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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*Résumé*

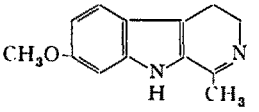
On a contrôlé des femmes enceintes, atteintes d'éclampsie et, chez un groupe d'entre elles, la présence d'autoanticorps contre le placenta, le foie, les reins et le myocarde. On a constaté un taux significativement plus élevé d'autoanticorps chez les femmes dont la grossesse a été compliquée d'éclampsie.

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

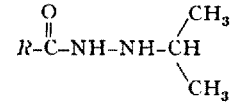
Up to now two principal classes of monoamine oxidase (MAO) inhibitors are known to interfere with monoamine metabolism in the brain. The first group has a very long duration of action and consists mainly of hydrazine derivatives. The second group has a shorter duration of action and contains compounds 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.

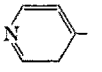
For theoretical and practical reasons it seemed to be of interest to determine whether an interaction exists between harmaline and hydrazides concerning monoamine metabolism in the brain. Therefore, the effect of harmaline on the 5HT and NE rise in brain caused by two different MAO inhibitors of the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

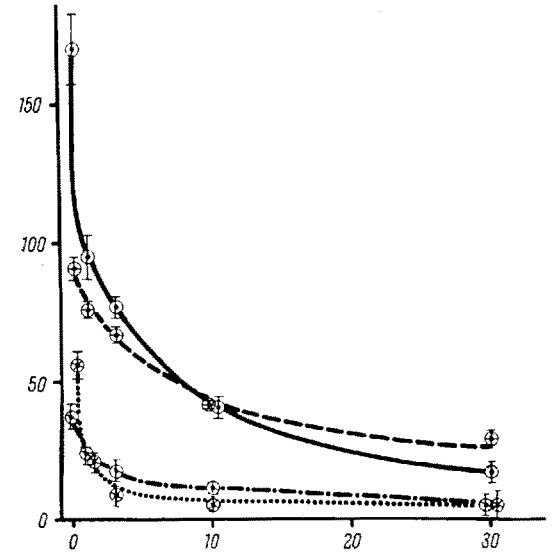
[2] S. Udenfriend, H. Weissbach, and D. F. Bogdanski, Ann. N. Y. Acad. Sci. *66*, 602 (1957); J. Pharmacol. exp. Ther. *120*, 255 (1957). – A. Pletscher, Exper. *12*, 479 (1956); Helv. physiol. pharmacol. Acta *14*, C76 (1956); Schweiz. med. Wschr. *87*, 1532 (1957). – P. A. Shore and B. B. Brodie, Science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

brains of animals after the combined hydrazide-harmaline treatment were not different from those of animals treated with the hydrazides alone.




Inhibition of the hydrazide-induced increase of 5-hydroxytryptamine (5HT) in the brain of rats and mice.

Ordinate: Percentage increase of 5HT in brain, as compared with untreated controls.

Abscissa: Harmaline dose in mg/kg.

The hydrazides were injected intraperitoneally in doses equimolecular to 100 mg/kg iproniazid 1 h prior to administration (intraperitoneal) of harmaline. Measurement of 5HT 16 h after application of the hydrazides. Animals treated with the hydrazides only (0 mg/kg harmaline) served as controls.

——— Hydrazide III, rats; – – – – – Iproniazid, rats;
····· Hydrazide III, mice; –·–·–· Iproniazid, mice.

Each point represents the average of 4–8 measurements. Vertical lines: standard deviation.

*Discussion.* The inhibition of the hydrazide-induced 5HT and NE rise in the brain after harmaline pretreatment is probably due to the fact that harmaline and the hydrazides compete for the same receptor site on the enzyme MAO. Thus, the short-acting harmaline probably blocks the receptor which then cannot be attacked by the long-acting hydrazide any more. Harmaline, however, does not reverse the action of hydrazides once the latter compounds have caused a monoamine rise in the brain. Thus, harmaline, given after the hydrazides, has no effect on the hydrazide-induced increase of the monoamines. This may be explained by the fact that hydrazides cause an irreversible damage to MAO, or that the hydrazide-enzyme bond is very strong and cannot be reversed by harmaline once it has taken place.

The above described antagonism between harmaline and hydrazides may serve as a tool to separate the hydrazide effects due to MAO inhibition from those caused by other mechanisms. Thus, the pharmacological effects of hydrazides which are counteracted by harmaline are probably due to MAO inhibition, whereas those effects which cannot be antagonized by harmaline must be caused by different mechanisms. Preliminary results show that some hydrazide-induced alterations of the reserpine and benzoquinolizine effects on brain are probably due to interference with monoamine metabolism. Iproniazid and compound III counteract some central nervous actions of reserpine and benzoquinolizines (e.g. potentiation of sedation and narcosis potentiation[6]). This effect of the hydrazides is abolished by pretreatment with harmaline. By further investigation along this line it may be possible to get additional evidence concerning the role of MAO inhibition in drug action.

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*Medical Research Department of F. Hoffmann-La Roche & Co. Ltd., Basel (Switzerland), October 31, 1958.*

*Zusammenfassung*

Vorbehandlung mit Harmalin hemmte den Anstieg von 5-Hydroxytryptamin (5HT) und Noradrenalin (NE) im Gehirn von Ratten und Mäusen, welcher durch zwei langdauernd wirkende Monoaminoxydasehemmer verursacht wurde (Isopropylhydrazide von Isonikotinsäure und α-Isopropylhydrazid von Glutaminsäure). Wurde Harmalin 6–8 h nach den Hydraziden appliziert, so konnte kein Absinken des durch das Hydrazid erhöhten Monoamin-Gehaltes beobachtet werden. Mit Hilfe dieses Antagonismus zwischen Harmalin und Hydraziden dürfte es möglich sein, mehr Kenntnis über die Rolle der Monoaminoxydase bei der Wirkung von Pharmaka zu gewinnen.

[6] M. CHESSIN, B. DUBNICK, E. R. KRAMER, and C. C. SCOTT, Fed. Proc. *15*, 409 (1956). – M. CHESIN, E. KRAMER, and C. C. SCOTT, J. Pharmacol. exp. Ther. *119*, 453 (1957). – H. BESENDORF and A. PLETSCHER, Helv. physiol. pharmacol. Acta *14*, 383 (1956). – P. A. SHORE and B. B. BRODIE, Proc. Soc. exp. Biol. Med., N. Y. *94*, 433 (1957). – A. PLETSCHER, Schweiz. med. Wschr. *87*, 1532 (1957). – A. PLETSCHER, H. BESENDORF, and H. P. BÄCHTOLD, Arch. exp. Path. Pharmak. *232*, 499 (1958).

## The Effect of Colchicine on Plasma Unesterified Fatty Acids[1]

Although the influence of colchicine on mitotic activity has been studied extensively, comparatively little attention has been paid to other pharmacological effects of this alcaloid[2,3]. STERNBERGER and FERGUSON[4] found that a single lethal intravenous dose of colchicine causes 'fat nephrosis', which is probably a manifestation of some derangement of lipid transport. Since in $CCl_4$ poisoning a similar derangement occurs in association with increased plasma unesterified fatty acid (UFA) concentrations[5,6], it was decided to investigate the effect of colchicine on UFA.

*Materials and Methods.* 4 mg of colchicine/kg of body weight were given intravenously to male, white rats, weighing 150–300 g. The control animals received equal amounts of physiological saline. All animals were exsanguinated under Nembutal anesthesia through the inferior vena cava 17–20 h after the injection. The blood was chilled immediately and the specific gravity determined[7].

[1] Supported by the National Heart Institute, Bethesda, Md.

[2] P. F. ROBINSON and R. R. RUNGE, Fed. Proc. *15*, 154 (1956).

[3] R. W. BALEK, J. J. KOCSIS, and E. M. K. GEILING, Fed. Proc. *15*, 397 (1956).

[4] S. S. STERNBERGER and F. C. FERGUSON, Cancer *7*, 607 (1954).

[5] G. L. SELDEN and U. WESTPHAL, Proc. Soc. Exp. Biol. Med., *89*, 159 (1955).

[6] J.J.SPITZER and H.I.MILLER, Proc. Soc. Exp. Biol. Med. *92*, 124 (1956).

[7] R. A. PHILLIPS, D. D. VAN SLYKE, V. P. DOLE, R. EMERSON P. B. HAMILTON, and R. M. ARCHIBALD, Bull. U.S. Army Med. Dept. *41*, 66 (1943).