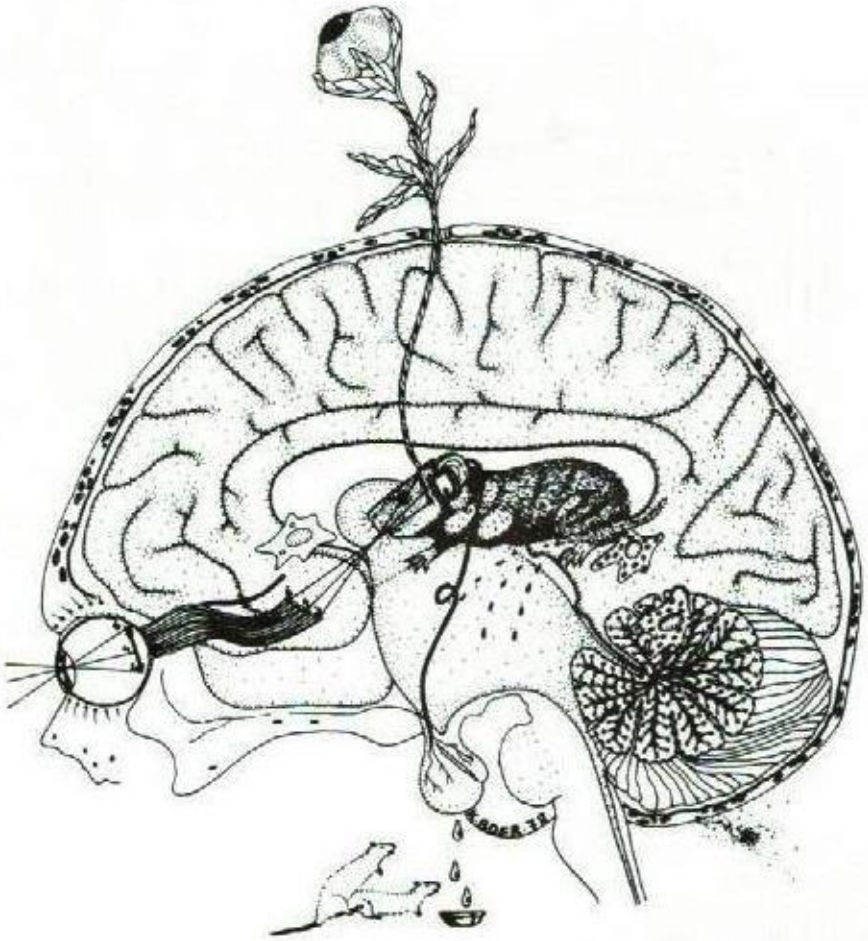
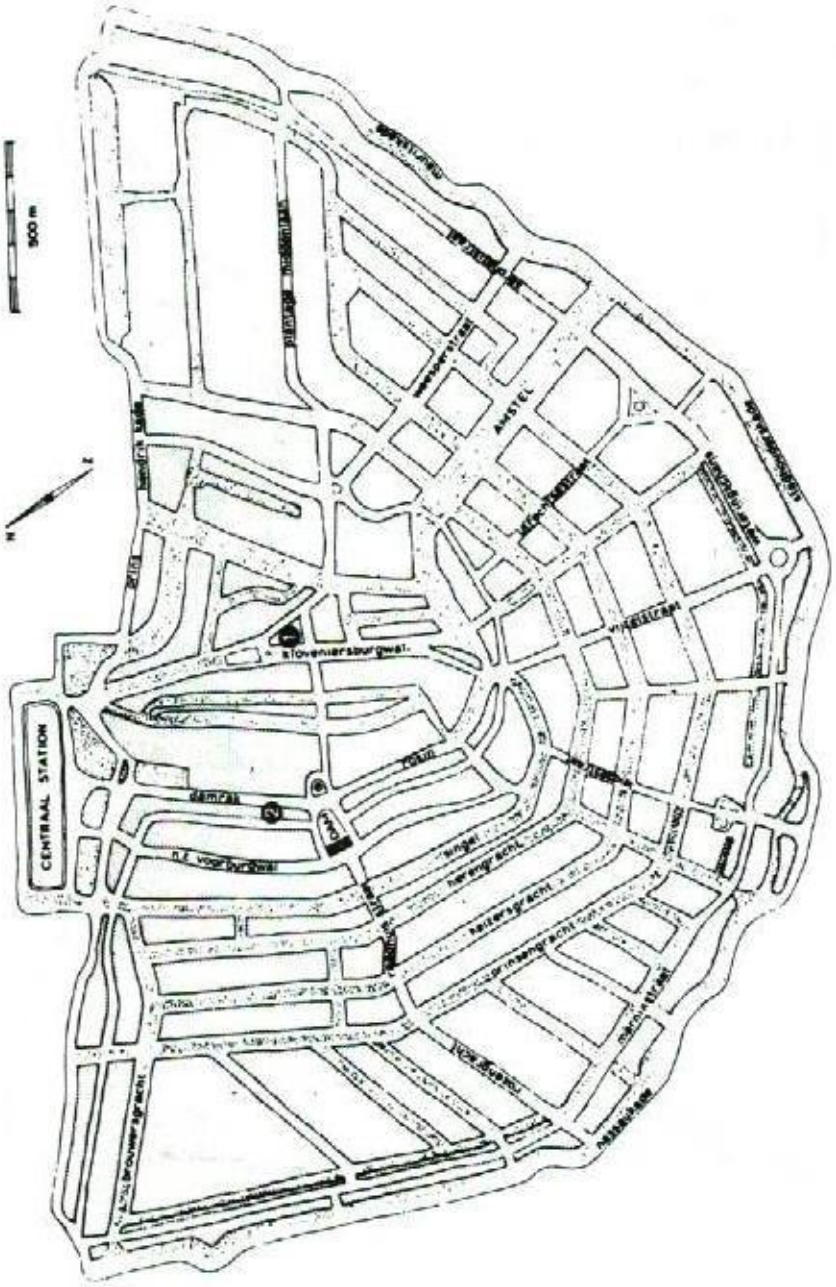
EPSG newsletter
Supplement 1
Editors: P. Pevet and E. Tapp
November 20-24, 1978

FIRST COLLOQUIUM OF THE EUROPEAN PINEAL STUDY GROUP

AMSTERDAM - THE NETHERLANDS





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Reprinted from:
The Pineal Gland of Vertebrates including Man
(Progress in Brain Research, Vol. 52)
Editors: J. Ariëns Kappers and P. Pevet

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Perspectives in pineal functions.

The main function of pineal body probably concerns the reproduction and other special cellular functions, particularly of bone marrow and neuroendocrine tissues.

These functions may be detected after a tolerably lasting latency, with moderate dosages (≤ mg 0,1 Kg b.w. of melatonin (MLT)). Some functions need being integrated by either Somatostatin, or α1-2-α bromocryptin (a synthetic inhibitor of prolactin secretion), as well as by ACTH and corticosteroids. MTL binds itself probably to specific sites of cellular membranes, of megacariocytes especially, with an ensuing platelet discharge. MLT can likewise interact with intracellular nucleotides and nucleosides (H-bond). The interactions of MLT with practically every somatic cell account for the general somatic, subjective and objective consequences of MLT treatment.

The admininstration of moderate doses of MLT to human beings, for periods lasting over five years, has never caused any trouble to appear, and has validly contributed in order that many blood diseases (trombocytopenia, thalassaemia, leukemia), and lung, bewel, uterus, etc., cancer had a more favorable course and prognosis.

Since MLT has no seemingly antiblastic action, some good results in malignant neoplastic diseases are conditioned by the simultaneous employment of moderate doses of antiblastic drugs, such as cyclophosphamide.

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Although "the profession of the pineal is to regulate reproduction whereas its avocation is to influence the functioning of other endocrine organs" (Reiter, 1977), yet some other target organs can be envisaged, and some new insights may be obtained. According to Di Bella et al. (1969) bipolar stimulation of the habenular nuclei (2 V; 40 Hz; square waves; 30-180 min duration) induces a transitory increase in number of blood platelets (Fig. 1). No other stimulated brain area produced any such increase, nor the injection of melatonin (MLT). The different responses may be tentatively attributed either to the secretion by the epithalamo-pineal complex of several indolederivatives (Axelrod, 1974), acting altogether differently than MLT alone, and/or to an activation of eventually melatonergic (Lerner et al., 1959) nerves to the bone marrow (Calvo, 1968; Calvo and Forteza-Vila, 1969). The long latency of the blood platelet increase suggests that MLT or the epithalamic indolamines induce an acceleration of the development from stem- to adult cells, and/or from megakaryocytoblast to mature megakaryocyte. An injection of a watery suspension of lyophilized pineals, from healthy rats killed with fluid N_2, produced inconstant variations in blood platelet number. Injections of watery suspensions of lyophilized epithalami, from the same rats, did, on the contrary, produce a rather uniform increase in blood platelet number.

Since enzymatic O-methylation of catecholamines requires S-adenosyl-methionine as a methyl donor (Axelrod, 1957), MLT was injected together with S-adenosyl-methionine (8-96 μM/kg b.w.). The results were inconsistent.

In splenectomized and epinephrectomized rats, injected MLT induced an enormous increase in number of "dusty" platelets (up to $12x10^6/\mu l$) in the circulating blood, like in some splenectomized, chronically thrombocytopenic patients.

Living megakaryocytes from rat bone marrow showed, in vitro, signs of

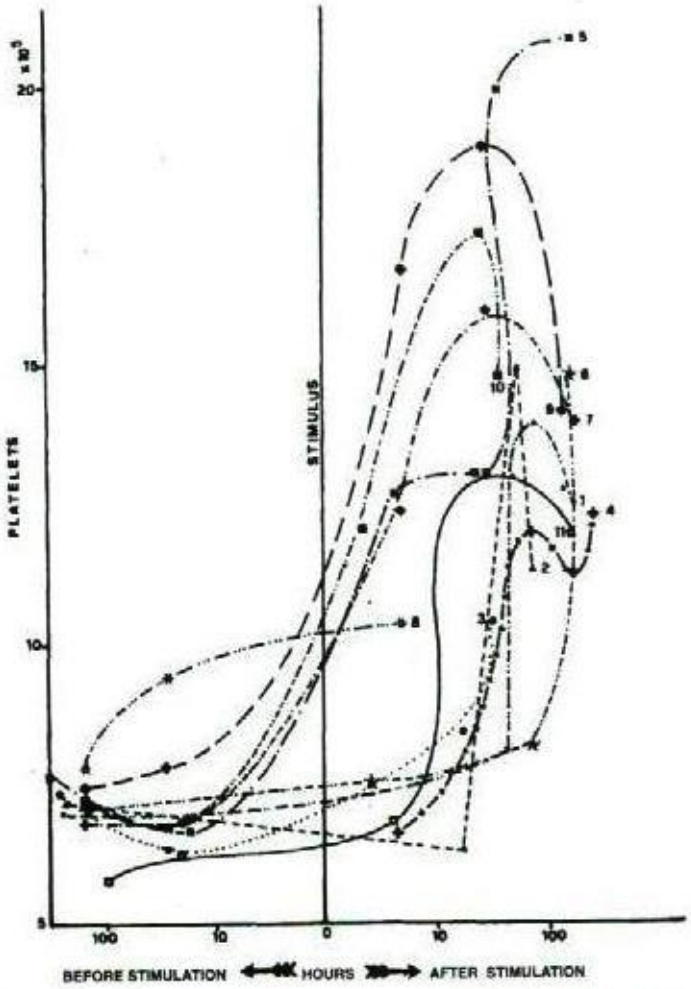

Fig. 1. Peripheral venous blood platelet count of male, adult Wistar rats, permanently implanted with silver electrodes in habenular nuclei of both sides. Platelet number was computed 19.5-321 hr before electrode implantation, as well as 2.25-238.89 hr afterwards. The stimulation was accomplished once (from 21 to 75.3 hr after electrode implantation), or twice, only in 6 over 11 rats (from 51.5 to 96.3 hr after electrode implantation). The blood platelet count was 714,500±78,900/µl (18 counts; M±SD) before the stimulation, and 1268,000±363,000/µl (34 counts; M±SD) after the stimulation; P<0.001. The stimulation (square waves; 2V) lasted 30-33 min in 8 rats and 180 in in 3 rats. The frequency was 40 Hz in 4 rats, and 80 Hz in 7 rats.

platelet discharge when MLT, or ADP, or both, were added. The impression is gained that the newly produced platelets reach either the interstitial spaces of the bone marrow, or the bone marrow blood sinusoids.

Since Pulvertaft (1958) has never observed platelet production in oxygenated bone marrow cultures unless the O_2 supply was stopped, the question

arises as to the relation between glycolysis and respiration, and the effect of indolamine derivatives on platelet production. However, if the smaller platelets are the older ones (Paulus, 1974) then MLT should promote, in splenectomized animals, a migration of platelets from the tissue depot blood to the circulating blood. In many thrombocytopenic patients, MLT has revealed itself to be a fully active substance. This finding is of practical importance as MLT has never shown any toxic effect in several thousands of extremely heterogeneous subjects, quite apart from fickle drowsiness. MLT has, moreover, a marked stimulatory effect on both the erythroid- and the myeloid-bone marrow cell compartments. The erythropoiesis-stimulating effect is revealed by an increased number of basophilic, polychromatic and orthochromatic erythoblasts as well as of reticulocytes, and by an increase of the blood erythrocyte number. This effect has been applied by giving thalassemic patients less blood transfusions.

The myeloid compartment too is vigorously stimulated by MLT. In a thalassemic 14-year-old young girl the number of white blood cells rose to 94,000 after 10 days of MLT administration.

MLT can therefore be very profitably used in leukopenia, in both chronic and acute lymphoblastic leukemia and during antiblastic chemotherapy. Attention must be paid to the fact that considerably lower dosages have to be used in myeloid than in lymphoid leukemia.

Cellular growth control by MLT is, however, not restricted to the bone marrow cell compartment; it extends to practivally all cells of the human body as is shown by both decreasing abnormal growth and stimulating depressed growth.

Abnormal cellular growth is depressed in the blast or immature myeloid or lymphoid cells, which appear in significantly smaller numbers both in the circulating blood and in bone marrow. It so happens that leukemic patients behave as if the disease had become either chronic or healed.

The growth of lung, stomach and breast cancers, as well as of lymphoma and bone sarcoma is equally depressed or discontinued so that the survival time of patients is longer and the symptoms become increasingly less severe.

MLT, at non-pharmacological dosages, does not seem to have a cytotoxic effect, but only a prevailingly cytostatic one. Any subjective or objective intolerance phenomena are absent, apart from some fickle drowsiness state, or a mild increase of libido in 30-40 year-old women.

In cancer patients the regulatory influence on cellular growth by MLT is strongly strengthened by simultaneous lowering of the levels of circulating GH (by means of somatostatin or *p*-oxypropiophenon) and prolactin.

The results of this combined therapy seem to be very good. However, when the cancer mass is very extensive and poorly vascularized or when the cancer cells grow on the poorly vascularized scars of a preceding intervention, the results of the cure are less favourable.

Since neither MLT nor GH exert any cytotoxic effect, a mild antiblastic cure could be simultaneously applied in order to accelerate the reduction or the disappearance of the neoplastic mass.

The following conclusions may be drawn:

(a) Cancer probably arises due to an imbalance of MLT, GH and prolactin.

(b) The viral, physical and chemical etiologic agents of cancer probably act by interfering with the same growth reactions as those promoted by the co-presence of GH and MLT.

(c) MLT probably extends its action to all body cells in the same manner as does GH.

(d) GH has widespread effects on the synthesis of proteins and nucleic acids (Kostyo and Isaksson, 1977), while indoleamines (Da Prada et al., 1971, 1978) and MLT (Di Bella et al., 1976) interfere with nucleic acid metabolism. Biochemically common pathways exist between the two kinds of compounds at the level of the growth processes of every body cell.

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DISCUSSION

R. MILINE: Did you observe mast cells after melatonin treatment?

L. DI BELLA: Mast cells are generaly, but not always increased in number in rat bone marrow after melatonin treatment.