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NEUROLOGICAL SYMPTOMS IN PHARMACOTHERAPY OF PSYCHOSES

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After introduction of the phenothiazines in the therapy of psychoses it was soon evident that these compounds produce a series of so-called extrapyramidal symptoms (*Labhardt*, 1954) besides the anti-psychotic effect.

It has been much discussed whether the extrapyramidal symptoms are a necessary condition for obtaining anti-psychotic effect (*Flügel*, 1956) or an inevitable consequence of the treatment (*Haase*, 1961), or a therapeutically beneficial effect of the phenothiazines on the central nervous system (*Bordeleau & Gratton*, 1958; *Delay & Deniker*, 1959). Several authors conclude that extrapyramidal symptoms are not necessary for obtaining anti-psychotic effect (*Faurbye et al.*, 1959; *Goldman*, 1961; *Cole & Clyde*, 1961), and *Uhrbrand & Faurbye* (1960) regard the extrapyramidal symptoms as harmful side effects and assert that they may be irreversible.

Cases with chronic extrapyramidal symptoms were also seen by *Sigwald et al.* (1959); *Kruse* (1960); *Chatagnon et al.* (1961); *Druckman, Seelinger & Thulin* (1962).

In the following are presented some investigations on the so-called extrapyramidal symptoms during long term treatment of psychoses with psychopharmaca and a discussion of the mechanism of their appearance.

Definition of drug-induced neurological symptoms

The literature about drug-induced neurological symptoms is confusing because many authors do not distinguish between the different symptoms. The common term "extrapyramidal symptoms" is often used although there is profound disagreement about what should be included in "the extrapyramidal system" and about the function of this ill-defined motor system (*Laursen*, 1963). Another common and vague term is "Parkinsonism" which now seems to mean more or less rigidity and now tremor or other involuntary movements. There is also disagreement about what akathisia and tasikinesia means.

In our investigations we have considered it necessary to give a definition of the single symptoms and register each symptom separately. We have adhered to the following definitions:

1. *Rigidity.* The first manifestations of muscular rigidity are oligomimia and slight stiffness of movements and posture, in more pronounced cases the fully developed Parkinsonian posture, in some cases backward or sideward posture.

2. *Disturbance of co-ordination.* The delicate and finely co-ordinated movements used in handwriting are disturbed according to *Haase* (1961). The handwriting is more stiff, the lines become shorter, the single letters are shorter or smaller, there is lessening of the right slant and signs of tremor. In-coordination of the fine movements after neuroleptic drugs is not directly observable, it only turns up in the handwriting.

3. *Dystonic movements* are in-coordinated spasmodic movements of the body and the limbs, torticollis, retrocollis, opisthotonus and oculogyric crises. The term "dystonic" is not a fortunate one as it is used in neurology in a different sense, but we have adhered to it since it is the most common term for these movements in the literature.

4. *Dyskinetic movements* are co-ordinated, involuntary, stereotyped, rhythmic movements and they are so in contrast to the in-coordinated, spasmodic dystonic movements. The dyskinetic movements can be localized to a single pattern of movements or be universally extended.

Facial dyskinesia consists of incessant rhythmic munching and masticatory movements of the jaw, grimaces of the lips and movements of the tongue with rhythmic protrusion outside the mouth or in the cheeks. These symptoms may appear singly or combined as the bucco-lingvo-masticatory triad.

Dyskinesia of the body appears when the patient is standing as swaying to and fro, in some cases with torsions of the body. In sitting position rocking movements and in pronounced cases nodding of the head in the opposite direction of the body movements.

Akathisia is inability to remain in sitting position.

Tasikinesia is the term for incessant tripping and shuffling movements of the feet so that the patient can not stand still, and in pronounced cases he is shifting the weight from one foot to the other.

5. *Tremor* is not a co-ordinated movement and therefore not a form of dyskinesia. Drug-induced tremor is a rather coarse rhythmic resting tremor, it appears generally in a single limb. The special form of "pill-rolling" tremor characteristic of paralysis agitans is not seen produced by drugs.

6. *Autonomic symptoms.* The most frequent autonomic symptoms are dryness of the mouth, stuffy nose and disturbance of the blood pressure regulation and disturbance of accomodation.

Drug-induced neurological syndromes

The different drug-induced neurological symptoms may appear singly or in combinations, and it is possible to distinguish between distinct combinations or syndromes.

Acute dystonia. The clinical picture of the syndrome of acute dystonia is dominated by dystonic movements. The syndrome starts abrupt and it has a dramatic and violent character somewhat similar to hysterical convulsions (*Labhardt,* 1954). Under opisthotonus there may be stridorous respiration with cyanosis and pronounced sweat and swelling and protrusion of the tongue. The syndrome appears generally after few doses of neuroleptics, i. e. during the first 2–3 days of the treatment, more frequently after the potent compounds as those with piperazine in the side chain than after the weaker ones and especially when the treatment is started with a big dose. *Ayd* (1961) states that "dyskinesia or dystonic reaction", which according to his description is equivalent to our term acute dystonia, is more frequent in younger persons than in elder and more frequent in males than in females (2:1). The syndrome can, in spite of its violent and dramatic character, be stopped in a few minutes by injection of anti-Parkinson drugs. Afterwards it is possible to continue the treatment with the provoking drug when the treatment is resumed with a smaller dose, which then is increased slowly, or by combination with an anti-Parkinson drug. Untreated the syndrome lasts a few hours until about 24 hours.

The rigidity syndrome is characterized by muscular rigidity with more or less pronounced alteration of posture, besides often tremor and autonomic symptoms. Rigidity often occurs in combination with the syndrome of tardive dyskinesia.

The syndrome may appear at any time during the treatment depending on the dosage and it seems always to be reversible. By cessation of the treatment it disappears in a few days. In some cases the syndrome may disappear during continued treatment. Generally, there is good effect of anti-Parkinson drugs.

Tardive dyskinesia is first and foremost characterized by the occurrence of dyskinetic movements, besides that tremor and autonomic symptoms may occur, and the syndrome is often combined with syndrome of rigidity. The dyskinetic movements may be more or less pronounced and may appear in different combinations, the clinical pictures can thus be rather different. Generally, tardive dyskinesia occurs only after treatment for a long time, it is seldom during the first six months and it may occur even after several years of symptom-free treatment. By treatment with the piperazine substituted phenothiazines the syndrome is more frequent and appears earlier. In some cases the syndrome starts a few days after cessation of the treatment.

Tardive dyskinesia is more frequent in elder persons and in patients with organic brain diseases (*Uhrbrand* & *Faurbye,* 1960) and according to *Ayd* (1961) the syndrome is more frequent in females than in males (2:1).

The syndrome disappears in most cases in 1–2 months by cessation of treatment, but it may continue chronically. Anti-Parkinson drugs have generally only poor effect.

DIAGNOSTIC PROBLEMS

Dyskinetic movements are not always easy to recognize because attention arrest them for a time when they are only sligthly pronounced. They may therefore not be present during a shorter interview or when the patient pays attention to his work. Dyskinetic movements are best seen when the patient is sitting unoccupied in his habitual surroundings without knowing that he is under observation.

Before introduction of modern pharmacotherapy of psychoses many chronic schizophrenic patients displayed mannerisms and grimaces which were mimic and often habitual expression of the autistic patients' psychotic experiences. These movements have generally not the same rhythmic character as the drug-induced dyskinetic movements. Psychotic manners and grimaces are now seldom in well treated schizophrenics but in some cases there may be difficulties in the differential diagnostic against drug-induced dyskinesia.

Neurological symptoms, especially rigidity with postural alterations and dyskinetic movements, are often seen in senile and arteriosclerotic demented patients who do not get drugs. These "spontaneous" dyskinetic movements are generally not as pronounced and distinct as the drug-induced and they do not disappear by attention. In senile arteriosclerotic patients without drugs "spontaneous" dyskinetic movements of the face are more frequent than movements of the body and the extremities. It is therefore possible to speak of a *"spontaneous" dyskinetic syndrome.*

OWN CLINICAL INVESTIGATIONS

Our own investigations concern the tardive dyskinetic syndrome. On a certain day all the patients were registered and the occurrence of the syndrome was noted.

In table 1 is seen the occurrence of dyskinesia in the total material of 417 female patients of the department whether they were under pharmacotherapy or not.

The symptoms were regarded as drug-induced if the patient had been under pharmacotherapy for at least one month when they occurred or if they appeared in the first 10 days after cessation of the treatment.

TABLE 1

Number of patients with dyskinetic symptoms in the total material of 417 female patients.

Diagnosis	Total no. of patients	"Spontaneous" dyskinesia	Dyskinesia after ECT	Dyskinesia of uncert. origin	Drug-induced dyskinesia	Total no. of patients with dyskinesia
Abuse of alc.	2	0	0	0	0	0
Drug addiction	3	0	0	0	0	0
General paralysis	11	2	0	2	2	6
Chron. epid. encephalitis	2	1	0	0	1	2
Post-traumatic cerebral syndrome	2	0	0	1	0	1
Senile & arteriosclerotic dementia	85	11	0	1	14	26
Manic-depressive psychosis	50	3	1	7	11	22
Schizophrenia	216	22	3	12	75	112
Epilepsy	4	0	0	0	1	1
Psychogenic psychosis	7	0	0	0	1	1
Atypical psychosis	15	0	0	1	3	4
Neurosis	4	1	0	0	0	1
Psychopathic personality	11	0	0	0	1	1
Oligophrenia	1	0	0	0	0	0
Organic psychosis	4	0	0	0	0	0
	417	40	4	24	109	177
		10 %	1 %	6 %	26 %	42 %

In 24 patients with dyskinesia it was not possible to establish the exact time of the onset of the symptoms. In these cases the relation of the symptoms to drug therapy is therefore uncertain.

Dyskinesia occurred in direct connection to electro-convulsive-treatment (ECT) in 4 patients.

The symptoms were considered as "spontaneous" in 40 patients, i. e., they did not occur in connection with ECT and the patients did not have drugs during the last month before the onset of the symptoms.

Table 2 shows the incidence of the single spontaneous and drug-induced neurological symptoms in schizophrenics and the incidence of the fully developed bucco-lingvo-masticatory triad, which is the most frequent combination of symptoms. In the patients with "spontaneous" symptoms the lip-tongue-jaw movements are more frequent than the other dyskinetic symptoms, which is not the case for patients with drug-induced dyskinesia, and drug-induced dyskinesia is often combined with tremor and rigidity while this is rare in "spontaneous" dyskinesia. Clinically there is also another difference, the spontaneous symptoms are less marked than the drug-induced and have no tendency to disappear under attention, unlike the drug-induced symptoms.

Table 3 demonstrates that there is an increasing number of patients with "spontaneous" dyskinesia after 50 years of age. This suggests that arterio-

TABLE 2

Frequency of the single neurological symptoms in 22 schizophrenics with "spontaneous" dyskinesia and in 75 schizophrenics with drug-induced dyskinesia.

	No. of schizophrenics with "spontaneous" dyskinesia		No. of schizophrenics with drug-induced tardive dyskinesia	
Dyskinesia of the lips	11		33	
Dyskinesia of the tongue	7		28	
Dyskinesia of the jaw	12		32	
Bucco-lingvo-masticatory triad		4		17
Dyskinesia of the body	3		38	
Akathisia	0		6	
Tasikinesia	1		19	
Tremor	3		23	
Rigidity	4		32	

TABLE 3

Number of patients with "spontaneous" dyskinesia divided into age-groups.

Age	Number	No. with "spontaneous" dyskinesia
< 30 years	17	0
30–39 –	21	3
40–49 –	43	0
50–59 –	85	6
60–69 –	101	12
> 70 –	150	19
	417	40

sclerotic and senile brain alterations are of significance for the occurrence of dyskinesia. The same prevails in table 4, which shows that there is also an increasing number of drug-induced tardive dyskinesia after the age of 50. The smaller number of schizophrenics over 70 years of age with drug-induced symptoms is presumably due to the less intensive treatment of elder schizophrenics.

The question is then whether other forms of brain damage are of significance for the manifestation of drug-induced neurological symptoms. In table 5 the effect of prefrontal leucotomy is investigated. In the two groups of schizophrenics with and without prefrontal leucotomy but with similar age distribution there is no difference in the incidence of drug-induced dyskinesia.

In table 6 the significance of ECT is investigated. Among schizophrenics previously treated with one or more series of ECT the rate of drug-induced symptoms is 44 per cent, in the group without former ECT the incidence is

TABLE 4

Schizophrenics with "spontaneous" and drug-induced dyskinesia divided into age-groups.

Age	No. of schiz.	No. with "spontaneous" dyskinesia	No. with drug-induced dyskinesia	
< 30 years	7	0	4	
30–39 –	13	3	2	28 %
40–49 –	23	0	6	
50–59 –	61	5	27	
60–69 –	64	7	25	42 %
> 70 –	48	7	11	22 %
Total	216	22	75	

TABLE 5

Occurrence of drug-induced tardive dyskinesia in schizophrenics with and without prefrontal leucotomy.

Age	Schizophrenics with ECT and with leucotomy		Schizophrenics with ECT and without leucotomy	
	Total no.	No. with drug-induced dyskinesia	Total no.	No. with drug-induced dyskinesia
< 50 years	18	8	15	3
50–59 –	30	12	20	12
60–69 –	15	7	17	8
> 70 –	4	2	8	4
	67	29	60	27

TABLE 6

Occurrence of drug-induced tardive dyskinesia in schizophrenics with and without previous series of ECT.

Age	Schizophrenics with ECT		Schizophrenics without ECT	
	Total no.	No. with drug-induced dyskinesia	Total no.	No. with drug-induced dyskinesia
< 50 years ..	33	11	10	1
50–59 – ..	50	24	10	3
60–69 – ..	32	15	32	10
> 70 – ..	12	6	34	5
	127	56 (44 %)	86	19 (22 %)

only 22 per cent although the patients in this group are older in average which should give some disposition for drug-induced symptoms. This suggests that brain damage from former ECT is of significance for the manifestation of drug-induced dyskinesia. It may, however, be questioned whether the two groups are quite comparable. ECT was formerly mainly given to disturbed patients, and the patients in the ECT-treated group may perhaps also have had more intensive drug treatment because of disturbance than the other group. On the other hand some disturbed patients will react better to drugs than more quiet patients and therefore require a minor dosage. It is, however, our estimate that the intensity of the drug treatment has been much the same in the two groups. It is not possible to evaluate the intensity of the treatment exactly since the dosage has varied from time to time according to the clinical condition, and many of the patients have been treated with different drugs.

The time of onset of tardive dyskinesia in relation to the duration of the treatment is seen in table 7. Only few cases begin during the first six months of drug treatment, and many appear even after several years of treatment.

The drugs we have used are seen in table 8. Many of the patients have been treated with more than one drug. The table does not indicate the

TABLE 7

Duration of treatment before the onset of tardive dyskinesia.

Duration of treatment	No. of schizophrenics with drug-induced dyskinesia
< 1/2 year	3
1/2–1 –	6
1–3 years	32
> 3 –	34

TABLE 8

The drug-induced tardive dyskinetic syndrome in relation to the provoking drugs.

Drug	No. of schizophrenics treated	No. of schizophrenics with drug-induced dyskinesia
Chlorpromazine	185	47
Perphenazine	62	12
Thioridazine	74	10
Prochlorperazine	21	4
Haloperidol	15	2

frequency with which the drugs produce tardive dyskinesia, it only states the frequency with which the drugs have been used.

Neurological examination. 8 patients with a pronounced and consistent bucco-lingvo-masticatory triad were selected for special investigations because this triad is the most frequent and most marked combination of tardive dyskinesia. The neurological examination showed:

1. The dyskinetic movements were strikingly stereotyped in the individual patient.
2. The pattern of dyskinesia was much the same in all the patients.
3. The patients had not themselves noticed the dyskinetic movements.
4. All the patients had strikingly lively deep reflexes.
5. None of the patients had cerebellar or Parkinson symptoms.
6. None of the patients displayed neurological symptoms apart from the dyskinetic movements.
7. The dyskinetic movements stopped in most of the patients when they concentrated on performing a voluntary movement, for instance backward bending of the head.

The fact, that the pattern of dyskinesia is so constant in the single patient and so much alike in all the patients suggests that this dyskinetic triad is the result of a disturbance in the regulation of the motor function with a definite neurological pattern in the central nervous system.

Roentgenological examination of the skull and pneumography displayed in 6 of 7 patients some cortical or diffuse cerebral atrophy, which was not different from that commonly seen in schizophrenics of the same age group.

Electromyography (prof. *Buchthal*) was performed in two patients with the bucco-lingvo-masticatory triad.

Pt. E. A. P.: Simultaneous registration from left and right orbicularis oris superior and left masseter: In absence of voluntary innervation brief tetanic discharges are seen synchronically in left and right orbicularis superior and less pronounced in masseter. Voluntary innervation of the facial muscles produces an interference pattern and in most cases the spontaneous activity in the masseter muscles stops. The rhythmic activity which is characteristic for mb. Parkinson is not seen.

Pt. A. M. N.: Simultaneous registration from left and right orbicularis superior and masseter: Sporadic spontaneous activity is seen as motor unit potentials in left and right orbiscularis oris superior but no activity in masseter. By voluntary innervation interfering activity is seen in orbicularis oris but no rhythmic discharges, and in contrast to what was found in right masseter pronounced activity was seen in left masseter by voluntary innervation.

Conclusion: The activity in absence of voluntary innervation is essentially different from that seen for instance in Parkinsonism, the characteristic regular rhythm is not seen, the activity is similar to that seen in athetosis.

COMMENTS

The frequency and the significance of drug-induced neurological symptoms

The frequency of drug-induced tardive dyskinesia in our material is on the same level as most statements in the literature. *Ayd* (1961) found in his great

statistic "extrapyramidal symptoms" in 47.8 per cent of 1,942 females and in 29.6 per cent of 1,833 males. The frequency after chlorpromazine was 35 per cent, after perphenazine 36 per cent, after trifluoperazine 60 per cent (average of men and women). The incidence of acute dystonia was in *Ayd*'s statistic 1.5 per cent in females and 3.1 per cent in males.

The frequency and the rapidity of the onset of neurological symptoms is in our experience and according to the literature dependent on the dosage and the chemical structure of the drug. Neurological symptoms are hardly to avoid in using the very potent thioproperazine (*Delay & Deniker,* 1959). *Wilson, Parker & Handy* (1960) gave an anti-Parkinson drug in combination with perphenazine in order to avoid the occurrence of what they call "acute dystonia" (retrocollis, torticollis and akathisia). But in spite of that, "dystonia" occurred in 66 of 184 patients, i. e. 36 per cent. According to their description the symptoms were mainly "acute dystonia" (in our sense) although akathisia also occurred. They started with 16 mg perphenazine per day, which in 7–10 days was increased to 64–128 mg per day. The very high frequency of acute symptoms and the admixture of dyskinetic symptom was presumably due to the rapid increase in dosage of a potent drug. It is, however, a common experience that there are fewer acute neurological symptoms when the dose is increased slowly (*Goldman,* 1961; *Ravn,* 1962).

Gratton (1960) states that drug-induced "Parkinsonism" is more frequent in females than in males, and in females more frequent before than after the menopause. Addition of oestrogen hormone to patients treated with trifluoperazin precipitated Parkinsonism within 24–48 hours and improved the anti-psychotic effect. *Hyvert* (1956) states that the anti-psychotic effect of neuroleptics in chronic psychoses is better in females than in males and that the result in men can be improved by addition of oestrogen hormone.

The statement that the clinical results are better in females than in males seems not evident according to the literature. While Parkinsonism according to *Gratton* should be more frequent before than after the menopause, the opposite is seen for tardive dyskinesia in our investigation (table 4). Considering the different rates of dyskinesia in men and women according to *Ayd*'s investigation it seems, however, evident that the sex hormone balance plays a role for the occurrence of these symptoms.

There is wide disagreement about what the occurrence of neurological symptoms means for the anti-psychotic effect, as mentioned in the introduction. It seems, however, evident that many psychotic patients get cured or symptomfree without displaying any neurological symptoms (*Cole & Clyde,* 1961). And it seems also evident that there are some cases of chronic schizophrenia where the results are better when pronounced neurological symptoms occur (*Delay & Deniker,* 1959; *Denham & Carrick,* 1961). But that does not prove that the neurological symptoms are necessary for the anti-psychotic

effect, it shows that with the to day known drugs it is in some cases necessary to increase the dose so high in order to get the best possible clinical results that neurological symptoms are inevitable.

The mechanism of the three drug-induced neurological syndromes

The three syndromes are so different with regard to onset, occurrence, clinical picture and course that one is compelled to assume that the syndromes have different mechanism and different cerebral localization.

Acute dystonia. The characteristic traits of acute dystonia are the special "dystonic" movements which are not seen in the other syndromes. Further, the abrupt onset after a few doses and that the syndrome does not occur later in the treatment even if the treatment is continued with the provoking drug. This mode of occurrence is in our opinion best explained by the effect of the drugs on the cellular and intracellular membranes.

Roizin et al. (1959) have demonstrated that chlorpromazine produces alterations in the size and structure of brain cell mitochondria. *Spirtes* & *Guth* (1961) have in direct investigations demonstrated that chlorpromazine in low concentration has a pronounced inhibiting effect on the permeability for water and water-soluble ions of mitochondria isolated from brain cells and liver cells of rats.

Gey & *Pletscher* (1961) have in rats shown that chlorpromazine and chlorprothixene, which do not themselves affect the brain content of amines, inhibit the increase in the brain of 5-hydroxy-tryptamine, dopamine and noradrenaline caused by MAO-inhibitors, and that the drugs inhibit the increase of brain 5-hydroxy-tryptamine after administration of 5-hydroxytryptophane, and that the two drugs counteract reserpine-induced decrease of 5-hydroxytryptamine, noradrenaline and dopamine in the brain. They conclude that this is best explained by the hypothesis, that the drugs diminish the permeability of the cellular membranes.

It has further been demonstrated that chlorpromazine does not inhibit the penetration of MAO-inhibitors into the brain, and that it does not inhibit the enzymes mono-amine-oxydase and decarboxylase in vivo (*Costa et al.*, 1960; *Ehringer et al.*, 1960). This points also to a reduced permeability of cellular and intra-cellular membranes.

Wase, Christensen & *Polley* (1956) demonstrated that labelled chlorpromazine in the brain was almost exclusively localized in the lipid fraction, which is an essential component of membranes.

There is thus much in favour of the hypothesis that phenothiazines inhibit the permeability of cellular and intra-cellular membranes. This theory could presumably explain that acute dystonia appears when the treatment is started with a large dose, which suddenly changes the internal ion-milieu and function of the brain cells, and that dystonia does not appear when the provoking drug

afterwards is given again in a smaller dose which is increased slowly so that the cells get opportunity to adapt themselves to the change of membrane permeability. The theory explains also why acute dystonia solely occurs in the first few days of treatment and not later when the cells are adapted.

We assume thus that acute dystonia is the result of a sudden change of cell function in the relevant neural structures.

The rigidity syndrome. Muscular rigidity may occur after a few days of treatment or at any time depending on the dose and the chemical structure of the drug, it may occur isolated or in combination with dyskinesia.

The mono-amine dopamine undoubtedly plays a certain role in the function of the basal ganglia. It has been evinced that dopamine is especially concentrated in nucleus caudatus and nucleus lentiformis. Since dopamine hardly is there for nothing it must be thought to have a special function. Animal experiments have shown that reserpine depletes dopamine and produces akinesia, and that administration of dopa, the pre-cursor of dopamine, does increase the brain content of dopamine and cause excitation of the animals (*Carlson, Lindquist* & *Magnusson,* 1957).

In regard of these investigations on animals *Carlson* (1959) has launched the theory that dopamine is involved in the control of motor function in the so-called extrapyramidal diseases in man.

Ehringer & *Hornykiewics* (1960) have demonstrated abnormally low dopamine content in the caudate nucleus of patients with "Parkinsonism". *Barbeau* & *Sourkes* (1961) and *Barbeau, Murphy* & *Sourkes* (1961) found that "Parkinson patients" had markedly low urinary excretion of dopamine while patients with "striatal" syndromes had high excretion of dopamine in the urine. *Birkmayer* & *Hornykiewicz* (1961) showed that intravenous administration of 50–100–150 mg l-dopa abolished akinesia in "Parkinson patients", and the MAO-inhibitor isocarboxazide increased and prolonged the effect of dopa injection.

In contrast to that *McGeer et al.* (1961) saw very little effect of perorally dl-dopa on drug-induced Parkinsonism, although they gave as much as 4–32 grams per day.

The diminished permeability of cellular membranes produced by chlorpromazine may explain this contrast.

In Parkinson patients, where the membrane permeability presumably is normal, administration of dopa can restore the diminished dopamine content of the caudate nucleus and thus normalize the cell function. In drug-induced Parkinsonism administration of dopa has no effect, in the first instance because dopa does not penetrate into the cells, second because the dopamine content of the basal ganglia is not diminished.

The seemingly contradictory fact that rigidity can be induced both by reserpine which depletes dopamine from the intracellular stores and by chlor-

promazine which does not deplete dopamine but inhibits its release might be explained in this way, that as well depletion as inhibition of release prohibits the special function of dopamine, and therefore both drugs induce rigidity. It is furthermore a clinical experience, that combination of chlorpromazine and reserpine is liable to induce severe rigidity.

We come thus to the hypothesis that the rigidity syndrome depends upon inhibition of a special function of dopamine, presumably mainly in the caudate nucleus, in Parkinson's disease because of diminished dopamine content, in drug-induced rigidity because of confinement of dopamine in the intracellular stores. This theory is in accordance with the dose dependency of the rigidity syndrome.

Tardive dyskinesia. It is characteristic that chlorpromazine-induced tardive dyskinesia rarely occurs during the first months of the treatment, and that the syndrome in many cases appears for the first time after several years of treatment without neurological symptoms. Tardive dyskinesia appears in some cases a few days after cessation of the treatment. Tardive dyskinesia stops in most cases in 1–2 months after cessation of the treatment, but may continue chronically. Piperazine substituted phenothiazines as thioproperazine may provoke dyskinetic movements immediately at the beginning of the treatment.

Tardive dyskinesia differ in these characteristic traits from rigidity, and the syndrome is not so direct dose dependent as is rigidity.

Animal experiments and neuro-surgical experience indicate that rigidity and hyperkinetic phenomena in so-called extrapyramidal diseases have different brain localization, they can at any rate be affected rather independently of each other by stereotactical operations on different regions of the brain (*Bucy,* 1961). From own animal experiments and a critical survey of the literature *Laursen* (1963) concludes that lesions confined to the corpus striatum (nucleus caudatus, putamen and globus pallidus) have no effect on motor activity in animals, including primates, but lesions in corpus striatum combined with lesions in the cortex or the internal capsule produce spasticity, akinesia and tremor. Stimulation of the head of the caudate nucleus in cats produces head turning and circling movements to the side opposite of the side of stimulation, the cats look as if they are searching for something. Other motor reactions to stimulation of the caudate nucleus were presumably due to spread of the current to neighbouring tissues. The theories about the mechanism of motor function is thus under revision, especially after *Laursen*'s important investigations.

While rigidity presumably can be attributed to a diminished special function of dopamine mainly in the caudate nucleus according to *Carlson*'s theory, the dyskinetic movements must depend on another pattern of neural structure which perhaps also involves the cortex. This suggests that dyskinesia can not be referred to augmented dopamine content in the caudate nucleus,

and the hyperactivity seen in animals with increased dopamine content of the basal ganglia is thus not equivalent to tardive dyskinesia. Furthermore, increase of dopamine in human by means of MAO-inhibitors produces stimulation of the central nervous system but not dyskinesia.

Another current theory about the drug-induced involuntary movements is that they are due to a disturbed balance between adrenergic and cholinergic central mechanisms (*Sirnes,* 1963; *Pakkenberg,* 1963). The foundation of this rather vague theory is that the anti-psychotic drugs have anti-adrenergic properties and their use should thus create cholinergic preponderance, and further, that all anti-Parkinson drugs of reasonable effectivity have anti-cholinergic properties. This theory is not satisfactory, mainly because the effect of anti-Parkinson drugs of drug-induced tardive dyskinesia is rather poor and inconstant.

The phenomenon that dyskinesia can appear a few days after cessation of treatment must somehow be due to the disappearance of the drugs from the central nervous system. It has been proposed that the mechanism of dyskinesia should be, that dyskinetic movements had been suppressed by rigidity and were released when the rigidity disappeared by cessation of the treatment. That may be the explanation in some cases. We have, however, seen dyskinesia start by cessation of treatment in cases where the patient did not display any apparent rigidity. Furthermore, anti-Parkinson drugs should, if this theory was correct, provoke or worsen dyskinesia by suppression of rigidity, but that is not the case.

Several authors state that phenothiazines inhibit cytochrome oxidase, oxidative phosphorylation and ATP-ase in isolated brain slices, but the concentration of the drugs was in most experiments much higher than clinical dosage. *Decsi* (1961) points out, however, that the distribution of chlorpromazine in the brain is uneven and he maintains that a dose of 5 mg/kg must reach a level in hypothalamus which causes a strong inhibition of the enzymes and he shows that there is a close parallelism between the inhibitory effect in-vitro of phenothiazines on the enzymes and the tranquilizing effect in vivo.

The oxygen consumption of the total brain determined by the method of *Kety* & *Schmidt* is about 3.2–3.7 cc O_2/100 g brain/minute in normal persons under the age of 50 years. In elder persons the cerebral oxygen consumption is in most cases lower, and *Lassen, Munck* & *Tottey* (1957) have demonstrated that there is a close relationship between the degree of arteriosclerotic demens and diminution of oxygen consumption. *Heyck* (1962) demonstrated that the cerebral oxygen consumption was normal in patients, mostly schizophrenics, under 50 years of age during long term treatment with perazine 300–1,000 mg per day, but in 6 patients being 53–69 years old treated in the same way with perazine the cerebral oxygen consumption was on average 1.7

cubic centimeter oxygen per 100 grams of brain per minute. Since the cerebral oxygen consumption is not reduced in younger persons by long term treatment with perazine according to *Heyck,* it is not likely that the reduction in elder persons is directly on the respiratory enzymes, the effect is more likely indirect by interference with the membrane permeability.

It may be assumed that the explanation of the severe reduction of cerebral oxygen consumption in *Heyck*'s investigations is, that perazine has a more pronounced effect on brain cells already damaged by alterations of age and cerebral vascular changes than on brain cells in younger persons. The reduction of cerebral oxygen consumption happens about the age of 50 which is also the age limit for the increase in frequency of drug-induced tardive dyskinesia.

This suggests that tardive dyskinesia is precipitated by localized cerebral hypoxia and that would explain why rather many cases of tardive dyskinesia only become manifest after several years of symptom-free treatment, i. e. when the patient aquire cellular and vascular changes of age. Further may be mentioned, that all phenothiazines inhibit tissue respiration in in-vitro experiments.

These considerations lead to the hypothesis that tardive dyskinesia has a special neural pattern the site of which is not apparent and that the syndrome is precipitated by localized cerebral hypoxia. The origin of this hypoxia seems in some cases, especially by the piperazine substituted phenothiazines, to be due to diminished permeability of cellular membranes, in other cases the hypoxia seems to be due to a combination of structural changes of age and diminished membrane permeability.

SUMMARY

The neurologic side-effects in pharmacotherapy of psychoses appear in distinct syndromes.

1. *The syndrome of acute dystonia* consists of spasmodic movements of the limbs, torticollis, retrocollis, opisthotonus, oculogyric crises, swelling and protrusion of the tongue and stridorous respiration. The syndrome starts abruptly after a few doses of psychopharmaca, and stops in a few hours after cessation of the treatment or can be stopped in a few minutes by injection of anti-Parkinson drugs. Afterwards the treatment can be continued with the provoking drug, when the treatment is resumed with a smaller dose, which then is increased slowly. The syndrome is more frequent in males than in females.

The cause of acute dystonia is presumably a drug-induced decrease of permeability of cellular membranes which disturbs cellular function in the relevant cerebral structures.

2. *The syndrome of rigidity* consists of muscular rigidity with alteration of posture. The syndrome is directly dependent on the dose and the potency of the drug. The cause of the syndrome is presumably a disturbance of a special function of dopamine mainly in the caudate nucleus.

3. *The syndrome of tardive dyskinesia* consists mainly of automatic, stereotyped, rhythmic movements in a single muscle pattern or more universally. The syndrome appears generally late in the treatment, often after several years of treatment, and it may appear a few days after cessation of treatment. It disappears in most cases in 1–2 months after cessation of treatment but it may continue chronically. The syndrome is more frequent in patients over the age of fifty than in younger patients and it is more frequent in patients which previously have had series of ECT than in patients without earlier ECT, and the syndrome is more frequent in females than in males. Tardive dyskinesia seems to be due to localized cerebral hypoxia in a special neural pattern which presumably involves the cortex.

While there is clinical evidence of the existence of the three drug-induced neurological syndromes the theories about the mechanism of their manifestation are of course simplified and imperfect, and even if they should be confirmed by further investigations there are presumably still unknown factors to take in consideration.

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