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Platelet research in psychiatry

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Summary. The platelet is one of the most researched biological markers in psychiatry. Characteristics of MAO activity, 5-HT uptake, imipramine and α_2-adrenergic receptor binding, for example, are similar in platelet and CNS. Methodological factors are not negligible, and range from diagnostic specificity and drug effects to the normal physiological variability of age and hormone-related changes, circadian and seasonal rhythms. As yet, there are no clear state or trait platelet markers in affective disorders and schizophrenia that can be unequivocally used to detect vulnerability to the illness, predict therapeutic response, define clinical diagnostic entities or follow the course of the illness. However, platelet markers are increasingly being used in careful studies to monitor psychopharmacological effects (an in vivo assay of all active metabolites), different ligands can be specific markers for certain aspects of a psychiatric illness (e.g. α_2-adrenergic receptors and weight loss), and this homogeneous preparation of human cells is an increasingly important tool in studying mechanisms in pathophysiology. More longitudinal studies are required to establish functional relationships between platelet variables and psychopathology.
Key words. Platelet; psychopathology; MAO activity; 5 HT uptake; imipramine binding; α_2-adrenergic receptors; drug effects.

The search for markers for psychopathology

The serendipitous advent of psychopharmacological agents, and elucidation of the metabolic pathways of the first putative neurotransmitters, resulted in the formulation of precise, testable hypotheses of affective disorders and schizophrenia. Drugs had been found to act on specific symptoms: their modulation of CNS monoamines invoked causal theories. These discoveries led to an entirely new perspective of mental illness – equivalent to a new paradigm – and has shaped the views of clinicians and scientists alike. These discoveries also led to direct measurement of neurotransmitters and their metabolites in man. However, the difficulty of postmortem or cerebrospinal fluid studies, compared with the ease of blood sampling and its possibility of sequential observations, led to the use of different blood cells as possible peripheral representations of central processes. It was the remarkable parallels in a number of properties of the platelet to those in the CNS – the 'neuronal model' concept of Pletscher [82] – that initiated the more dynamic studies in psychiatric illness that will be discussed here. This review does not intend to replicate recent in-depth surveys [21, 33, 49, 58, 73, 82, 93, 101, 102] and makes no pretension to be comprehensive. Instead, I shall adumbrate certain issues that may be critical for an adequate use of platelet markers in psychiatry.

As with post-mortem neurochemistry or CSF metabolites, methodological factors and issues of 'normal' variability were extensively investigated only after the initial flurry of excitement for a new finding was damped by non-replication of the finding by other groups. These methodological factors are not negligible, and additionally, the range of physiologic changes provides important clues to pathophysiology.

Abbreviations: MAO, monoamine oxidase; MAOI, monoamine oxidase inhibitor; 5HT, serotonin; DHE, dihydroergocriptine; cAMP, cyclic adenosine 3′-5′ monophosphate; CNS, central nervous system.

Diagnostic difficulties

The search for markers in psychiatry is perhaps even more desperate than in other fields. In a medical model of mental illness, the brain is the substrate, there is an expectation that some output of the brain can be measured as a differential diagnostic aid, as a predictor for therapeutic response to one or another treatment, and as a monitor of the clinical course of the illness. The difficulties of diagnosis need to be explicitly recognised in research on biological markers, since homogeneity of patient populations is a prerequisite for specificity:

- conceptual: disease model or spectrum model?
- descriptive or diagnostic language with aetiological implications (e.g. 'endogenous' vs 'neurotic' depression)
- the distinction between 'trait' and 'state' markers
- the phase of the illness studied

- illness specificity or symptom specificity?
- variable reliability of individual diagnostic criteria or clinical state rating items

The 'Diagnostic and Statistic Manual' (DSM-III) is one effort to improve diagnostic methodology in research, and replace aetiological with operational criteria for symptoms[4]. This tool has certainly allowed better comparisons of patient populations across studies and across schools.

Methodological considerations

For the use of the platelet as a model for CNS neurotransmitter function, it is necessary that rigorous studies document in which cases the model is accurate and in which cases it is not[82]. It has even been suggested that the presence of a neurone-specific enolase in platelets is evidence that they may form part of the nervous system[21].
If the biochemical and pharmacological characteristics of a given variable in platelets are parallel to those in the CNS, this does not necessarily mean that in vivo, physiologically, the two are related, or even correlated. It cannot be assumed that platelet changes found in psychopathological states are not due to peripheral modulation. Therefore it is important to know under which conditions changes in the platelet accurately reflect changes in the brain.

Examples of problems

A. Ligands for α_2-adrenergic receptors. Both agonist and antagonist ligands, of varying selectivity, have been used to label platelet α_2-adrenergic receptors. An antagonist such as yohimbine labels 50% more sites than an agonist ligand: it is not known which sites are the relevant ones to the clinical questions being asked. Thus discrepant results in binding characteristics associated with a given psychiatric illness may relate primarily to the particular radioligands used[49, 81, 128].

B. Platelet preparation, platelet protein. Because of the heterogeneity of platelet populations, slightly different preparation methods yield different results. Platelet rich plasma, or platelet membranes, heavy or light platelets, all show differential 5 HT concentration or MAO activity[26, 47] or modifications in the number of imipramine binding sites[34], their affinity[11] or both[8]. This predicates caution in comparing the findings in studies using different preparations. Interpretation of platelet results should be carried out with the awareness that factors such as platelet mean age – i.e. turnover rate – can affect these values and may be altered as a consequence of basic platelet physiology and not be intrinsic to the illness under investigation[26].

'Normal' variability

There are a number of factors that may add to variance in clinical studies. Their importance lies not only in methodology, but in certain parallels with the characteristics of some psychiatric illnesses, such as changes in a platelet marker with age, sex, hormonal status, diet, weight, time of day or time of year.
An exemplary summary of some platelet markers indicates that some, though not all, do show significant changes in different physiological states (table 1).

Table 1. Selected platelet variables

Factor	MAO activity	[5-HT]	5 HT uptake	Imipramine-binding
Age	Tendencies towards an increase			
Women/Men	Higher	=	=	=
Menstrual cycle changes	Yes	Yes	Yes	No
Diurnal rhythm	No	Yes	Yes	Yes
Seasonal rhythm	No	Yes	4 Yes 1 No	5 Yes 4 No
Genetics (twin concordance)	Yes	?	Yes	Yes

Selected platelet measures

A) MAO activity. MAO studies in mono- and dizygotic twins and control pairs indicate genetic control[75]. Environmental factors on MAO are negligible[24, 88], compared with a genetic heritability in male twins of 0.78 [cited in Cloninger et al.[24]). The level of MAO may be a predictor of vulnerability to psychological disturbance: in the general population, low platelet MAO activity seems to correlate with psychiatric morbidity, neurotic personality, and suicidal behaviour in relatives[18, 52]. MAO is lower in men than in women[71, 90, 127], is lower during the premenstrual phase and lower in pregnancy and post-partum[127]. MAO increases with age[71]. There do not appear to be marked circadian or seasonal changes in a given individual[125, 127].
It is puzzling that the MAO-B form of the enzyme, that does not metabolise 5 HT, is found in platelets. The human brain possesses relatively more MAO-B than MAO-A activity[70], with characteristics identical to the enzyme in platelets, which is why it has been used as an index of CNS neurotransmitter function in affective disorders. However, there is no correlation between platelet MAO and MAO from several areas of post-mortem brains from the same subjects[120]. According to Oreland, MAO is genetically determined by the same set of genes that regulates the level of 5 HT turnover in the CNS, so that a possible rationale for measuring platelet MAO activity is that it indirectly reflects serotonergic function in the brain[77].
There is a long history of clinical studies reviewed in[58, 73, 93]. Many have shown that platelet MAO is lower in bipolar depressed patients than in either unipolar depressed patients or controls. Others have shown higher MAO activity in unipolar than non-endogenous or reactive depression. There may be a more consistent relationship between certain clinical syndromes rather than diagnostic categories. For example, low MAO activity occurs in patients with suicidal behaviour, high MAO activity correlates with anxiety. MAO activity appears to be stable over time and clinical state. However, family studies indicate it may be low in both ill and well relatives of depressed patients. There are some negative findings, as well as a MAO activity increase related to clinical improvement. Low MAO activity may not be specific for affective illness, as it has been found lower in schizophrenia and alcoholism and higher in Alzheimer patients.
In spite of the discrepancies in the findings in depression (that do not seem to be explicable by methodological differences alone), a certain pattern is apparent, and parallels to the findings in normal physiology can be drawn. Low MAO activity is found in predisposed personalities and in situations of hormonal change; low MAO activity is more often found in clinical states related to suicidal behaviour (that is more prevalent in men). Suicidality, in turn, has been repeatedly related to low 5 HT turnover as measured in the CNS of suicide victims or in CSF 5 HIAA[10]. Thus low platelet MAO activity may indeed be a risk factor for psychopathology.

B) 5 HT uptake. Platelet 5 HT uptake shows intraindividual consistency and high concordance in twin studies; there do not appear to be age, sex or menstrual cycle differences[58, 121], though a recent study has found high 5 HT uptake in the premenstrual phase[112]. There may be subtle hormonal modulation: e.g. the inhibitory effect of tricyclics is greater for women than for men, and is dependent on the

phase of the menstrual cycle[121]. A number of studies have shown a variety of diurnal changes in either V_{max} or affinity or both[46, 67, 85, 86, 95, 126]; no studies have used sufficient time points or subjects to provide a clear pattern (and a negative finding with two time points is not necessarily so[6]). Seasonal variations have been observed by most[7, 31, 111, 125] but not by all[58] authors.

Even though low values in 5 HT uptake are remarkably consistently found in depression [25, 31, 32, 41, 46, 58, 61, 64, 66, 85, 86, 97, 104, 115], a decrease in 5 HT uptake is not specific for any syndrome or symptom. A decrease in V_{max} is also found in schizophrenia[59, 68, 94, 130] though not always[5], anxiety disorders[79], though not always[76], anorexia nervosa[118], Alzheimer's and Parkinson's disease[109].

C) Imipramine binding. Platelet [^{3}H]-imipramine binding has characteristics identical to those reported for rat and human brain[54, 87]. Family studies report high concordance[78]. There do not appear to be differences between men and women[45, 54] nor at different stages of the menstrual cycle[83]. No age relationships[109] or a slight negative correlation[54] with age have been noted. However a diurnal rhythm in imipramine binding in healthy subjects has recently been reported[74]. The issue of seasonality is a moot one, for most studies of this new 'marker' have been aware of the methodological relevance of seasonal change, and have analysed their data accordingly. Rather than clarify possible discrepancies, more have arisen: of the 9 studies with at least one year of data, five found seasonal changes[30, 31, 45, 91, 119] and four did not[22, 36, 96, 113]. Changes in imipramine binding in different patient populations are less ubiquitous than changes in 5 HT uptake. No changes are found in schizophrenia[130], panic attacks[79, 96], Alzheimer's or Parkinson's disease[109]. Nine groups have found a decrease in depression[9, 12, 15, 16, 55, 56, 74, 78, 84, 108, 109, 114, 117, 131], two additionally a decreased number of imipramine binding sites in the brain of suicides[80, 105]. In contrast, nine studies report no differences[22, 30, 31, 40, 43, 45, 72, 113, 119]. Even an increase in platelet imipramine binding in depressives[62] or suicide attempters[117] or in the brains of suicides[65] has been observed. Imipramine binding does not appear to be correlated with diagnostic criteria[40], but an indication that it is related to depth of depression has been noted[22, 74, 114].

Imipramine binding changes appear to be more selective for depression than those of 5 HT uptake. One study of agoraphobia/panic discorders has measured lowered imipramine binding[57]; three have found no change[79, 96, 116]. Anorectic patients have also shown lower imipramine binding than controls[118].

A comparison of those studies where parallel measurement of 5 HT uptake and imipramine binding have been made indicate that these parameters do not usually show parallel changes in spite of being considered closely related (table 2).

D) α_2-Adrenergic receptors. The characteristics of platelet and brain α_2-adrenoceptors appear similar biochemically but not necessarily functionally[42]. Platelet α_2 adrenoceptors and cAMP production are higher in men than women in one study[50]; the opposite was found in another study[48]. Some studies have shown changes with the menstrual cycle[1, 48], others not[106]. The findings with age are conflicting[17, 19, 48]. A diurnal rhythm has not been found in one study[48] but measured in another[35]. Since many different radioligands, agonists and antagonists have been used to label platelet α_2-adrenoceptors with discrepant results, this constitutes a major problem in establishing normative values.

In studies of affective disorders, the number of α_2-adrenoceptor binding sites measured with clonidine has given contradictory results: decreased in unipolar depression[23], but increased in elderly depressed patients[28] or those with major depressive disorder[37]. Using DHE as ligand, binding was lower in depression in one study[128], but higher in another (although with decreased cAMP production[50, 98]). Yohimbine binding appears unaltered in depression[27, 103].

Table 2. Parallel measurement of 5 HT uptake and imipramine binding compared with a control group

Patient group	5 HT uptake	Imipramine binding	Reference
Depression	↓	↓	Suranyi-Cadotte et al.[109]
Depression	↓	=	Egrise et al.[31]
Depression	↓	=	Wood et al.[130]
Schizophrenia	↓	=	Rotman et al.[93]
Schizophrenia	↓	=	Wood et al.[130]
Anorexia nervosa	=	↓	Weizman et al.[118]
Panic attacks	↓	=	Pecknold and Suranyi-Cadotte[79]
Alcoholic cirrhosis	↓	=	Ahtee et al.[2]
Alzheimer's disease	↓	=	Suranyi-Cadotte et al.[109]
Parkinson's disease	↓	=	Suranyi-Cadotte et al.[109]

One study in panic attacks has found clonidine binding lower than in both depressed patients and controls[20].

Diet and weight are an important normative factor, since α_2-adrenoceptors increase with weight loss in obesity[107]. In anorexia nervosa, similar findings of increased α_2-adrenoceptor binding have been reported[44, 51, 60], together with platelet hyperaggregability[60] or increased stimulation of adenylate cyclase[51].

α_2-Adrenergic receptor function in schizophrenic patients indicated increased DHE binding but decreased cAMP production[50]. Some schizophrenic patients with lower clonidine binding tended to have more negative symptoms; however, no correlation with yohimbine binding was found[92]. Another study has shown that yohimbine binding was lower in schizophrenic patients[1]. Clonidine binding in the locus coeruleus of schizophrenic patients tended to be lower than controls[53].

Other studies have found increased yohimbine binding in panic disorder[3] or no change in Parkinson's disease[48].

The methodological problems related to α_2-adrenergic receptor binding need clarification, and longitudinal studies are necessary before any conclusion about α_2-adrenergic receptor function in psychiatric illness can be drawn[49].

E) Other platelet markers. Although a number of other measures in platelets have been studied, the results are inhomogeneous and their relevance questionable. For example, platelet 5 HT has been extensively studied[69, 93, 95, 101, 104, 122–124, 126], but there appears to be even less functional correlation with CNS function than that possible for 5 HT membrane uptake mechanisms.

A typical 'newer' example is that of vasopressin-1 receptors. As soon as their characteristics were described, a study in a group of bipolar depressed patients was carried out that found no differences[13]. Subsequent interest in this potential marker was thus damped, and no comprehensive attempt at establishing adequate 'normal' values has been carried out.

State or trait markers?

It is difficult enough to find biological state markers that are present only in the active phase of the illness – reliable, replicable across patients and across international differences, of sufficient magnitude to be a meaningful and not only a statistical entity, and a phenomenon that can be integrated within a conceptual framework of the disorder. That goal itself has hardly been achieved in psychopathology. This has not daunted the ambitious to search for trait markers in

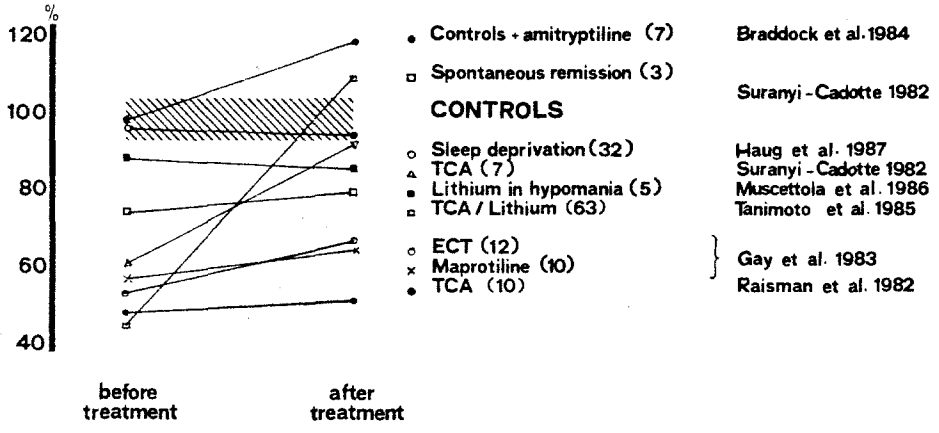

Figure 1 A. Pharmacotherapy and imipramine binding (from [14, 39, 43, 72, 84, 110, 114]).

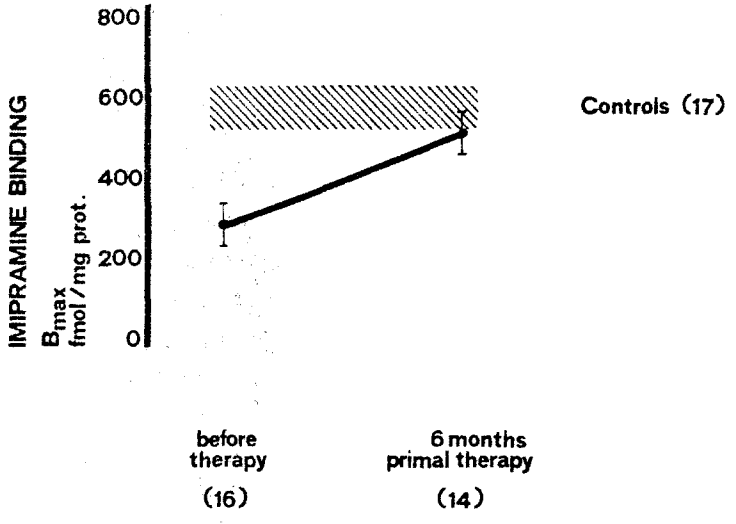

Figure 1 B. Psychotherapy and imipramine binding (from Rose and Murphy[91]).

psychiatry, for its promise is much greater – to detect vulnerability to the illness, to predict favourable response to treatment, and to corroborate clinical diagnostic entities. For any biological abnormality identified in patients to be a trait marker, certain criteria must be fulfilled[89]. First, this factor must be associated with an increased likelihood of the disorder; second, the factor must be heritable; third, the factor must not be transmitted independently of the illness within pedigrees; fourth, the factor must be present independent of clinical state.

Most studies show that MAO activity appears to remain individually stable independent of clinical state. However, MAO activity does not differentiate between clinical syndromes. 5 HT uptake is sensitive to psychopharmacological agents, and thus is not useful to differentiate between drug effects and clinical state. Since imipramine binding, in contrast, does not appear to be greatly modified by drug treatment, a comparison of imipramine binding before and after clinical improvement may reveal 'state' vs 'trait' characteristics. At the moment, it rather indicates the difficulties and discrepancies in such marker studies. Figure 1 A summarises a number of studies of imipramine binding before and after treatment (and remission). Low values before treatment may stay low after treatment, characteristic of a 'trait' marker. They may also increase towards control values, characteristic of a 'state' marker. Figure 1 B represents an unusual and original approach in this field: to overcome the dichotomy between psycho- and pharmacotherapy, this group asked themselves if a proposed biological marker for the depressive syndrome was also found in patients beginning a rather extreme form of psychotherapy. Indeed, imipramine binding was 50% lower than in healthy subjects, and approached normal values after six months primal therapy[91]. These results open up a new dimension, breaking down conventional barriers between concepts often considered incompatible.

Drug effects

A comprehensive review of psychotropic drug effects on platelets is outside the scope of this paper. Nevertheless, in all platelet measures the issue of treatment modification is not unimportant. Since the aim of research in this field is to delineate biological markers of the illness and not epiphenomena of treatment or its withdrawal, carefully controlled studies, and comparison of untreated with treated patients are essential. For example the effect of lithium is to decrease α_2-adrenergic receptors[20, 128], inhibit phosphatidylinositol-specific phospholipase C and adenylate cyclase activity[29], decrease 5 HT uptake[63] but increase the aggregatory response[129]. Tricyclics also decrease α_2-adrenergic recep-

tors[38, 100], whereas a MAO-inhibitor did not[99]. In contrast, imipramine binding seems somewhat resistant to drug-induced change [fig. 1 A].

An important use of platelets is to monitor drug therapy, in particular the tricyclics and MAOI. Most antidepressant drugs inhibit 5 HT uptake after chronic treatment; platelet 5 HT content is thus decreased rapidly. Even a selective NA uptake inhibitor such as maprotoline has been found to modify platelet 5 HT concentrations after long-term administration[69, 122]. The clinical usefulness of these measurements has not been sufficiently recognised – as a functional estimate of drug efficacy, of perhaps more relevance than measurement of the drug levels themselves, since all metabolites of a drug concertedly modify the membrane uptake in an in vivo system.

A role can be envisaged for platelet MAO assays in the near future for the newer, reversible MAOI: to monitor drug compliance, to determine a dosage increase when insufficient MAO inhibition, and also to have a measure of true therapy-resistant cases (no clinical response in spite of adequate MAO inhibition)[102].

Thus the platelet may be finally more useful as a monitor of pharmacological effects in vivo than as a tool to analyse the CNS mechanisms of action of chronically applied psychopharmacological agents via the peripheral model.

Perspectives

The failure to find unequivocal platelet markers for psychiatric illnesses has a number of causes. First, for many years diagnostic differences resulted in inhomogeneity of patient groups and inability to compare across psychiatric schools and national boundaries. Recognition of these problems led to a concerted effort to replace aetiological with operational criteria of symptoms. This is a prerequisite for any search for biological markers of a syndrome. Second, a natural ambition to be the first researcher finding 'the' marker for depression or schizophrenia or agaraphobia resulted in too many 'instant' studies. Description of a new assay was immediately followed by a clinical investigation. Other groups did not replicate the findings, and it was only much later – if at all – that the somewhat pedantic work of delineating normative values was then carried out. Third, assay problems, whether related to actual platelet preparation methods, or the specificity of the ligand or substrate used in a receptor or enzyme assay, are not a minor detail; interpretation of results is crucially dependent on knowing the conditions under which the measurement was made. Fourth, our biochemical models of psychiatric syndromes are perhaps far too reductionist to fit reality. Of markers for schizophrenia, Zubin has said: '... they resemble more the hair colour reflectance measure than the phenylalanine concentration in blood plasma, and that is why we need to be satisfied with patterns of markers rather than search for pathognomonic markers.'[132]. Remembering that there is a massive redundancy in all these neurotransmitter systems – spare receptors abound, enzymes are present in great excess – it is perhaps too much to expect that large differences between control and patient populations be found in parameters that are so buffered for homeostasis.

I have deliberately emphasised the difficulties. Not to induce behavioural despair, but rather to demand a new approach, a new quality to such research. The impetus provided by Pletscher's work on platelet characteristics has enormously advanced our understanding of neurotransmitter mechanisms. The advantages of platelets as a model for illnesses considered related to these neurotransmitters in the CNS, is obvious. We have a more homogeneous, and a more accessible population of cells than in the brain, to study dynamical changes in certain well-defined aspects of neurotransmitter metabolism or receptor function; a physiological or second messenger response can be measured in the same preparations; and, perplexed enough with the shortcomings of animal models of psychic syndromes, we have access to tissue of human origin. I doubt whether 'the' marker for a psychiatric syndrome exists; the search should be weighted rather differently, and be less ambitious. It is to be hoped that proper attention to detail may now yield insights into precisely defined aspects of psychopathology via the pathophysiology of the platelet.

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Platelets as models: Use and limitations

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Key words. 5-Hydroxytryptamine; 5 HT uptake; neurotransmitters; platelet receptors; 5 HT-storage; LDL activation; phosphatidyl-inositol metabolites; $(Ca^{2+})_i$.

The idea of using platelets as an experimental system for neuropharmacology originated in 1955 when experiments with reserpine, an indole alkaloid from *Rauwolfia serpentina,* were carried out. This drug, which was used in the treatment of mental disorders (e.g. schizophrenia), was found to cause a marked depletion of 5-hydroxytryptamine (5 HT) in the brain of rabbits[6]. Since a few years before this discovery, platelets had been reported to contain 5 HT, the suggestion was made that they might be useful for elucidating the mode of action of *Rauwolfia* alkaloids. Indeed, reserpine was then shown to cause a decrease of the 5 HT content in platelets in vivo[7] and in vitro[4], and the in vitro experiments indicated that this decrease was due to a release of the amines from the cells (fig. 1). Later on, various synthetic drugs not related to *Rauwolfia* alkaloids were found to cause a decrease of cerebral 5 HT, and all these compounds also released the amine from platelets. Tetrabenazine, a derivative belonging to the group of 1,2,3,4,6,7-11 bH-benzo(a)quinolizines, was the first synthetic derivative shown to exhibit this effect (fig. 1)[4].

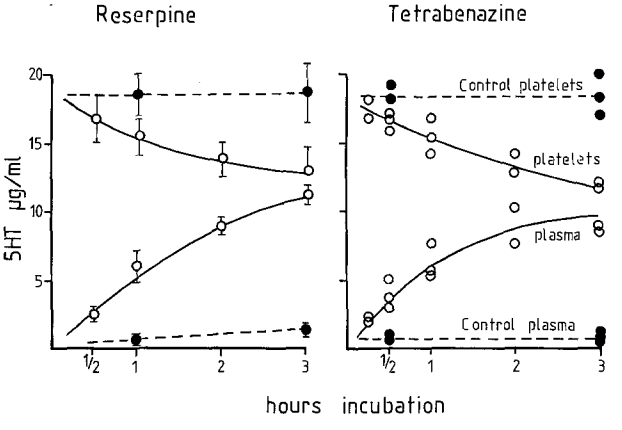

Figure 1. Effect of reserpine (1 µg/ml) and tetrabenazine (20 µg/ml) on the 5 HT content of blood platelets and plasma at 37 °C. The drugs were added to platelet-rich plasma (PRP) at zero time (taken from 4, 3).

Since platelets had also been shown to exhibit a specific uptake of 5 HT at the plasma membrane similar to that in cerebral neurons, the platelets were proposed to be a potential model for 5 HT neurons[3,5].

In the following years the use of platelets as models developed further and many of the speakers in this symposium have made essential contributions to this concept. On the basis of the results presented in this symposium and of other findings, I will try to give a short review and summary of the present knowledge about the neurotransmitter elements of platelets and their potential use as models for other tissues, especially the central nervous system.

Some neurotransmitter elements of human blood platelets are summarized in figure 2. They include an uptake system for 5 HT, intracellular storage organelles (dense bodies),