In rats which consumed small quantities of nicotine no switching to consumption of cocaine solution took place during this period. Switching of the animals of group 2 of this kind took place only after 4 months of consumption of nicotine solution (Tables 2 and 3).

Switching of the rats to drinking cocaine solution on withdrawal of the nicotine solution from them is evidence mainly that prolonged consumption of nicotine leads to the development of physical dependence, as takes place during consumption of other substances inducing toxicomania: The times of development of dependence were connected with the quantity of nicotine consumed daily. In the present experiments, in rats consuming a mean dose of 1.788 mg/kg nicotine daily, dependence developed after 8 weeks, whereas in rats with a daily consumption of nicotine of 1.226 mg/kg it developed after 16 weeks.

These data thus indicate that animals may in principle develop nicotine toxicomania by voluntary consumption of nicotine. Animals consuming nicotine can be used as an experimental model for the study of the pathogenetic mechanisms of development of nicotine toxicomania and preclinical evaluation of the effectiveness of new chemical compounds for use in the treatment of addiction to tobacco smoking.

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β-ENDORPHIN AND ENDOGENOUS ETHANOL BLOOD LEVELS IN PATIENTS WITH ALCOHOLISM

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A series of model experiments on rats has shown that animals predisposed to the development of ethanol dependence possess a number of particular behavioral, neurochemical, and biochemical features [1-3]. However, it is not yet clear which of these characteristics are of predominant importance in the formation of alcoholsm. Since studies on animals have revealed the possible role of endogenous ethanol (EE) and of some neuropeptides in the development of experimental alcoholism [3, 5], it is of considerable interest to study these parameters in patients with chronic alcoholism.

The aim of this investigation was to study EE and β-endorphin (β-E) levels and their possible pathogenetic role in patients with chronic alcoholism.

EXPERIMENTAL METHOD

Altogether 58 men aged 25-42 years with stage II of chronic alcoholism were studied; their alcohol tolerance was high, and had remained constant during the last 3-6 years before the investigation. By depth and structure of the borderline psychopathological disorders which were observed in the patients outside the period of abstinence, the patients were divid-

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TABLE 1. EE and β-E Levels and Coefficients of Correlation (r) between Them in Different Subgroups of Alcoholics and Normal Subjects

Group of subjects	EE, μg/ml	Coefficient of correlation (r)	β-E, fmoles/ml
Healthy controls	19,3	+0,62*	15,7
Alcoholics			
altogether	14,5	+0,07	17,2
1-subgroup	16,3	+0,65*	14,4
2-nd »	14,3	—0,5*	14,4
3-rd »	14,0	+0,26	16,7
4-th »	14,7	+0,20	24,8**

Legend. *) r differs significantly from 0, $P < 0.05$; **) significant difference from control, $P < 0.05$.

ed into four subgroups: 1) with no psychopathological manifestations or with readily reversible asthenovegetative symptoms, 2) with reactive or cyclothymic-like subdepressions, 3) with psychopathic disorders, and 4) with atypical subdepressions against the background of characterologic personality disorders. The patients were studied 30-40 days after admission to the clinic, and during the 5 days before investigation all pharmacologic methods of treatment were withheld. Blood (6 ml) was taken from the cubital vein at the same time of day (10 a.m.), 2 h after breakfast. The β-E concentration was determined by radioimmunoassay using kits from Amersham Corporation (England). The EE concentration was determined by gas chromatography on a Soviet LKhM-8 MD chromatograph by the method described previously [3]. The control group consisted of 54 normal subjects. The data were subjected to statistical analysis by Student's t test. Correlation analysis was carried out by the usual methods [4] on a "Diehl Alphatronic" microcomputer.

EXPERIMENTAL RESULTS

As Table 1 shows, no significant differences were found between β-E levels in patients with alcoholism as a whole and normal subjects. However, there was significantly higher β-E levels in the subgroup of patients with the severest grade of psychopatholic disorders, namely atypical subdepressions against the background of characterologic personality changes. These disturbances, in the form of long-lasting monotonous states of depression with elements of inertia, apathy, and anxiety were observed in emotionally impoverished patients without initiative, who had lost most of their previous interest and social connections. In patients with relatively mild psychopathologic disorders (asthenovegetative, psychopathic, cyclothymic-like) the basal β-E levels did not differ significantly from the control. In alcoholics and normal subjects wide variability of the basal EE concentrations was observed, although it fluctuated within the same limits (Fig. 1). Unlike normal subjects of the control group, in whom the distribution of EE concentrations was bimodal in character, in the chronic alcoholics EE levels were shifted toward the region of lower concentrations, and their distribution was monomodal. No significant differences in EE concentrations could be found between patients with different levels of psychopathologic disorders.

Correlation analysis (Table 1) showed positive correlation between the EE and β-E concentrations in normal subjects and in the subgroup of alcoholics who either had no psychopathologic disorders or they were very mild and easily reversible. Negative correlation was found in the subgroup of patients with cyclothymic-like affective disorders. Both in the alcoholics as a whole and in subgroups with psychopathic and atypical affective disorders, significant correlation was not found between the parameters studied.

These results agree with the observations of Naber et al. [7], who found no difference in the basal β-E concentrations between chronic alcoholics (not subdivided on the basis of clinical criteria) and normal subjects. It must be noted that the peripheral β-E level also was raised in patients not addicted to alcohol, in psychopathogic disorders similar to those observed in our own patients of the 4th subgroup [8]. This, in our view, is evidence that psychopathologic disorders in chronic alcoholism and in other mental diseases may have common pathogenetic mechanisms.

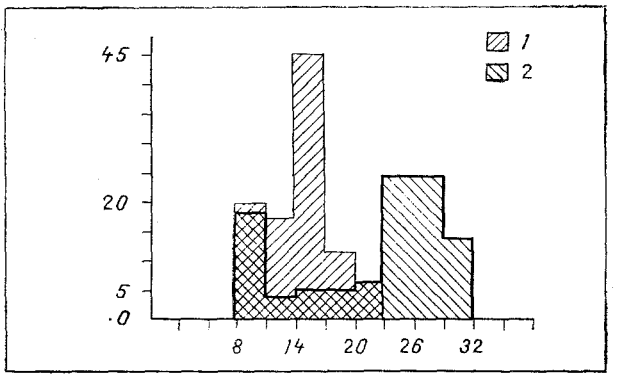

Fig. 1. Distribution of blood EE levels in chronic alcoholics (1) and normal subjects (2). Abscissa, EE level (in μg/ml; ordinate, number of subjects (in per cent).

The fall in the EE concentration in chronic alcoholics may perhaps be due to induction of ethanol-oxidizing enzyme systems as a result of chronic alcoholic poisoning. However, data showing that the background EE level is lower in inbred mice with genetically determined alcoholic motivation suggest that activity of ethanol-metabolizing enzyme systems is increased *ab initio*. Chronic alcoholic poisoning, by changing activity of ethanol-oxidizing enzyme systems, also leads to a change in shape of the EE concentration distribution curve in alcoholics.

The raised peripheral β-E level discovered in one of the groups of alcoholics in these experiments was evidently not connected with the pathogenetic mechanisms of development of the alcoholic addiction syndrome proper in these patients, but may probably reflect formation of psychopathologic disorders in chronic alcoholic poisoning.

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