Résumé

Le *myo*-Inositol, en concentration de 0,2%, active la biosynthèse de la benzylpénicilline par des suspensions mycéliales de *P. chrysogenum* dans le tampon de phosphate et d'acétate de phényl. L'action stimulante est inhibée par le 2,4-dinitrophénol, cyanure ou arsénite en concentrations de 0,0006 *M*, 0,005 *M* et 0,005 *M* respectivement. Le *myo*-Inosose-2 en concentration de 0,2% est comparable à l'inositol en sa stimulation de biosynthèse de la pénicilline; la D-glucuronolactone ne présente aucun effet notable en concentration de 0,2%, mais à 0,5%, elle a un effet stimulant. Le *P. chrysogenum* est capable d'accroissement dans un milieu synthétique contenant 2% d'inositol comme seule source de carbonne et le polysaccharide du mycelium fournit après hydrolyse presque uniquement du glucose.

Immunology of Toxemias of Pregnancy
I. Findings of Organ-Specific Antibodies

An abundant literature on the pathogenesis of preeclamptic conditions appears to support the assumption that pathologic immunological mechanisms are participating in the genesis of these conditions. It was the purpose of the present investigation to establish whether antibodies directed against tissues of human body can be demonstrated during pregnancy and, if so, to assess their relationship to the clinical conditions of pregnant women.

Materials and Method. Observations were made on 113 pregnant women of whom, in the course of their pregnancy, 66 were found to suffer from preeclampsia. The remaining 47 women were used as controls. Serological tests for antibodies were carried out in each case as soon as the symptoms of preeclampsia had become apparent as well as on occasion of any examination during pregnancy. Sera were obtained by centrifugation immediately after sampling and stored at – 25°C. Tests for the presence of antibodies were undertaken at the latest within 72 h after sampling by the method of collodion agglutination as described elsewhere[1,2]. The employed antigens were kidney, placenta, liver, and myocardium tissues taken from human bodies in the manner indicated *ibidem*.

Results. Correlation between the incidence of preeclampsia and the findings of antibodies is illustrated by Figure 1. Columns above the central line represent the numbers of positive findings. The results are given separately for the control group, for the mild form of preeclampsia and for its severe form. Statistical evaluations show an association between the incidence of preeclampsia and the findings of the different organ-specific antibodies, with the only exception of those to placenta tissue. This association is, of course, not absolute, as antibodies were detected also in several pregnant women without apparent symptoms of preeclampsia and *vice versa*. It may be pointed out, though, that an analysis of the 13 positive cases of women without apparent symptoms of preclampsia has shown that in six of them the pregnancy took a thoroughly normal course, only whilst the remaining seven developed pathological disorders, *viz.*: other types of toxemia of pregnancy (3 cases), albumin in urine with pathological casts (2 cases), hyperemesis (5 cases), the ratened abortion (1 case), premature labour (3 cases), delayed parturition (4 cases), still birth (4 cases). These complications were combined indifferent ways in the seven pregnant women.

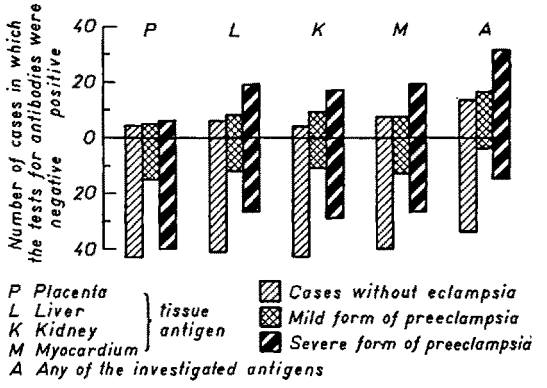

Fig. 1. – Incidence of Preeclampsia in Relation to Production of Autoantibodies

Figure 2 demonstrates a certain association between the occurrence of severe form of preeclampsia and the presence of a higher titre of antibody.

The investigation aimed further at establishing whether the presence of antibodies has any bearing upon the timing of the delivery and on live or still births. A statistically significant correlation between the findings of antibody to myocardium and kidney tissues and the occurrence of still births has been established; no such correlation has been found for the timing of delivery.

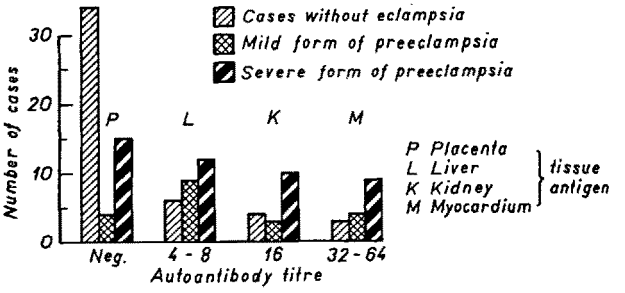

Fig. 2. – Severity of Preeclampsia in Relation to Titre of Autoantibodies

Discussion. Presence of autoantibody[3] has been demonstrated in 47 pregnant women out of a total of 66 preeclamptics. As, in the majority of cases, the test for autoantibody was carried out only once, the possibility cannot be precluded that a repetition of the test might have substantially increased the rate of positive autoantibody findings. This is borne out by the experience gained in separate cases where a repetition of the test was performed. While looking for rational explanations of negative findings in preeclampsia, the possibility should not be neglected that, at the time of collecting blood samples,

[1] V. WAGNER and J. ŠEBA, Dermatologica *112*, 25 (1956).

[2] V. WAGNER, V. REJHOLEC, and V. MALÝ, Ann. rheum. Dis. *15*, 364 (1956).

[3] From the data presented it is by no means clear whether the antibodies are produced following isoimmunization by antigens from the foetus, or by autoimmunization by changed antigenic composition of tissues of pregnant women. The label 'autoantibodies' is therefore tempting though representing only the personal opinion of the authors.

autoantibody may already have been produced but may have been fixed in the tissues.

Autoantibody has been detected also in 13 cases out of a total of 47 pregnant women without preeclampsia. It was already pointed out that seven of these 13 women presented different pathological symptoms not far removed from those observed in preeclampsia. Especially striking is the fact that the pregnancy of four out of these seven women resulted in still births.

The results show that the presence of autoimmunization processes in preeclamptic conditions can be demonstrated. It is true that, for the time being, it is not possible to present an all-embracing picture of the formation of autoantibodies in pathological pregnancy or to assess their exact role in the genesis of the disease. Only further investigations can solve this problem.

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Institute for Microbiology, Medical Clinic, Clinic for Gynecology and Obstetrics of the University of Pilsen and Institute for Medical Organization of the Karl-University of Prague, September 3, 1958.

Résumé

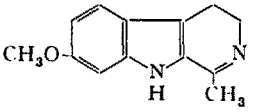
On a contrôlé des femmes enceintes, atteintes d'éclampsie et, chez un groupe d'entre elles, la présence d'autoanticorps contre le placenta, le foie, les reins et le myocarde. On a constaté un taux significativement plus élevé d'autoanticorps chez les femmes dont la grossesse a été compliquée d'éclampsie.

Antagonism between Harmaline and Long-Acting Monoamine Oxidase Inhibitors Concerning the Effect on 5-Hydroxytryptamine and Norepinephrine Metabolism in the Brain

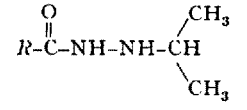
Up to now two principal classes of monoamine oxidase (MAO) inhibitors are known to interfere with monoamine metabolism in the brain. The first group has a very long duration of action and consists mainly of hydrazine derivatives. The second group has a shorter duration of action and contains compounds of various chemical structures, e.g. phenylethyl amines (amphetamine) and harmaline. Several hydrazides, e.g. isonicotinic acid isopropylhydrazide (iproniazid [1]), cause an increase of the 5-hydroxytryptamine (5HT) and norepinephrine (NE) content of the brain which lasts for several days [2]. Harmaline also causes a rise in the level of monoamines in the brain which, however comes back to normal after a few hours [3]. This action is probably due to MAO inhibition which is of long or short duration in the case of hydrazides and harmaline respectively.

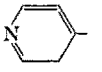
For theoretical and practical reasons it seemed to be of interest to determine whether an interaction exists between harmaline and hydrazides concerning monoamine metabolism in the brain. Therefore, the effect of harmaline on the 5HT and NE rise in brain caused by two different MAO inhibitors of the hydrazide type was investigated.

Experimental. Rats and mice were injected (intraperitoneally) with various doses of harmaline (I) 1 h prior to intraperitoneal administration of two MAO inhibitors of the hydrazide type (II and III [4]).



I harmaline



II *R*: 

isonicotinic acid isopropyl-hydrazide (iproniazid)

III *R*: $HOOC-CH_2-CH_2-CH(NH_2)-$

L-glutamic acid-α-isopropyl-hydrazide

The 5HT content of the brains was measured 16 h after the hydrazide application. Furthermore, determinations of the NE content in the brain of mice pretreated with harmaline 1 h prior to the administration of compound III were carried out. In other animals, the hydrazides were given 6 to 8 h prior to the injection of harmaline and the 5HT content was measured 8 to 16 h after the harmaline administration. Animals treated with hydrazides alone, as well as untreated animals, served as controls.

5HT and NE measurements were carried out by spectrophotofluorimetric methods [5]. The NE in the final extracts was oxidized with potassium ferricyanide at pH 6.

Results

(1) Treatment with harmaline 1 h prior to the administration of iproniazid or compound III antagonized the hydrazide-induced increase of 5HT in the brains of mice and rats. This antagonism was dependent on the harmaline dose (Figure) and could be seen if the hydrazides were administered anywhere from 1/2 to 6 h after harmaline. If the hydrazides were injected more than 6 to 8 h after harmaline, this antagonism did not appear.

(2) The hydrazide-induced increase of norepinephrine in the brain of mice was antagonized by harmaline also. Thus, 16 h after intraperitoneal injection of 113 mg/kg of compound III (equimolecular to 100 mg/kg iproniazid) the norepinephrine content of the brain showed a significant rise of $47 \pm 8\%$ as compared to untreated animals ($p < 0{\cdot}01$). Compound III (113 mg/kg) administered 1 h after 10 mg/kg of harmaline did not cause an increase of NE in the brain at all ($0 \pm 5\%$ as compared with untreated controls).

(3) If harmaline was administered 6 to 8 h after the hydrazides, the hydrazide-induced increase of 5HT could not longer be counteracted. Thus, the 5 HT contents of the

[1] Trade name: Marsilid.

[2] S. Udenfriend, H. Weissbach, and D. F. Bogdanski, Ann. N. Y. Acad. Sci. *66*, 602 (1957); J. Pharmacol. exp. Ther. *120*, 255 (1957). – A. Pletscher, Exper. *12*, 479 (1956); Helv. physiol. pharmacol. Acta *14*, C76 (1956); Schweiz. med. Wschr. *87*, 1532 (1957). – P. A. Shore and B. B. Brodie, Science *127*, 704 (1958).

[3] S. Udenfriend and H. Weissbach, Proc. Soc. exp. Biol. Med., N. Y. *97*, 748 (1958). – S. Udenfriend, B. Witkop, B. G. Redfield, and H. Weissbach, *Biochemical Pharmacology 1*, 160, Pergamon Press Ltd., London (1958).

[4] Compound III was synthetized by Dr. B. Hegedüs, Chemical Research Department of F. Hoffmann-La Roche & Co. Ltd.

[5] D. F. Bogdanski, A. Pletscher, B. B. Brodie, and S. Udenfriend, J. Pharmacol. exp. Ther. *117*, 82 (1956). – P. A. Shore and J. S. Olin, J. Pharmacol. exp. Ther. *122*, 295 (1958).