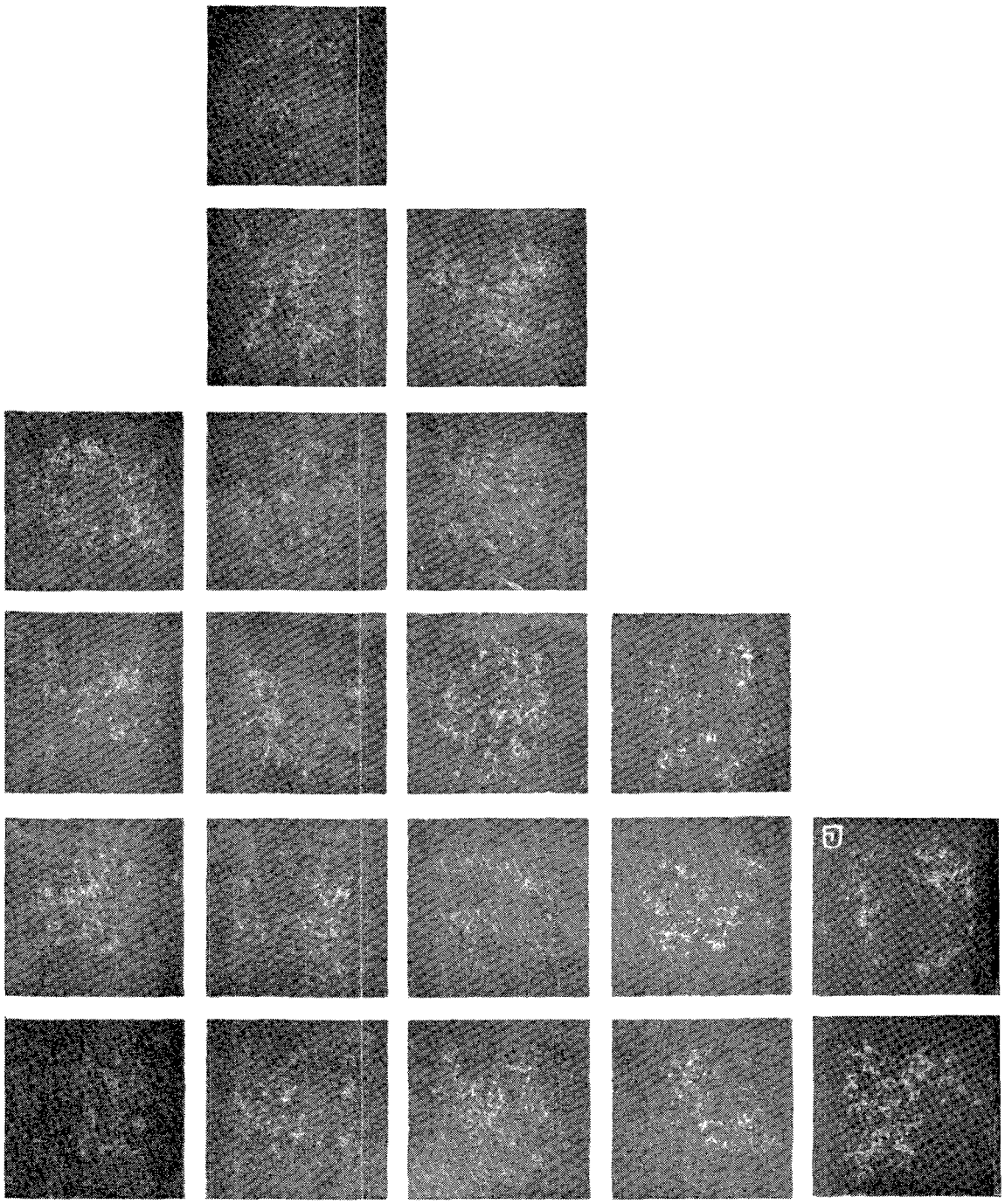
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SOME CURRENT VIEWS ON BRAIN MONOAMINES*

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* The following abbreviations are used: 5HT (5-Hydroxytryptamine) ; 5HTP (5-Hydroxytryptophan); NE (Norepinephrine); Dopamine (3-4 Dihydroxyphenylethylamine); DOPA (3-4 Dihydroxylphenylalanine); MAO (Monoamine oxidase); MMT (α-methyl-m-tyrosine); α-MMTyramines (total of decarboxylation products of MMT).

While it is true that we are far from understanding the functions of catecholamines and 5 HT in brain, the problem is taking on a clearer perspective. At first the efforts of biochemists, physiologists, pharmacologists and psychiatrists to bridge biochemistry with normal and abnormal brain function yielded much disorganized information but served to pinpoint many of the obstacles to interdisciplinary approach. These have arisen largely from misunderstandings about the meaning of words and concepts among the various disciplines. It is not surprising that semantic difficulties should give rise to unsuitable experiments which lead to faulty conclusions all too quickly incorporated into textbooks.

The interdisciplinary approach to the problem of monoamines has raised many other difficulties, only a few of which will be mentioned:

1) Analytical: Despite the availability of simple physiochemical techniques for defining the specificity of analytical methods, monoamines are all too often measured under conditions in which an experimental drug interferes with the assay.

2) Interpretation of *in vitro* results: Inferences are often drawn from biochemical data measured *in vitro* results: Inferences are often drawn from biochemical data measured *in vitro* which does not take into consideration the structural organization of the living cell. If cell compartmentalization is ignored, the conclusion might be reached that MAO is unimportant in the metabolism of NE *in vivo*, based on data describing the low affinity of the amine for the enzyme in tissue homogenates.

3) Failure to apply physicochemical criteria to data obtained from *in vivo* experiments: Rates calculated from steady-state values instead of values shortly after zero time can result in the conclusion that the hypothalamus has a relative high permeability to NE ; the lipoid character of cellular and intracellular membranes is often disregarded ; physiological storage is frequently not distinguished from physicochemical binding ; saturation of a process may not be recognized as two opposing processes becoming equal ; it is usually inferred that an inhibitor blocks the endogenous formation of an amine on the basis of *in vitro* blockade of an enzyme that forms it ; conclusions are ofttimes based on data obtained *iu vitro* in the presence of considerable concentrations of irreversibly-acting inhibitors like reserpine or MAO inhibitors when the results might be due to a direct action of inhibitor molecules with a cellular component rather than the effects of nonreversible inhibition.

The biochemist, for example, uses words like "irreversible", "energy", and "adapt", assuming that they have the same connotation in other disciplines. We suspect that the psychiatrist is puzzled how a biochemist can con-

ceive of a drug acting irreversibly for one week and how a microbiologist can describe the "behavior" of a microorganism, while the biochemist is baffled by the problem of how much work "psychic energy" can accomplish. The use of words lacking a common meaning or not exactly defined can lead to improperly designed experiments and improperly interpreted data. Yet, despite all the above mentioned difficulties there has been gratifying progress in our knowledge about the function of brain monoamines.

A number of reviews have discussed the possibility that 5 HT and NE have a neurohormonal function in brain (1—6). They have one, perhaps essential, property of neurohormones*(2) in being readily available for physiological need, and at the same time protected from enzymatic inactivation and uncontrolled overspill receptor sites (7). This characteristic of a neurohormone permits a neuron to function as an electrochemical transducer in this sense intracellular storage depots receive a nerve impulse and respond to it by liberating graded amounts of biologically active amines which in turn rIgulate neuronal activity.

Moreover, the uneven distribution of 5 HT (8—9) and NE (10) in various brain regions suggests that these amines might be involved in the regulation of subcortical function. Detailed studies have shown that catecholamines and 5HT are found together in most parts of the brain(9). However, important exceptions are the limbic system with its high amount of 5 HT(11) and little NE(12), and the corpus striatum (13) which contains almost all the dopamine present in brain.

Studies of the formation of monoamines in the developing brain also indicate their importance in subcortical function. For example, newborn rats and rabbits are helpless and are deficient in the biochemical mechanisms providing for the synthesis and storage of brain amines. As a result they have almost no brain NE and a level of brain 5 HT which is only a fraction that of the adult. The amine levels progressively rise for about 3 weeks when they approach those of the adult; at this time the animals show well-developed patterns of behavior. In contrast, the neonatal guinea pig has well-developed patterns of behavior and brain amine levels equal to those of the adult(14).

In this paper I deal mainly with processes that make up the amine storage unit, namely, synthesis, storage mechanisms, release and metabolism, and with drugs that directly or indirectly affect amine reactive sites by blocking these processes.

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* By neurohormone is meant either a transmitter substance, released from nerve endings and activating the postsynaptic membrane, or a substance enhancing or inhibiting (modulating) the action of a transmitter.

NATURE OF MONOAMINES STORAGE PROCESSES

A discussion of the effects of drugs on amine storage should be prefaced by some remarks on the nature of the process. The concept that 5 HT and NE are stored was introduced to explain the stability of the amines in tissues; in fact storage can be regarded as the final step in the formation of amines, making them available for physiological release.

In recent years arguments have arisen concerning the question of bound (stored)and free monoamines, and their measurement, whether or not they have been freed by a drug. Unless defined these terms are about as meaningful as those of freedom and bondage at the economic and political level. To describe amines as "bound" or "free" without defining these indefinite words can only result in misunderstanding and confusion between disciplines. To the pharmacologist, the term binding applied to an amine has the connotation of not being freely available to synaptic sites and to inactivating enzymes. For the biochemist, bound amine has another connotation—the actual combination of amine with a cell constituent. The latter definition has led to the formulation that the amine in the supernatant of brain homogenate represents unstored amine in the intact brain. Inferences on whether a drug releases brain NE or 5 HT are often based on the amounts of amines in the supernatant. However, conclusions based on this definition of binding may have no physiological meaning.

For example, the biochemist will tell the pharmacologist that MAO inhibitors not only block MAO, but also prevent reserpine from releasing brain monoamines. But the pharmacologist, has just given reserpine to a rabbit, pretreated with a MAO inhibitor, and reports "the animal is about as tranquil as a cat on a hot tin roof". Naturally he concludes that the excitation results from free amines made available to reactive sites and stabilized by blockade of MAO. Similarly the pharmacologist tells the biochemist that reserpine causes a slow release of 5 HT from platelets. But the chemist has just homogenized platelets and found no evidence of 5 HT being bound in the first place. The physical chemist will question the conclusions of both: he agrees with the pharmacologist that reserpine releases 5 HT from platelets, but not that the release is slow. On the basis of kinetic studies he concludes that reserpine releases 5 HT rapidly (from the confines of the 5 HT pump), and that the slow diffusion of 5 HT into plasma merely reflects what every physical chemist knows, that a highly polar substance slowly passes through a lipoid boundary.

These divergent views can be reconciled only by defining the terms "bound" and "free". Since the words must describe a physiological function, the definitions should have a physiological meaning, related in some way to availability

of amines to reactive sites and inactivating enzymes. If they are not free to get metabolized or to reach receptors they are stored. Storage is a better term than binding since it implies potential availability and avoids the chemical meaning of binding.

The nature of amine storage has been greatly clarified by recent studies on the uptake of 5 HT into platelets(15). After it was shown by investigations in our laboratory (16) that reserpine releases 5 HT from a platelet suspension *in vitro* in a molar ratio of drug to indole of several hundred to one, it became difficult to visualize that reserpine had blocked anything except a carrier mechanism. Indisputable proof that reserpine prevents 5 HT uptake by blocking an active transport system was provided by kinetic data, and was supplemented by experiments showing that ouabain and certain metabolic inhibitors poison the process(17).

The storage of amines is obviously a more complex process in nervous tissue where sites of formation, storage and inactivation are all together, not to mention the further complication of the presence of amine-containing granules (18).

Since reserpine blocks active transport in platelets(15), it is not unreasonable to suspect that it blocks a similar process in the nervous system. The view that platelets "store" 5 HT in a form that becomes free after rupture of cells is accepted with equanimity, though many workers are loathe to concede that brain tissue might also store some 5 HT in a form that becomes free after homogenization of brain cells. Since there is no evidence that reserpine acts directly on granules(18, 19) let us look into the possibility that storage in the CNS is basically similar to that in platelets and that granules are merely an ancillary part of the overall process.

Fortunately we are helped by the concepts of biochemists like H. Waelsch (20) who have demonstrated that cellular metabolites are stored in metabolic compartments or pools which are only evident in the intact cell. Thus labeled amino acids are taken up by active transport into a metabolic pool, and mix more slowly with a reserve pool which is in equilibrium with the metabolic pool. Similarly an amine in brain cells might be present in two pools as suggested by Hillarp for the adrenal medulla(21).

The granules might hold large amounts of an amine, complexed with intragranular components, and would correspond to the reserve pool of the amino acids. This pool might be in a state of equilibrium with a second, more mobile pool from which the amine might be released by nerve impulses according to physiological need. On energetic grounds it might be presumed that this amine pool

is separated from MAO by an intracellular membrane which would also keep the amine relatively unavailable to reactive sites. The mobile pool might be maintained by a specialized transport process like that for 5 HT in platelets. Favoring this view are kinetic studies by Dengler *et al.*(22) showing that brain and heart slices take up labeled NE against a concentration gradient, and that the uptake of NE is blocked by reserpine and poisoned by ouabain and various metabolic inhibitors. Particularly significant is their finding that labeled amine does not readily mix with a large part of the total NE in tissue.

Fig. 1 schematically describes the storage unit which involves the synthesis, storage and metabolism of NE in brain cells. The scheme is not meant to have any physical counterpart in the brain, but is intended to use physicochemical principles to integrate metabolic processes with structure as well as

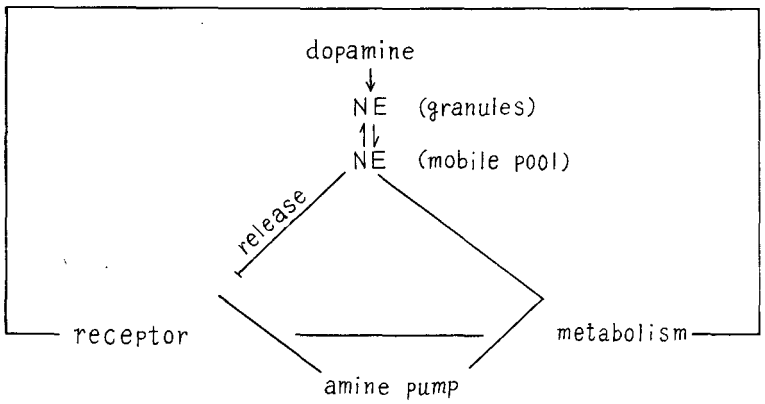


Fig. 1. Schematic diagram showing a proposed arrangement of the storage process. It consists of a lipoid membrane with an amine pump to control passage of monoamines from the storage pool to receptor and metabolic sites. The physiological release of the amines from the mobile pool is regulated by nerve impulses which in some unknown way change membrane permeability. The amines in granules are a reserve pool, in equilibrium with the mobile pool.

to explain: 1) Functional integration of active transport with amine-containing granules. 2) Separation of amines from reactive sites and from MAO. 3) Self-regulation of the content of brain amines. 4) Rise in brain amine levels after a MAO inhibitor. 5) Release of amines and prevention of their uptake by reserpine.

NE equilibrates between mobile and granule pools which are surrounded by a lipoid membrane. Contiguous to the membrane are the reactive sites and the MAO(which presumably surrounds the membrane). An increased demand for

monoamines is met by drawing on the mobile store; replacement is made by synthesis, or from granules should the demand temporarily outstep formation. The amine can penetrate by two processes: active transport which can also be regarded as a pump to maintain the high level of NE formed inside; the second process is passive diffusion. The diffusion coefficient across the lipoid membrane is quite low since the amine is highly polar. However, the amine leaves the cell at a rate proportional to the concentration gradient, consequently at high levels diffusion will be rapid enough to counteract the active uptake, and the content of NE will reach an equilibrium level.

In this scheme, MAO has a key role of controlling the amount of amines in the storage pool in the face of continuous synthesis. This role can be explained on kinetic grounds. Normally the enzyme inactivates NE and keeps the amine outside the membrane at a low level. As a result, MAO facilitates diffusion and the level reaches a steady-state well before saturation of the transport system. After blockade of MAO, the NE level outside the membrane increases, as a result the concentration gradient will also decrease and diffusion slows down. The level of amines in the pools will then rise until the rate of diffusion and synthesis are once more equal. Of considerable interest are recent electron microscopic studies which show that in the nerve cell mitochondria(which contain MAO) are located around a compartment which appears to contain the granules(23).

The question arises why blockade of MAO at peripheral nerve endings does not usually increase the levels of amines. The answer is probably related to the permeability of peripheral nerve endings as compared to the blood-brain barrier. After blockade of MAO, diffusion into the blood stream is presumably rapid enough to prevent a rise in the amine content.

DRUGS ACTING ON MONOAMINES REACTIVE SITES IN BRAIN

Table 1 shows the various ways in which drugs can effect NE reactive sites, peripherally or centrally. I was tempted to include a similar table for 5 HT but there would be too many gaps and guesses. But I think it is fair to say that such a table will be available for 5 HT in the not too distant future.

DRUGS THAT MIMIC AND BLOCK THE ACTION OF NOREPINEPHRINE

A number of compounds called sympathomimetic agents, for example, neosynephrine, appear to act by mimicking the action of NE at peripheral nerve endings. These substances are generally structurally related to NE.

Sympathomimetic agents which cross the blood-brain barrier can act like

NE both peripherally and centrally. When they act centrally they produce behavioral and pharmacological responses similar to those of dopamine (from administered DOPA). These amphetamine-like effects have been attributed to stimulation of central adrenergic mechanisms. But it does not seem logical to attribute the action of these compounds to a mimicking of dopamine in the corpus striatum. As described later, NE released from sites of action and stabilized by MAO blockade elicits similar but much more potent effects. Since dopamine from DOPA forms throughout the whole brain it presumably mimics the action of NE at reactive sites throughout the brain.

Table 1. Action of Drugs on NE Reactive Sites

Type of Action	Peripheral	Central
Mimics action at reactive sites	Neosynephrine	Desoxyephedrine
Blocks action at reactive sites	Dibenamine	Chloropromazine
Blocks synthesis	—	—
	decarboxylase inhibitor	decarboxylase inhibitor
	dopamine hydroxylase inhibitor	dopamine hydroxylase inhibitor
Blocks metabolism	MAO inhibitor	MAO inhibitor
Blocks physiological release	Bretylium	—
Blocks storage (non-competitive)	Reserpine Guanethidine α-methyl-m-tyrosine	Reserpine α-methyl-m-tyroseine
Blocks storage (competitive)	Cocaine Imipramine	— —

DRUGS AFFECTING SYNTHESIS OF BRAIN MONOAMINES

5 HT, NE and dopamine are formed directly in brain, as would be expected from the relative impermeability of the blood-brain barrier to these amines(24). For all practical purposes only two catecholamines are present in mammalian brain: Dopamine and NE. Almost all the dopamine is in the corpus striatum (13) while NE is located largely in the brain stem(10).

The main steps in the biosynthesis of catecholamines are as follows:

Tyrosine ⟶ Dopa ⟶ Dopamine ⟶ NE

Enzymes for the last two reactions have now been found in brain(24).

5 HT is formed from tryptophan as follows:

Tryptophan ⟶ 5-Hydroxytryptophan ⟶ 5-Hydroxytryptamine

The presence of the enzyme that converts tryptophan to 5 HTP has not yet been demonstrated in brain.

A substance that inhibits the formation of NE or 5 HT might turn out to be an interesting physiological tool as well as of possible therapeutic value. Inhibition of NE could be accomplished by means of substances that prevent the hydroxylation of tyrosine, the decarboxylation of DOPA, or the hydroxylation of dopamine; that of 5 HT by agents which inhibit hydroxylation of tryptophan and decarboxylation 5 HTP.

Attempts have been made to block amine synthesis by means of decarboxylase inhibitors. This approach is complicated by the fact that DOPA and 5 HTP are decarboxylated by the same enzyme(12, 25). Consequently, a substance that blocks the formation of 5 HT will also prevent that of NE. A more serious difficulty results from the large excess of the decarboxylase enzyme in brain, so that to block the formation of monoamines, the enzyme must be inhibited completely.

In this regard we are learning to distrust the conclusion that an enzyme inhibitor blocks the endogenous formation of an amine *in vivo* on the basis of enzyme activity measured in brain homogenates. Thus, the formation of NE takes place in a number of steps each one of which supplies the substrate for the next step. If one of these steps is rapid, the enzyme activity might be in excess of that needed to form all the substrate needed by a slow step. Even though most of the enzyme is blocked by the inhibitor, sufficient amounts of substrate might be available for a subsequent slow step.

To determine whether an inhibitor blocks the endogenous synthesis of an amine, it is necessary to measure its effect in the living organism. Many compounds inhibit DOPA decarboxylase but this enzyme is present in brain in such large excess that it must be almost completely blocked to affect the formation of endogenous NE. For example, the brain level of NE is strikingly lowered by the potent decarboxylase inhibitors α-methyldopa(26, 27, 28) and α-methyl-m-tyrosine(27, 28, 29). At first this effect was thought to be consequent to decarboxylase inhibition, but as described later it is now believed that it results from impariment of catecholamine storage.

To block NE formation it might be more practical to look for compounds that inhibit the enzymes that hydroxylate tryptophan and dopamine. Such inhibitors might be highly specific since the two hydrolyses are different(30, 31, 32). In addition the blockade of synthesis will be proportional to the degree of inhibition because hydroxylation is a slow step in the formation of the amines. The conversion of tyrosine to DOPA is also a slow step and a compound that inhibits this conversion might also be of considerable interest.

At the present moment it is not known what would happen if a drug should

completely block the formation of either NE or 5 HT. The decline in amine levels will not necessariiy be rapid since this will depend on the rate of utilization of the stored amines which in turn depends on nervous activity.

DRUGS AFFECTING METABOLISM OF MONOAMINES

Few will disagree that MAO has an important role in the inactivation of 5 HT (33), but its role in the metabolism of catecholamines is controversial. Recent biochemical and electron microscopic(23) studies indicate that MAO has a special topographical arrangement with the amine storage processes. The relative importance of MAO and catechol-O-methyltransferase(COMT)(34) often has been based on relative affinities for NE in tissue homogenates. However, neither enzyme seems particularly important in terminating the action of NE released at peripheral sympathetic nerve endings.

Unlike acetylcholine released at skeletal muscle, NE need not be rapidly inactivated. Indeed the action of NE is relatively long lasting, it might even be undesirable for NE to be rapidly metabolized after release on its reactive sites.

O-methylation is the principal pathway in the metabolism of circulating catecholamines(35) ; the enormous activity of the liver seems well suited for this role(36). But this does not mean that COMT has an important physiological role since other enzymes can also inactivate circulating catecholamines. In fact, it is unlikely that COMT is essential since circulating catecholamines are still rapidly metacolized when COMT is completely blocked(37).

MAO has the vital role of regulating the amount amine of in the storage pool. Such a function for MAO, suggested by this laboratory a number of years ago, would explain why blockade of MAO results in a rise in amine levels of brain and sympathetic ganglia and retards the disappearance of these amines after their release by reserpine. In contrast, the blockade of COMT does not cause a rise in brain amines nor protect the amines from enzymatic inactivation after their release by reserpine(38).

MAO Inhibitors

After MAO blockade, the stores of brain amine increases 2 to 3 times(33). At the steady-state, the amine levels in mobile and granule pools should rise proportionately-the levels reach a new plateau when the rate of passive diffusion from the mobile pool exactly counteracts the transport mechanism. The newly-formed amines will then over-run on reactive sites. However, the physiological responses are difficult to interpret since physiological adjustment by release of stored amines is still possible despite blockade of MAO.

An MAO inhibitor could cause central excitation, directly or indirectly,

from its action on MAO(5). A number of studies show that in general the drugs act indirectly by a damage of the enzyme that persists long after the drug disappears from the body. On the basis of present evidence there is nothing to be gained in opposing the view that the stimulation is caused by free monoamines in brain. However, due to a misconception that excitation is elicited by endogenous 5 HT released at its reactive sites in brain (see later), the problem has been raised whether the stimulatory actions of MAO inhibitors are caused by free 5 HT or by free NE.

In the rabbit brain, the rather slow formation of NE relative to 5 HT after blockade of MAO has enabled us to show a close association between central excitation and the elevation in NE level* for a considerable number of MAO inhibitors, both hydrazines and non-hydrazines(39). It is particularly pertinent that blockade of MAO in dogs and cats elevates brain 5 HT but not NE. Possible reasons why NE does not rise shall not be discussed here, but the important point is that MAO inhibitors do not cause excitation in these animals(5).

Additional and perhaps more direct evidence that after MAO blockade, free NE is responsible for excitation is obtained by first depleting amine stores in rabbits by means of reserpine and then 3 hours later blocking MAO with the potent inhibitor MO 911**. There is a significant rise in the levels of free dopamine and 5 HT which peak within one hour, without the animals recovering from the effects of reserpine. The NE rises much more slowly; in about 3 hours it shows a small but definite rise and the effects of reserpine are completely counteracted (unpublished observations). These results also suggest that free NE is considerably more active than free dopamine in antagonizing reserpine effects.

Irrespective of their structure, clinically used MAO inhibitors generally lower blood pressure and in man the effect on blood pressure parallels the degree of MAO blockade(41). Several workers suggest that the blood pressure change results from inhibition of synaptic transmission due to blockade of MAO at peripheral sympathetic ganglia(42, 43). However, Costa *et al.* have shown that complete inhibition of MAO does not decrease synaptic transmission in sympathetic ganglia (44). It is possible that the central pharmacological effects of MAO

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* The rabbit (white New Zealand) is a particularly good animal to measure the effects of MAO blockade since there is a good separation in the times that 5HT and NE brain levels reach a plateau. These animals do not show much change in normal activity but a surprising hyperactivity is elicited by environmental stimuli, such as shaking the cage violently or prodding with a stick.

** MO 911 N-methyl-N-benzyl-2-propynylamine given by courtesy of Abbott Laboratories(40).

blockade result from free 5 HT. Since blockade of MAO in cats causes a rise in brain 5 HT but not in NE(5), it is of particular interest that MAO blockade elicits orthostatic hypotension in this species(45).

A number of characteristics of MAO inhibitors must be considered in evaluating their effects in animals and man.

1) In early animal studies it was not recognized that reletively weak inhibitors, like iproniazid and niamid, appeared to block brain MAO almost completely by *in vitro* assay, but *in vivo* there was still sufficient activity to prevent a rise in brain NE. As a result, an investigator might assume that a single dose of iproniazid blocks MAO completely without altering behavioral patterns. On giving another dose of the inhibitor, he might then find that behavorial changes now occur. The conclusion that in addition to blockade of MAO some other mechanism is implicated would be wrong. Such difficulties in applying *in vitro* data to *in vivo* effects have made it necessary to devise methods of determining whether the enzyme is completely blocked *in vivo*. The realization by biochemists that in order to equate behavioral changes to enzyme inhi bition it might be necessary to check the degree of functional blockade *in vivo* has been one of the unpleasant facts of life shown by studies with brain amines.

2) Some MAO inhibitors exert pharmacological effects due to the action of drug molecules *per se*(5). For example, catron(JB 516) exerts a short-lasting amphetamine-like effect which terminates before blockade of MAO reaches a maximum. Parnate(SKF 385)(46) and α-ethyltryptamine(Monase)(47) can exert long-lasting amphetamine-like actions. In fact much of the action of the latter drug may be due to this direct action. Generally, MAO inhibitors are of the "hit and run" nature; the drugs literally destroy the MAO and the resulting effects last long after the original drug has disappeared from the body(48). In animal studies it is usually preferable to use a rapidly-metabolized inhibitor and thus avoid any direct effects of the drug molecules. In addition hydrazines should be avoided since they might react irreversibly with other enzymes such as diamine oxidase. In our laboratory, we have used MO 911; this compound is a potent MAO inhibitor which exerts no stimulatory action *per se* and is not a hydrazine(44).

3) There is a considerable species difference in the reaction to MAO inhibitors. After complete blockade of the enzyme, excitation will be determined by the rate at which the NE level rises in brain(5). In mice, rabbits and cats, brain 5 HT rises rapidly. In mice, the NE level rises more rapidly than in other laboratory animals, though it is less rapid than that of 5 HT (this laboratory unpublished observations). On the other hand, NE in New Zealand white rabbits

rises quite slowly, and in cats it does not rise at all. Investigators using only one species might draw quite different conclusions concerning the potency and the latency in onset of action of MAO inhibitors. Researchers working with mice might conclude on the basis of a single brain level of amines that MAO blockade causes rapid excitation and a rapid rise in levels of both amines, and that the excitation is due to both amines; the rabbit specialist might be more positive in stating that NE is the important amine; the cat expert might conclude that MAO inhibitors do not do much of anything. Thus with MAO inhibitors it is especially difficult to generalize on the basis of results with a single animal species.

4) Because of the rapid action of certain MAO inhibitors (Catron and MO 911) the capacity of the brain to synthesize 5 HT may be approximated from the rise in level after administration of these inhibitors. The rise in 5 HT is much more rapid than that of NE, but failure to apply physicochemical principles can lead to incorrect conclusions. Relative rates of formation should be determined not from the plateau level, but from the rise shortly after giving the inhibitor, before processes of disappearance become appreciable. For example, if levels of 5 HT and NE in the mouse rise to the same level in one hour, it cannot be concluded that they are formed at equal rates. Comparison of the amounts formed in a few minutes might show that the 5 HT is formed much more rapidly than NE.

Another common mistake is to conclude that monoamines block their own synthesis because after blockade of MAO a plateau in monoamine level is attained in a few hours. While this could possibly be true, a simpler explanation could be given based on the view that equilibrium between two opposing rates occurs when they become equal. Disappearance of the amine by diffusion or by the action of another enzyme, ordinarily slow, will gradually increase as the concentration of free amine increases until the disappearance rate becomes equal to that of formation.

Another example of failure to distinguish an equilibrium level from a rate has even led to the conclusion that reserpine inhibits the synthesis of 5 HT. This view was based on data showing that in reserpinized animals the rise of brain amines one hour after treatment with a MAO inhibitor is less than in normal animals. This conclusion does not take into account that the rate may be the same, but the equilibrium level lower because of impairment of storage.

If reserpine is given shortly after blockade of MAO, NE and 5 HT liberated by reserpine are no longer inactivated nor can they readily disappear into the

blood stream because of the low permeability of the blood-brain barrier to the amines. Accordingly, the amines become freely available to reactive sites. Evidence described later indicates that the free NE is responsible for the physiological antagonism of the reserpine sedation. Among other interpretations of the failure of reserpine to produce either sedation or a decline in brain amines is that MAO inhibitors not only block MAO, but prevent the action of reserpine in releasing brain amines. Such an interpretation is possible only by ignoring the excitatory effects of this drug combination (49), by ignoring blood-brain barrier and by disregarding the failure of MAO inhibitors to prevent release of 5 HT from platelets and NE from peripheral nerve endings. Failure to give a non-physiological meaning to the term storage, and to apply physico-chemical considerations has resulted in literally dozens of papers arguing this point. When tritiated NE is administered after a MAO inhibitor the amount of amine retained by storage processes in treated animals is much greater than that of controls(50). One can ignore the importance of blocking MAO in these studies only by giving the inhibitors the property of enhancing the amine pump.

Clinical aspects of MAO inhibitors

The "irreversible" mode of action of MAO inhibitors poses the problem of dosage regulation since the effects of these inherently dangerous drugs are related not to plasma levels, but to the extent of MAO blockade. It is difficult to decide if a poor clinical response is caused by underdosage, or if side effects arise from overdosage. Since there are now available simple clinical tests such as the increase in urinary tryptamine or tyramine (51), it is now advisable to determine the degree of MAO activity during the adminstration of MAO inhibitors. This precaution might be particularly valuable in avoiding toxic effects in susceptible individuals and in assessing the therapeutic value of MAO blockade in depressed patients. Like reserpine the slow onset of action with MAO inhibitors is not due to the slow action of the drug, but to the way it is administered. An adequate effect might be attained in a single dose, but this would bring all the dangers of overshooting the mark and produce undesired hyperexcitation of long duration.

DRUGS AFFECTING MONOAMINES STORAGE PROCESSES

Non-competitive inhibitors

Reserpine impairs the active transport systems which maintain NE and 5 HT in their mobile pools. As a result, the amines diffuse through the storage membrane and are metabolized by MAO surrounding the storage process. Since

the two pools are in a state of equilibrium, the intragranular amines will also reach MAO, via the mobile pool. Although 5 HT is the better substrate for MAO, the content of both brain amines declines at the same rate. This result suggests that diffusion across the storage membranes rather than metabolism is a slow step in the disappearance. Despite the liberation of considerable amounts of NE after reserpine administration the increase in adrenergic activity is not marked since most of the amine is released onto MAO ; in contrast, when nerve impulses are acting on storage membrane, it is probable that the amine is released mainly onto reactive sites.

The action of reserpine is non-reversible since it does not depend on drug concentration in brain. Reserpine appears to destroy the storage process, and the amines accumulate again only after the process is restored. The effects persist long after the drug has disappeared from the body (52), since the pharmacological action is not caused by the drug molecules *per se*, but by the extent to which storage is blocked.

The observation that traces of labeled reserpine (.008γ/g) are present in brain 48 hours after drug administration has been interpreted as valid evidence that reserpine acts *per se* rather than indirectly (53). Since the radioactivity in these experiments was no higher in 8 hours when the animal showed the greatest sedation, than in 48 hours when the animal had recovered, one must assume that the labeled material was, at least in part, bound to non-specific brain constituents. But accepting the premise that some of the counts were due to a complex of reserpine with the storage receptor, the action would still be a non-reversible one, since the drug is so tightly complexed that neither the receptor nor the drug retain their original identity. Indeed it is difficult to imagine an " irreversible " reaction of drug with body structures which does not result in some persistent residue of a drug-receptor interaction.

The problem often arises whether reserpine acts on two different mechanisms since it acts immediately on platelets in preventing the uptake of 5 HT but only slowly effects its release. However, it is unnecessary to create two mechanisms. After blocking the active transport system, platelets immediately cease to take up 5 HT but a slow passage of the amine from platelets is an inescapable consequence of its low lipoid solubility.

The hypotensive drug, guanethidine, releases NE from peripheral sympathetic neurons but has relatively little effect on 5 HT (54). The drug presumably because it does not enter the brain, it does not affect brain NE. The mechanism by which guanethidine releases NE appears to differ from that of reserpine. For example, it takes a considerably longer time for the guanethidine

to deplete heart NE. The possibility has been considered that it acts on the mechanism whereby the nerve impulse triggers the release of catecholamine and depletes the amine by eliciting a sustained activation of the normal process of physiological release. In accord with this view, guanethidine no longer depletes heart NE(55) in rats pretreated with bretylium, a compound which suppresses the release of NE caused by nerve stimulation(56). However, bretylium does not prevent the depletion of NE by reserpine suggesting that reserpine and guanethidine block the storage by different mechanisms.

As described later, certain analogues of NE, for example α-methyl-m-tyramine also block storage of NE by a nonreversible reaction, but their precise mechanism has not been elucidated.

Clinical aspects

Many physicians believe that reserpine has a slow onset of action because it often takes several weeks before the drug shows a clinical effect. As a matter of fact, the drug acts quite rapidly. The difficulty in controlling reserpine therapy stems from the peculiar way the drug acts. The action of most drugs is readily reversible and the intensity of the effects is dependent on tissue levels. Such drugs rapidly bring about the desired clinical effect which can be easily adjusted by a change in dosage. However, the action of reserpine, despite its rapid disappearance from the body, is not readily reversible and it has been described as a "hit and run" drug because the biological effects persist long after treatment has stopped. For this reason large "priming" doses of reserpine are rarely administered for fear of overshooting the mark and producing prolonged signs of overdosage. To avoid this danger, reseripine is administered in small daily doses; although the drug is present only transiently each day, its effects accumulate and reach a plateau after days or even weeks. Even when given in this way, reserpine is not easy to handle since the biological response may peak at too high an intensity.

Because of these considerations, we have collaborated with Dr. A. Plummer of Ciba to develop reversibly acting derivatives of reserpic acid. As a result of these studies, ethers of methyl reserpate such as the simple methyl ether, have been developed which exert short-lasting and non-accumulative reserpine-like action(57). Dr. A. Pletscher and his group(58) have shown that a number of synthetic benzoquinolizine derivatives also exert short-lasting effects(59).

Competitive inhibitors of storage processes

A number of other drugs including cocaine (60), imipramine (61), and desmethylimipramine(62), antagonize *in vivo* and *in vitro* the uptake of administered NE by tissues and thereby prolong its action. Desmethylimipramine is particularly potent, inhibiting the uptake of NE in brain slices by about 50% at 10^{-9}M. Since imipramine and cocaine do not release appreciable amounts of NE, the inference has been made that release and uptake of the amines are brought about by entirely different processes. However, kinetic considerations show that imipramine and cocaine could compete for NE with the storage process. In fact, Titus (62) in our laboratory, has shown that desmethylimipramine inhibits the uptake of NE, the degree of blockade depending on the ratio of the respective plasma levels. Calculation of the data of Muscholl indicates similar results from cocaine(60). Actually, if a drug like cocaine blocks the uptake from plasma of NE (5γ/liter) it would release only negligible amounts of the amine if inside the storage pool NE was 100 times more concentrated. Tyramine and amphetamine also inhibit the uptake of NE (61). In large doses these substances release some of the amine. Since these analogues of NE readily penetrate lipid membranes, it is possible that their liberating action is in part due to a direct action on the granules(63).

(To be continued.)

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Assay of substance P on goldfish intestine in a microbath (Gaddum J.H. & Szerb J.C.) **17**(3) 451-463, 1961

Effect of chlorpromazine on septal hyperactivity in the cat (Raitt J.R., Nelson

J.W. & Tye A.) **17**(3) 473-478, 1961

Effects of injection of mepesulphate into the cerebral ventricles of cats (Joseph A.D.) **17**(3) 533-538, 1961

Effects of organophosphorus compounds, oximes and atropine injected into the third ventricle of unanaesthetized dogs (Edery H.) **18**(1) 19-28, 1962

Increase of pentobarbitone metabolism induced in rats pretreated with some centrally acting compounds (Kato R. & Chiesara E.) **18**(1) 29-38, 1962

An investigation of the action of tyramine and its interrelationship with the effects of other sympathomimetic amines (Nasmyth P.A.) **18**(1) 65-75, 1962

A ganglion stimulating action of neostigmine (Mason D.F.J.) **18**(1) 76-86, 1962

Effect of drugs on the noradrenaline content of brain and peripheral tissues and its significance (Sanan S. & Vogt M.) **18**(1) 109-127, 1962

Actions of bretylium and guanethidine on the uptake and release of ^{3}H-noradrenaline (Hertting G., Axelrod J. & Patrick R.W.) **18**(1) 161-166, 1962

Effect of reserpine on the acetylcholine content of the heart, the ileum and the hypothalamus of the dog (Malhotra C.L. & Das P.K.) **18**(1) 190-193, 1962

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The diphasic effect of N-methyl-3-piperidyl-(N', N')-diphenylcarbamate (MPDC) on the metabolism of hexobarbital (Serrone D.M. & Fujimoto J.M.) **133**(1) 12-17, 1961

Influence of chlorpromazine and chlorprothizene on the cerebral metabolism of 5-hydroxytryptamine, norepinephrine and dopamine (Gey K.F. & Pletscher A.) **133**(1) 18-24, 1961

Adenine nucleotide, catecholamine and protein contents of whole adrenal glands and heavy granules of reserpine-treated fowl (Burack W.R., Draskoczy P.R. & Weiner N.) **133**(1) 25-33, 1961

The effect of synaptic blocking agents on reserpine-induced alterations in adrenal medullary and urinary catecholamine levels (Mirkin B.L.) **133**(1) 34-40, 1961

The development of supersensitivity to norepinephrine after pretreatment with reserpine (Fleming W.W. & Trendelenburg U.) **133**(1) 41-51, 1961

The depressor effect of serotonin and tryptamine on chicken blood pressure (Bunag R.D. & Walaszek E.J.) **133**(1) 52-56, 1961

Interaction of serotonin with vasoconstrictor agents in the vascular bed of the denervated dog forelimb (Hurwitz R., Campbell R.W., Gordon P. & Haddy F.J.) **133**(1) 57-62, 1962

Modification of the chronotropic action of sympathomimetic amines by reserpine in the heart-lung preparation of the dog (Liebman J.) **133**(1) 63-69, 1961

SC-10049 : A catecholamine bronchodilator and hyperglycemic agent (Van Arman C.G., Miller L.M. & O'Malley M.P.) **133**(1) 90-97, 1961

Excitatory effects of thiocyanate on spinal cord (Goto K. & Esplin D.W.) **133**(1) 129-136, 1961

Antiemetic activity of *d*-lysergic acid diethylamide (Dhawan B.N. & Gupta G. P.) **133**(1) 137-140, 1961

Cardiac activities of several monoamine oxidase inhibitors (Lee W.C., Shin Y. H. & Shideman F.E.) **133**(2) 180-185, 1961

The physiological role of acetylcholinesterase (AChE) in sympathetic ganglia (Volle R.L. & Koelle G.B.) **133**(2) 223-240, 1961

Effects of general anesthesia on peripheral blood levels of carbohydrate and fat metabolites and serum inorganic phosphorus (Henneman D.H. & Bunker J.P.) **133**(2) 253-261, 1961

Demonstration of tolerance and physical dependence in the dog following a short-term infusion of morphine (Martin W.R. & Eades C.G.) **133**(2) 262-270, 1961

Effects of meprobamate on operant behavior in rats (Kelleher R.T., Fry W., Deegan J. & Cook L.) **133**(2) 271-280, 1961

The absence of blood-brain barrier from certain areas of the central nervous system (Wilson C.W.M. & Brodie B.B.) **133**(3) 332-334, 1961

A comparison of the anticonvulsant activity of mepivacaine and lidocaine (Berry C.A., Sanner J.H. & Keasling H.H.) **133**(3) 357-363, 1961

A biometric study of the effects of ammonium acetate on electroshock convulsions (Rosenthal F., Timiras P.S. & Roberts K.E.) **133**(3) 364-370, 1961

Monoamine oxidase inhibition by isocarboxazid (Schwartz M.A.) **135**(1) 1-6, 1962

A sensitive assay of monoamine oxidase activity *in vitro* : application to heart and sympathetic ganglia (Lovenberg W., Levine R.J. & Sjoerdsma A.) **135**(1) 7-10, 1962

The effects of reserpine on uptake of epinephrine in brain and certain areas outside the blood-brain barrier (Wilson C.W.M., Murray A.W. & Titus E.) **135**(1) 11-16, 1962

The effect of a number of central depressant drugs upon brain 5-hydroxytryptamine levels in the rat (Bonnycastle D.D., Bonnycastle M.F. & Anderson E.G.) **135**(1) 17-20, 1962

Central inhibition of vasomotor activity by guanethidine (Kaneko Y., McCubbin J.W. & Page I.H.) **135**(1) 21-24, 1962

Some pharmacological effects of two tetrahydrocannabinols (Dagirmanjian R. & Boyd E.S.) **135**(1) 25-33, 1962

The release of posterior pituitary hormone in the rat by nicotine and lobeline (Grewal R.S., Lu F.C. & Allmark M.G.) **135**(1) 84-88, 1962

Studies on cellular adaptation to morphine and its reversal by nalorphine in cerebral cortical slices of rats (Takemori A.E.) **135**(1) 89-93, 1962

The mechanism of serotonin and tryptamine induced vasodepression in the chicken (Buñag R.D. & Walaszek E.J.) **135**(2) 151-155, 1962

Spinal cord site of action of resorcinol isomers that produce symyathetic circulatory stimulation (Gatgounis J. & Walton R.P.) **135**(2) 174-179, 1962

Catecholamine content of the cat nictitating membrane following procedures sensitizing it to norepinephrine (Kirpekar S.M., Cervoni P. Furchgott R.F.) **135**(2) 180-190, 1962

Effect of temperature on toxicity and distribution of pentobarbital and barbital in rats and dogs (Setnikar I. & Temelcou O.) **135**(2) 213-222, 1962

Studies on the mechanism of meprobamate tolerance in the rat (Phillips B.M., Miya T.S. & Yim G.K.W.) **135**(2) 223-229, 1962

The influence of pentobarbital and ether narcosis on the brain concentration of various esters with acetylcholine activity (Hosein E.A. & Ara R.) **135**(2) 230-232, 1962

Strain difference in response of mice to damphetamine (Weaver L.C. & Kerley T.L.) **135**(2) 240-244, 1962

The effect of acute ethanol intoxication on chloroform-induced liver damage (Kutob S.D. & Plaa G.L.) **135**(2) 245-251, 1962

Cross-cellular adaptation to methadone and meperidine in cerebral cortical slices

from morphinized rats (Takemori A.E.) **135**(2) 252-255, 1962

Passage of lipid-insoluble substances from crerbrospinal fluid to blood (Prockop L.D., Schanker L.S. & Brodis B.B.) **135**(3) 266-270, 1962

Some effects of sodium gamma-hydroxybutyrate on the central nervous system (Drakontides A.B., Schneider J.A. & Funderburk W.H.) **135**(3) 275-284, 1962

Tolerance to morphine I. Effects on catecholamines in the brain and adrenal glands (Maynert E.W. & Klingman G.I.) **135**(3) 285-295, 1962

Tolerance to morphine II. Lack of effects on brain 5-hydroxytryptamine and γ-aminobutyric acid (Maynert E.W., Klingman G.I. & Kaji H.K.) **135**(3) 296-299, 1962

Tolerance to morphine III. Effects on catecholamines in the heart, intestine and spleen (Klingman G.I. & Maynert E.W.) **135**(3) 300-305, 1962

The relationship between distribution and pharmacological activity of hexamethonium-N-methyl C^{14} (McIsaac R.J.) **135**(3) 335-343, 1962

Blockade of the ganglionic stimulant action of 5-hydroxytryptamine (Gyermek L. & Bindler E.) **135**(3) 344-348, 1962

The effect of reserpine and mecamylamine on experimental atheromatosis in the normotensive and hypertensive rat (Smith T.H.F. & Rossi G.V.) **135**(3) 367-373, 1962

Amer. J. Physiol.

Adrenal medullary and adrenal cortical response to stimulation of diencephalon (Goldfien A. & Ganong W.F.) **202**(2) 205-211, 1962

Liberation of antidiuretic hormone following hypothalamic stimulation in the dog (Fang H.S., Liu H.M. & Wang S.C.) **202**(2) 212-216, 1962

Bone, bone marrow, and brain oxygen (Misrahy G.A., Hardwick D.F., Brooks C.J., Garwood V.P. & Hall W.P.) **202**(2) 225-231, 1962

Reserpine and adrenocortical function in chickens (Newcomer W.S.) **202**(2) 337-339, 1962

Estrous and circadian periodicity and electroshock convulsions in rats (Woolley D.E. & Timiras P.S.) **202**(2) 379-382, 1962

Outflux of various phosphates during membrane depolarization of excitable tissues (Abood L.G., Koketsu K. & Miyamoto S.) **202**(3) 469-474, 1962

Localization of gold in mouse brain in relation to gold thioglucose obesity (Debons A.F., Silver L., Cronkite E.P., Johnson H.A., Brecher G., Tenzer D. & Schwartz I.L.) **202**(4) 743-750, 1962

Muscarinic synapses in the hypothalamus (Stein L. & Seifter J.) **202**(4) 751-756, 1962

Active transport of iodide by choroid plexus of the rabbit *in vitro* (Welch K.) **202**(4) 757-760, 1962

J. cell. comp. Physiol.

Microelectrode study of taste receptors of rat and hamster (Kimura K. & Beidler L.M.) **58**(2) 131, 1961

Cortical intracellular synaptic potentials (Choh-Luh Li) **58**(2) 153, 1961

J. Physiol.

Contractures and permeability changes produced by acetylcholine in depolarized denervated muscle (Jenkinson D.H. & Nicholls J.G.) **159**(1) 111-127, 1961

The effect of subarachnoid injections of Cu^{2+} in pigeons (Davies A., Peters R. A. & Walshe J.M.) **159**(1) 32 P-33 P, 1961

Inhibition of the methylation of histamine in cat brain (White T.) **159**(2) 191-197, 1961

Some effects of histamine and two histamine metabolites on the cat's brain (White T.) **159**(2) 198-202, 1961

Further purification of an active lipid acid from rabbit brain (Ambache N. & Reynolds M.) **159**(2) 63 P-64 P, 1961

Blood-brain barrier and extracellular space (Davson H., Kleeman C.R. & Levin E.) **159**(2) 67 P-68 P, 1961

The effect of calcium and magnesium on the spontaneous release of transmitter from mammalian motor nerve endings (Hubbard J.I.) **159**(3) 507-517, 1961

Ann. med.-psychol.

Perturbations du métabolisme du glucose chez les schizophrénes (Jarosz M.) **119-2**(4) 633-650, 1961

Clin. chim. Acta

The renal clearance of phenylpyruvate (Vink C.L.J. & Kroes A.A.) **6**(6) 813-818, 1961

A spectrophotofluorimetric method for the determination of serotonin(5-hydroxytryptamine) in plasma (Crawford N. & Cohen S.) **7**(1) 114-121, 1962

Neurology (Minneap.)

A study of subdural effusions in an infant (Rabe E.F., Elyynn R.E., Dodge P. R.) **12**(2) 79-92, 1962

Some metabolic studies of sporadic and familial periodic paralysis (Norris F.H. Jr.) **12**(3) 208-212, 1962

Psychiat. et Neurol.

A propos d'un médicament relaxant.antitréorique : Le rôle de la rectivité afférentielle dans les trémors et mouvements involuntaires (Benmiloud K., Garrone G., Gunn-Séchehaye A., Desaugy D. & Vauthier C.) **143**(2) 126-137, 1962

Résultats expérimentaux d'un nouveau médicament, relaxateur myo-psychique : le Control-OM (OM-518/méphénoxalone) (Kaufmann R.Z.) **143**(2) 138-153, 1962

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ニュース

第5回 国際神経化学シンポジウム プログラム

"COMPARATIVE NEUROCHEMISTRY"
ST. WOLFGANG, AUSTRIA
10—15 JUNE, 1962

Monday, 11 June

STRUCTURAL CHARACTERIZATION OF THE NERVOUS SYSTEM IN DIFFERENT SPECIES

Morning	
V. Hamburger	Review: Structural differences that underlie behavioural differences in different species.
Margaret Murray	Myelin formation and neuron histogenesis in tissue culture.
J.D. Robertson	Contact relationships of cell membranes in different species.
Afernoon	
F. Knowles	Review: The organization of the nervous system in different phyla.
G.B. David	The cytoplasmic network in neurones of vertebrate and invertebrate species.
Rita Levi-Montalcini and P.O. Angeletti	The sympathetic nerve growth factor.
G.A. Horridge	Structure and function in the elementary nervous system.
General Discussion	The significance of structural variation in different specis.

Tuesday, 12 June

CHEMICAL COMPOSITION AND METABOLISM OF NERVOUS TISSUES IN DIFFERENT SPECIES

Morning	
W.C. McMurray and R.J. Rossiter	Lipids of the vertebrate and invertebrate nervous system.
R. Paoletii	Regulation of lipid metabolism in different species.
A. Lowenthal, M. von Sande, D. Karcher and J. Richard	Proteins and enzymes of the central nervous system in different species.
M.K. Gaitonde	Metabolism of lipoproteins in different species.

L. Amaducci	The distribution of proteolipids in different species.
F.O. Schmitt	Protein synthesis in neurons and glia.

Afternoon

P. Mandel	Distribution and metabolism of RNA in the vertebrate central nervous system.
A. Lajtha	Blood-brain barrier and active transport of amino acids.
Y. Tsukada	Distribution of amino acids in the brain in different species.
Nora Frontali	Synthesis of GABA from ^{14}C-substrates by brain homogenates of vertebrate and invertebrate species.
E. Roberts	Comparative neurochemistry of amino acids.
General Discussion	Variation of chemical composition and metabolism of nervous tissues in different species.

Wednesday, 13 June

CHEMICAL COMPOSITION AND METABOLISM (continued)

Morning

S. Berl, S.C. Cheng and H. Waelsch	Carbon dioxide fixation in vertebrate and invertebrate nervous tissue.
R. Balazs	Operation of the Krebs cycle in nervous tissue of different species.
E. Egana and M.I. Velarde	Effect of H_2O_2 on the respiration of normal and irradiated central nervous system of the rat.
H.H. Hillman	The ionic composition of the nervous system in different species.
R.V. Coxon	The blood-brain barrier to urea in different species.
General Discussion	Variation of energy metabolism and ionic composition.

Afternoon free

Thursday, 14 June

CHEMICAL ASPECTS OF FUNCTION IN THE NERVOUS SYSTEM

Morning

A.V. Palladin	The metabolism of the brain during hibernation.
L.C. Mokrasch and H.J. Grady	Respiratory and glycolytic enzymes and cholinesterase in relation to hibernation.
H. Heller	Class and species differences in the distribution of hypothalamo-neurohypophyseal active peptides.
Lucie Arvy	Enzyme distribution in the hypophysis in different species.
H.E. Colhoun	Pharmacologically active substances in insects.
M. Schachter	The distribution of acetylcholine and other active substances in insects.

Afternoon

J.H. Welsh	The distribution of 5TH in the vertebrate nervous system.
O. Hornykiewicz	The distribution and metabolism of 5HT and catecholamines in the brain of different species.
B.B. Brodie and D. Bogdanski	Formation, storage and metabolism of 5HT and catecholamines in the amphibian brain.
Nancy J. Lane	Neurosecretory function in the gastropoda.
D.B. Carlisle	What makes the shrimp's heart beat faster? (Neurochemical mechanisms in crustacea).
Catherine Hebb	The distribution of acetylcholine and choline acetylase in vertebrate tissues.
General Discussion	Variation of functional mechanisms in different species.

Friday, 15 June

COMPARATIVE NEUOROPHARMACOLOGY

Morning

Martha Vogt	Some species difference in responses to drugs.
S. Szara	Behavioural correlates of 6-hydroxylation and the effect of psychotropic tryptamine derivatives on brain 5HT levels.
Margaret Murray	Actions of drugs and toxic substances on nerve cells in tissue culture.
H. Sobotka	Different responses of lower and higher vertebrates to a neurotoxic agent, holothurin.
Maria Wollemann and Katona Ferenc	Colour film: Effects of phenothiazine derivatives in invertebrates.
M. Mirolli and J.H. Welsh	Actions of reserpine and LSD on the behaviour of molluscs.

Afternoon

E. Bueding	Neurochemical mechanisms in relation to anthelmintic action.
G.R. Pscheidt and H.E. Himwich	Comparative studies of the effects of monoamine oxidase inhibitors in different species.
General Discussion	Variation in response of different species to pesticides and drugs.

IBRO (International Brain Research Organization) の活動：フエローシツプ，研究チーム

ＩＢＲＯ の今年度の Bulletin No. 1 によると，いよいよ今年から上記の活動をはじめる．1962—63年度は限られた数のフエローシップにつき旅費の支給，研究チームに対する援助が行われる．

1963—64年度には，フエローシップの数も20—25人になる見込．詳細は事務局に問合せられたい．我国では阪大吉井（生理）教授を中心に，ＩＢＲＯの国内連絡をはかるよう計画がすゝめられている．

レーダーバーグ博士との懇談会

本年4月末文部省の招聘により来日中であつたスタンフォード大学教授 Joshua Lederberg 博士（微生物遺伝学）より日本の神経化学者と是非懇談したいとの申し入れがあり，期日も切迫していたので東京附近在住の常任委員の方々の御参集を頂き，5月9日同博士を囲んで懇談会を行つた．

レーダーバーグ博士の話によると，ケネディー大統領から，米国で年々増加しつゝある精神薄弱の対策に就いて諮問があり，専門家によるパネルが構成されて目下その実態調査と治療予防に関する研究計画の答申を準備中である由で，同氏もその一人として生化学的な立場からこの問題の研究を始めたいとのことであつた．既に同氏は遺伝生化学の面では大きな業績を残し，ノーベル賞授賞者として有名であるが，神経化学に対しても積極的な情熱をもつており，既に文献的に豊富な知識を貯え，特に記憶の物質的レベル（分子生物学）での探求に大きな興味をもつている様に感じられた．

同氏の当面の研究目標は脳蛋白質の一次，二次構造を追究することにより脳の機能との関連をつかもうとしており，電気泳動や免疫化学的方法によつて脳蛋白の単離を試みるそうである．そしてこの面から Mental Retardation の問題に取り組む予定だそうで既に神経化学者を雇い入れる予定もある由．

彼自身今まで神経化学の仕事は全くないのであるが，米国での国家的要請と，彼自身の生物学的な興味から，かなり本気でこの問題に取り組むであろうことが考えられる．この様に米国でも一流の学者によつて神経化学の研究が本格的に取り上げられる様になつたことは，我々にとつても大きな刺激となるし又神経化学の将来にも大きな力を与えることになるであろう．（塚田記）

関東神経化学合同集談会記録

（昭和37年3月28日）

染色体異常による疾患について

長畑正道
（東大・医・小児科・精神科）

人類の染色体数については，ごく最近に至るまで，その数は男女とも48或は男47，女48と云われ確定されるに至らなかつた．しかし1956年 Tjio 及び Levan が人胎芽の肺の線維芽細胞の組織培養を行い，男女とも46の染色体を有することを発表した．以後 Ford 等の追試により確認されるに至つた．1959年に至り Kleinfelter 症候群，蒙古症などに染色体数の異常があることが見出され大きく注目される様になつた．人の染色体を検査するには，組織培養法を用い（材料は血液，骨髄血，皮膚その他），Colchicine を作用させて細胞分裂を中期の段階で止め，低張液処理により細胞を膨化させ，染色固定を行い，更に標本を強く圧迫して，染色体を光学的に同一平面上に並べることによつて容易に観察される．

人類の正常の染色体像は常染色体22対，性染色体1対，合計46個で，男ではＸＹの性染色体を有し，女ではＸＸの性染色体を有している．染色体の長さ，Centromere の位置により，また付随体の有無などを参考として，No. 1 より No. 22 の常染色体とＸ或はＹの性染色体に分類し命名するよう国際的にきめられている．

人類にみられる染色体異常は数の変化と構造の変化（転座，欠失，重複）とがあるが，かかる異常が，常染色体にみられる場合と，性染色体にみられる場合とがある．そこでかかる異常について概略を述べる．

1．常染色体の異常

(1) 蒙古症：1959年に Lejeune 等により No. 21の染色体が1つ多く trisomy をなし，総計47の染色体数を有することが発表された．以後 Jacobs, Böök 等も同様の事実を確認し略ゝ確定されるに至つた．しかし1960年に至り Polani が染色体数46の蒙古症を報告し，No. 14と No. 21の相互転座があることが見出された．また Carter, Penrose 等はかかる転座は家族性にみられることのあることを報告している．No. 21の転座の相手として，こう云つたNo. 13—15のグループの他に No. 21—22のグループを選ぶことのあることを Fraccaro 等が報告している．蒙古症では No. 21の trisomy か，転座による実質的なNo. 21の trisomy か．何れかの場合に限られることが確定している．筆者等の行つた研究では6例の蒙古症ではすべて No. 21の trisomy で，転座によるものはなく，転座によるものはかなり少い様である．

類蒙古症については種々の報告があるが，むしろ性染色体の異常がみられることが少くない．しかし No. 21が2つあるものと3つあるものの Mosaicism のみられた報告があり，かかる例が真の意味での類蒙古症と考えられる．

(2) No. 16—18 trisomy 症候群および No. 13—15 trisomy 症候群：No. 16～18のグループに属する trisomy を Edward 等が最初に報告し，特異な顔貌，小顎，耳の低位，心室中隔欠損，指の奇型などが特徴的であるとされている．その後 Smith, Crawford, van Wijck 等の報告があり，最近東大小児科に於て同様の症例が見出されている．No. 13—15のグループの trisomy について Patan 等が報告している．無眼，兎唇，口蓋裂，多指，心室中隔欠損等があり，これも同様の症例が2－3報告されている．以上2つの症候群は染色体異常と臨床像がよく対応しているものである．

(3) その他：Sturge-Weber 症候群に於て No. 22に trisomy がみられることを Hayward 等が報告したが，その後の追試ではかかる例はなく，筆者等の1例でも異常を認めなかつた．また Turner は，分裂病様小児に No. 22の trisomy のみられたことを報告している．家族性にみられた脳性小児麻痺に異常に大きいX染色体がみられた例，脊椎に各種の異常のみられる Polydyspondylism に No. 22と No. 13の転座があり，染色体数が45しかないと云う報告もある．Marfan 症候群に於て異常に大きい付随体のみられたことを Tjio 等が報告している．その他 Macroglobulinemia に No. 1に類似した染色体が1つ多いと云う報告もある．かかる代謝異常による疾患で染色体異常が見出されることは興味ある問題と思われる．

その他，人における3倍体の例を Penrose 等が流産した胎児にみとめ，また Böök 等は Lipomatosis 孔脳，合指のみられた例で2倍体と3倍体のキメラと考えられる症例を報告した．

2．性染色体の異常

倭小睾丸．無精子症，女性化乳房のみられる男性は Kleinfelter 症候群とよばれるが，かかる例ではＸＸＹの染色体構造を有していることを Jacobs 等が報告している．しかしその後，XY/XXY/XXYY，XXY/XXXXY/XXXXY，の，Mosaicism，ＸＸＸＹ，ＸＸＹＹ，ＸＸＹy等の報告がある．他方外形は女性で，侏儒，翼状頚，外反肘等のみられる Turner 症候群に於て Ford 等はＸＯなる性染色体を有することをみいだした．その後 X(x)，ＸＸＸ/ＸＯ等のみられることもしられている．その他超女性 super female として Jacobs 等が不規則な月経を有する女性にＸＸＸなる性染色体を有することを報告している．猩々蝿でＸＸＸが super female であることに因んでつけたものである．またＸＸ/ＸＸＸの Mosaicism がみられた報告もある．

3．悪性腫瘍と染色体異常

悪性腫瘍に染色体異常がみられることは古くより知られている．人の各種の癌で染色体数が正常と異り42—84あり，形もＶ型，Ｊ型，棒型，環状などがあり，Centromere も2つあるものが知られている．そ

の他，急性の白血病の場合に染色体の数の異常がみられることが少くなく，46—50と2n より多い場合がある．慢性白血病では No. 21～22のグループに属する4つの染色体のうち，1つが欠失により小さくなつていることが高率にみられ，Ph_1，染色体とよばれている．かかる染色体異常と Carcinogenesis とどの様な関係があるかは未だ不明であるが，注目されている問題である．

4．結　び

染色体異常は先天性異常と惡性腫瘍の研究に1つの光をなげかけた問題である．しかしかかる染色体異常が人類に於て如何にして発生するかと云うことが現在の所殆んど判つていない．また蒙古症の如く染色体数が正常と異る場合，それが代謝の上に如何なる影響を及ぼすかと云う問題も殆んど未解決である．現在の段階では，猩々蝿の研究者達がすでに40年前に到達した水準に今日漸く達したにすぎない．この領域の研究成果は遺伝学の原理の解明と相まつて，臨床医学の上に於てますます切実な問題となつて来ることと考えられる．

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