Chlorpromazine exerts stronger suppressive action on the instrumental responses motivated by social than by alimentary reward

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Abstract. Experiments were performed on six dogs over-trained before treatment, in differentiation of two instrumental responses, i.e. reinforced either by food or by sensory-social reward (petting by the experimenter). Chlorpromazine was injected intramuscularly (1.5 mg/kg) in two separate series. In the first series the drug was given four times during two weeks (twice a week). In the second series, it was injected every day for four consecutive days. Chlorpromazine produced a decrease of performance and an increase of response latencies and errors but this effect was much more evident with social than with alimentary reward. The effect of the drug was similar in both variants of the experiment, although it was more pronounced in the second than in the first series. Food intake was not changed. The motor and autonomic disturbances produced by the drug were not correlated with the decrease in instrumental performance. It is suggested that chlorpromazine acts rather on motivational or rewarding processes than on hunger drive or instrumental performance as such.

Key words: chlorpromazine, alimentary-social differentiation, instrumental performance, motivation, reward
INTRODUCTION

Chlorpromazine is a drug, which besides various effects (like antihistamine, antiadrenergic, and others) suppresses the dopaminergic system. As dopamine (DA) is considered as one of the more important mediators of the reward system (Wise 1982, Hoebel et al. 1983, Hoebel 1985), chlorpromazine may exert an inhibitory effect on motivation and hedonic processes. The works of Xenakis and Sclafani (1981) and Weatherford et al. (1988) on the effect of DA antagonists also suggest that dopamine is important in hedonic sensory processes during food consumption and evaluation of food palatability.

Experiments of Hernandez and Hoebel (1988), on stimulation of the hypothalamic (LH) feeding zone, strongly suggest the important role of dopamine in hedonic processes related to food. It was shown that feeding, as well as electrical stimulation of the LH "food center", produces an increase in DA turnover and an increase of extracellular DA content (Hernandez et al. 1987).

According to these authors, dopamine turnover increases in nucleus accumbens, but not in striatum. They suggested that feeding is rewarding because it produces the release of DA into nucleus accumbens (see also Heffner et al. 1977, 1980, Hoebel et al. 1983, Hunter et al. 1988).

It is however not clear which of the components of the alimentary act: drive, consumption, motor, autonomic functions, or the whole set of ingestive processes (oral, gastrointestinal, enzymatic and so on) depends on dopaminergic mechanisms. Usually as positive reinforcement, food reward has been used without any comparison with other rewards in the same conditions. As most of the investigations on the role of dopamine in hedonic processes concern the alimentary behaviour, in order to verify the role of dopamine in the general reward mechanisms in comparison with specific motivations, it seemed important to study the role of dopamine using different rewards. For such purpose we undertook the investigations on the effect of chlorpromazine (as a dopamine antagonist) on the sensory-social reward as compared with alimentary reward of instrumental performance. These two rewards were earlier proved to have equal reinforcing value for the instrumental performance in dogs (Fonberg et al. 1981). We attempted to answer the question whether chlorpromazine would affect to different extent alimentary or social motivation, or instrumental performance as such.

The present experiments on chlorpromazine are the continuation of our long-term studies on the effect of pharmacological treatments on various forms of motivated behaviour such as aggressive, defensive, alimentary, sexual and social behaviour. In the last few years emphasis was given to the effect of antidepressants, stimulants and neuroleptics on two positive motivations, i.e. alimentary and social (Fonberg 1979, 1980, 1985, 1989, Zagrodzka et al. 1981, 1987, Korczyński and Fonberg 1979, Fonberg et al. 1980, Kostarczyk et al. 1986, Kostarczyk and Fonberg 1988).

Recently a new type of differentiation was introduced i.e. differentiation of two instrumental responses to two conditioned stimuli (CSi), reinforced either by food or by social reward. Such procedure offers the opportunity to distinguish between the effect of different drugs on purely instrumental performance and a differential effect on two different motivations, both belonging to the positive hedonic system. On the other hand, the use of two different positive rewards, in the same experimental session and on the same subject, allows to distinguish the general hedonic mechanisms independently of the specificity of the particular rewards. It also allows to separate changes in motivational processes from motor disturbances, as these last should equally affect the instrumental performance reinforced by food or social reward independently of the kind of reinforcement.

METHODS

Experiments were performed on six male mongrel dogs housed in individual cages 2m x 3m. They were fed once a day with 1 kg of cereal mixed with meat.
Instrumental training

Dogs were trained in differentiation of two tones reinforced by two different rewards, i.e. either by food or by tactile-social contact. A tone of 500 Hz and a tone of 1,000 Hz were applied as conditioned signals (CSI) in random order and their duration was 10s in every trial. The tone of 1,000 Hz was used as CS for the instrumental response reinforced by food (CSA) and the tone of 500 Hz as CS for the instrumental response reinforced by social reward (CSS). Both tones were of the same intensity. In order to exclude leg preference, in different dogs either the right or the left fore paw was trained for the social reinforcement and respectively other fore-paw was used for alimentary reinforcement. In four dogs the right fore paw was associated with social reward and the left fore paw with alimentary reward, while in the remaining two dogs the right fore paw was reinforced by food and the left by social reinforcement. The instrumental response consisted of lifting the proper leg and putting it on the food tray during 10s of CS presentation, contingent upon such performance the reward was immediately administered. And thus the reinforcement was dependent on the performance. Alimentary reward consisted of mashed cooked meat mixed with bread powder, supplied in the automatically moving bowls on the food tray, in the amount of 50 grams in each bowl. The social reward consisted of petting the dog by the experimenter (stroking, i.e., "passing the hand overgently" on the head and back).

Experimental sessions were performed five times weekly. During one experimental session, CSI (CSA and CSS), followed by an appropriate response and an appropriate reward, were combined during the same experimental session, again in a random sequence. In three dogs, the alimentary responses were trained first and in the remaining three, socially reinforced responses were first established. The aim of such procedure was to counterbalance the effect of initial training ("law of primacy", Konorski and Szwajkowski 1952). Training in the alimentary-social differentiation, after the combining of the two responses, lasted several months. The dogs were overtrained.

Chlorpromazine administration

Chlorpromazine (Phenactil-Polfa) was injected intramuscularly at a dose of 1.5 mg/kg. Two separate treatment series were performed.

SERIES I

Chlorpromazine was administered four times over 2 weeks (twice a week). Experiments were performed 5 times a week. Four experimental sessions with chlorpromazine treatment were compared with 4 sessions before the treatment and 4 sessions after chlorpromazine treatment (Fig. 1, Series I). Performance during the days between injections was also taken into account (Fig. 4).

SERIES II

Chlorpromazine was injected on four consecutive days and the performance during the treatment was compared with four experimental sessions before and four sessions after chlorpromazine treatment (Fig. 1, Series II). The number of correct responses, their latency (Fig. 2), and number of errors, i.e. performance of the alimentary response to CSS (stimuli for social reward) and of the social response to CSA (alimentary stimuli) were recorded (Fig. 3). The general behaviour, i.e. mobility, emotional signs and autonomic changes was also observed and estimated qualitatively.
Statistical analysis

Statistical analysis was performed on raw number of correct responses for each dog, during 4 days before chlorpromazine treatment and four days during chlorpromazine administration. The Chi-Square Test for differences in probabilities, 2 x 2, was used (see Conover 1971).

RESULTS

Alimentary-social differentiation

It was possible to establish the proper performance of two instrumental responses to two CSi reinforced either by food or by sensory-social rewards presented at random order during the same experimental session. Individual differences were observed. Training lasted from 10 to 65 experimental sessions. At the end of training most dogs achieved differentiation perfectly. Few errors were made accidentally by some dogs.

The effect of chlorpromazine

GENERAL BEHAVIOUR

Chlorpromazine produced similar autonomic and motor symptoms during both series of experiments. In most dogs pupillary dilatation and lacrimation was observed and in some dogs squinting. Motor disturbances related to body balance and other motor functions were also noted, i.e. in some dogs reeling, unsteady gait, and difficulties in going up and down the stairs. Cataleptic postures were never observed. All these disturbances were not always present but fluctuated from session to session and from dog to dog.

GENERAL SYMPTOMS OBSERVED IN THE REFLEX CHAMBER

Most dogs showed a decrease of muscular tonus (hanging down on the harness) and seemed to be drowsy, occasionally yawning, panting and lolling. Nevertheless, all dogs reacted in a normal way to external stimuli and were fully capable of walking and performing the instrumental movements. Similarly to the behaviour outside the chamber, the motor and autonomic disturbances in the reflex chamber were observed not in all dogs and not in every experimental session. In general, the intensity of the autonomic and motor changes did not increase during successive sessions, but rather tended to decline in the course of treatment.

Instrumental performance

I SERIES

Changes in alimentary responses.

Instrumental performance slightly decreased in three dogs under chlorpromazine treatment, while in other three such a decrease was not observed. In general, the mean of the alimentary responses was 97.2% of the pretreatment level (Fig. 1, difference not significant). The mean response latency of instrumental alimentary responses did not vary (Fig. 2). Four dogs seemed to move slower, but two other dogs performed even faster. Two dogs sometimes overkept their forepaw on the food tray after CSi. Errors (responses to the alimentary CSi with the forepaw trained for social reward) did not increase (Fig. 3).

Changes in socially reinforced responses.

Social instrumental responses were evidently disturbed. The performance dropped to 68.5% of the pretreatment level (see Fig. 1), and this change was highly significant (T=23.43; P<0.001). The dogs also made more errors, i.e. they responded with the "alimentary" paw to the social CSi. In one dog instrumental performance was completely abolished on the third day of the treatment. Such a change was not the consequence of motor disturbances, as in this dog no changes in mobility and muscular tonus were observed during this session. The response latency of performance increased in all dogs (Fig. 2).

The observations of the dogs' general behaviour indicated that the contact with the experimenter was profoundly impaired. The paws were given unwillingly
Chlorpromazine suppresses the instrumental responses

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**Fig. 1.** The effect of chlorpromazine on the instrumental performance reinforced by food or by social reinforcements. Bars represent correct responses for whole group (mean from four experimental sessions): a. before treatment by chlorpromazine; b. during treatment (striped bars); c. after treatment.

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**Fig. 2.** The effect of chlorpromazine on the latencies of instrumental reactions. Bars represent mean latencies for whole group from four sessions: a. before treatment by chlorpromazine; b. during treatment (striped bars); c. after treatment.
Fig. 3. Bars represent the percent of errors in relation to correct instrumental responses. Mean for the whole group from four sessions: a. before chlorpromazine treatment; b. during treatment (striped bars); c. after treatment.

Fig. 4. The course of instrumental performance in Series I. Curves demonstrate number of correct responses (mean for the whole group) during consecutive experimental sessions before, during, and after treatment by chlorpromazine. Arrows indicate days of chlorpromazine injections.
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Fig. 5. The course of instrumental performance in Series II. Curves demonstrate number of correct responses (mean for the whole group) during consecutive experimental sessions, before, during, and after chlorpromazine treatment. Arrows indicate day of chlorpromazine injections.

and with hesitation and the usual friendly facial expression directed toward the experimenter was absent. Some dogs even turned their head away from the experimenter's hand. In the face of such negativistic social attitude, the lack or decrease of performance of social responses, elongated latencies and alimentary errors to social CSi appeared to be caused by a decrease in social motivation rather than by motor or gnosis disturbances.

II SERIES

Changes in the alimentary responses.

Changes in alimentary performance were more obvious and marked than during the first series. Instrumental responses after chlorpromazine treatment decreased to 77.1% of the pretreatment level (Fig. 1 \( T=27.00; P<0.001 \)). The decrease of performance was observed in all dogs, and one subject did not respond at all on the second day of the treatment. Errors did not increase significantly (Fig. 3). Therefore, the decreased number of correct responses was due to the lack of performance, and not to a shift in performance between right and left forepaw. The latencies of the instrumental responses were prolonged in all dogs (Fig. 2). In addition, the time of eating was occasionally prolonged in some dogs. Two dogs overkept their mouths in the empty bowls after eating. One dog licked the empty bowls and another one overkept his forepaw on the food-tray after discontinuation of CSA.

Changes in socially reinforced responses.

Social instrumental responses were greatly impaired in all dogs. The performance decreased to 50.9% of pretreatment level (Fig. 1). The dogs made more errors, i.e. responded with the "alimentary leg" to CSSi (Fig. 3). Two dogs did not respond at all (one during the second and another one during the fourth session of treatment). Differences between the number of correct responses before and during chlorpromazine administration were statistically highly significant (\( T=56.97; P<0.001 \)).
The latency of performance increased in all dogs (Fig. 2). It appeared that the contact with the experimenter was profoundly impaired. The dogs which usually turned their head toward the experimenter during CSi, now turned it away from him. A lack of friendly expression and of tail wagging was also noted.

It should be underlined that the autonomic, motor and other disturbances described above did not occur in all dogs regularly. In the same dog, they could vary between different experimental sessions as well as during the same session and not be manifested by the same subject during I and II series. All observed symptoms were not stable but fluctuating and some occurred only occasionally. In contrast, the disturbances in the instrumental responses were observed regularly and they were not parallel to the disturbances in general motor behaviour. For example in some dogs, in which instrumental performance was strongly depressed, the autonomic and motor changes were rarely observed, while in others, in which general motor and autonomic disturbances were marked, the instrumental performance, in particular that of alimentary responses was satisfactory. The autonomic and motor changes were rather more marked during the first two days of chlorpromazine treatment and tended to decrease or disappear. The main decrease of performance occurred on the second or third (Figs. 4 and 5) day of treatment, when the autonomic and motor disturbances tended to disappear. There were however individual differences in this respect. After treatment there was fast recovery of the performance and autonomic and motor disturbances never overlasted the treatment.

DISCUSSION

The present experiments put some new bricks to build the understanding of the motivated behaviour. First, it was demonstrated that it is possible to establish the differentiation of two instrumental conditioned responses motivated by two positive rewards, i.e. alimentary and sensory-social. In comparison with the alimentary-avoidance differentiation (Fonberg 1968), in the present experiment greater individual differences were observed. In some dogs the training proceeded faster than in alimentary-avoidance differentiation, but in some other more slowly. This did not depend on the primacy of the initial training (either social or alimentary). As shown by Fonberg et al. (1981), these two reinforcements are of comparable motivational values. Such conclusion was drawn from the evidence that the speed of acquisition of instrumental responses was similar in the group of dogs in which alimentary reward was applied, as in the group with social-sensory reinforcement. It should be underlined that in that research the conditioned stimuli for social or alimentary responses were the same as in the present study, and both tones used as CSi were of the same intensity.

During our considerable work on dogs we noticed that, as a rule, there are evident individual differences among subjects concerning various situations and different experimental procedures, as well as the value of reinforcement and susceptibility to the drug. For this reason, in order to compare the effects of pharmacological manipulations on social and alimentary motivations, it was important to observe both responses on the same subjects and during the same experimental session.

The present experiments demonstrated that alimentary-social differentiation offers a better comparison of the effect of chlorpromazine on these two motivations than could be obtained from observations of the social or alimentary performance of the separate groups of dogs. In this last case it would not be possible to discriminate the effect on motor mechanisms from that on specifically motivated performance.

Another value of this work was to use the dog as the experimental subject. An unusually strong social and emotional bond between dog and man makes the dog an ideal subject for the studies on hedonic and motivational effect of various drugs.

The main achievement of the present work was to demonstrate that chlorpromazine produced the suppression of both socially and food motivated performance. And, in spite of individual differences
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Chlorpromazine suppresses the instrumental responses (see Fig. 1). The effect of treatment was in general more evident during the II Series, when chlorpromazine was applied in a sequence during four consecutive days. It might point to the cumulative effect of chlorpromazine. However, the effect was evident from the first day of drug administration and the greatest drop of performance occurred on the third day of the continuous treatment, and tended to decline. Therefore it cannot be stated that the suppressive effect progressed steadily (see Figs. 4 and 5). These results are different from the work of Hoffemeister (1975) who found that the negative reinforcing effects of chlorpromazine were observed not earlier than after 3 days of drug use, and progressed with time. This author, however, used not only a different dose of chlorpromazine, but also different subjects (rhesus monkeys) than we did. In his work the negative sensations due to deep autonomic and motor changes might be gradually conditioned.

Beside the general decrease of performance, chlorpromazine produced the elongation of response latencies and an increase of errors. The procedure of alimentary-social differentiation may suggest that the decrease of correct responses and increase of errors depends on the disturbances in switching the responses of the right and left forepaw to two different CSi. Disturbances in switching produced by chlorpromazine were observed by Evenden (1986). But as underlined by Evenden, the reduction in switching concerned only high rates of responding and in our experiments different CSi were divided by minutes. And what is the most important, errors in the present experiment concerned the performance of alimentary responses to CSS (social) and not vice versa (Fig. 3). This fact, together with greater decrease of socially reinforced responses, also speaks for the conclusion that the errors resulted from the more pronounced suppression of social than alimentary motivation. Stimulus damping (Bradley 1963), if it would be the cause of changes in instrumental performance as well as in errors, would be similar for alimentary and social responses. On the other hand, from observations on humans it is known that chlorpromazine may enhance hunger or appetite which may counteract the suppressive effect on alimentary responses. We did not observe an evident increase in appetite and food intake. Some dogs in the reflex-chamber licked out the bowl or kept the "alimentary" paw on the foodtray longer than usually and performed, as pointed above, "alimentary" responses to social CSi. This may suggest an increase in appetite. As shown by Rusk and Cooper (1988), use of the agonist of D2 receptors produced a reduction of food consumption, and in particular a reduction in eating sweat, very palatable food and a decrease of operant behaviour reinforced by food. In view of these results, and the results of other authors confirming the same line, it may be expected that chlorpromazine (as D2 antagonist) would enhance food consumption and hedonic value of sensory gustatory processes. Our results did not confirm such assumptions. Also the data of several authors (Berger 1972, Giardini 1985) who observed taste aversion by chlorpromazine, are contradictory to Rusk and Cooper's results. In the present experiment chlorpromazine produced the decrease of motivated performance also with alimentary reinforcement. However, it must be stressed once more that the suppressive effect of chlorpromazine was much more evident in social responses. It concerned not only the number of social responses but also their latencies and errors (Figs. 2 and 3). All these results speak for the conclusion that either social motivation, or the hedonic value of social reward was impaired more than alimentary.

Further support for such conclusion was furnished by the observation that the general attitude toward the experimenter and toward the reward he offered was changed. The dogs turned their heads away from the experimenter instead of directing it toward him, and their facial expression changed to unfriendly. Our recent results (Fonberg and Korczyński in preparation) have shown that the need for social reward (petting by the experimenter) decreased under chlorpromazine, whereas the amount of food intake remained unchanged.
The action of chlorpromazine is very complex, it exerts its effect both on D1 and D2 receptors, and it is probable that one of them is more involved in the motivational and the other in the rewarding processes. It might also be some specificity of D1, D2 and other dopamine receptors in relation to different motivations. There are, however, no direct proofs to support such suggestions. Chlorpromazine is antagonistic not only to dopaminergic but also to adrenergic mechanisms, which are involved in hedonic processes. Inhibition of adrenergic mechanisms may have the suppressing effect on motivational and rewarding processes (see Stein 1964, 1969, Stein and Wise 1971). Anticholinergic and antihistaminic effect of chlorpromazine might be responsible for some autonomic changes observed in our experiment. The well known effect of chlorpromazine and other antidopaminergic drugs on motor system was also evident in our experiment. However, motor disturbances were not noted consistently and were not observed in all dogs, and if they appeared, they did not interfere with instrumental responses. Therefore, the decrease in instrumental performance cannot be attributed to motor disturbances. Moreover, the degree of decrease of instrumental performance was not related to motor or autonomic disturbances. It should be also emphasized that the dogs, in the same experimental session, may refuse to perform social instrumental responses, but perform quite well instrumental alimentary reactions. If motor disturbances would be the cause of decrease of conditioned instrumental performance as such, the decrease should be equal for social and alimentary responses. Differences concerning social and alimentary responses and lack of correlations between motor disturbances and instrumental performance strongly speak for the changes in motivational, and not motor mechanisms. The fact that chlorpromazine may serve as the negative reinforcement for active avoidance and produces an increase of bar-pressing (Hoffmeister 1975, see also Bignami 1978, Giardini 1985 a, b) testifies that motor disturbances are not responsible for the effect of chlorpromazine. Therefore, it may be inferred that the decrease of conditioned instrumental performance was due to the suppressing effect of chlorpromazine on motivational or rewarding processes.

Our present results support to some extent the dopamine hypothesis of reward (Wise 1982, Hoebel 1985). Chlorpromazine as dopamine antagonist consequently may produce suppression of reward mechanisms, which is exibited by a decrease of motivated instrumental performance. Although our present experiment seems to support the dopamine theory of hedonaesthesia, our previous experiments on amphetamine (which is a dopamine agonist), are not so clear (Fonberg 1985, Kostarczyk and Fonberg 1988). Although the need for petting and the positive attitude towards the experimenter was augmented by amphetamine, both alimentary and social instrumental responses were diminished. On the other hand, the avoidance responses were also diminished during amphetamine treatment (Fonberg, Kostarczyk and Kolakowska 1983), which may support the hedonaesthesia hypothesis.

It is noteworthy that the avoidance responses in neurotic dog were ameliorated during chlorpromazine treatment, which was related to the decrease of neurotic anxiety state (Fonberg 1989). The dopamine theory of reward has, however, another weak point. Already several years ago it was clearly demonstrated that neuroleptics block dopamine receptors (Van Rossum 1966). Chlorpromazine is acting on D1 as well as on D2 receptors. The blocking of D2 receptors is related to antipsychotic action of neuroleptics. The dopamine hypothesis of schizophrenia (Carlson 1987, Seeman 1987), based on the increased proliferation of D2 receptors, seems to be contradictory to the reward hypothesis of dopamine (Wise 1982). It is known that schizophrenics are sad, inert, apathetic, that external and internal stimuli loose their rewarding properties, life looses for them its sense, joy and value. If neuroleptics have the genuine antipsychotic action, it should be expected that they would have the capacity to restore the normal emotional state. If, however, the rewarding mechanisms are related to dopamine, and neuroleptics block dopamine receptors, the emotional symptoms of de-
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expression, and sadness should be rather exacerbated. Our present work demonstrated that chlorpromazine produces a decrease in motivational or rewarding mechanisms. In particular, in the case of social reinforcement it is obvious that reward (petting by the experimenter) lost its positive emotional, motivational and hedonic values. Other data (Berger 1972, Hoffmeister 1975, Bignami 1978, Giardini 1985) point out that chlorpromazine may serve as negative reinforcer for avoidance responses as well as produce taste aversion, i.e. results in suppression of hedonic processes.


If neuroleptics do not ameliorate the deep emotional and motivational processes, their beneficial effect is only symptomatic i.e. paliative and superficial.

It may be possible that chlorpromazine’s action on D2 receptors abates some schizophrenic symptoms, while the blocking of D1 receptors is selectively anti-hedonic. The increased density of D2 receptors observed in schizophrenia, led to supposition that a blockade of these receptors might be beneficial. On the other hand, it is possible that not the hyperfunction of D2 but disturbances in interaction between D1 and D2 (see Seeman et al. 1989) are the most important for pathological changes. It may also be possible that the proliferation of D2 receptors does not reflect the basic mechanism underlying schizophrenia, but that it reveals compensatory mechanisms, directed to extrapyramidal motor system, in order to compensate for the drive deficit.

The role of dopamine is very complex and involves emotional and motivational processes as well as motor, autonomic and endocrine functions. Its role in the integration between neocortical and subcortical structures may be also essential (see Carlson 1987).

The symptoms observed in schizophrenia as well as pathological symptoms ascribed to dopamine hyperfunction may be caused not by increased activity of dopamine neurones, but by disturbed dopamine interaction with other neurotransmitters. From the results of many studies it follows that not only dopamine, but also noradrenaline play an important role in motivated behaviour as well as in schizophrenia (Stein and Wise 1971, Van Kammen and Antelman 1984). In view of the multiple role of chlorpromazine (which beside antidopaminergic effect has also antiadrenergic, antihistaminic, anticholinergic and antiserotonergic properties), the suggestion that the most important aspect is the balance between various neurotransmitters is convincing.

In conclusion, the prevalent suppressive effect of chlorpromazine on socially reinforced responses observed in our experiment suggests that chlorpromazine exerts a prominent deteriorating effect on hedonic processes and social relations. This also suggests in consequence that the criteria for application of neuroleptics in schizophrenics who already have a low level of drive and who are ahedonic and unsocial, should be revised (see also Bignami 1991, Emerich and Sandberg 1991). In fact, in recent years the sociopsychiatric, psychodynamic, psychoterapeutic, and existentialistic schools have increasingly denied that neuroleptics have a genuine therapeutic action in schizophrenia (for review see Warner 1985). In this respect, although obviously with great precaution, the results of the experiments on animals (see also Bignami 1978, Wise 1982, Fonberg 1989) should be taken into account, and better integrated with clinical data.

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