NARCOBIOTIC ACTIVITY AND THE MODE OF ACTION OF CHLORPROMAZINE

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SINCE the therapeutic indications for the use of chlorpromazine are very varied, the clinician should know something about the experimental work on its mode of action. This article is an attempt to present a short account of some of these studies, which have been described in specialised French periodicals.

The history of the subject will not be dealt with here. It is enough to know that in 1935 the search began for a therapy against the " phenomena of Reilly "*, which have been the object of a considerable amount of research in France for the past 20 years, although they remain little known in Anglo-Saxon countries[24]. Study of their pathogenesis led to the discovery of antihistamine therapy, which, despite its interest, did not have any preventive effects on the " phenomena of Reilly ". It was only after 17 years that the first convincing results were obtained with chlorpromazine, and although they are far from being perfect, they represent an important therapeutic advance[19].

An account of the researches that led up to the discovery of chlorpromazine can be found in another article[14].

This article will deal with the researches on narcobiotic action which represents the essential mode of action of this drug. The characteristic feature of this action is an inhibition of the fundamental metabolic processes of living matter, essential to the normal activity of all cells.

Chlorpromazine has the most powerful narcobiotic action of all drugs examined up to the present time.

General principles of narcobiotic action

Since it is generally agreed that living cells are more resistant to aggression if their activity is diminished, I have, with various collaborators, undertaken a search for a pharmacological action capable of inhibiting cellular activity, throughout the entire range of living matter, from the lowest unicellular organisms to the most highly developed species of the animal kingdom[1 14].

These researches have involved considerable experimental work[1-9]. The organisms upon which they have been carried out can be classified as follows:—

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*See glossary.

Organisms whose living nature is doubtful.
  Ultra-microscopic virus.
  Bacteriophages.
Unicellular organisms (" protistes "*) and fungi (these latter being classed by Langeron amongst the " protistes ").
  Anaerobic and aerobic bacteria.
  Infusoria.
  Microscopic fungi.
Multicellular vegetable organisms.
  Seeds.
  Roots of plants.
Animal organisms intermediate between the unicellular and the vertebrates.
  Echinoderms.
  Procordes.
Vertebrates.
  Fishes.
  Mammals.

We have been able to demonstrate a pharmacological action which depresses all types of cellular activity. Only ultra-microscopic viruses and bacteriophages are practically unaffected and this fact lends support to the opinion that these are not living matter.

The studies have been carried out with both old and new drugs. The most active have been the chlorohydrate of chloro-3(dimethyl amino-3 propyl) 10 phenothiazine, and the chlorhydrate of chloro-3 (diethyl amino-3 propyl) 10 phenothiazine. The first of these is now known as chlorpromazine. We have also demonstrated this kind of activity in other chemical series, but none show the potency of the aminated derivatives of phenothiazine.

This special action is independent of any other physiological properties of these compounds. Thus, the most active are classified pharmacologically sometimes amongst the anti-adrenaline, sometimes the anti-histamine, and sometimes the anti-parkinson drugs.

The term " narcobiotique " has been chosen to designate this action ($\eta\alpha\rho\chi\omega\varsigma$ = numbness $\beta\iota\omega\varsigma$ = life) because it corresponds to an action which benumbs certain metabolic processes which are universal and indispensable for the activity of all living organisms.

Tests to measure narcobiotic activity

As narcobiotic action affects all living cells one can therefore study it and measure it on any type of organism. In practice the interpretation of results on higher animals can be difficult because of their complexity both in structure and regulatory mechanisms (these will be discussed later). For this reason narcobiotic activity is measured for preference on very simple organisms which do not possess a nervous system.

Narcobiotic activity can only be established if its universality can be demonstrated. As it is not practicable to study the action of

*See glossary.

a series of drugs on all types of living things, a few crucial tests have been devised which cover a wide range of vital cellular processes, and thus establish the universality of the action. At the same time they allow the elimination of certain types of narcotic activity with which the process might be confused. These tests are as follows:—

Reduction in the rapidity of absorption of grains of carmine by an infusoria, *Tetrahymena piriformis* (showing an action exerted on the functional activity of cytoplasm).

Reduction of the rate of development of the embryo of the sea urchin (showing an activity exerted on nuclear division).

Reduction of activity of an anaerobic microbe: *e.g.* Vibrion septique (showing an action independent of oxidative processes).

Study of mitostatic action on a plant (root of *Pisum sativum* or *Allium cepa*). This last test allows an easy preliminary and rapid trial of any substance requiring investigation.

Although we have studied the same action on many other biological materials, the tests already described are in practice sufficient. One important point, however, should be noted: no one test by itself can establish the existence of a narcobiotic action.

Narcobiotic action should also be distinguished from narcotic actions which correspond to a simple action on the physical structure of the cell. In this connection the study of "pharmodynamic activity" (which is calculated as the ratio between the molecular concentration in saturated solution and the active concentration) reveals a unique characteristic of narcobiosis.

In the classification of narcotics by Overton and Ferguson, a coefficient of "pharmacodynamic activity"* of less than 0.01 indicates a specific and chemical mechanism, whilst a higher coefficient indicates a physical and non-specific mechanism. In every instance, all the "indifferent" or non-specific narcotics have a coefficient clearly higher than 0.01. However, the coefficient of activity of chlorpromazine lies between 0.0002 and 0.00002, which is remarkably low. Nevertheless its narcobiotic action is essentially non-specific. This fact gives a particular character to narcobiotic action which deserves careful notice.

In practice only those substances which have a coefficient of pharmacodynamic activity which is clearly less than 0.01 should be included amongst the narcobiotics.

Particular characteristics of narcobiotic action with regard to the other phenomena of narcosis.

The precise meaning of the term narcosis has never been established. That is why very different opinions exist as to how far one should include the many different phenomena which have been brought

*See glossary.

together under this general term. Thus in the course of the important " International symposium on the mechanism of narcosis "[10] some speakers envisaged principally an action on the nervous system of the higher animals, whilst others visualised an action on cellular function without any special connection with the nervous system. Even if narcotic action were confined to the nervous system local analgesic action would be included by some, whilst others would limit it to an exclusively central and hypnotic action. One of the organisers of the symposium, P. Gavaudan, took as a standard method of experimental study of narcosis the mitoclasic* action of colchicine (the absence of fusorial retraction in the course of mitosis being attributed to a phenomenon of narcotic type). Sulphonamides and antibiotics have also been described as narcotics, because they diminish or inhibit cellular activity, in a reversible manner. These last types of narcosis are regarded as being " specific ", in contrast with " non-specific " narcosis such as is brought about by ether or chloroform, or by substances acting by a mechanism corresponding to the lipoid theory of Meyer and Overton.

Whatever may be the mechanism, the tests already indicated allow a distinction to be made easily between narcobiotic action and the other phenomena of narcosis. For example:—

Colchicine arrests the development of the roots of plants, but does so by a process of " mitoclasis ", and not " mitostasis " as observed with narcobiotic action. Other tests show that it exhibits no true narcobiotic action.

The barbiturates only show activity in the test of absorption of grains of carmine by infusoria in concentrations in the neighbourhood of 1/100 whilst chlorpromazine is active in concentrations of 1/300,000. The action on electro-encephalographic tracings, and their therapeutic properties show effectively that these substances do not act in the same way as chlorpromazine.

Deprivation of oxygen can only produce a state of narcosis in aerobic organisms, but narcobiotic action affects anaerobes in addition. Thus the mechanisms of their action are very different.

The "indifferent narcotics" (like alcohol) have a coefficient of thermodynamic activity greater than 0.01.

Relative variability of narcobiotic action with cellular activity

Narcobiotic action is not only universal, activity is revealed in the same strength on all living cells. For example, the inhibitory action of chlorpromazine becomes irreversible at concentrations in the neighbourhood of 2 or 3×10^{-4}, equally on a plant; on an infusoria; on a fungus, or on a microbe[1], on the cells of the higher animals.

Only a few microbes belonging to the Coliform bacilli are notably less sensitive to this action, which only becomes irreversible at a concentration in the neighbourhood of 2 to 5×10^{-3}. This appears connected with certain enzymatic features—themselves exceptional—of these germs.

*See glossary.

As one might expect, the action is more marked when cellular activity is high. Thus it is most marked on the cells of the sea urchin's embryo, which are in a state of very active division, and on the other hand it is almost negligible on spores which are in a state of " latent life ", to use the expression of Claude Bernard. The inactivity is just as marked on spores of fungi as on microbic spores, though the non-sporulated forms of both are sensitive to narcobiotic action. These last facts confirm that it is the vital activity of cells which is most affected.

Physiological characteristics of narcobiotic action on higher animals.

Whilst studying narcobiotic action on fishes placed in an external environment containing the drug (as one does when experimenting on lower organisms), we have noticed that activity appears at concentrations of the same order as those which induce the onset of action on infusoria and the sea-urchin's egg. If, however, the drug is administered by the parenteral route, the active doses are comparable to those which are active on the mammals. The connection between the active concentration for unicellular organisms on the one hand, and the dose active on higher animals (mammals) on the other, has thus been established through fishes[5]. However, in the higher animals, certain parts of the brain are much more sensitive to narcobiotic action than the rest of the organism. Generally speaking the cells of the nervous system are more sensitive to narcotic action than other cells. However, the histological structure of certain parts of the brain gives a particular characteristic to narcobiotic action. It is necessary to insist on this because otherwise it is difficult to understand how a universal cellular activity can exert a special action on specific parts of the brain.

This reinforcement of activity appears in a few regions which I have called the "système complexe"* and above all in the "reticular formations "*[11 8]. It is essentially the consequence of the special arrangement in " networks " or " in series " of certain neuronal systems. This arrangement multiplies the individual effect of narcobiotic action on each neurone throughout the entire system, since, due to their depression, ability both to receive and transmit impulses is impaired. Thus on passage through a multisynaptic system, an impulse will become progressively attenuated and finally its intensity will fall below the threshold value and fail to elicit a response.

In other words if a system is made up of a network of cells functionally disposed in series (as in the sense of electric cells connected in series), the inhibitory action, although acting individually on each cell, must of necessity multiply in the course of the passage of the nervous impulse from one to the other. This is what one observes in fact in the reticular formations (whence their name).

I have arrived at these conclusions for reasons which can briefly be summarised here.

*See glossary.

Narcobiotic action in the higher animal is characterised by a depression of those functions which are to a considerable degree dependent on the activity of the reticular formations of the brain. These include the general tone of encephalic activity, central control of thermoregulation, and the vomiting centre.

A feature of drugs that possess a more or less strong narcobiotic action is that the intensity of their action on functions mediated through the reticular formations bears little or no relation to the degree of their other physiological actions (antihistamine, antiadrenaline, or antiacetylcholine), but is proportional to their narcobiotic activity measured on lower organisms devoid of any nervous system.

> Consider for example promethazine (Phenergan) and chlorpromazine (Largactil). Although the first may be antihistamine and the second antiadrenaline both have an analgous action on the brain. At the same time their action on lower organisms is similar. Thus promethazine is two or three times less active than chlorpromazine both on the brain and on lower organisms. The constant parallelism between the action of these drugs which one finds present throughout the whole range of biological material tested (confirming the difference in activity between the two compounds) cannot be attributed to mere chance.
>
> Inversely, 883 F. and 933 F. (belonging to the benzodioxane series), although they possess an anti-adrenaline action just as powerful as that of chlorpromazine, are much less active on the higher centres. The narcobiotic action measured on lower organisms is correspondingly less. Clinical study shows that their therapeutic efficacity remains very feeble. The particular clinical value of chlorpromazine cannot therefore be explained by its anti-adrenaline activity.

The researches of Castaigne[12] [13], confirmed by other authors, have shown that chlorpromazine and promethazine share the property of markedly depressing the reaction of the pituitary to non-specific aggresions transmitted by nervous means. Our experiments have enabled us to note that the intensity of this action on pituitary activity is proportional to narcobiotic activity estimated on organisms without a nervous system.

The experimental study of a series of compounds has shown us that the addition of a quaternary ammonium radicle to a drug showing narcobiotic action decreases very markedly and equally both the action on the brain, and on organisms without a nervous system.

Experimental facts are so numerous, and in such close agreement, that one is justified in drawing the following conclusions:—

The inhibitory action of narcobiotics on cellular activity in the brain, corresponds to their inhibitory activity on cellular activity in general. This explains the similarity between the results obtained on lower forms of life (even on microbes) and on the brain of higher animals.

Narcobiotic action is most marked on nervous tissues of " reticular type ", whether or not belonging to the classic " reticular formations ".

The predominant action is directly bound to the histological structure of these systems, whose cells are functionally arranged in " series " and the more marked the reticular structure the more marked the action.

Formerly I had based the foregoing conclusions partly on theoretical deductions which depended on the universal character of narcobiotic action. Several experimental facts have subsequently progressively confirmed this conception.

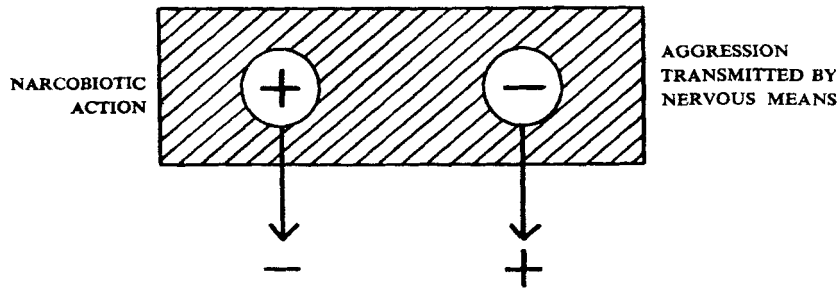
Hiebel Bonvallet and Dell have confirmed by direct experiment on the brain that the central depressant effects of chlorpromazine are due to its action on the reticular regions belonging to the " ascending activator system " of Magoun and Moruzzi.

A recent clinical observation is particularly interesting. During narcobiotic therapy in psychiatry progressively increasing doses have been used (up to 600 - 800 mg. per day) and these have resulted in the frequent appearance of all the symptoms of Parkinson's disease. It is enough to reduce the dose slightly in order to make these manifestations disappear, and they re-appear if the dose is increased to its former level. Now the extra-pyramidal system is made up of relatively fewer relays than are found in the pyramidal system. Thus, in the smallest dose which is effective on the reticular formations, chlorpromazine has no action on the extra-pyramidal tracts, but at higher dosage these tracts (composed of multi-neuronal systems in " series " and in " networks " particularly in the substantia nigra) are affected whilst the pauci-synaptic pyramidal system is not depressed. The result is a state of Parkinsonism which does not correspond to any particular pathological lesion, but is due simply to the reversible and physiological action of chlorpromazine. This confirms in a remarkable way the general conception already elaborated to the extent that one feels that it should have been anticipated on theoretical grounds[28].

The recent careful experiments of Malmejac shows that the conditional salivary reflex is more sensitive to narcobiotic action than the inborn salivary reflex, whilst this in its turn is more sensitive than the psycho-motor reflex, and finally that the simple encephalic vaso-motor reflexes are still less sensitive. Thus it is seen that the degree to which these different types of reflex are sensitive to narcobiotic action depends on the number of neuronal connections which are involved, and the greater the number of synaptic connections, the greater the susceptibility of the reflex[28].

It is necessary to insist on an important complementary point. In the " reticular formations " are found excitor systems or " facilitators " which increase the tone of other parts of the nervous system, as well as " inhibitory " systems whose excitation involves the

inhibition of other regions. If an inhibitory system is depressed, inhibition will be less effective, and the ultimate effect will appear as a relative excitation of the regions under its control. Thus when narcobiotic action inhibits " inhibitory systems " it brings about a relative excitation in the corresponding part of the nervous system. Nevertheless, the general tone of the nervous system remains constantly more or less depressed because the action of the " facilitator " systems predominates normally over the action of " inhibitory " systems, in the reticular formations.



+ = Facilitatory centre.
− = Inhibitory centre.

Scheme of the mechanism of narcobiotic action on nervous formation composed of antagonistic systems.

1. Inhibition produced by narcobiotic action provokes
   (*a*) a relative depression of facilitatory centres
   (*b*) a relative excitatory effect on inhibitory centres.
2. In depressing the activity of these two groups of systems which are antagonistic, chlorpromazine acts simultaneously in two opposite directions, in such a way that the global equilibrium of encephalic tone is little changed.
3. On the other hand the activity of the antagonistic systems being strongly depressed, the reactivity of nervous centres to aggression transmitted by nervous means is considerably reduced.

It should also be recalled that narcobiotic action does not affect metabolic processes involving the consumption of oxygen. This explains why chlorpromazine does not in any significant manner decrease basal metabolism in the higher animal nor the consumption of oxygen " in vitro " of tissues (like kidney and liver) whose cells are individually independent of each other.

Therapeutic consequences

Narcobiotic action has been specially sought with the object of finding a therapy of the non-specific reactions which follow aggression particularly those affecting directly or indirectly visceral nerve fibres (phenomena of Reilly).

From a therapeutic point of view the consequences of the facts which have been discussed are as follows:—

Narcobiotic action allows the powerful depression of the reactivity of the " reticular formations " which in the brain control the tone of the entire nervous system. As a result the reactions which follow aggression are considerably diminished.

Furthermore, in stronger concentrations, the reaction of the pituitary, and by its intermediary, the reaction of the other endocrine glands, can be markedly diminished.

Altogether, narcobiotic action can considerably decrease the intensity, and thus the harmfulness of a great part of the non-specific neuro-endocrine reactions to aggression.

Nevertheless this result is obtained whilst the general equilibrium of the nervous system remains relatively little depressed. For example, in man, the function of " awakefulness " is only slightly depressed, the subject remaining " present " when questioned. This general fact is explained because the depression is operative at the same time on both the facilitator and inhibitor systems, which are antagonistic, and thus the total nervous equilibrium remains relatively slightly depressed.

The mode of action of chlorpromazine

Some clinicians have attempted to explain the action of this drug in terms of theories which have not been confirmed experimentally. Thus the powerful "ganglion blocking action" of chlorpromazine has been spoken of as being capable of bringing about " nervous disconnection ". But no experiment to prove such disconnection has been described, and we have actually demonstrated that chlorpromazine has no ganglion-blocking action[15 16] and this has been confirmed by others[25 26 27].

It has also been suggested that chlorpromazine by virtue of its hypothermic properties could transform a homeotherm into a poikilotherm, and that the hypothermia represents the actual therapeutic action. However, experimentation has shown that the homeotherm, under the influence of this drug, does not in the least resemble a poikilotherm[17] and that subjects are better protected against aggressions when they are warmed than when they are cooled[18 19 13 20].

The activity of chlorpromazine has also been ascribed to a reduction of basal metabolism. Experimentally it has been shown that the therapeutic action is present not only when basal metabolism is normal, but even when the consumption of oxygen is increased under the influence of cooling.

Of greater interest was the hypothesis put forward by Terzian, who, basing it on the analogy between the sleep produced by chlorpromazine and natural sleep, supposed that there was a special action on the reticular formations whose activity controlled the function of " wakefulness "[22]. More recently G. Hiebel, M.

Bonvallet and P. Dell have succeeded in demonstrating the truth of the hypothesis formulated by Terzian, by means of electro-encephalographic tracings obtained in animals submitted to transection of the brain sometimes in front, and sometimes behind the reticular formations of the midbrain[23]. These authors have also shown that adrenaline can also stimulate wakefulness by a direct action on the reticular formations. They attribute the depressive action of chlorpromazine on the centre of wakefulness to its anti-adrenaline action.

These experiments are extremely interesting, because they demonstrate the action of the drug on a function which is in part under the dependence of the reticular substance. Nevertheless they are not sufficient to explain the therapeutic efficiency of chlorpromazine, especially in the preventive treatment of non-specific reactions of the organism to aggression.

The action on the function of " wakefulness " does not provide the complete explanation, since the therapeutic action is obtainable in a subject who is awake. (This is particularly striking in the guinea pig which does not sleep even under very large doses of chlorpromazine). Also, if it were so, chlorpromazine would be less active than the most powerful hypnotics known, which have not shown the slightest therapeutic effect against the pathological lesions produced by aggression.

On the other hand, whilst not denying the possibility of chlorpromazine acting on the reticular formations by virtue of its anti-adrenaline property, this itself cannot explain the particular therapeutic efficiency of the drug, as the following points will indicate:

The concentration of adrenaline in the blood stream is always very low, and, in the opinion of some, is not present at all. Even when it is increased following an aggression, it remains low and fleeting, and the concentration falls far short of the figures capable of causing significant pathological lesions.

The drugs of the benzodioxane series which possess an anti-adrenaline action as powerful as chlorpromazine should be as active as chlorpromazine in therapy, but their therapeutic activity is practically nil.

Conversely certain drugs—like promethazine—possess therapeutic properties which are common with chlorpromazine, though they possess no notable anti-adrenaline action. However, they do show a powerful narcobiotic action. This action is less than that of chlorpromazine according to the tests of measurement, and similarly their therapeutic action is less.

All this leads to the conclusion that chlorpromazine owes its remarkable therapeutic properties to its powerful narcobiotic action, since it is the only pharmacological action, apart from its anti-adrenaline action, which might be active in therapeutic dosage.

In this connection distinction must be made between the therapeutic effects which follow when the drug is administered in high dosage.

Whilst lower dosage acts exclusively through the medium of the reticular formations (which control centres of wakefulness, heat-regulation, and contain centres of vomiting, diuresis, vaso-motor tone, etc.) higher doses can act on other parts of the " complex nervous system " which control notably the reactivity of the hypophysis to aggressions transmitted by nervous means, whilst still higher concentrations act directly on effector cells which do not belong to the complex system.

These facts explain:

Why chlorpromazine acts above all by means of its depressive action on the activity of the reticular formations.

Why it can be shown to be very active therapeutically in considerably decreasing the reactivity of the nervous system (and thus in part the activity of the endocrine system).

Why this powerful action on nervous activity is not accompanied by an equally great modification of the general equilibrium of the nervous system, and in particular the " comportment " of the subject, and is not accompanied by any notably profound hypnotic action.

Glossary

" *Phenomena of Reilly* ".
This expression designates all of the non-specific phenomena which can be produced by widely differing types of aggression (bacterial toxins, simple and complex chemical compounds, physical agents, etc.), and which were described and studied in some detail by J. Reilly and his colleagues (1934)[1].
The same phenomena were described later by H. Selye under the title " Reaction of Alarm " in his " General Syndrome of Adaptation "[1]. But the pathogenic conception of the French School (based on a nervous disturbance giving rise secondarily to an endocrine reaction) is very different from the conception of Selye. Moreover, according to Ph. Decourt, the general syndrome of adaptation does not exist[2 3].
The studies on the pathogenesis of the Phenomena of Reilly, and the attempts to prevent them, which began in 1935, led to the discovery of antihistamine therapy, and later to narcobiotic therapy.

" *Pharmacodynamic Activity* ".
Property of a substance which has an action on a living cell (such a drug usually possesses several different pharmacodynamic actions, but most often only one or two of these are sufficiently strong to be able to act in the dosage used clinically.

" *Protistes* ".
A group of organisms which includes the unicellular plants and animals.

" *Mitoclasic* ".
Action on mitoses which is characteristic of colchicine. It shows itself above all by the fact that the fragments of the chromosomes are no longer drawn along the spindles towards the two opposite poles of the cell in the process of division. The consequences of this are the existence of several nests in the same cell.

" *Mitostasic* ".
Action which shows itself uniquely by a slowing up of mitoses (or a reversible suspension in higher concentrations) without any other anomaly in the evolution of the mitosis.

" *Reticular formations* ".
Parts of the C.N.S. are made up of a network of numerous neurones with short intercommunicating associative fibres. It is now known that they play an important part in the general tone of nervous activity which is still incompletely elucidated and which is at present still the object of numerous researches.

" *Système complexe* ".

A generally isolated system, and defined by the author as including nervous cells, neuro-secretory and endocrine, which has essentially metabolic functions (meaning in a general sense anabolic and catabolic activity), and does not transmit any specific message (motor or sensory) in the nervous system.

The reticular formations are part of the "Système complexe". This is contrasted by the author with the " Système Hierachise ", which, on the contrary, has the important function of transmitting specific messages from one point of the nervous system to another.

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