meet the criteria for any of the previous listed types, or for more than one. Patients who were initially diagnosed as being disorganized, catatonic or paranoid schizophrenics, often become "chronic undifferentiated schizophrenics" in a later stage.

Reliability and validity. Spitzer *et al.* (1978) give a survey of the reliability (interrater agreement) of the different systems for the diagnosis of "schizophrenia": an acceptable reliability can be reached. No data are available, to my knowledge, on the reliability of the differential diagnoses of the various subtypes of schizophrenia. The validity of the various diagnostic systems for schizophrenia cannot be determined at the moment, because there is no independent test for "real" schizophrenia, let alone for the various subtypes of schizophrenia. Gift *et al.* (1980) have demonstrated, however, that in the various diagnostic systems, emphasis is laid on different symptoms of schizophrenia. It has recently been attempted to relate symptomatical differences between schizophrenics to differences in neurochemical, neurological and other "biological" measures (Wyatt *et al.*, 1981). The subtype "paranoid schizophrenia" is considered to be the most homogeneous subtype, both symptomatically and neurochemically (Section 8.1.2.).

Hypotheses on etiology. "Various areas of neuroscience, and not at least the realms of schizophrenia research, appear to follow swings of fashion. After much emphasis on the role of dopamine supersensitivity in the development of schizophrenia, noradrenaline is now considered by some as being a more crucial neurotransmitter in this disorder" (Ter Haar, 1979a). Apart from DA and NE, other compounds and processes have been suggested as a cause of forms of schizophrenia: ACh, GABA, endorphins, prostaglandins, melatonin, gluten, immunological disorders and virus infections (Ter Haar, 1979b; Malek-Ahmadi and Callen, 1980; Horrobin, 1980; Berger, 1981). It is at the

moment far from clear whether these presumed causes are really causes, and, if so, whether they are related or not, and whether they act simultaneously or in succession. I will restrict myself here to the involvement of NE and DA in schizophrenia.

8.1.2. *Brain changes in schizophrenics*

Morphology of the brains of schizophrenics. With the various histological techniques used up to this moment, remarkably few changes in brain morphology in schizophrenics have been reported. The melanogenesis in the brain, eyes and skin of some schizophrenics is probably due to the skin pigment melanin, and not to the CA-specific neuromelanin (cf. Greiner and Nicholson, 1965). Some weak association has been described between symptoms of schizophrenia and the presence of Lewy bodies (Sections 8.3. and 10.). To reliably ascribe schizophrenic symptoms to brain damage a much more detailed analysis than that of Bowman and Lewis (1980) is necessary.

Central NE in paranoid schizophrenia. All the recent studies about the NE content of brain nuclei and the CSF in paranoid schizophrenic patients are in agreement that the NE content is increased (Farley *et al.*, 1978; 1979; Carlsson, 1979; Hornykiewics, 1979 (cited by Ter Haar, 1979a), Kleinman *et al.*, 1979; Lake *et al.*, 1980a). An increase in the NE content, which may be up to 3 times, has been found both in LC terminal regions (mesencephalon, nucleus interstitialis striae terminalis, ventral septum, corpora mammilaria) and in presumed non-LC terminal regions (nucleus accumbens). The increase in the CSF NE content is probably not due to antipsychotic drug treatment (cf. Lipsky, 1980; Lake *et al.*, 1980b). A normal brain DBH activity and CSF MHPG content has been found in paranoid schizophrenics (Wise and Stein, 1975; Peters, 1979). These biochemical measures alone cannot indicate whether the central NE transmission is disturbed in paranoid schizophrenia, and if so, what sort of disturbance there is. The levels of DA, homovanillic acid and 3,4-dihydroxyphenylacetic acid, which are related to the DA transmission, have been reported as being unchanged in paranoid schizophrenia (Kleinman *et al.*, 1979). The peripheral (sympathetic) NE transmission is also disturbed in paranoid schizophrenic patients: platelet MAO activity and plasma DBH activity are reduced (Schildkraut *et al.*, 1976; Potkin *et al.*, 1978; Wyatt *et al.*, 1978; Baron *et al.*, 1980, DeLisi *et al.*, 1980, Meltzer *et al.*, 1980).

Central NE in non-paranoid schizophrenia. No change in the NE content of brain nuclei in non-paranoid schizophrenics have been described (Farley *et al.*, 1979); this might explain why smaller, not statistically significant, changes in NE levels are found in brain regions of a large group of schizophrenics without further subclassification (cf. Bird *et al.*, 1979; Farley *et al.*, 1979). An increase in the CSF NE content has also been found in chronic schizophrenics without further subclassification (Gomes *et al.*, 1980). The activities of enzymes related to the NE transmission (TH, dopa-decarboxylase, catechol-O-methyltransferase (COMT) and DBH) in the brains of schizophrenics are reduced according to a number of authors (Wise and Stein, 1973, 1975; Wyatt *et al.*, 1975, 1978), but unchanged according to others (Cross *et al.*, 1978; Lerner *et al.*, 1978). The mean urinary MHPG content of chronic schizophrenic patients (without schizoaffective or paranoid features) did not differ from that of controls, but the variation was much larger, which indicates a heterogeneous composition of this group of schizophrenics (Taube *et al.*, 1978). An increase in the content of free MHPG, and a decrease in conjugated MHPG has been found in the hypothalamus of psychotic patients, including paranoid and undifferentiated schizophrenics (Kleinman *et al.*, 1979).

8.2. DRUG-INDUCED PSYCHOTIC MANIFESTATIONS

Introduction. Psychotic manifestations (confusions, delusions, hallucinations) can be induced by administration of some drugs to man. Some of these drugs directly influence the central NE transmission; their effects will be mentioned below.

Amphetamine-induced psychosis. Amphetamines cause mental disturbances resembling acute paranoid schizophrenia (Carlsson, 1977; Crow, 1979; Kokkinidis and Anisman, 1980). Amphetamines increase the release of both NE and DA, but from a comparison of the effectiveness of the d- and l-isomers, a number of authors concluded that NE rather than DA is involved in the amphetamine-induced psychoses (Sulser and Robinson, 1978; Mason, 1979b; Hornykiewics, 1979; cited by Ter Haar, 1979a).

l-Dopa-induced psychosis. l-Dopa alone in a high dose, or l-dopa plus a MAO-inhibitor administered to Parkinsonian patients has been reported as causing psychotic manifestations: confusions, delusions, hallucinations (Jenkins and Groh, 1970; Marsh and Markham, 1973; Birkmayer, 1976). These psychoses are probably really l-dopa-induced, since they disappeared after discontinuation of l-dopa administration. The NE content of several brain regions is increased in psychotic l-dopa-treated Parkinsonians, compared to non-psychotic l-dopa-treated Parkinsonians (Birkmayer *et al.*, 1974, 1976, 1977). In psychotic l-dopa-treated Parkinsonians, the NE content of the LC terminal regions gyrus cinguli, and raphe nuclei was also far above that of asymptomatical controls. It was also increased in the SN and nucleus rubber, and in the amygdala, which is a LC terminal region. The DA content of most brain regions in psychotic l-dopa-treated Parkinsonians was similar to that in non-psychotic l-dopa-treated Parkinsonians; it was increased only in the SN, and in the predominantly LC terminal regions gyrus cinguli and raphe nuclei: in the latter two cases it probably concerns precursor DA in LC terminals. The l-dopa-induced psychoses are probably caused by a l-dopa-induced increase in the level of NE rather than DA (Birkmayer *et al.*, 1974).

8.3. Psychotic Manifestations in Parkinson's/Lewy Body Disease

The frequency of occurrence of Lewy bodies in the brains of "patients with psychosis or mental deficiency" is similar to that in a large sample of individuals without predominance of psychiatric symptoms (Woodard, 1962; cf. Forno, 1969). No Lewy bodies were found in 77 cases of "organic psychosis other than Alzheimer's disease". In cases of Alzheimer's disease, Lewy bodies occur as frequently (10%) as in the whole population of elderly individuals (Section 3.2.). Lewy bodies are however much more frequent (28%) in cases of "mental disturbance without established morphological basis" (Woodard, 1962). The clinical features found in these cases with Lewy bodies are paranoia, violence, confusion, affective disorders, and relatively minor and often late intellectual deterioration (Woodard, 1962). (Quantitative (WAIS) investigation indicate however a clear intellectual impairment in idiopathic Parkinson's (Lewy body) disease, see Section 4.4.) Parkinsonian patients have a high score on an index for schizophrenia, but "clinically, the patients show Parkinsonism, not schizophrenia" (Hoehn *et al.*, 1976; cf. Sections 4.3. and 10.).

8.4. Drug-treatment of Psychotic Manifestations

Antipsychotic drugs. A variety of drugs is used to diminish psychoses in schizophrenics and other patients (reviews Sulser and Robinson, 1978; Carlsson, 1978). Despite a remarkable antipsychotic effect of these drugs in a number of patients, "large drug studies have shown that at most only 50% (of schizophrenic patients) derive some benefit from pharmacotherapy" (Sulser and Robinson, 1978). This is not unexpected: only if schizophrenia is in some respect a neurochemical entity, attempts to develop a specific antipsychotic drug, or to formulate a single theory on the origin and termination of psychoses, can be sucessful. At the moment, there are no grounds to assume that the schizophrenias are a neurochemical entity; on the contrary, the data available indicate a neurochemical heterogeneity of the group of schizophrenics (Taube *et al.*, 1978). In this section, attention will be paid to groups of antipsychotic drugs which directly influence the NE transmission: propranolol and neuroleptics.

Propranolol. A number of investigations indicate improvements in schizophrenics by administration of high doses of propranolol (Roberts and Amacher, 1978; Lindström and

Persson, 1980; but not King *et al.*, 1980). A substantial improvement has been reported in paranoid schizophrenics particularly (Yorkston *et al.*, 1977; Bigelow *et al.*, 1979); propranolol is reported as being an equally effective antipsychotic drug as chlorpromazine (Yorkston *et al.*, 1981). At the moment, it is uncertain whether the antipsychotic effect of propranolol is due to its blockade of central β-adrenoceptors, or to other effects (peripheral actions, membrane stabilizations or antiserotonergic action, cf. Weinstock and Weiss, 1980).

Neuroleptics: DA and NE transmission. For many years it has been the broadly accepted theory that neuroleptics exert their antipsychotic effect through a blockade of DA receptors (Sulser and Robinson, 1978; Carlsson, 1978; Peroutka and Snyder, 1980). Besides blocking the DA receptors, the neuroleptics are antagonists both of β- and α_2-adrenoceptors (Sulser and Robinson, 1978). Neuroleptics antagonize the NE-induced suppression of cerebellar Purkinje cells, and the NE-induced accumulation of cyclic AMP, which effects both come about via β-adrenoceptors (Palmer *et al.*, 1971, 1972, Freedman and Hoffer, 1975). Neuroleptics increase the release of NE by blockade of α_2-adrenoceptors (Arbilla *et al.*, 1978; Gross and Schumann, 1980). At least part of the therapeutic action of neuroleptics could be due to their blockade of β- and α_2-adrenoceptors.

8.5. NE AND DA IN SCHIZOPHRENIA

Some circumstantial evidence can be presented and will be summarized here that a change in the central NE transmission is a cause of some forms of schizophrenia (besides and/or together with other causes, Section 8.1.1.).

1. Some correlations between changes in the central NE transmission and the occurrence of some forms of schizophrenia have been described. (1) In paranoid schizophrenic patients, the brain NE content is increased. (2) In schizophrenic patients, the brain DBH activity is decreased. (3) In cases of Lewy body disease, paranoid features were prominent. (4) In psychotic l-dopa-treated Parkinsonian patients, the most prominent changes were in the NE transmission. It remains to be investigated which regions of NE cell bodies and NE terminals are primarily involved in schizophrenia.
2. No indications have been published thus far that changes in the central NE transmission precede schizophrenia or psychoses.
3. The effects of some manipulations of the central NE transmission are in line with the hypothesis that a change in the central NE transmission is a cause of symptoms of schizophrenia: (1) the antipsychotic effect of neuroleptics and propranolol, and (2) the induction of psychotic manifestations by amphetamines and l-dopa.

It should be noted that the pharmacological evidence in favour of the DA hypothesis of schizophrenia (the effects of neuroleptics, amphetamines and l-dopa) is also in agreement with a NE hypothesis of schizophrenia; in contrast to NE however, no broadly confirmed changes in the central DA transmission in schizophrenic patients have been found. The relationships between a NE hypothesis of schizophrenia and the "function" of the LC, as concluded from animal studies, will be discussed in Section 10.

9. Affective Disorders; Mood

9.1. DEFINITION AND DIAGNOSIS

"*Affective disorders*". Patients with affective disorders are characterized by depressive and/or manic periods (cf. Feighner *et al.*, 1972, DSM-III, 1980). A patient in a depressive period is depressed, sad, hopeless, etc. On the other hand, a patient in a manic episode is characterized by a remarkably elevated, euphoric or irritable mood. One speaks about "affective disorders", if the depressive or manic symptoms are of sufficient severity to

interfere with social functioning, and if other mental disorders such as schizophrenia or phobic neuroses are absent (cf. DSM-III, 1980).

Classification and differential diagnosis. Patients with affective disorders are further distinguished on a number of dimensions (Katz and Hirschfeld, 1978):

1. unipolars versus bipolars: the former have only depressed periods, while in the latter depressed and manic periods occur.
2. endogenous versus non-endogenous: "endogenous depression" refers to a syndrome involving early morning awaking, anorexia and weight loss, psychomotor disturbance, severe depression of the mood, and lack of reactivity; these symptoms are not due to external circumstances.
3. schizophrenia-related depression, and schizoaffective disorder (for definitions see Spitzer *et al.*, 1978 and Arana, 1978).
4. primary versus secondary: in secondary depression, there is a pre-existing non-affective psychiatric disease, or another disease which could cause the affective symptoms (Feighner *et al.*, 1972).

Cluster analysis of depressed patients has revealed 4 subtypes: bipolar, psychotic, severe endogenous and less severe endogenous (Andreasen and Grove, 1980). (The subgroup "severe endogenous depression" is broadly the same as "major depressive illness" according to DSM-III (1980) or "depression" according to Feighner *et al.* (1972).) These symptomatological differences between depressed patients are reported to correlate with biochemical measures (Schildkraut *et al.*, 1979).

Reliability and validity. The reliability (interrater agreement) of the DSM-III criteria for major depressive disorder and bipolar depression is acceptable, but it is rather weak for schizo-affective and minor depressive disorders (Spitzer *et al.*, 1975). The validity of the diagnostic criteria for affective disorders cannot be determined, because there is no independent, and generally accepted, "test" to determine to which disease the patient "really" belongs. Biochemical measures and the outcome of drug treatment might become part of such independent tests (cf. Schildkraut *et al.*, 1979).

"Biological" affective disorders. "We note a major gap between the nature of the "biological" depressives (endogenous and bipolar) on the one hand, and that of the "psychogenic" depressives (primarily neurotic, some secondary, some unipolar) on the other" (Katz and Hirschfeld, 1978). This section will be limited principally to the bipolar and major depressive disorders (or endogenous unipolar depression), i.e. to the groups about which a relatively great deal of biochemical and pharmacotherapeutic knowledge is available.

Symptoms in depression. A depressed mood is not the only characteristic of endogenous depression; other symptoms are found in affect, thinking, behavior and somatic activities: feelings of guilt and worthlessness, hostility, anxiety–tension, cognitive loss, loss of interest, somatic complaints, motor retardation and bizarre thoughts (Katz and Hirschfeld, 1978; Nelson and Charney, 1981). The intellectual impairments of depressed patients are similar to, but less severe than, those in Parkinsonian patients (Loranger *et al.*, 1972a).

9.2. Brain Changes in Affective Disorders

Unipolar endogenous depression: "NE-" and "5-HT-depression". The group of unipolar endogenous depressed patients is reported as being heterogeneous with respect to biochemical measures. A subgroup of patients with low urinary MHPG contents (which reflects CNS NE metabolism, see references in Schildkraut, 1978; Garver and Davis, 1979), and one with normal contents could be distinguished; an inverse relationship exists between the contents of urinary MHPG, and the levels of CSF 5-hydroxyindoleacetic acid (5-HIAA, the main metabolite of 5-HT; Goodwin *et al.*, 1978; Schildkraut, 1978; Schildkraut *et al.*, 1979; Halaris and DeMet, 1979; Taube *et al.*, 1978; Garver and Davis, 1979; but not Ridges *et al.*, 1980). Endogenous unipolar depression with low urinary MHPG contents is called "NE-depression", while it is called "5-HT-depression"

when the CSF 5-HIAA level is low. Patients of these two forms of unipolar endogenous depression respond differently to treatment with various antidepressant drugs (see below). When the symptoms of "NE-depression" have disappeared, urinary MHPG levels appear to have increased to normal values (Shaw *et al.*, 1973; Sweeney *et al.*, 1979). The urinary MHPG content was related to mood rather than to retardation or agitation (Schildkraut, 1978; Taube *et al.*, 1978). Although the data on urinary MHPG content in unipolar endogenous depression are fairly consistent, contradictory data have been published on CSF MHPG levels in depressed patients (see Schildkraut, 1978). For the whole group of unipolar endogenous depressed patients (without differentiation between NE- and 5-HT depression), a decrease in the brain NE content has been reported only for a few regions (amygdala, nucleus ruber), while a decrease in the level of free MHPG has been found in more regions (globus pallidus, hypothalamus, corpora mammilaria, SN, raphe, nucleus accumbens; Birkmayer *et al.*, 1976; Riederer and Birkmayer, 1980). The CSF DBH activity is reported as being normal in unipolar endogenous depressed patients (Lerner *et al.*, 1978).

Bipolar patients. The levels of plasma and urinary MHPG in bipolar patients correlate with their mood (Bond *et al.*, 1972; Jones *et al.*, 1973; Schildkraut, 1978; Garver and Davis, 1979; Halaris and DeMet, 1979). The urinary MHPG content of bipolars in the depressed phase is lower than that of controls, and in the manic phase equal to the controls' content. The changes in MHPG content are reported as preceding the changes in mood; the MHPG content is related to mood rather than to agitation and retardation (Schildkraut, 1978; Taube *et al.*, 1978). Although DBH probably is released together with NE (cf. Van Dongen, 1980b, pp. 174–175), the CSF DBH activity in bipolar patients is diminished during the manic phase (Lerner *et al.*, 1978).

9.3. PHARMACOTHERAPY OF DEPRESSION; ANTIDEPRESSANTS

Tricyclic antidepressants in "NE-depression". The subgroup of depressed patients who react relatively well to treatment with tricyclic antidepressant drugs, is characterized by endogenous symptoms (Goodwin *et al.*, 1978; Katz and Hirschfeld, 1978). Patients with NE- and 5-HT-depression react differently to the various tricyclic antidepressants (Fawcett and Siomopoulos, 1971; Beckman and Goodwin, 1975; Goodwin *et al.*, 1975; Garver and Davis, 1979; Halaris and DeMet, 1979; Rosenbaum *et al.*, 1980). The symptoms of patients with NE-depression are diminished predominantly by treatment with secondary tricyclic antidepressant drugs (mainly desmethylimipramine, DMI), rather than the tertiary ones (amitriptyline, chlorimipramine and imipramine, IMI, which is however metabolized to DMI, Garver and Davis, 1979). The urinary MHPG content of patients with NE-depression is increased by administration of DMI or IMI. Such patients show temporary improvement after treatment with d-amphetamine.

Antidepressant drugs: mechanism of action. The effects of acute and chronic administration of tricyclic antidepressants are different. The most prominent effect of acute administration of secondary tricyclic antidepressant drugs is the blockade of the re-uptake of NE, while for the tertiary antidepressants it is the blockade of the 5-HT re-uptake (Lewi and Colpaert, 1976; Carlsson and Lindquist, 1978, U'Prichard *et al.*, 1978; Goodwin *et al.*, 1978; Garver and Davis, 1979; Maggi *et al.*, 1980; Rehavi *et al.*, 1980). Chronic administration tricyclic antidepressants causes a decrease in the number of central adrenoceptors (β_1 and α_2; Section 1.2.); the secondary tricyclic antidepressants are more effective in this respect than the tertiary ones (Tang *et al.*, 1981). After chronic administration of other clinically effective antidepressants (mianserin, zimilidine) the NE-induced accumulation of cyclic AMP is reduced; this might be due to a decrease in the number of β-adrenoceptors (Clements-Jewery, 1978), or to other, still unknown, processes (Sellinger-Barnette *et al.*, 1980; Mishra *et al.*, 1980). Evidence has been presented that such antidepressant-induced decrease in the effects of NE is related to their therapeutic action in NE-depression, rather than their blockade of the NE-reuptake (cf. Sulser *et al.*, 1978; Maas, 1979).

1. The time course of the DMI-induced decrease in the effects of β-adrenoceptor agonists is similar to the time-course of DMI's therapeutic action (Huang *et al.*, 1980).
2. In animals, a common property of tricyclic and non-tricyclic antidepressants is a decrease in the effects of NE, rather than a blockade of the reuptake (Banerjee *et al.*, 1977; Clements-Jewery, 1978; Sellinger-Barnette *et al.*, 1980; Mishra *et al.*, 1980).
3. The behavioral effects of the α_2-adrenoceptor agonist clonidine in depressed patients are reduced by DMI, with a time-course, similar to the time course of DMI's therapeutic effects (Checkley *et al.*, 1981).

9.4. Pharmacotherapy of Mania

There is evidence that in bipolar patients in the manic phase, the NE release and its effects are increased as compared to the depressed phase, and that this increase is a cause of the manic phase. During the manic phase, plasma and urinary MHPG are increased as compared to the depressive phase (Section 9.2.), and manic symptoms are diminished by propranolol (at least partly by blockade of β-adrenoceptors; Emrich *et al.*, 1979), DBH inhibitors (fusaric acid in mild hypomania; Sacks and Goodwin, 1974) and by lithium (which among other things antagonizes the NE-induced accumulation of cyclic AMP, cf. Van Dongen, 1981; Gerbino *et al.*, 1978).

9.5. Affective Disorders in Parkinson's Disease

Occurrence of depression in Parkinson's disease. A high incidence of depression (37–90%) has been reported in Parkinsonian patients (the idiopathic as well as the postencephalitic and arteriosclerotic forms; Warburton, 1967; Mindham, 1970; Celestia and Wanamaker, 1972; Brown and Wilson, 1972; Andersen *et al.*, 1980). Depression has been reported in untreated and l-dopa-treated Parkinsonian patients. The depression in Parkinsonian patients has rarely been described in more detail; Damasio *et al.* (1970) have reported "endogenous" and "reactive" forms of depression in Parkinsonism (cf. "biological concomitants" of depression, Brown and Wilson, 1972; Andersen *et al.*, 1980). The reactive form of depression is effectively treated by l-dopa, and the endogenous depression by tricyclic antidepressants (Damasio *et al.*, 1970; Mindham, 1970; Celestia and Wanamaker, 1972; Andersen *et al.*, 1980).

Depression and motor impairments. The depression and motor impairments in Parkinson's disease are not caused by loss of identical nerve cells, and the depression is only incidentally an effect of the motor impairments (reactive depression).

1. Depression and motor impairments are poorly correlated: (1) the correlation between the severity of the motor symptoms and of the depression is small, and (2) in Parkinsonian patients, more depression has been found than in other, physically more disabled, patients (Robins, 1976); consequently, the motor symptoms alone cannot explain the depression in Parkinsonian patients.
2. The depression can precede the motor impairments and *vice versa.*
3. The depression and motor impairments can be, and often are, treated independently: l-dopa diminishes the akinesia and rigidity leaving the depression in many cases unaffected (Marsh and Markham, 1973; Hoehn *et al.*, 1976), and tricyclic antidepressants diminish the depression and not the motor symptoms (Mindham, 1970; Andersen *et al.*, 1980).

No mania in Parkinson's disease. While depression is part of the natural history of Parkinson's disease, mania is almost completely absent (Mindham, 1970); the low (1%) incidence of bipolar affective disorder in l-dopa-treated Parkinsonian patients (Mendlewicz *et al.*, 1976) may be attributed either to l-dopa treatment, or to misdiagnosis of Parkinson's disease (cf. Pollock and Hornabrook, 1966). It is tempting to conclude that the cause of depression in Parkinson's disease differs from that of depression in bipolar affective disorder.

9.6. CONCLUSIONS ON AFFECTIVE DISORDERS

Hypothetical causes of affective disorders. The hypothetical somatic causes of affective disorders are disturbances in the central NE and 5-HT transmission, in the cell membranes, in hormone action or in amino acid transport across the blood-brain barrier (Goodwin *et al.*, 1978; Carlsson, 1979; Garver and Davis, 1979). It remains to be settled whether these presumed causes are related or not, and whether they act simultaneously or in succession.

Central NE in endogenous "NE depression" and bipolar disorder. A number of studies indicate that a change in the central NE transmission is a cause of "NE depression" and of the bipolar affective disorder.

1. Some measures of the central NE transmission correlate with mood: (1) during depression in endogenous NE-depressive and bipolar patients, the urinary MHPG content is low, and (2) after recovery from depressive illness, urinary MHPG appears to be increased. It has to be investigated which NE region is primarily involved in NE-depression.
2. The changes in urinary MHPG are reported to precede the changes in mood (Taube *et al.*, 1978; Schildkraut, 1978).
3. The effects of various drugs which influence the central NE transmission (tricyclic and non-tricyclic antidepressants, d-amphetamine) on endogenous NE depression are in line with the hypothesis that a change in the central NE transmission is a cause of the change in the mood.

Since there is no broadly accepted theory on brain processes and mood, the hypothetical relationship between the central NE transmission and depression cannot be in line, or conflicting, with such theory.

What is wrong with central NE in endogenous NE-depression? The question was whether the effects of activity of the NE cells were too great or too small in endogenous NE-depression (cf. Sulser *et al.*, 1978; Maas, 1979; Willner and Montgomery, 1980). At the moment it is broadly accepted that antidepressant drugs are clinically effective by diminishing the effects of central NE, so it is obvious that the effects of central NE are too great in endogenous NE-depression, and that this change in the central NE transmission is a cause of depression. Many speculations can be made on the molecular or cellular mechanism of this increase in the effects of the activity of the NE cells: ranging from a disturbed input of the NE cells, via a disturbed transmission by these cells, to disturbances in the NE target cells (cf. Fig. 2). A hypertrophy of the central adrenoceptors seems to be the most plausible explanation of endogenous "NE-depression". The MHPG and NE levels in some brain regions are reduced, so the models 1 to 5 (Fig. 2) are less probable, because these models predict an enhancement in these measures. It is plausible to conclude that in endogenous NE-depression (1) the release of central NE is someway reduced, and (2) this reduction causes hypertrophy of the central adrenoceptors. The effects of such hypertrophy of the central adrenoceptors can be diminished either by drugs decreasing the number of central adrenoceptors (secondary tricyclic antidepressants), or by drugs that otherwise diminish the effects of NE-induced activation of the central adrenoceptors (cf. Mishra *et al.*, 1980).

Central CA and depression in Parkinson's disease. Analogously as in endogenous NE depression, the "endogenous" depression in Parkinsonian patients can be an effect of loss of central NE cells. Loss of central DA and NE cells has been well demonstrated in Parkinson's disease; this cell loss most probably causes an increase in the central receptors for DA and NE. Analogously as in endogenous NE-depression, NE rather than DA is thought to be involved in depression in Parkinson's disease. NE cell loss is then a remote cause, and hypertrophy of central adrenoceptors a proximate cause, of depression in Parkinson's disease.

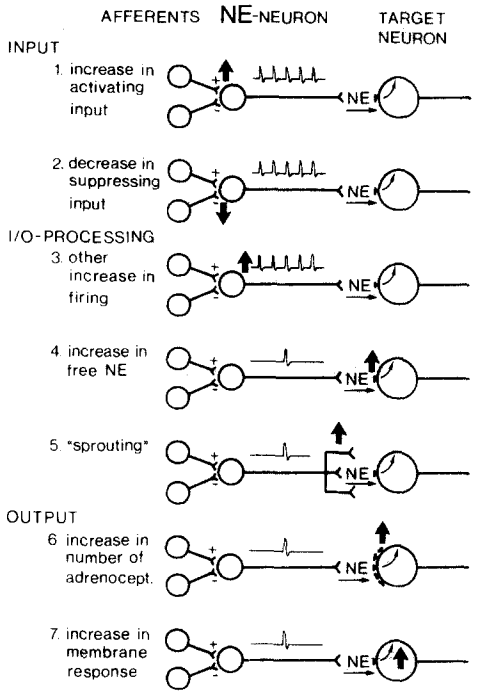

FIG. 2. Schematic survey of different hypothetical causes of the increase in the effects of activity of central NE neurons in endogenous NE depression. 1. Increase in the activity of activating afferent neurons. 2. Decrease in the activity of suppressing afferent neurons. 3. A change in the information processing in the NE neuron, such that its firing rate is increased in the presence of an unchanged input. 4. An increase in the level of free NE in the presence of an unchanged firing rate of the NE neurons, caused by either (a) an increase in the amount of NE released by a single action potential, (b) a decrease in the degradation of free NE, or (c) a decrease in the re-uptake of free NE. 5. "Sprouting" leading to hyperinnervation. 6. An increase in the number of adrenoceptors. 7. An increase in the response of the target neuron of the NE cell in the presence of an unchanged number of adrenoceptors.

10. The "Function" of the LC; Intellectual and Memory Impairments, Confusions, Delusions and Hallucinations

Introduction. Several theories on the "function" of the LC have been formulated in the course of time; these theories were mainly (or exclusively) based on animal studies. In this section, the conclusions from such experimental investigations on the LC will be compared with the results from research correlating clinical symptoms with changes in the human LC and central NE transmission.

The "relevance?/stand-by function" of the LC. The effects of environmental stimuli on the LC cells' activity (Foote *et al.*, 1980), AND the effects of the activity of the LC cells on their target cells (Van Dongen, 1981), and thereby on the CNS's information processing and behavior, have been generalized to the "relevance?/stand-by function" of the LC (Van Dongen, 1980b). According to this hypothesis, the LC cells are saying metaphorically: "Something important may be going on; observe what is going on (dorsal LC), and stand by to react (ventral LC)". This message is carried by the LC fibers during active waking, when the LC cells are most active, and not during paradoxical sleep and dreaming, when the LC cells are silent (Foote *et al.*, 1980; Van Dongen, 1980b, pp. 40–42). The LC cells are not simply excitatory or inhibitory, but their action is selectively enhancing or diminishing the effects of various other neurotransmitters (cf. Van Dongen, 1981). The "relevance?/stand-by function" of the LC is more or less in line with the "attention function" of the LC as suggested by Mason, based mainly on studies of the effects of lesions of the ascending LC fibers (Mason, 1979a, b; McNaughton and Mason, 1980). It is however difficult to infer the "normal function" of a brain region from malfunctions

after its destruction (Gregory, 1961; Van Dongen and Van den Bercken, 1981), so I prefer the "relevance?/stand-by function" since this is based on the normal effects of the environment on the LC cells' activity, and on the normal effects of the LC cells' activity on the CNS. (I have admitted already that the relevance?/stand-by function in its present form is too general, but the data available do not yet permit a more specific formulation.)

Other theories on the LC's "function". Several other hypotheses on the LC's "function" are considered to be less probable (see the reviews by Amaral and Sinnamon, 1977; Clark, 1979; Ramm, 1979; Mason, 1979a, b; McNaughton and Mason, 1980; Van Dongen, 1980b). These are:

1. atonia: the hypothesis that activity of the LC cells causes atonia during paradoxical sleep (Jouvet, 1972),
2. reward: the hypothesis that electrical stimulation of the LC fibers causes self-stimulation behavior (Crow, 1972),
3. anxiety: the hypothesis that electrical stimulation of the LC cells causes flight or defense (Redmond, 1977; cf. Section 7.),
4. stress: the hypothesis that activity of the LC cells causes a reduction in the response to stressors (the "stress-dampening function", Amaral and Sinnamon, 1977; cf. Van Dongen, 1980b).

The hypothesis that the LC is involved in frustrative non-reward (cf. McNaughton and Mason, 1980) applies only to a subset of the effects of the LC's activity: to a subset of the LC's terminal regions and to a subset of situations in which the LC cells are active.

Summary; syndromes and symptoms. The LC and the central NE transmission appear to be disturbed in the following syndromes: Parkinson's, Alzheimer's and Hallervorden–Spatz disease, paranoid schizophrenia and in endogenous "NE depression". The involvement of the LC and/or central NE in progressive supranuclear palsy, Korsakoff's disease, epilepsy and other forms of schizophrenia and affective disorders are less clear. The following symptoms are generally found in diseases in which a disturbance in the LC has been well demonstrated: impairments of perceptual organization and memory, disorientation, confusions, delusions, hallucinations and changes in personality and mood. The occurrence of these symptoms will be related to the "relevance?/stand-by function" of the LC. No further remarks on the LC and NE in depression will be made below: because there is no broadly accepted theory on the relationship between brain processes and mood, such remarks would be too speculative.

Intellectual and memory impairments. LC cell loss will be followed by an increase in the number of the adrenoceptors in the denervated region, and possibly by sprouting of other LC fibers re-innervating the denervated region (Section 1.2., Fig. 1). Despite such compensatory actions, the amount of information that can be transported by the remaining LC fibers is reduced after LC cell loss, since the information capacity of a neuronal system is tightly coupled to the number of neurons (Kulikowski, 1971). With an increase in age, however, the compensatory changes in the central adrenoceptors are probably reduced (cf. Scheff *et al.*, 1978). Consequently, the effects of dysfunction, decay or cell loss in the LC will become evident as symptoms. According to the relevance?/stand-by function, any disturbance in the LC and the central NE transmission will disturb the information processing in vast areas of the CNS, sensory as well as integrative and executive. When an animal or man with such disturbed LC is confronted with a simple task, this task can still be done, but more difficult tasks cannot be completed any more. In Parkinsonian patients, an impairment in the reaction to novel or unfamiliar stimuli has been found, and a loss of LC cells; LC cells are most active in the presence of novel or unfamiliar stimuli, and the activity of the LC cells is thought to improve the cerebral information processing. So it is plausible that cell loss in the LC is a cause of an impaired reaction to novel or unfamiliar stimuli. An overall deterioration of the CNS's information processing will cause not only intellectual, but also memory impairments; the latter not due to a selective impairment of memory, but rather to a decay of the neuronal messages to be remembered and/or to retrieve the stored information.

Confusions, delusions and hallucinations. When still more LC cells are lost, the symptoms will become more severe; a severe LC cell loss is suggested to be a cause of the so-called "dementia" as observed in Parkinsonian patients with the prominent characteristics of disorientation, confusions, delusions and hallucinations. Disorientation and confusion could, at least partly, be due to a further deterioration in the CNS information processing after a more severe LC cell loss. The LC cells are active during behavioral activity during waking, and silent during paradoxical sleep. Let us now make the speculation that NE from the LC is a cue for the CNS which neural activities are representations of a real outside world, and which are merely dreams: neural activity simultaneous with central adrenoceptor activation is taken to be a representation of a real world, while neural activity without central adrenoceptor activation is considered to reflect dreaming. When LC cells have died, and the CNS has compensated for this cell loss, the distinction between waking and dreaming will be reduced or non-existant: waking and dreaming will become indistinguishable for the CNS, and the resulting symptoms will be confusions, delusions and hallucinations.

Summary

1. The locus coeruleus (LC) is quantitatively the most important noradrenergic (NE) nucleus in the brain. The LC and the central NE transmission appear to be disturbed in the following diseases: idiopathic and post-encephalitic Parkinson's disease, Hallervorden–Spatz disease, Alzheimer's disease, paranoid schizophrenia and endogenous "NE depression" (i.e. a form of endogenous depression characterized by low levels of urinary MHPG).
2. In the brains of idiopathic Parkinsonian and Hallervorden–Spatz patients, Lewy bodies and cell loss in the LC are present. The Parkinsonian motor symptoms are probably not caused by dysfunctions of the LC.
3. The LC of patients with postencephalitic Parkinson's or Alzheimer's disease shows neurofibrillary tangles and cell loss.
4. In paranoid schizophrenia, the brain NE content is increased; such increase has been found in terminal regions of the LC and others.
5. In endogenous NE depression, the NE levels in some LC target regions are reduced; it is suggested that hypertrophy of central adrenoceptors ("supersensitivity") is a cause of endogenous NE depression.
6. The involvement of the LC and the central NE transmission in the following diseases is less certain: Korsakoff's disease, progressive supranuclear palsy, epilepsy, anxiety states, and other forms of schizophrenia and affective disorders than paranoia and endogenous "NE-depression".
7. The following symptoms are often found in diseases with disturbances in the LC and the central NE transmission: impairments of perceptual organization and memory, disorientation, confusions, delusions and hallucinations. It is suggested that dysfunctions of the LC are a cause of these symptoms. This suggestion is in line with conclusions on the LC's "function" from animal studies.
8. Changes in mood (depression) and personality have been found in endogenous NE depression, and in Parkinson's and Alzheimer's disease. These symptoms might be caused by disturbances in the LC and the central NE transmission.

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References

ADAMS, R. D., VAN BOGAERT, L. and VAN DER EECKEN, H. (1964) Striato-nigral degeneration. *J. Neuropath. exp. Neurol.* **23,** 584–608.

ADOLFSSON, R., GOTTFRIES, C. G., ORELAND, L., ROOS, B. E. and WINBLAD, B. (1978) Reduced levels of catecholamines in the brain and increased activity of monoamine oxidase in platelets in Alzheimer's disease: Therapeutic implications. In: *Alzheimer's disease: Senile dementia and related disorders*, pp. 441–451. Eds. R. KATZMAN, R. D. TERRY and K. L. BICK. Raven Press, New York.

ADOLFSSON, R., GOTTFRIES, C. G., ROOS, B. E. and WINBLAD, B. (1979) Changes in the brain catecholamines in patients with dementia of Alzheimer type. *Brit. J. Psychiat.* **135,** 216–223.

ALBERT, M. L., FELDMAN, R. G. and WILLIS, A. L. (1974) The "subcortical dementia" of progressive supranuclear palsy. *J. Neurol. Neurosurg. Psychiat.* **37,** 121–130.

ALBERT, M. L. (1978) Subcortical dementia. In: *Alzheimer's disease: Senile dementia and related disorders*, pp. 173–180. Eds. R. KATZMAN, R. D. TERRY and K. L. BICK. Raven Press, New York.

ALVORD, E. C., JR., FORNO, L. S., KUSSKE, J. A., KAUFMAN, R. J., RHODES, J. S. and GOETOWSKI, C. R. (1974) The pathology of Parkinsonism: A comparison of degenerations in cerebral cortex and brain stem. *Adv. Neurol.* **5,** 175–193.

ALZHEIMER, A. (1907) Ueber eine eigenartige Erkrankung der Rindhirne. *Allg. Z. Psychiatr.* **64,** 146–148.

AMARAL, D. G. and SINNAMON, H. M. (1977) The locus coeruleus: neurobiology of a central noradrenergic nucleus. *Prog. Neurobiol.* **9,** 147–196.

ANDÉN, N.-E. and FUXE, K. (1971) A new dopamine-β-hydroxylase inhibitor: effects on the noradrenaline concentration and on the action of l-Dopa in the spinal cord. *Brit. J. Pharmacol.* **43,** 747–756.

ANDERSEN, J., AABRO, E., GULMANN, N. HJELMSTED, A. and PEDERSEN, H. E. (1980) Antidepressive treatment in Parkinson's disease. *Acta neurol. Scand.* **62,** 210–219.

ANDREASEN, N. C. and GROVE, W. M. (1980) Cluster analysis and the subtyping of affective disorders. *Psychopharmacol. Bull.* **16, 4,** 36–38.

APPENZELLER, O. and GOSS, J. E. (1971) Autonomic deficits in Parkinson's syndrome. *Arch. Neurol.* **24,** 50–57.

ARANA, J. D. (1978) Schizophrenic psychoses. In: *Clinical psychopathology*, pp. 123–155. Eds. G. U. BALIS, L. WURMSER and E. MCDANIEL. Butterworth Inc., Boston.

ARBILLA, S., BRILEY, M. S., DUBOCOVICH, M. L. and LANGER, S. Z. (1978) Neuroleptic binding and their effects on the spontaneous and potassium-evoked release of ^{3}H-dopamine from the striatum and of ^{3}H-noradrenaline from the cerebral cortex. *Life Sci.* **23,** 1775–1780.

BANERJEE, S. P., KUNG, L. S., RIGGI, S. J. and CHANDA, S. K. (1977) Development of β-adrenergic receptor subsensitivity by antidepressants. *Nature* **268,** 455–456.

BANNISTER, R. and OPPENHEIMER, D. R. (1972) Degenerative diseases of the nervous system associated with autonomic failure. *Brain* **95,** 457–474.

BARBEAU, A. (1969) L-Dopa therapy in Parkinson's disease. *Can med. Ass. J.* **101,** 791–800.

BARBEAU, A. (1978) The last ten years of progress in the clinical pharmacology of extraphyramidal symptoms. In: *Psychopharmacology: A generation of progress*, pp. 771–776. Eds. M. A. LIPTON, A. DIMASCIO and K. F. KILLAM. Raven Press, New York.

BARDEN, H. (1969) The histochemical relationship of neuromelanin and lipofuscin. *J. Neuropath. exp. Neurol.* **28,** 419–441.

BARON, M., PERLMAN, R. and LEVITT, M. (1980) Paranoid schizophrenia and platelet MAO activity. *Amer. J. Psychiat.* **137,** 1465–1466.

BARTHOLINI, G. and PLETSCHER, A. (1968) Cerebral accumulation and metabolism of ^{14}C-dopa after selective inhibition of peripheral decarboxylase. *J. Pharmacol. exp. Ther.* **161,** 14–20.

BAZELON, M., FENICHEL, G. M. and RANDALL, J. (1967) Studies on neuromelanin. I. A melanin system in the human adult brainstem. *Neurol.* **17,** 512–519.

BECKMAN, H. and GOODWIN, F. K. (1975) Antidepressant response to tricyclics and urinary MHPG in unipolar patients. *Arch. gen. Psychiat.* **32,** 17–21.

BEHEIM-SCHWARZBACH, D. (1952) Ueber Zelleib-Veränderungen im Nucleus coeruleus bei Parkinson-Symptomen. *J. nerv. ment. Dis.* **116,** 619–632.

BEMPORAD, J. R. and PINSKER, H. (1974) Schizophrenia: The manifest symptomatology. In: *American handbook of psychiatry. Vol. 3. Adult clinical psychiatry*, pp. 524–550, Eds. S. ARIETI and E. B. BRODY. Basic Books, New York.

BERGER, B., TASSIN, J. P., RANCUREL, G. and BLANC, G. (1980) Catecholaminergic innervation of the human cerebral cortex in presenile and senile dementia. Histochemical and biochemical studies. In: *Enzymes and neurotransmitters in mental disease*, pp. 317–328. Eds. E. USDIN, T. L. SOURKES and M. B. H. YOUDIM. John Wiley and Sons, Chichester.

BERGER, P. A. (1981) Biochemistry and the schizophrenias. Old concepts and new hypotheses. *J. nerv. ment. Dis.* **169,** 90–99.

BERGSTROM, D. A. and KELLAR, K. J. (1979) Adrenergic and serotonergic receptor binding in rat brain after chronic desmethylimipramine treatment. *J. Pharmacol. exp. Ther.* **209,** 256–261.

BERNADT, M. W., SILVERSTONE, T. and SINGLETON, W. (1980) Behavioral and subjective effects of beta-adrenergic blockade in phobic subjects. *Brit. J. Psychiat.* **137,** 452–457.

BERNHEIMER, H., BIRKMAYER, W., HORNYKIEWICZ, O., JELLINGER, K. and SEITELBERGER, F. (1973) Brain dopamine and the syndromes of Parkinson and Huntington. *J. neurol. Sci.* **20,** 415–455.

BETHLEM, J. and DEN HARTOG JAGER, W. A. (1960) The incidence and characteristics of Lewy bodies in idiopathic paralysis agitans (Parkinson's disease). *J. Neurol. Neurosurg. Psychiat.* **23,** 74–80.

BIGELOW, L. B., ZALCMAN, S., KLEINMAN, J. E., WEINBERGER, D. E., LUCHINS, TALLMAN, J., KAROUM, F. and WYATT, R. J. (1979) Propranolol treatment of chronic schizophrenia: Clinical response, catecholamine metabolism and lymphocyte β-receptors. In: *Catecholamines: Basic and clinical features*, pp. 1851–1853. Eds. E. USDIN, I. J. KOPIN and J. BARCHAS. Pergamon Press, New York.

BIRD, E. D., SPOKES, E. G. and IVERSEN, L. L. (1979) Brain norpepinephrine and schizophrenia, 1. *Science* **204**, 93–94.

BIRKMAYER, W., DANIELCZYK, W., NEUMACHER, E. and RIEDERER, P. (1974) Nucleus rubber and L-DOPA psychosis: biochemical post mortem findings. *J. neural Transm.* **35**, 93–116.

BIRKMAYER, W. (1976) Medical treatment of Parkinson's disease: General review, past and present. In: *Advances in Parkinsonism*, pp. 407–423. Eds. W. BIRKMAYER and O. HORNYKIEWICZ. Roche, Basle.

BIRKMAYER, W., JELLINGER, K. and RIEDERER, P. (1977) Striatal and extrastriatal functions. In: *Psychobiology of the striatum*, pp. 141–153. Eds. A. R. COOLS, A. H. M. LOHMAN and J. H. L. VAN DEN BERCKEN. North-Holland publishing Company, Amsterdam.

BJÖRKLUND, A., BAUMGARTEN, H. G., LACHENMAYER, L. and ROSENGREN, E. (1975) Recovery of brain noradrenaline after 5,7-dihydroxytryptamine-induced axonal lesions in the rat. *Cell Tiss. Res.* **161**, 145–155.

BJÖRKLUND, A. and LINDVALL, O. (1979) Regeneration of normal terminal innervation patterns by central noradrenergic neurons after 5,7-dihydroxytryptamine-induced axotomy in the adult rat. *Brain Res.* **171**, 271–294.

BJÖRKLUND, A. and STENEVI, U. (1979) Regeneration of monoaminergic and cholinergic neurons in the mammalian central nervous system. *Physiol. Rev.* **59**, 62–100.

BJORKLUND, A., SEGAL, M. and STENEVI, U. (1979) Functional reinnervation of rat hippocampus by locus coeruleus implants. *Brain Res.* **170**, 409–426.

BLACK, I. B. and PETITO, C. K. (1976) Catecholamine enzymes in the degenerative neurological disease idiopathic orthostatic hypotension. *Science* **192**, 910–912.

BLESSED, G., TOMLINSON, B. E. and ROTH, M. (1968) The association between quantitative measures of dementia and of senile change in the cerebral gray matter of elderly subjects. *Brit. J. Psychiat.* **114**, 797–811.

BLESSED, G. (1980) Clinical aspects of the senile dementias. In: *Biochemistry of dementia*, pp. 1–14. Ed. P. J. ROBERTS. John Wiley and Sons, Chichester.

BOGERTS, B. (1981) A brainstem atlas of catecholaminergic neurons in man, using melanin as a natural marker. *J. comp. Neurol.* **197**, 63–80.

BOLLER, F. (1980) Mental status of patients with Parkinson disease. *J. clin. Neuropsychol.* **2**, 157–172.

BOND, P. A., JENNER, F. A. and SAMPSON, G. A. (1972) Daily variations in the urine content of 3-methoxy-4-hydroxyphenylglycol in two manic-depressive patients. *Psychol. Med.* **2**, 81–85.

BORNSTEIN, B., SANDBANK, U. and FRIED, Y. (1966) Hallervorden–Spatz disease with Lewy type inclusions. *Confin. Neurol.* **27**, 397–405.

BOWEN, D. M. (1980) Biochemical evidence for selective vulnerability in Alzheimer's disease. In: *Biochemistry of dementia*, pp. 77–90. Ed. P. J. ROBERTS. John Wiley and sons, Chichester.

BOWMAN, M. and LEWIS, M. S. (1980) Sites of subcortical damage in diseases which resemble schizophrenia. *Neuropsychol.* **18**, 597–602.

BRODY, H. (1976) An examination of cerebral cortex and brainstem aging. In: *Neurobiology of aging*, pp. 177–181. Eds. R. D. TERRY and S. GERSHON. Raven Press, New York.

BROWN, G. L. and WILSON, W. P. (1972) Parkinsonism and depression. *South med. J.* **65**, 540–545.

BROWNING, R. A. and MAYNERT, E. W. (1978) Effect of intracisternal 6-hydroxy-dopamine on seizure susceptibility in rats. *Europ. J. Pharmacol.* **50**, 97–102.

BRUN, A. and GUSTAFSON, L. (1976) Distribution of cerebral degeneration in Alzheimers disease—Clinico-pathological study. *Arch. Psychiat. Nervenkr.* **223**, 15–34.

BUGIANI, O., MANCARDI, G. L., BRUSA, A. and EDERLI, A. (1979) The fine structure of subcortical neurofibrillary tangles in progressive supranuclear palsy. *Acta neuropath.* **45**, 147–152.

BUNNEY, W. E., JANOWSKY, D. S., GOODWIN, F. K., DAVIS, J. M., BRODIE, H. K., MURPHY, D. L. and CHASE, T. N. (1969) Effect of L-dopa on depression. *Lancet* **I**, 885–886.

CARLSSON, A. (1977) Does dopamine play a role in schizophrenia? *Psychol. Med.* **7**, 583–597.

CARLSSON, A. (1978) Mechanism of action of neuroleptic drugs. In: *Psychopharmacology: A generation of progress*, pp. 1057–1070. Eds. M. A. LIPTON, A. DIMASCIO and K. F. KILLAM. Raven Press, New York.

CARLSSON, A. and LINDQVIST, M. (1978) Effect of antidepressant agents on the synthesis of brain monoamines. *J. neural Transm.* **43**, 73–92.

CARLSSON, A. (1979) The impact of catecholamine research on medical science and practice. In: *Catecholamines: Basic and clinical frontiers*, pp. 4–19. Eds. E. USDIN, I. J. KOPIN, J. BARCHAS. Pergamon Press, New York.

CASTAIGNE, P., LAPLANE, D., AUTRET, A., BOUSSER, M. G., GRAY, F. and BARON, J.-C. (1977) Syndrome de Shy et Drager avec troubles du rhythme respiratoire et de la vigilance. *Rev. Neurol.* **133**, 455–466.

CEDARBAUM, J. M. and AGHAJANIAN, G. K. (1977) Catecholamine receptors on locus coeruleus neurons: pharmacological characterization. *Europ. J. Pharmacol.* **44**, 375–385.

CELESTIA, G. G. and WANAMAKER, W. M. (1972) Psychiatric disturbances in Parkinson's disease. *Dis. nerv. Syst.* **33**, 577–583.

CHALMERS, J. P., BALDESSARINI, R. J. and WURTMAN, R. J. (1971) Effects of L-DOPA on brain norepinephrine metabolism. *Proc. natl. Acad. Sci. USA* **68**, 662–666.

CHECKLEY, S. A., SLADE, A. P., SHUR, E. and DAWLING, S. (1981) A pilot study on the mechanism of action of desipramine. *Brit. J. Psychiat.* **138**, 248–251.

CHIBA, T., JEW, J. Y. and WILLIAMS, T. H. (1979) Ultrastructural evidence for remodelling in a central noradrenergic pathway following electrolytic lesioning. *Brain Res.* **171**, 77–84.

CLARK, T. K. (1979) The locus coeruleus in behavior regulation: Evidence for behavior-specific versus general involvement. *Behav. Biol.* **25**, 271–300.

CLEMENTS-JEWERY, S. (1978) The development of cortical β-adrenoceptor sub-sensitivity in the rat by chronic treatment with trazodone, doxepin and mianserine. *Neuropharmacol.* **17**, 779–781.

CONSTANTINIDIS, J. (1978) Is Alzheimer's disease a major form of senile dementia? Clinical, anatomical and genetic data. In: *Alzheimer's disease: Senile dementia and related disorders*, pp. 15–26. Eds. R. KATZMAN, R. D. TERRY and K. BICK. Raven Press, New York.

COOLS, A. R. and VAN ROSSUM, J. M. (1980) Multiple receptors for brain dopamine in behavior regulation: Concept of dopamine-E and dopamine-I receptors. *Life Sci.* **27,** 1237–1254.

CORCORAN, M. E. and MASON, S. T. (1980) Role of forebrain catecholamines in amygdaloid kindling. *Brain Res.* **190,** 473–484.

COTZIAS, G. C., PAPVASILION, P. S. and GELLER, R. (1969) Modification of Parkinsonism—Chronic treatment with L-dopa. *New Engl. J. Med.* **280,** 337–345.

CROSS, A. J., CROW, T. J., KILLPACK, W. S., LONGDEN, A., OWEN, F. and RILEY, G. R. (1978) The activities of brain dopamine-β-hydroxylase and catechol-O-methyltransferase in schizophrenics and control. *Psychopharmacol.* **59,** 117–122.

CROW, T. J. (1972) A map of the rat mesencephalon for electrical self-stimulation. *Brain Res.* **36,** 265–273.

CROW, T. J., SPEAR, P. J. and ARBUTHNOT, G. W. (1972) Intracranial self-stimulation with electrodes in the region of the locus coeruleus. *Brain Res.* **36,** 275–287.

CROW, T. J. (1979) What is wrong with dopaminergic transmission in schizophrenia? *Trends Neurosci.* **2,** 52–53.

DAHLSTRÖM, A. and FUXE, K. (1964) Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. *Acta physiol. Scand. suppl.* 232.

DAMASIO, A. R., ANTIMES, J. L. and MACEDO, C. (1970) L-dopa, parkinsonism and depression. *Lancet* **II,** 611–612.

DE BONI, U. and CRAPPER MCLACHLAN, R. D. (1980) Senile dementia and Alzheimer's disease: A current view. *Life Sci.* **27,** 1–14.

DEFENDINI, R., MARKESBERY, W. R., MASTRI, A. R. and DUFFY, P. E. (1973) Hallervorden–Spatz disease and infantile neuroaxonal dystrophy: Ultrastructural observations, anatomical pathology and nosology. *J. neurol. Sci.* **20,** 7–23.

DELISI, L. E., WISE, C. D., POTKIN, S. G., ZALCMAN, S., PHELPS, B. H., LOVENBERG, W. and WYATT, R. J. (1980) Dopamine-β-hydroxylase, monamine oxidase, and schizophrenia *Biol. Psychiat.* **15,** 899–916.

DEN HARTOG JAGER, W. A. (1969) Sphingomyelin in Lewy inclusion bodies in Parkinson's disease. *Arch. Neurol.* **21,** 615–619.

DEN HARTOG JAGER, W. A. (1970) Histochemistry of adrenal bodies in Parkinson's disease. *Arch. Neurol.* **23,** 528–533.

DE REUCK, J., DE COSTER, W. and VAN DER EECKEN, H. (1980) Parkinsonism in patients with cerebral infarcts. *Clin. Neurol. Neurosurg.* **82,** 177–185.

DOMINO, E. F., DREN, A. T. and GIARDINA, W. J. (1978) Biochemical and neurotransmitter changes in the aging brain. In: *Psychopharmacology: A generation of progress*, pp. 1507–1515. Eds. M. A. LIPTON, A. DIMASCIO, K. F. KILLAM. Raven Press, New York.

DOOLING, E. C., SCHOENE, W. C. and RICHARDSON, E. P. (1974) Hallervorden–Spatz syndrome. *Arch. Neurol.* **30,** 70–83.

DSM-III (1980) Diagnostic and statistical manual of mental disorders (third edition). American Psychiatric Association, Washington.

DUFFY, P. E. and TENNYSON, V. M. (1965) Phase and electron microscopic observations of Lewy bodies and melanine granules in substantia nigra and locus coeruleus in Parkinson's disease. *J. Neuropath. exp. Neurol.* **24,** 398–414.

EHRINGER, H. and HORNYKIEWICZ, O. (1960) Verteilung von Noradrenalin und Dopamin (3-Hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des extrapyramidalen System. *Klin. Wschr.* **38,** 1236–1239.

EMRICH, H. M., VON ZERSSEN, D., MÖLLER, H.-J., KISSLING, W., CORDING, C., SCHIETSCH, H. J. and RIEDEL, E. (1979) Action of propranolol in mania: Comparison of the effects of the d- and l-stereoisomer. *Pharmakopsychiatrie Neuropyschopharmak.* **12,** 295–304.

FAHN, S., LIBSCH, L. R. and CUTLER, R. W. (1971) Monoamines in the human striatum: Topographic distribution in normal and in Parkinson's disease and their role in akinesia, rigidity and tremor. *J. neurol. Sci.* **14,** 427–455.

FARLEY, I. J. and HORNYKIEWCIZ, O. (1976) Noradrenaline in subcortical brain regions of patients with Parkinson's disease and control subjects. In: *Advances in Parkinsonism*, pp. 178–185. Eds. W. BIRKMAYER and O. HORNYKIEWICZ. Roche, Basle.

FARLEY, I. J. and HORNYKIEWICZ, O. (1977) Noradrenaline distribution in subcortical areas of the human brain. *Brain Res.* **126,** 53–62.

FARLEY, I. J., PRICE, K. S., MCCULLOCH, E., DECK, J. H. N., HORDYNSKI, W. and HORNYKIEWICZ (1978) Norepinephrine in chronic paranoid schizophrenia. Above-normal levels in limbic forebrain. *Science* **200,** 456–457.

FARLEY, I. J., PRICE, K. S., MCCULLOCH, E., DECK, J. H. N., HORDYNSKI, W. and HORNYKIEWICZ (1979) Reply to Bird *et al.* (1979) and to Taylor (1979). *Science* **204,** 94.

FARMER, P. M., PECK, A. and TERRY, R. D. (1976) Correlations among numbers of dendritic plaques, neurofibrillary tangles, and the severity of senile dementia. *J. Neuropathol. exp. Neurol.* **35,** 367.

FAWCETT, J. and SIOMOPOULOS, V. (1971) Dextroamphetamine response as a possible predictor of improvement with tricyclic therapy in depression. *Arch. gen. psychiat.* **25,** 247–255.

FEIGHNER, J. P., ROBINS, E., GRUZE, S. B., WOODRUFF, R. A., WINOKUR, G. and MUNOZ, R. (1972) Diagnostic criteria for use in psychiatric research. *Arch. gen. Psychiat.* **26,** 57–63.

FILE, S. E., DEAKIN, J. F. W., LONGDEN, A. and CROW, T. J. (1979) An investigation of the role of the locus coeruleus in anxiety and agonistic behavior. *Brain Res.* **169,** 411–420.

FLOR-HENRY, P. (1969) Psychosis and temporal lobe epilepsy. *Epilepsia*, **10,** 363–394.

FLOR-HENRY, P. (1972) Ictal and interictal psychiatric manifestations of epilepsy. *Epilepsia*, **13,** 773–783.

FLORU, L. (1977) Use of beta-blocking agents in psychiatry and neurology. *Fortschr. Neurol. Psychiat.* **45,** 112–127.

FOLEY, J. M. and BAXTER, D. (1958) On the nature of pigment granules in the cells of the locus coeruleus and substantia nigra. *J. Neuropathol. exp. Neurol.* **17,** 578–586.

FOOTE, S. L., ASTON-JONES, G. and BLOOM, F. E. (1980) Impulse activity of locus coeruleus neurons in awke rats and monkeys is a function of sensory stimulation and arousal. *Proc. natl. Acad. Sci. USA* **77,** 3033–3037.

FORNO, L. S. (1969) Concentric hyalin intraneuronal inclusions of the Lewy type in the brains of elderly persons (50 incidental cases): Relationship to Parkinsonism. *J. Amer. ger. Soc.* **17,** 557–575.

FORNO, L. S. and ALVORD, E. C., JR. (1974) Depigmentation in the nerve cells of the substantia nigra and locus coruleus in Parkinsonism. In: *Advances in neurology. Vol. 5. Second Canadian–American conference on Parkinson's disease*, pp. 195–202. Eds. F. H. MCDOWELL and A. BARBEAU. Raven Press, New York.

FORNO, L. S. and NORVILLE, R. L. (1976) Ultrastructure of Lewy bodies in the stellate ganglion. *Acta neuropathol.* **34,** 183–197.

FORNO, L. S., BARBOUR, P. J. and NORVILLE, R. L. (1978) Presenile dementia with Lewy bodies and neurofibrillary tangles. *Arch. Neurol.* **35,** 818–822.

FORNO, L. S. and NORVILLE, R. L. (1981) Synaptic morphology in the human locus coeruleus. *Acta neuropathol.* **53,** 7–14.

FREEDMAN, R. and HOFFER, B. J. (1975) Phenothiazine antagonism of the noradrenergic inhibition of cerebellar Purkinje cells. *J. Neurobiol.* **6,** 277–288.

GARVER, D. L. and DAVIS, J. M. (1979) Biogenic amine hypotheses of affective disorders. *Life Sci.* **24,** 383–394.

GERBINO, L., OLESHANSKY, M. and GERSHON, S. (1978) Clinical use and mode of action of lithium. In: *Psychopharmacology: A generation of progress*, pp. 1261–1275. Eds. M. A. LIPSON, A. DIMASCIO and K. F. KILLAM. Raven Press, New York.

GERMAN, D. C. and BOWDEN, D. M. (1975) Locus coeruleus in Rhesus monkey (*Macaca mulatta*): A combined histochemical, Nissl and silver study. *J. comp. Neurol.* **161,** 19–30.

GHATAK, N. R., NOCHLIN, D. and HADFIELD, M. G. (1980) Neurofibrillary pathology in progressive supranuclear palsy. *Acta neuropathol.* **52,** 73–76.

GIFT, T. E., STRAUSS, J. S., RITZLER, B. A., KOKES, R. F. and HARDER, D. W. (1980) How diagnostic concepts of schizophrenia differ. *J. nerv. ment. Dis.* **168,** 3–8.

GILLESPIE, D. D., MANIER, D. H. and SULSER, F. (1979) Electroconvulsive treatment: rapid subsensitivity of the norepinephrine receptor coupled adenylate cyclase system linked to down regulation of β-adrenergic receptors. *Comm. Psychopharmacol.* **3,** 191–195.

GOMES, U. C. R., SHANLEY, B. C., POTGIETER, L. and ROUX, J. T. (1980) Noradrenergic overactivity in chronic schizophrenia: Evidence based on cerebrospinal fluid noradrenaline and cyclic nucleotide concentrations. *Brit. J. Psychiat.* **137,** 346–351.

GOODWIN, F. K., BRODIE, H. K., MURPHY, D. L. and BUNNEY, W. E. (1970) L-dopa, catecholamines and behaviour. *Biol. Psychiat.* **2,** 341–366.

GOODWIN, F. K., COWDRY, R. W. and WEBSTER, M. H. (1978) Predictors of drug response in the affective disorders: Toward an integrated approach. In: *Psychopharmacology: A generation of progress*, pp. 1277–1288. Eds. M. A. LIPTON, A. DIMASCIO and K. F. KILLAM. Raven Press, New York.

GOTTFRIES, C. G. (1980) Biochemistry of dementia and normal ageing. *Trends Neurosci.* **3,** 55–57.

GRAHAM, D. G. (1978) Oxidative pathways for catecholamines in the genesis of neuromelanin and cytotoxic quinones. *Mol. Pharmacol.* **14,** 633–643.

GRAHAM, D. G. (1979) On the origin and significance of neuromelanin. *Arch. Pathol. Lab. Med.* **103,** 359–362.

GRANT, S. J., HUANG, Y. H. and REDMOND, D. E., JR. (1980) Benzodiazepines attenuate single unit activity in the locus coeruleus. *Life Sci.* **27,** 2231–2236.

GRAY, T. and REWCASTLE, N. B. (1967) Parkinsonism and striatonigral degeneration. *Can. med. Ass. J.* **97,** 240.

GREENBLATT, D. J. and SHADER, R. I. (1978) Pharmacotherapy of anxiety with benzodiazepines and β adrenergic blockers. In: *Psychopharmacology: A generation of progress*, pp. 1381–1390. Eds. M. A. LIPTON, A. DIMASCIO and K. F. KILLAM. Raven Press, New York.

GREENFIELD, J. G. and BOSANQUET, F. D. (1953) The brain-stem lesions in Parkinsonism. *J. Neurol. Neurosurg. Psychiat.* **16,** 213–226.

GREGORY, R. L. (1961) The brain as an engineering problem. In: *Current problems in animal behaviour*, pp. 307–330. Eds. W. H. THORPE and O. L. ZANGWILL, Cambridge University Press, London.

GREINER, A. C. and NICHOLSON, G. A. (1965) Schizophrenia-melanosis. Cause or side-effect? *Lancet* **II,** 1165–1167.

GROSS, G. and SCHÜMANN, H.-J. (1980) Enhancement of noradrenaline release from rat cerebral cortex by neuroleptic drugs. *Naunyn–Schmiedeberg's Arch. Pharmacol.* **315,** 103–110.

GUYENET, P. G. and AGHAJANIAN, G. K. (1979) ACh, substance P and met-enkephalin in the locus coeruleus: pharmacological evidence for independent sites of action. *Europ. J. Pharmacol.* **53,** 319–328.

HAEFELY, W. E. (1978) Behavioral and neuropharmacological aspects of drugs used in anxiety and related states. In: *Psychopharmacology: A generation of progress*, pp. 1359–1374. Eds. M. A. LIPTON, A. DIMASCIO and K. F. KILAM. Raven Press, New York.

HAKIM, A. M. and MATHIESON, G. (1979) Dementia in Parkinson disease: A neuropathologic study. *Neurol.* **29,** 1209–1214.

HALARIS, H. E. and DEMET, E. M. (1979) Studies of norepinephrine metabolism in manic and depressive states. In: *Catecholamine: Basic and clinical frontiers*, pp. 1866–1868. Eds. E. USDIN, I. J. KOPIN and J. BARCHAS. Pergamon Press, New York.

HARTMAN, E. and KELLER-TESCHKE, M. (1979) The psychological effects of dopamine-β-hydroxylase inhibition in normal subjects. *Biol. Psychiat.* **14,** 455–462.

HASSLER, R. (1938) Zur Pathologie der Paralysis agitans und des Postenzephalitischen parkinsonismus. *J. Psychol. Neurol. Lpz.* **48,** 387–476.

HEFTI, F. and MELAMED, E. (1980) L-DOPA's mechanism of action in Parkinson's disease. *Trends Neurosci.* **3,** 229–231.

HIRANO, A. and ZIMMERMAN, H. M. (1962) Alzheimer's neurofibrillary changes: A topographic study. *Arch. Neurol.* **7**, 227–242.

HIRANO, A., ARUMUGASAMY, N. and ZIMMERMAN, H. M. (1967) Amyotrophic lateral sclerosis: A comparison of Guam and classical cases. *Arch. Neurol.* **16**, 357–363.

HIROSAWA, K. (1968) Electron microscopic studies on pigment granules and locus coeruleus of Japanese monkey (*Macaca fuscata yakui*). *Z. Zellforsch.* **88**, 187–203.

HOEHN, M. M., CROWLEY, T. J. and RUTLEDGE, C. O. (1976) Dopamine correlates of neurological and psychological status in untreated Parkinsonism. *J. Neurol. Neurosurg. Psychiat.* **39**, 941–951.

HORNYKIEWICZ, O. (1975) Parkinson's disease and its chemotherapy. *Biochem. Pharmacol.* **24**, 1061–1065.

HORROBIN, D. (1980) A singular solution for schizophrenia. *New Scientist* **85**, 642–644.

HORTON, R., ANLEZARK, G. and MELDRUM, B. (1980) Noradrenergic influences on sound-induced seizures. *J. Pharmacol. exp. Ther.* **214**, 437–442.

HOTSON, J. R. and LANGSTON, J. W. (1976) Disulfiram induced pathology. *Arch. Neurol.* **33**, 141–142.

HUANG, H. Y., MAAS, J. W. and HU, G. H. (1980) The time-course of noradrenergic pre- and postsynaptic activity during chronic desipramine treatment. *Europ. J. Pharmacol.* **68**, 41–48.

IKEDA, K., IKEDA, S., YOSHIMURA, T., KATO, H. and NAMBA, M. (1978) Idiopathic Parkinsonism with Lewy-type inclusions in cerebral cortex. A case report. *Acta neuropath.* **41**, 165–168.

IKEDA, K., HORI, A. and BODE, G. (1980) Progressive dementia with "diffuse Lewy-type inclusions" in cerebral cortex. A case report. *Arch. Psychiat. Nervenkr.* **228**, 243–248.

INGVAR, D. H., BRUN, A., HAGBERG, B. and GUSTAFSON, L. (1978) Regional cerebral blood flow in the dominant hemisphere in confirmed cases of Alzheimer's disease, Pick's disease, and multi-infarct dementia: Relationship to clinical symptomatology and neuropathological findings. In: *Alzheimer's disease: Senile dementia and related disorders*, pp. 203–211. Eds. R. KATZMAN, R. D. TERRY and K. L. BICK. Raven Press, New York.

IOSELIANI, T. K., CHOKHELI, K. G. and MGALOBLISHVILI, N. R. (1979) Effect of electrical stimulation of the locus coeruleus on the threshold of hippocampal paroxysmal activity. *Soobshch. Akad. Nauk Gruz. SSR* **93**, 169–172 (in Russian).

ISHII, T. (1966) Distribution of Alzeimer's neurofibrillary changes in the brain stem and hypothalamus of senile dementia. *Acta neuropath.* **6**, 181–187.

ISHINO, H. and OTSUKI, S. (1975) Distribution of Alzheimer's neurofibrillary tangles in the basal ganglia and brain stem of progressive supranuclear palsy and Alzheimer's disease. *Folia Psychiat. Neurol. Japon.* **29**, 179–187.

ISSIDORIDES, M. R., MYTILINEAU, C., WHETSELL, W. O. and YAHR, M. D. (1978) Protein-rich cytoplasmatic bodies of substantia nigra and locus coruleus. Comparative study in Parkinsonian and normal brain. *Arch. Neurol.* **35**, 633–637.

IZUMI, K., INOUE, N., SHIRABE, T., MIYAZAKI, T. and KUROIWA, Y. (1971) Failed levo-dopa therapy in striato-nigral degeneration. *Lancet* **I**, 1355.

JACOBY, R. J. and LEVY, R. (1980) Computed tomography in the elderly. 2. Senile dementia: Diagnosis and functional impairment. *Brit. J. Psychiat.* **136**, 256–269.

JELLINGER, K. and DANIELCZYK, W. (1968) Striato-nigrale degeneration. *Acta neuropathol.* **10**, 242–257.

JELLINGER, K. (1976) Neuropathological aspects of dementias resulting from abnormal blood and cerebrospinal fluid dynamics. *Acta neurol. Belg.* **76**, 83–102.

JENKINS, R. B. and GROH, R. H. (1970) Mental symptoms in Parkinsonian patients treated with L-dopa. *Lancet* **II**, 177–180.

JOBE, P. C., GEIGER, P. F., RAY, T. B., WOODS, T. W. and MIMS, M. E. (1978) The relative significance of spinal cord norepinephrine and 5-hydroxytryptamine in electrically-induced seizure in the rat. *Neuropharmacol.* **17**, 185–190.

JONES, F., MAAS, J. W., DEKIRMENJIAN, H. and FAWCETT, J. A. (1973) Urinary catecholamine metabolites during behavioral changes in a patient with manic-depressive cycles. *Science* **179**, 300–302.

JONES, B. E., HAPER, S. T. and HALARIS, A. E. (1977) Effects of locus coeruleus lesions upon cerebral monoamine content, sleep-wakefulness states and the response to amphetamine in the cat. *Brain Res.* **124**, 473–496.

JONSSON, G., PYCOCK, C., FUXE, K. and SACHS, C. (1974) Changes in the development of central noradrenaline neurons following neonatal administration of 6-hydroxydopamine. *J. Neurochem.* **22**, 419–426.

JONSSON, G., WIESSEL, F.-A. and HALLMAN, H. (1979) Developmental plasticity of central noradrenaline neurons after neonatal damage—Changes in transmitter functions. *J. Neurobiol.* **10**, 337–354.

JOUVET, M. (1972) The role of monoamines and acetylcholine-containing neurons in the regulation of the sleep-waking cycle. *Ergebn. Physiol.* **64**, 166–307.

KALINOWSKY, J. B. (1975) Electric and other convulsive treatments. In: *American handbook of psychiatry*. Vol. V, pp. 531–547. Eds. S. ARIETI, D. X. FREEDMAN and J. E. DYRUD. Basic Books, New York.

KASTIN, A. J., BUZEMCHAK, B., TOMPKINS, R. G., SCHALLY, A. V. and MILLER, M. C. (1976) Melanin in the rat brain. *Brain. Res. Bull.* **1**, 567–572.

KATZ, M. M. and HIRSCHFELD, R. M. A. (1978) Phenomenology and classification of depression. In: *Psychopharmacology: A generation of progress*, pp. 1185–1195. Eds. M. A. LIPTON, A. DIMASCIO, K. F. KILLAM. Raven Press, New York.

KATZMAN, R. (1976) The prevalence and malignancy of Alzheimer's disease: a neuropathologic investigation. *Arch. Neurol.* **33**, 217–218.

KATZMAN, R., TERRY, R. D. and BICK, K. L. (1978) *Alzheimer's disease: Senile dementia and related disorders. Aging. vol. 7*, Raven Press, New York.

KEBABIAN, J. W. and CALNE, D. B. (1979) Multiple receptors for dopamine. *Nature*, **277**, 93–96.

KELLER, H. H., BARTHOLINI, G. and PLETSCHER, A. (1974) Enhancement of noradrenaline turnover in rat brain by L-dopa. *J. Pharm. Pharmacol.* **26**, 649–651.

KETY, S. S., JAVOY, I., THIERRY, A. A. M., JULON L. and GLOWINSKI, J. (1967) A sustained effect of electroconvul-

sive shock on the turnover of norepinephrine in the central nervous system of the rat. *Proc. natl. Acad. Sci. USA* **58,** 1249–1254.

KIDD, M. (1963) Paired helical filaments in electron microscopy of Alzheimer's disease. *Nature*, **197,** 192–193.

KING, D. J., TURKSON, S. N. A., LIDDLE, J. and KINNEY, C. D. (1980) Some clinical and metabolic aspects of propranolol in chronic schizophrenia. *Brit. J. Psychiat.* **137,** 458–468.

KLEIN, D. F., ZITRIN, C. M. and WOERNER, M. (1978) Antidepressants, anxiety, panic and phobias. In: *Psychopharmacology: A generation of progress*, pp. 1401–1410. Eds. M. A. LIPTON, A. DIMASCIO, K. F. KILLAM. Raven Press, New York.

KLEINMAN, J. E., BRIDGE, P., KAROUM, F., SPECIALE, S., STAUB, R., ZALCMAN, S. GILLIN, J. C. and WYATT, R. J. (1979) Catecholamines and metabolites in the brains of psychotic and normals: Post-mortem studies. In: *Catecholamines: Basic and clinical frontiers*, pp. 1845–1847. Eds. E. USDIN, I. J. KOPIN and J. BARCHAS. Raven Press, New York.

KOKKINIDIS, L. and ANISMAN, H. (1980) Amphetamine models of paranoid schizophrenia: An overview and elaboration of animal experimentation. *Psychol. Bull.* **88,** 551–579.

KONKOL, R. J., BENDEICH, E. G. and BREESE, G. R. (1978) A biochemical and morphological study of the altered growth pattern of central catecholamine neurons following 6-hydroxydopamine. *Brain Res.* **140,** 125–136.

KOSAKA, K. (1978) Lewy bodies in cerebral cortex. Report of three cases. *Acta neuropathol.* **42,** 127–134.

KOSAKA, K. and MEHRAEIN, P. (1979) Dementia–Parkinsonism syndrome with numerous Lewy bodies in senile plaques in cerebral cortex. *Arch. Psychiat. Nervenkr.* **226,** 241–250.

KRISTENSEN, V., OLSEN, M. and THEILGAARD, A. (1977) Levodopa treatment of pre-senile dementia. *Acta psychiat. Scand.* **55,** 41–51.

KULIKOWSKI, J. J. (1971) Information channels of the senses. In: *Bionics. The nervous system as a control system*, pp. 97–142. Ed. R. GAWROŃSKY. Elsevier Amsterdam.

LAKE, C. R., STERNBERG, D. E., VAN KAMMEN, D. P., BALLENGER, J. C., ZIEGLER, M. G., POST, R. M., KOPIN, I. J. and BUNNEY, W. E. (1980a) Schizophrenia: Elevated cerebrospinal fluid norepinephrine. *Science*, **207,** 331–333.

LAKE, C. R., STERNBERG, D. E., VAN KAMMEN, D. P., BALLENGER, J. C., ZIEGLER, M. G., POST, R. M., KOPIN, I. J. and BUNNEY, W. E. (1980b) Reply to Lipsky, 1980, *Science*, **210,** 97.

LANGER, S. Z. (1980) Presynaptic receptors and the modulation of neurotransmission: pharmcological implications and therapeutic relevance. *Trends Neurosci.* **3,** 110–112.

LAXER, K. D., SOURKER, T. L., FANG, T. Y., YOUNG, S. N., GOUTHIER, S. G. and MISSALA, K. (1979) Monoamine metabolites in the CSF of epileptic patients. *Neurol.* **29,** 1157–1160.

LEFKOWITZ, R. J. (1978) Identification and regulation of alpha- and beta-adrenergic receptors. *Fed. Proc.* **37,** 123–129.

LERNER, P., GOODWIN, F. K., VAN KAMMEN, D. P., POST, R. M., MAJOR, L. F., BALLENGER, J. C. and LOVENBERG, W. (1978) Dopamine-β-hydroxylase in the cerebrospinal fluid of psychiatric patients. *Biol. Psychiat.* **13,** 685–694.

LEVITT, P. and MOORE, R. Y. (1979) Origin and organization of brainstem catecholamine innervation in the rat. *J. comp. Neurol.* **186,** 505–528.

LEVITT, P. and MOORE, R. Y. (1980) Organization of brainstem catecholamine hyperinnervation following neonatal 6-hydroxydopamine treatment in the rat. *Anat. Embryol.* **158,** 133–150.

LEWI, P. J. and COLPAERT, F. C. (1976) On the classification of antidepressant drugs. *Psychopharmacol.* **49,** 219–224.

LEWY, F. H. (1912) Paralysis agitans: I Pathologische Anatomie. In: *Handbuch der Neurologie. Vol. 3*, pp. 920–933. Ed. M. LEWANDOWSKY. Springer Verlag, Berlin.

LIBET, B., GLEASON, C. A., WRIGHT, E. W., JR. and FEINSTEIN, B. (1977) Suppression of an epileptiform type of electrocortical activity in the rat by stimulation in the vicinity of locus coeruleus. *Epilepsia*, **18,** 451–462.

LIDDON, S. C. and SATRAN, R. (1967) Disulfiram (Antabuse) psychosis. *Amer. J. Psychiat.* **123,** 1284–1289.

LIBERMAN, A., DZIATOLOWSKI, M., KUPERSMITH, M., SERBY, M., GOODGOLD, A., KOREIN, J. and GOLDSTEIN, M. (1979) Dementia in Parkinson disease. *Ann. Neurol.* **6,** 355–359.

LINDSTRÖM, L. H. and PERSSON, E. (1980) Propranolol in chronic schizophrenia: A controlled study in neuroleptic-treated patients. *Brit. J. Psychiat.* **137,** 126–130.

LIPKIN, L. E. (1959) Cytoplasmatic inclusions in ganglion cells associated with Parkinsonian states. **Amer. J.** *Pathol.* 35, 1117–1133.

LIPSKY, J. J. (1980) Elevated cerebrospinal fluid norepinephrine in schizophrenics: confounding effects of treatment drugs. *Science*, **210,** 97.

LLOYD, K. G., DAVIDSON, L. and HORNYKIEWICZ, O. (1975) The neurochemistry of Parkinson's disease: Effect of L-DOPA therapy. *J. Pharmacol. exp. Ther.* **195,** 453–464.

LONDON, E. D. and BUTTERBAUGH, G. G. (1978) Modification of electroshock convulsive responses and thresholds in neonatal cats after brain monoamine reductions. *J. Pharmacol. exp. Ther.* **206,** 81–90.

LORANGER, A. W., GOODELL, H., MCDOWELL, F. H., LEE, J. E., SWEET, R. D. (1972a) Intellectual impairment in Parkinson's syndrome. *Brain*, **95,** 405–412.

LORANGER, A. W., GOODELL, H., LEE, J. E. and MCDOWELL, F. (1972b) Levodopa treatment of Parkinson's syndrome. Improved intellectual functioning. *Arch. gen. Psychiat.* **26,** 163–168.

MAAS, J. W. (1979) Neurotransmitters and depression. Too much, too little, or too unstable? *Trends Neurosci.* **2,** 306–308.

MAEDA, T. and WEGMAN, R. (1969) Infrared spectrometry of locus coeruleus and substantia nigra pigments in human brain. *Brain Res.* **14,** 673–681.

MAGGI, A., SCHMIDT, M. J., GHETTI, B. and ENNA, S. J. (1979) Effect of aging on neurotransmitter receptor binding in rat and human brain. *Life Sci.* **24,** 367–374.

MAGGI, A., U'PRICHARD, D. C. and ENNA, S. J. (1980) Differential effects of antidepressant treatment on brain monoaminergic receptors. *Europ. J. Pharmacol.* **61,** 91–98.

MALEK-AHMADI, P. and CALLEN, K. E. (1980) Endorphins and schizophrenia—narcotic antagonists in the treatment of chronic schizophrenia. *Gen. Pharmacol.* **11,** 149–152.

MANIER, D. H., GILLESPIE, D. D. and SULSER, F. (1980) Development of and recovery from subsensitivity of the noradrenergic cyclic AMP generating system in brain. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **313,** 113–118.

MANN, D. M. A. and YATES, P. O. (1974) Lipoprotein pigments—their relationship to aging in the human nervous system. II. The melanin content of pigmented nerve cells. *Brain,* **97,** 489–498.

MANN, D. M. A. and YATES, P. O. (1979) The effects of ageing on the pigmented cells of the human locus coeruleus and substantia nigra. *Acta neuropath.* **47,** 93–98.

MANN, D. M. A., LINCOLN, J., YATES, P. O., STEMP, J. E. and TOPER, S. (1980) Changes in the monoamine containing neurons of the human central nervous system in senile dementia, *Brit. J. Psychiat.* **136,** 533–541.

MARKHAM, C. H. (1974) The "On–off" side-effect of L-dopa. *Adv. Neurol.* **5,** 387–396.

MARSDEN, C. D. and HARRISON, M. J. G. (1972) Outcome of investigation of patients with presenile dementia. *Brit. med. J.* **2,** 249–252.

MARTILLA, R. J. and RINNE, U. K. (1976) Dementia in Parkinson's disease. *Acta neurol. Scand.* **54,** 431–441.

MASON, S. T., ROBERTS, D. C. S. and FIBIGER, H. C. (1978) Noradrenaline and neophobia. *Physiol. Behav.* **21,** 353–361.

MASON, S. T. (1979a) Noradrenaline: reward or extinction. *Neurosci. Biobehav. Rev.* **3,** 1–10.

MASON, S. T. (1979b) Noradrenaline and behaviour. *Trends Neurosci.* **2,** 82–84.

MASON, S. T. and CORCORAN, M. E. (1979a) Seizure susceptibility after depletion of spinal or cerebellar noradrenaline with 6-OHDA. *Brain Res.* **166,** 418–421.

MASON, S. T. and CORCORAN, M. E. (1979b) Depletion of brain noradrenaline, but not dopamine, by intracerebral 6-hydroxydopamine potentiates convulsions induced by electroshock. *J. Pharm. Pharmacol.* **31,** 209–211.

MASON, S. T. and CORCORAN, M. E. (1979c) Noradrenaline and seizures. *Science,* **203,** 1265.

MASON, S. T. and CORCORAN, M. E. (1979d) Catecholamines and convulsions. *Brain Res.* **170,** 497–508.

MASON, S. T. and FIBIGER, H. C. (1979a) Noradrenaline, fear and extinction. *Brain Res.* **165,** 47–56.

MASON, S. T. and FIBIGER, H. C. (1979b) Current concepts. 1. Anxiety—Locus coeruleus disconnection. *Life Sci.* **25,** 2141–2148.

MATUSSEK, N., BENKERT, O., SCHNEIDER, K., OTTEN, H. and POHLMEIER, H. (1970) L-dopa plus decarboxylase inhibitor in depression. *Lancet* **II,** 660–661.

MAYNERT, E. W., MARCZYNSKI, T. J. and BROWNING, R. A. (1975) The role of the neuro-transmitters in the epilepsies. *Adv. Neurol.* **13,** 79–147.

MCENTEE, W. J. and MAIR, R. G. (1978) Memory impairment in Korsakoff's psychosis: A correlation with brain noradrenergic activity. *Science,* **202,** 905–907.

MCENTEE, W. J. and MAIR, R. G. (1980) Korsakoff's amnesia: A noradrenergic hypothesis. *Psychopharmacol. Bull.* **16, 2,** 22–24.

MCGEER, P. L. and MCGEER, E. G. (1976) Enzymes associated with the metabolism of catecholamines, acetylcholine and GABA in human controls and patients with Parkinson's disease and Huntington's chorea. *J. Neurochem.* **26,** 65–76.

MCGEER, E. G. (1978) Aging and neurotransmitter metabolism in the human brain. In: *Alzheimer's disease: senile dementia and related disorders,* pp. 427–440. Eds. R. KATZMAN, R. D. TERRY and K. L. BICK. Raven Press, New York.

MCMILLEN, B. A., WARNACK, W., GERMAN, D. C. and SHORE, P. A. (1980) Effects of chronic desipramine treatment on rat brain noradrenergic responses to α-adrenergic drugs. *Europ. J. Pharmacol.* **61,** 239–246.

MCNAIR, D. M. and FISHER, S. (1978) Separating anxiety from depression. In: *Psychopharmacology: A generation of progress,* pp. 1411–1418. Eds. M. A. LIPTON, A. DIMASCIO and K. F. KILLAM. Raven Press, New York.

MCNAMARA, J. O. (1978) Selective alterations of regional β-adrenergic receptor binding in the kindling model of epilepsy. *Exp. Neurol.* **61,** 582–591.

MCNAUGHTON, N. and MASON, S. T. (1980) The neuropsychology and neuropharmacology of the dorsal ascending bundle—A review. *Prog. Neurobiol.* **14,** 157–219.

MEIER, M. J. and MARTIN, W. F. (1970) Intellectual changes associated with levodopa therapy. *J. Amer. med. Ass.* **213,** 465–466.

MELTZER, H. Y., NASR, S. J. and TONG, C. (1980) Serum dopamine-β-hydroxylase activity in schizophrenia. *Biol. Psychiat.* **15,** 781–788.

MENDLEWICZ, J., YAHR, F. and YAHR, M. D. (1976) Psychiatric disorders in Parkinson's disease treated with L-dopa: A genetic study. In: *Advances in Parkinsonism,* pp. 103–107. Eds. W. BIRKMAYER and O. HORNYKIEWICZ. Roche, Basle.

MEYERS, K. R., DORENKAMP, D. G. and SUZUKI, K. (1974) Amyotrophic lateral sclerosis with diffuse neurofibrillary changes—Report of a case. *Arch. Neurol.* **30,** 84–89.

MINDHAM, R. H. S. (1970) Psychiatric symptoms in Parkinsonism. *J. Neurol. Neurosurg. Psychiat.* **33,** 188–191.

MINNEMAN, K. P., DIBNER, M. D., WOLFE, B. B. and MOLINOFF, P. B. (1979) β_1- and β_2-adrenergic receptors in rat cerebral cortex are independently regulated. *Science,* **204,** 866–868.

MISHRA, R., JANOWSKY, A. and SULSER, F. (1980) Action of mianserin and zimelidine on the norepinephrine receptor coupled adenylate cyclase system in brain: subsensitivity without reduction in β-adrenergic receptor binding. *Neuropharmacol.* **19,** 983–988.

MODIGH, K. (1966) Long-term effects of electroconvulsive shock therapy on synthesis, turnover and uptake of brain monoamines. *Psychopharmacol.* **49,** 179–185.

MOORE, R. Y. and BLOOM, F. E. (1979) Central catecholamine neuron systems: Anatomy and physiology of the norepinephrine and epinephrine systems. *Ann. Rev. Neurosci.* **2,** 113–168.

MORRIS, M. J., ELGHOZI, J.-L., DAUSSE, J.-P. and MEIER, P. (1981) α_1- and α_2-adrenoceptors in rat cerebral cortex: Effect of frontal lobotomy. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **316,** 42–44.

MOSES, H. L., BEAVER, D. L., GARROTE, C. E. and SCHUFFMAN, S. S. (1966) Light and electron microscopic studies of pigment in human and Rhesus monkey substantia nigra and locus coeruleus. *Anat. Rec.* **155**, 167–184.

MURPHY, D. C., BRODIE, H. K., GOODWIN, F. K. and BUNNEY, W. E., JR. (1971) Regular induction of hypomania by l-dopa in "bipolar" manic depressive patients. *Nature*, **229**, 135–136.

NAGATSU, T., KATO, T., NAGATSU, I., KONDO, Y., INAGAKI, S., IIZUKA, R. and NARABAYASHI, H. (1979) Catecholamine-related enzymes in the brain of Parkinsonian patients. In: *Catecholamines: Basic and clinical frontiers*, pp. 1587–1589. Eds. E. USDIN, I. J. KOPIN and J. BARCHAS. Pergamon Press, New York.

NASHOLD, B. S., JR., WILSON, W. P. and SLAUGHTER, G. (1974) The midbrain and pain. In: *Advances in neurology. Vol. 4. International symposium on pain, Seattle*, pp. 191–196. Eds. I. BONICA and J. JOSEPH. Raven Press, New York.

NELSON, J. C. and CHARNEY, D. S. (1981) The symptoms of major depressive illness. *Amer. J. Psychiat.* **138**, 1–13.

NOTT, P. N. and FLEMINGER, J. J. (1975) Presenile dementia: the difficulties of early diagnosis. *Acta psychiat. Scand.* **51**, 210–217.

NYGREN, L. G. and OLSON, L. (1977) Intracisternal neurotoxins and monoamine neurons innervating the spinal cord: Acute and chronic effects on cell and axon counts and nerve terminal densities. *Histochem.* **52**, 281–306.

OHAMA, E. and IKUTA, F. (1976) Parkinson's disease: Distribution of Lewy bodies and monoamine neuron systems. *Acta neuropath.* **34**, 311–319.

OLPE, H. R. and SCHELLENBERG, A. (1980) Reduced sensitivity of neurons to noradrenaline after chronic treatment with antidepressant drugs. *Europ. J. Pharmacol.* **63**, 7–14.

PALMER, G. C., ROBINSON, G. A. and SULSER, F. (1971) Modification by psychotropic drugs of the cyclic adenosine monophosphate response to norepinephrine in rat brain. *Biochem. Pharmacol.* **20**, 236–239.

PALMER, G. C., ROBINSON, G. A. and SULSER, F. (1972) Modification by psychotropic drugs of the cyclic AMP response to norepinephrine in the rat brain *in vitro*. *Psychopharmacol.* **23**, 201–211.

PANDEY, G. N., HEINZE, W. J., BROWN, B. D. and DAVIS, J. M. (1979) Electroconvulsive shock treatment decreases β-adrenergic receptor density in rat brain. *Nature*, **280**, 234–235.

PAUL, S. M. and CREWS, F. T. (1980) Rapid desensitization of cerebral cortical β-adrenergic receptors induced by desmethylimipramine and phenoxybenzamine. *Europ. J. Pharmacol.* **62**, 349–350.

PEROUTKA, S. J. and SNYDER, S. H. (1980) Relationship of neuroleptic drug effects at brain dopamine, serotonin, α-adrenergic and histamine receptors to clinical potency. *Am. J. Psychiat.* **137**, 1518–1522.

PERRY, E. K., TOMLINSON, B. E., BLESSED, G., BERGMANN, K., GIBSON, P. H. and PERRY, R. H. (1978) Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. *Brit. med. J.* **2**, 1457–1459.

PETERS, J. G. (1979) Dopamine, Noradrenaline and serotonin spinal fluid metabolites in temporal lobe epileptic patients with schizophrenic symptomatology. *Europ. Neurol.* **18**, 15–18.

POLLOCK, M. and HORNABROOK, R. W. (1966) The prevalence, natural history and dementia of Parkinson's disease. *Brain*, **89**, 429–448.

POTKIN, S. G., CANNON, H. E., MURPHY, D. C. and WYATT, R. J. (1978) Are paranoid schizophrenics biologically different from other schizophrenics? *New Engl. J. Med.* **298**, 61–66.

PRADHAN, S. N. (1980) Central neurotransmitters and aging. *Life Sci.* **26**, 1643–1656.

PRO, J. D., SMITH, C. H. and SUMI, S. M. (1980) Presenile Alzheimer disease: Amyloid plaques in the cerebellum. *Neurol.* **30**, 820–825.

QUATRONE, A., CRUNELLI, V. and SAMANIN, R. (1978) Seizure susceptibility and anticonvulsant activity of carbamazepine, diphenylhydantoin and phenobarbital in rats with selective depletions of brain monoamines. *Neuropharmacol.* **17**, 643–648.

QUEIROZ, L. DE S., NUCCI, A. and PELLEGRINI-FILHO, A. (1977) Motor neuron disease with neurofibrillary tangles in a Brazilian woman. *J. neurol. Sci.* **33**, 21–29.

RAJPUT, A. H. and ROZDILSKY, B. (1976) Dysautonomia in Parkinsonism: a clinico-pathological study. *J. Neurol. Neurosurg. Psychiat.* **39**, 1092–1100.

RAMM, P. (1979) The locus coeruleus, catecholamines, and REM sleep: A critical review. *Behav. neural Biol.* **25**, 415–448.

RANCK, J. B., JR. (1975) Which elements are excited in electrical stimulation of mammalian central nervous system: a review. *Brain Res.* **98**, 417–440.

REDMOND, D. E., JR., HUANG, Y. H., SNYDER, D. R. and MAAS, J. W. (1976) Behavioral effects of stimulation of the nucleus locus coeruleus in the stump-tailed monkey (macaca arctoides). *Brain Res.* **116**, 502–510.

REDMOND, D. E., JR. (1977) Alteration in the functions of the nucleus locus coeruleus: A possible model for studies of anxiety. In: *Animal models in psychiatry and neurology*, pp. 293–306. Eds. I. HANIN and E. USDIN. Pergamon Press, New York.

REDMOND, D. E. and HUANG, Y. H. (1979) Current concepts. 2. New evidence for a locus coeruleus–norepinephrine connection with anxiety. *Life Sci.* **25**, 2149–2162.

REHAVI, M., RAMOT, O., YAVERTZ, B. and SOKOLOVSKY, M. (1980) Amitriptyline: long-term treatment elevates α-adrenergic and muscarinic receptor binding in mouse brain. *Brain Res.* **194**, 443–454.

REZNIK, M., FRANCK, G. and ROUSSEAU, J.-J. (1980) Le syndrome de Shy and Drager. Confrontation anatomoclinique. *Acta neurol. Belg.* **80**, 271–286.

RIDGES, A. P. (1980) Amine metabolism in depressive illness and it relationship to the response to antidepressant drugs. In: *Enzymes and neurotransmitters in mental disease*, pp. 229–245. Eds. E. USDIN, T. L. SOURKES and M. B. H. YOUDIM. John Wiley and Sons, Chichester.

RIEDERER, P., BIRKMAYER, W., RAUSCH, W.-D., JELLINGER, K. and DANIELCZYK, W. (1979) CNS and adrenal gland tyrosine hydroxylase and the influence of drug treatment on cAMP-activity in Parkinson's disease. Human post-mortem studies. In: *Catecholamines. Basic and clinical frontiers*, pp. 1625–1628. Eds. E. USDIN, I. J. KOPIN and J. BARCHAS. Pergamon Press, New York.

RIEDERER, P. and BIRKMAYER, W. (1980) A new concept: Brain area specific imbalance of neurotransmitters in depression syndrome—Human brain studies. In: *Enzymes and neurotransmitters in mental disease*, pp. 261–280. Eds. E. USDIN, T. L. SOURKES and M. B. H. YOUDIM. John Wiley and Sons, Chichester.

ROBERTS, P. and AMACHER, E. (1978) *Propranolol and schizophrenia. Proceedings of a Conference sponsored by the KROC Fund, held December 1976, at its Headquarters in St. Ynez Valley, California*; Liss, New York.

ROBINS, A. H. (1976) Depression in patients with Parkinsonism. *Brit. J. Psychiat.* **128,** 141–145.

ROBINSON, D. S. (1975) Changes in monoamine oxidase and monoamines with human development and aging. *Fed. Proc.* **34,** 103–107.

ROBINSON, S. E., BERNEY, S., MISHRA, R. and SULSER, F. (1979) The relative role of dopamine and norepinephrine receptor blackade in the action of anti-psychotic drugs: metoclopramide, thiethylperazine, and molindone as pharmacological tools. *Psychopharmacol.* **64,** 141–147.

RODGERS, A. D. and CURZON, G. (1975) Melanin formation by human brains *in vitro*. *J. Neurochem.* **24,** 1123–1129.

ROGAWSKI, M. A. and AGHAJANIAN, G. K. (1980) Modulation of lateral geniculate neurone excitability noradrenaline iontophoresis or locus coeruleus stimulation. *Nature*, **287,** 731–734.

RON, M. A., TOONE, B. K., GARRALDA, M. E. and LISHMAN, W. A. (1979) Diagnostic accuracy in presenile dementia. *Brit. J. Psychiat.* **134,** 161–168.

ROSENBAUM, A. H. SCHATZBERG, A. F., MARUTA, T., ORSULAK, P. J., COLE, J. O., GRAB, E. L. and SCHILDKRAUT, J. J. (1980) MHPG as a predictor of antidepressant response to imipramine and maprotiline. *Amer. J. Psychiat.* **137,** 1090–1092.

ROSENBLUM, W. I. and GHATAK, N. R. (1979) Lewy bodies in the presence of Alzheimer's disease. *Arch. Neurol.* **36,** 170–171.

ROTH, M. (1978) Diagnosis of senile and related forms of dementia. In: *Alzheimer's disease; Senile dementia and related disorders*, pp. 71–85. Eds. R. KATZMAN, R. D. TERRY and K. L. BICK. Raven Press, New York.

ROY, S. and WOLMAN, L. (1969) Ultrastructural observations in Parkinsonism. *J. Pathol.* **99,** 39–44.

ROZDILSKY, B., CUMMINGS, J. N. and HUSTON, A. F. (1968) Hallervorden–Spatz disease. Late adult and infantile types. *Acta neuropath.* **10,** 1–16.

ROZDILSKY, B., BOLTON, C. F. and TAKEDA, M. (1971) Neuroaxonal dystrophy: A case of delayed onset and protracted course. *Acta neuropath.* **17,** 331–340.

SACHS, C. and JONSSON, G. (1975) Effects of 6-hydroxydopamine on central noradrenaline neurons during ontogeny. *Brain Res.* **99,** 277–292.

SACK, R. L. and GOODWIN, F. K. (1974) Inhibition of dopamine-β-hydroxylase in manic patients. *Arch. gen. Psychiat.* **31,** 649–654.

SCHEFF, S. W., BERNARDO, L. S. and COTMAN, C. W. (1978) Decrease in adrenergic axon sprouting in the senescent rat. *Science*, **202,** 775–778.

SCHILDKRAUT, J. J. (1975) Norepinephrine metabolism after short- and long-term administration of tricyclic antidepressant drugs and electroconvulsive shock. *Adv. biochem. Psychopharmacol.* **13,** 137–153.

SCHILDKRAUT, J. J., HERZOG, S. M., ORSULAK, P. J., EDELMAN, S. E., SHEIN, H. M. and FRAZIER, S. H. (1976) Reduced platelet monoamine oxidase in a subgroup of schizophrenic patients. *Amer. J. Psychiat.* **133,** 438–440.

SCHILDKRAUT, J. J. (1978) Current status of the catecholamine hypothesis of affective disorders. In: *Psychopharmacology: A generation of progress*, pp. 1223–1234. Eds. M. A. LIPTON, A. DIMASCIO and K. F. KILLAM. Raven Press, New York.

SCHILDKRAUT, J. J., ORSULAK, P. J., SCHATZBERG, A. F., GUDEMAN, J. E., COLE, J. O. LABRIE, R. A. and RHODE, W. A. (1979) Biochemical discrimination of subtypes of depressive disorders. In: *Catecholamines: Basic and clinical frontiers*, pp. 1860–1862. Eds. E. USDIN, I. J. KOPIN and J. BARCHAS. Pergamon Press, New York.

SCHMIDT, R. H., KASIK, S. A. and BHATNAGAR, R. K. (1980) Regenerative critical periods for locus coeruleus in postnatal rat pups following intracisternal 6-hydroxydopamine: a model for noradrenergic development. *Brain Res.* **191,** 173–190.

SCHOBER, R., LANGSTON, J. W. and FORNO, L. S. (1975) Idiopathic orthostatic hypotension. *Europ. Neurol.* **13,** 177–188.

SCHWARTZ, J. C., COSTENTIN, J., MARTRES, M. P., PROTAIS, P. and BAUDRY, M. (1978) Modulation of receptor mechanisms in the CNS: hyper- and hyposensitivity to catecholamines. *Neuropharmacol.* **17,** 665–686.

SELBY, G. (1968) Cerebral atrophy in Parkinsonism. *J. neurol. Sci.* **6,** 517–559.

SELLINGER-BARNETTE, M. M., MENDELS, J. and FRAZER, A. (1980) The effect of psychoactive drugs on beta-adrenergic receptor binding sites in rat brain. *Neuropharmacol.* **19,** 447–454.

SHARPE, J. A., REWCASTLE, N. B., LLOYD, K. G., HORNYKIEWICZ, O., HILL, M. and TASKER, R. R. (1973) Striato-nigral degeneration. Response to Levodopa therapy with pathological and neurochemical correlation. *J. neurol. Sci.* **19,** 275–286.

SHAW, D. M., O'KEEFE, R. O., MACSWEENEY, D. A., BROOKBANK, B. W. L., NOGUERA, R. and COPPEN, A. (1973) 3-Methoxy-4-hydroxyphenylglycol in depression. *Phychol. Med.* **3,** 333–336.

SHIMIZU, N., KATOH, Y., HIDA, T. and SATOH, K. (1979) The fine structural organization of the locus coeruleus in the rat with reference to noradrenaline contents. *Exp. Brain Res.* **37,** 139–148.

SIMON, H., LE MOAL, M. and CARDO, B. (1975) Self-stimulation in the dorsal pontine tegmentum in the rat. *Behav. Biol.* **13,** 339–347.

SLABY, A. E. and WYATT, R. J. *Dementia in the presenium*, C. C. Thomas, Springfield, Illinois.

SPITZER, R. L., ENDICOTT, J. and ROBINS, E. (1975) Research diagnostic criteria (RDC) for a selected group of functional disorders; *Manual prepared for CRB-NIMH Collaborative Studies on Depression.*

SPITZER, R. L., FLEISS, J. L. and ENDICOTT, J. (1978) Problems of classification: Reliability and validity. In: *Psychopharmacology: A generation of progress*, pp. 857–869. Eds. M. A. LIPTON, A. DIMASCIO and K. F. KILLAM. Raven Press, New York.

SPYRAKI, C. and FIBIGER, H. C. (1980) Functional evidence for subsensitivity of noradrenergic α_2 receptors after chronic desipramine treatment. *Life Sci.* **27,** 1863–1868.

STADLAN, E. M., DUVOISIN, R. and YAHR, M. (1966) The pathology of Parkinsonism. In: *Neuropathology. Proceeding of the fifth international congress on neuropathology, ICS 100*, pp. 569–571; Excerpt medica, Amsterdam.

STEELE, J. C., RICHARDSON, J. C. and OLZSZEWSKI, J. (1964) Progressive supranuclear palsy, *Arch. Neurol.* **10**, 333–359.

SULSER, F. and ROBINSON, S. E. (1978) Clinical implications of pharmacological differences among antipsychotic drugs (with particular emphasis on biochemical central synaptic adrenergic mechanisms). In: *Psychopharmacology: A generation of progress*, pp. 943–954. Eds. M. A. LIPTON, A. DIMASCIO and K. F. KILLAM. Raven Press, New York.

SULSER, F., VETULANI, J. and MOBLEY, P. L. (1978) Mode of action of antidepressant drugs. *Biochem. Pharmacol.* **27**, 257–261.

SUNG, J. H., MASTRI, A. R. and SEGAL, E. (1979) Pathology of Shy–Drager syndrome. *J. Neuropath. exp. Neurol.* **38**, 353–368.

SVENSSON, T. H. and USDIN, T. (1978) Feedback inhibition of brain noradrenaline neurons by tricyclic antidepressants: α-Receptor mediation. *Science*, **202**, 1089–1091.

SWANSON, L. W., and HARTMAN, B. K. (1975) The central adrenergic system. An immunofluorescence study of the localization of cell bodies and their efferent connections in the rat utilizing dopamine-B-hydroxylase as a marker. *J. comp. Neurol.* 163, 467–505.

SWANSON, L. W. (1976) The locus coeruleus: a cytoarchitectonic, Golgi and immunohistochemical study in the albino rat. *Brain Res.* **110**, 39–56.

SWEENEY, D. R., MAAS, J. W. and PICHAR, D. (1979) Urinary 3-methoxy-4-hydroxyphenethelene glycol and state variables in affective disorder. In: *Catecholamines: Basic and clinical frontiers*, pp. 1917–1919. Eds. E. USDIN, I. J. KOPIN, J. BARCHAS. Pergamon Press, New York.

TANG, S. W., SEEMAN, P. and KWANG, S. (1981) Differential effects of chronic desipramine and amitriptyline treatment on rat brain adrenergic and serotonergic receptors. *Psychiat. Res.* **4**, 129–138.

TAUBE, S. L., KIRKSTEIN, L. S. SWEENEY, D. R., HENINGER, G. R. and MAAS, J. W. (1978) Urinary 3-methoxy-4-hydroxyphenylglycol and psychiatric diagnosis. *Amer. J. Psychiat.* **135**, 78–81.

TER HAAR, M. B. (1979a) Noradrenaline and schizophrenia. *Trends Neurosci.* **2**, **7**, IV.

TER HAAR, M. B. (1979b) Schizophrenia. *Trends Neurosci.* **2**, **9**, XIII.

TEYCHENNE, P. F., LAKE, C. R., ZIEGLER, M. G., PLOTKIN, C., WOOD, J. H. and CALNE, D. B. (1977) Central and peripheral deficiency of norepinephrine in Parkinson's disease and the effect of L-DOPA therapy. *Soc. Neurosci. Abstr. 7th Ann. Meeting*, 417.

THAPEDI, I. M., ASHENHURST, E. M. and ROZDILSKY, B. (1971) Shy–Drager syndrome. *Neurol.* **21**, 26–32.

TODOROV, A. B., GO, R. C. P., CONSTANTINIDIS. J. and ELSTON, R. C. (1975) Specificity of the clinical diagnosis of dementia. *J. neurol. Sci.* **26**, 81–98.

TOMLINSON, B. E., BLESSED, G. and ROTH, M. (1970) Observations on the brains of demented old people. *J. neurol. Sci.* **11**, 205–242.

TOMLINSON, B. E. (1980) The structural and quantitative aspects of the dementias. In: *Biochemistry of dementia*, pp. 15–52. Ed. P. J. ROBERTS. John Wiley and Sons, Chichester.

TOMLINSON, B. E., IRVING, D. and BLESSED, G. (1981) Cell loss in the locus coeruleus in senile dementia of Alzheimer type. *J. neurol. Sci.* **49**, 419–428.

TOMONAGA, M. (1977a) Neurofibrillary changes observed in the subcortical areas of the aged brain. Special reference on their fine structure. *Jap. J. Geriatr.* **14**, 60–67 (in Japanese).

TOMONAGA, M. (1977b) Ultrastructure of neurofibrillary tangles in progressive supranuclear palsy. *Acta neuropath.* **37**, 177–181.

TOMONAGA, M. (1980) Morphological changes of locus coeruleus in the senile human brain. *Jap. J. Geriatr.* **16**, 545–550 (in Japanese).

TOMONAGA, M. (1981) Neurofibrillary tangles and Lewy bodies in the locus coeruleus neurons of the aged brain. *Acta neuropath.* **53**, 165–168.

U'PRICHARD, D. C., GREENBERG, D. A., SHEEHAN, P. P. and SNYDER, S. H. (1978) Tricyclic antidepressants: Therapeutic properties and affinity for α-noradrenergic binding sites in the brain. *Science*, **199**, 197–198.

U'PRICHARD, D. C. and ENNA, S. J. (1979) *In vitro* modulation of CNS β-receptor number by antidepressants and β-antagonists. *Europ. J. Pharmacol.* **59**, 297–302.

U'PRICHARD, D. C., BECHTEL, W. D., ROUOT, B. M. and SNYDER, S. H. (1979) Multiple apparent alpha-noradrenergic receptor binding sites in rat brain. Effect of 6-hydroxydopamine. *Mol. Pharmacol.* **16**, 47–60.

U'PRICHARD, D. C., REISINE, T. D., MASON, S. T., FIBIGER, H. C. and YAMAMURA, H. I. (1980a) Modulation of rat brain α- and β-adrenergic receptor populations by lesion of the dorsal noradrenergic bundle. *Brain Res.* **187**, 143–154.

U'PRICHARD, D. C., REISINE, T. D., YAMAMURA, S., MASON, S. T., FIBIGER, H. C., EHLERT, F. and YAMAMURA, H. I. (1980b) Differential supersensitivity of β-receptor subtypes in rat cortex and cerebellum after central noradrenergic denervation. *Life Sci.* **26**, 355–364.

VANDERHAEGEN, J. J., PERIER, O. and STERNON, J. R. (1970) Pathological findings in idiopathic orthostatic hypotension. *Arch. Neurol.* **22**, 207–214.

VAN DONGEN, P. A. M. (1980a) Locus coeruleus region: Effects on behavior of cholinergic, noradrenergic, and opiate drugs injected intracerebrally into freely moving cats. *Exp. Neurol.* **67**, 52–78.

VAN DONGEN, P. A. M. (1980b) *The noradrenergic locus coeruleus. Behavioral effects of intra-cerebral injections, and a survey of its structure, functions and pathology.* Krips Repro, Meppel, The Netherlands.

VAN DONGEN, P. A. M. (1981) The central noradrenergic transmission and the locus coeruleus: A review of the data and their implications for neurotransmission and neuromodulation. *Prog. Neurobiol.* **16**, 117–143.

VAN DONGEN, P. A. M. and VAN DEN BERCKEN, J. H. L. (1981) Structure and function in neurobiology. A conceptual framework and the localization of functions. *Int. J. Neurosci.* (in press).

VAN ROSSUM, J. M. (1967) The significance of dopamine receptor blockade for the action of neuroleptic drugs. In: *Neuropsychopharmacology*, pp. 321–329. Ed. H. Brill. Excerpta medica, Amsterdam.

VICTOR, M. and BANKER, B. Q. (1978) Alcohol and dementia. In: *Alzheimer's disease: Senile dementia and related disorders*, pp. 149–170. Eds. R. KATZMAN, R. D. TERRY and K. L. BICK. Raven Press, New York.

VIJAYASHANKAR, N. and BRODY, H. (1979) Quantitative study of the pigmented neurons in the nuclei locus coeruleus and subcoeruleus in man as related to aging. *J. Neuropath. exp. Neurol.* **38,** 490–497.

VUIA, O. (1976) Striato-nigral degeneration and Shy-Drager syndrome (idiopathic orthostatic hypotension). *Clin. Neurol. Neurosurg.* **78,** 196–203.

WAGNER, H. R. and DAVIS, J. N. (1979) β-Adrenergic receptor regulation by agonists and membrane depolarization in rat brain slices. *Proc. natl. Acad. Sci USA* **76,** 2057–2061.

WARBURTON, J. W. (1967) Depressive symptoms in Parkinson Patients referred for thalamotomy. *J. Neurol. Neurosurg. Psychiat.* **30,** 368–370.

WATANABE, I., VACHAL, E. and TOMITA, T. (1977) Dense core vesicles around the Lewy body in incidental Parkinson's disease: an electron microscopic study. *Acta neuropath.* **39,** 173–176.

WEINSTOCK, M. and WEISS, C. (1980) Antagonism by propranolol of isolation-induced aggression in mice: Correlation with 5-hydroxytryptamine blockade. *Neuropharmacol.* **19,** 653–656.

WILLNER, P. and MONTGOMERY, T. (1980) Neurotransmitter and depression: too much, too little, too unstable—or not unstable enough? *Trends Neurosci.* **3,** 201.

WISE, C. D. and STEIN, L. (1973) Dopamine-β-hydroxylase deficits in the brains of schizophrenic patients. *Science,* **181,** 344–347.

WISE, C. D. and STEIN, L. (1975) Reply to Wyatt *et al.* (1975) *Science,* **187,** 370.

WISNIEWSKI, H., TERRY R. D. and HIRANO, A. (1970) Neurofibrillary pathology. *J. Neuropath. exp. Neurol.* **29,** 163–176.

WISNIEWSKI, H. M., NARANG, H. K. and TERRY, R. D. (1976) Neurofibrillary tangles of paired helical filaments. *J. neurol. Sci.* **27,** 173–181.

WISNIEWSKI, K., JERVIS, G. A., MORETZ, R. C. and WISNIEWSKI, H. M. (1979) Alzheimer neurofibrillary tangles in diseases other than senile and presenile dementia. *Ann. Neurol.* **5,** 288–294.

WISNIEWSKI, H. M. and IQBAL, K. (1980) Ageing of the brain and dementia. *Trends Neurosci.* **3,** 226–228.

WOLFE, B. B., HARDEN, T. K. SPORN, J. R. and MOLINOFF, P. B. (1978) Presynaptic modulation of beta adrenergic receptors in rat cerebral cortex after treatment with antidepressants. *J. Pharmacol. exp. Ther.* **207,** 446–457.

WOODARD, J. C. (1962) Concentric hyaline inclusion body formation in mental disease: Analysis of 27 cases. *J. Neuropath. exp. Neurol.* **21,** 442–449.

WREE, A., BRAAK, H., SCHLEICHER, A. and ZILLES, K. (1980) Biomathematical analysis of the neuronal loss in the aging human brain of both sexes, demonstrated in pigment preparations of the pars cerebellaris loci coerulie. *Anat. Embryol.* **160,** 105–119.

WYATT, R. J., SCHWARZ, M. A., ERDELYI, E. and BARCHAS, J. D. (1975) Dopamine-β-hydroxylase activity in brains of chronic schizophrenic patients. *Science,* **187,** 368–370.

WYATT, R. J., POTKIN, S. G., GILLIN, J. C. and MURPHY, D. L. (1978) Enzymes involved in phenylethylamine and catecholamine metabolism in schizophrenics and controls. In: *Psychopharmacology: A generation of progress*, pp. 1083–1095. Eds. M. N. LIPTON, A. DIMASCIO and K. F. KILLAM. Raven Press, New York.

WYATT, R. J., POTKIN, S. G., KLEINMAN, J. E., WEINBERGER, D. R., LUCHINS, D. J. and JESTE, D. V. (1981) The schizophrenia syndrome. Examples of biological tools for subclassification. *J. nerv. Ment. Dis.* **169,** 100–112.

YAGISHITA, S., ITOH, Y., AMANO, N., NAKANO, T. and SATOH, A. (1979) Ultrastructure of neurofibrillary tangles in progressive supranuclear palsy. *Acta neuropath.* **48,** 27–30.

YAGISHITA, S., ITOH, Y., AMANO, N. and NAKANO, T. (1980a) Atypical senile dementia with widespread Lewy type inclusion body in the cerebral cortex. *Acta neuropath.* **49,** 187–191.

YAGISHITA, S., ITOH, Y., AMANO, N. and NAKANO, T. (1980b) The fine structure of neurofibrillary tangles in a case of atypical presenile dementia. *J. neurol. Sci.* **48,** 325–332.

YAHR, M. D. (1969) Treatment of Parkinsonism with levodopa. *Arch. Neurol.* **21,** 343–354.

YORKSTON, N. J., ZAKI, S., PITCHER, D. R., GRUZELIER, J., HOLLANDER, J. H. and SERJEANT, H. G. S. (1977) Propranolol as an adjunct to the treatment of schizophrenia. *Lancet* **II,** 575–578.

YORKSTON, N. J., ZAKI, S. A., WELLER, M. P., GRUZELIER, J. H. and HIRSCH, S. R. (1981) DL-propranolol and chlorpromazine following admission for schizophrenia. A controlled comparison. *Acta psychiat. Scand.* **63,** 13–27.