Preliminary Investigations on the Influence of Reserpine Therapy on Adrenocortical Function in Schizophrenia[1]

HOAGLAND, RINKEL and HYDE[2] studied the metabolic effects of the administration of lysergic acid diethylamide and ACTH to schizophrenic patients. They have discussed the biochemical aspects of schizophrenia in relation to adrenaline and serotonin metabolism, and the comparatively poor response of the adrenals of schizophrenic patients to stimulation by ACTH. KLINE[3] has produced further evidence of the value of reserpine therapy in the symptomatic treatment of schizophrenia and other mental disorders. We have studied the urinary excretion of adrenal cortical steroids in 8 schizophrenic patients given graded doses of reserpine over a four-week period. The recently described rapid and simple method of APPLEBY, GIBSON, NORYMBERSKI and STUBBS[4] for the assessment of adrenocortical function has been used in these experiments. The method measures selectively the total 17-hydroxylated C_{21} adrenal steroids (17–OH, K. G. S.). Since difficulty is encountered in collecting complete 24 h specimens of urine from mentally disturbed and overactive patients, we have expressed our results as 3 day average rations of urinary 17–OH, K. G. S. to urinary creatinine.

The results are summarized in the Table.

The influence of reserpine therapy on urinary 17-OH, K.G.S./creatinine ratio in schizophrenic patients

Patient	Ratio of 17-OH, K.G.S./creatinine			
	No reserpine	Dosage of reserpine		
		after 2 weeks therapy with reserpine (1–1·5 mg/day)	3rd week (6 mg/day)	4th week (9 mg/day)
D.N.	0·0106	0·0106	–	0·0103
F.L.*	0·0217	0·0110	–	0·0140
F.R.*	0·012	0·0085	–	0·0080
M.Y.*	0·017	0·006	–	0·0203
P.H.*	0·0193	0·0110	–	0·0101
R.N.	0·0133	0·0100	–	0,0112
V.S.*	0·0360	0·0100	–	0·0160
W.N.	0·0218	0·0150	–	0·0180

A statistical analysis of our results shows a significant reduction from the control values in the 3-day average ratios of urinary 17–OH, K.G.S./creatinine at the 1–1·5 mg dosage level for reserpine ($P = 0{\cdot}02$–$0{\cdot}01$). The results obtained at the fourth weak compared with the controls are not highly significant ($P = 0{\cdot}1$–$0{\cdot}05$) indicating that further studies at the higher dosage levels are required. Since there was individual clinical variation in response to the chronic dosage with reserpine, it is not surprising to note a lack of uniformity regarding 17 OH, K.G.S. excretion at this phase of the treatment. Our results show quite clearly that the lower dosage level of reserpine did not elicit stimulation of the pituitary adrenal axis. GAUNT, RENZI, ANTONCHAK, MILLER, and GILMAN[5] showed that reserpine did not depress adrenal function in guinea pigs, but raised the question of the possibility of reserpine dampening the mechanism discharging ACTH in psychogenic stress.

GOODMAN, FLORSHEIM, and TEMPEREAU[6] have shown that after 25 days administration of reserpine, 11 out of 17 patients showed no eosinopenic response in the Thorn test. These results, while possibly indicating a reduced functional state of the hypothalamic-pituitary adrenal axis, should be accepted with reserve in view of the criticism of the eosinophil response test by TYLER, MIGEON, and CASTLE[7]. Furthermore, WINSOR[8] has demonstrated a lack of influence of reserpine treatment (0·5 mg dosage levels) on the adrenocortical response in normals.

In unpublished work, SPANNER, GINZEL, and BOSCOTT, have confirmed some of the results of HOAGLAND *et al.* relating to the increased adrenocortical activity in response to lysergic acid diethylamide, but as indicated by 17–OH, K.G.S. excretion. Furthermore, agents which we have studied which block the psychogenic effects of L.S.D. depressed also the adrenocortical activity simultaneously. The possibility that the sedation induced by reserpine in schizophrenic patients, is linked with a reduced output of adrenocortical steroids must therefore be considered.

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Zusammenfassung

Die Arbeit befasst sich mit der Harnausscheidung von Nebennierenrinden-Steroiden bei 8 schizophrenen Patienten vor und während der Behandlung mit allmählich ansteigenden Dosen von Reserpin. Eine statistisch nachweisbare Verringerung der Nebennierenrindenfunktion wurde während der Behandlung mit Reserpin beobachtet. Eine kritische Betrachtung dieser Ergebnisse wird vorgenommen.

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The Anticancerous Action of 6-Azauracil(3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine)

In the course of the last few years several analogs of the nucleic acids purine bases were tested in the chemotherapy of experimental neoplastic diseases. Some of these, e.g. 8-azaguanine and 6-mercaptopurine, have already found their application in clinical practice.

In this laboratory several analogs of the pyrimidine bases of the nucleic acids were studied and in the course of this research we have found that 6-azauracil, previously prepared by SEIBERT[1], exhibits a markedly pronounced antibacterial effect against *E. coli* in synthetic media. This effect may be abolished either by uracil or cytosine. The inhibitory action of 6-azauracil in the presence of uracil follows the law of strictly competitive inhibition[2,3]. In synthetic medium 6-azauracil also exerts a strongly synergistic effect with streptomycin. However, no inhibitory action by 6-azauracil was noted in experiments with animals infected with *Salmonella typhi*[4].

Table

	50% Mortality in days	P
Control	19·7	
6-azauracil	23·2	0·02
6-mercaptopurine	23·5	0·01

We have also tested the anticancerous effect of 6-azauracil by following the mortality curves of white mice (strain H) in groups of 10 animals inoculated intraperitoneally with 4,000,000 cells of the Ehrlich ascites carcinoma. 6-Mercaptopurine, which is known to have a marked anticancerous effect on this tumor[5], was given for comparison. The treatment was started 24 h after the transplantation of the tumor and was continued for 10 days. Because of the practical non-toxicity of 6-azauracil, a relatively high dose was used. The individual daily dose, given intraperitoneally, was 250 mg of 6-azauracil per kg and 30 mg of 6-mercaptopurine per kg. The 50% mortality of the animals was calculated by the method of REED and MUENCH[6]. The reliability of the values obtained was judged by the *t*-test. The results are given in the Table.

Although 6-mercaptopurine had in our experiments a lower cancerostatic effect than described in the literature[5], which may be due to the different strain of the Ehrlich ascites carcinoma used by us, the results show that the anticancerous effect of 6-azauracil is of the same order of magnitude as that of 6-mercaptopurine.

Since 6-azauracil is practically non-toxic and yet active against the Ehrlich ascites carcinoma *in vivo*, it seems probable that the neoplastic tissues differ in their metabolism of pyrimidine bases or nucleic acids, respectively. RUTMAN *et al.*[7] reached an analogous conclusion from a study of the distribution of C^{14}-marked uracil in various tissues of rats, where they found that only hepatoma contained appreciable amounts of the isotope. This uptake of uracil, exhibited solely by cancerous cells, would then explain the specific cancerostatic effect of its structural analog 6-azauracil.

The anticancerous activity is now being tested with other experimental tumors, and, because of its practical non-toxicity, clinical tests are envisaged.

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Zusammenfassung

Es wurde die kanzerostatische Wirkung des 6-Azauracils auf den Ehrlich-Aszites-Tumor beschrieben und mit der Wirkung des 6-Mercaptopurins verglichen.

Conséquences de la thymectomie sur la formule leucocytaire chez le cobaye

Il a été communiqué précédemment que chez le cobaye l'administration prolongée d'extrait de thymus de BEZSSONOFF et COMSA entraînait des modifications amples de la formule cytologique du sang, de la rate et de la moelle[1]. Ces modifications peuvent être résumées comme suit:

Les lymphocytes augmentent de nombre partout.

Les éosinophiles diminuent de nombre dans le sang et dans la rate. Elles augmentent dans la moelle. Ce sont surtout les formes mûres qui augmentent de nombre, de telle sorte qu'on a l'impression que l'hyperthymisation bloquait le débit des éosinophiles de la moelle vers le sang.

Ces remarques devaient être complétées par l'épreuve contraire, l'examen cytologique du sang chez le cobaye thymiprive.

Expérience. Chez 15 cobayes mâles de 170 à 190 g d'un élévage consanguin le thymus a été extirpé suivant la méthode décrite ailleurs[2]. Les animaux ont été examinés par la suite par groupes de 3 à 6, 12, 18, 24 et 30 jours après l'opération. Les examens cytologiques usuels ont été fait sur le sang prélevé par ponction du cœur. Le comptage différentiel est fait sur 200 cellules.

Les mêmes examens ont été faits sur 10 animaux normaux du même poids.

Les resultats sont résumées au Tableau.

Ont peut en dégager la conclusion suivante:

L'extirpation du thymus a pour conséquence une légère leucopénie, qui va en s'accentuant pendant 30 jours.

Cette leucopénie est essentiellement la suite de la baisse du taux des lymphocytes.

Le taux des éosinophiles augmente très mesurablement.

Ces deux modifications sont exactement de sens opposé à celles que l'on a pu observer chez le cobaye hyperthymisé.

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