We have also shown that the blood ADH cannot play an essential role in the elimination of exogenous ethanol in man, but activity of the enzyme is high enough to regulate the endogenous ethanol level [3].

In the last few years attempts have been made to associate differences in predisposition to alcohol consumption with the endogenous ethanol level [1]. According to data in [1], PW, IG, and PE animals have identical blood ADH activity. Consequently, the lower endogenous ethanol level in the tissues of PE animals than of PW rats [1] is due entirely to increased ADH activity in the liver. The blood ADH evidently does not participate in mechanisms responsible for the preference phenomenon in animals.

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EFFECT OF IMMUNOSTIMULANTS ON TUBULAR SECRETION OF XENOBIOTICS IN THE KIDNEY

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Secretion of organic substances by cells of the proximal portion of the renal tubules plays an essential role in the removal of foreign substances, including drugs, from the body and it is one of the important factors in pharmacokinetics. Features of similarity between tubular secretion and immune processes were observed in 1970 [1]. It was shown later that tubular secretion is subject to substrate induction [4, 8], which is linked with neogenesis of transport proteins. The secretory-transport system has been shown to recognize what is "its own" and what is "foreign," as a result of which endogenous substances are not secreted under ordinary conditions [2]. It has been shown in the writers' laboratory that immunosuppressants selectively inhibit tubular secretion [5, 11], even in the absence of any marked catabolic action. Meanwhile tubular secretion is enhanced by agents which stimulate protein biosynthesis: potassium orotate [6], retabolil (nandrolone) [10], and testosterone [9].

In the investigation described below the effect of immunostimulants with no anabolic action was studied on secretory transport; the bacterial lipopolysaccharide prodigiosan and the synthetic compound levamisole were used.

EXPERIMENTAL METHOD

Experiments were carried out on 45 noninbred albino rats weighing 180-220 g. Renal tubular secretion was determined as diodone excretion [7] several times in each animal: before the experiment began, on the day after each injection of the test substance, and 3 and

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TABLE 1. Effect of Prodigiosan on Tubular Secretion in Rats (M ± m, n = 6)

Experimental conditions	Diodone excretion, %/h	Diuresis, ml/h
Initial background	53,5±1,44	4,7±0,20
Injection of prodigiosan:		
1-st	58,4±1,90†	5,1±0,25
2 nd	64,9±2,34*	5,1±0,28
3-rd	64,2±2,85*	4,9±0,21
3 days after injection of prodigiosan	60,9±3,91	4,9±0,29
7 days after	53,4±1,96	5,2±0,46

*P < 0.001, †P < 0.05 compared with background.

TABLE 2. Effect of Levamisole (10 mg/kg) on Tubular Secretion in Rats (M ± m, n = 16)

Experimental conditions	Diodone excretion, %/h	Diuresis, ml/h
Initial background	60,5±2,49	5,2±0,28
Injection of levamisole:		
1-st	70,6±3,37*	5,8±0,36
2-nd	73,8±5,34*	6,4±0,56
3-nd	74,3±2,56†	6,0±0,41
3 days after injection of levamisole	77,2±2,97†	6,5±0,47*
7 days after	67,2±3,56	5,9±0,19*
10-12 days after	61,2±2,87	5,8±0,32

*P < 0.05, †P < 0.001 compared with background.

TABLE 3. Effect of Levamisole (50 mg/kg) on Tubular Secretion in Rats (M ± m, n = 9)

Experimental conditions	Diodone excretion, %/h	Diuresis, ml/h
Initial background	57,8±2,22	5,1±0,34
Injection of levamisole:		
1- st	57,0±3,61	4,9±0,61
2- nd	60,6±2,32	5,9±0,57
3- rd	58,5±4,11	6,1±0,74
3 days after injection of levamisole	55,2±2,00	5,2±0,58
7 days after	61,5±4,87	—

7 days or more after the end of the injections, Diodone excretion per hour was expressed as a percentage of the injected dose. The results were subjected to statistical analysis. Diuresis was measured at the same time, to give some idea of possible changes in urine excretion. Prodigiosan was injected subcutaneously in a dose of 50 μg/kg three times on alternate days, in an immunostimulating dose of 10 mg/kg, and in a dose of 50 mg/kg which does not have that effect.

EXPERIMENTAL RESULTS

The first injection of prodigiosan caused an increase in tubular secretion (Table 1). The maximal increase in diodone excretion amounted to 21%. Tubular secretion 1 week after the end of the prodigiosan injections did not differ from that observed initially. Diuresis remained stable throughout the experiment.

After the first injection of levamisole in a dose of 10 mg/kg diodone excretion increased by 17%; later it rose gradually to a maximum 3 days after the end of the injections,

when it was 28% higher than initially (Table 2). Stimulation of tubular secretion lasted longer than in the previous series of experiments. Not until 10-12 days after the end of the levamisole injections was it restored to normal. Stimulation of diuresis occurred only during the first few days after the end of levamisole injections. Diuresis is known not to be directly dependent on tubular secretion [2].

Since levamisole is an immunomodulator and since its effect depends on dose, a larger dose of the drug with no immunostimulant action was tested. Under these circumstances tubular secretion was unchanged (Table 3). Thus levamisole activates transport of foreign substances in the proximal portions of the renal tubules only in an immunostimulating dose.

Although the mechanism of the immunostimulant action of the test substances still remains largely unexplained, in our view there is a definite common factor in their action on tubular secretion and on the macrophage-lymphocytic system. For example, changes in the cyclic nucleotide concentrations in lymphocytes, with elevation of the cGMP level and lowering of the cAMP level under the influence of lipopolysaccharides and levamisole, have been reported [15]. At the same time, it has been shown that xanthines, which increase the intracellular cAMP concentration, reduce transport of substances to be secreted [13]. One explanation of the stimulating effect of levamisole on T lymphocyte function is its conversion *in vivo* into the more active compound oxo-mercaptophenylimidazolidine, which interacts with protein thiol groups of tuberculin, leading to the formation and improving the functioning of microtubules that are essential for normal leukocyte activity [12, 14]. Meanwhile evidence has been obtained that the microtubular system participates in the mechanism of secretory transport [3]. The possibility thus cannot be ruled out that the stimulating action of these substances on tubular secretion and on the macrophage-lymphocytic system of immunity possesses common mechanisms.

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