Clinical and experimental studies of entodermal antigen thus showed that it is present in the human oral mucosa in the same regions as those where it was first found in animals (dogs); the physicochemical properties of human and canine entodermal antigen also are similar in many respects. This suggests a possible general biological rule for its distribution in at least two representatives of mammals.

These investigations also showed that in man, entodermal antigen accumulates in saliva of the submandibulal and sublingual salivary glands during chronic recurrent diseases and remains in it in considerable quantities at all stages of development of the disease.

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EFFECT OF SOME NEW ANTIHISTAMINE DRUGS ON IMMUNOLOGIC REACTIVITY

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Many observations have shown [1, 2, 4, 5] that determination of the number of antibody-forming cells (AFC) and rosette-forming cells (RFC) in the blood and immunocompetent organs and detection of allergic reactions of delayed-type hypersensitivity (HDT) are objective tests with which to study immunologic reactivity and its changes under the influence of pharmacologic intervention.

The object of this investigation was an experimental study of the effect of new antihistamine drugs — phencarol (quinuclidyl-3-diphenylcarbinol) and bicarphen [quinuclidyl-3-di(ortho-tolyl)carbinol hydrochloride] — by comparison with the action of dimedrol (diphenhydramine hydrochloride) on immunologic reactivity *in vivo*. According to the results of pharmacological studies, phencarol has higher antihistamine activity than dimedrol, whereas bicarphen differs from phencarol in its longer antihistamine action and its high antiserotonin activity [3].

EXPERIMENTAL METHOD

Male BALB/c mice (135 animals) weighing 18-20 g and light colored guinea pigs (40 animals) weighing 350-400 g were used. The drugs were injected into the stomach in a volume of 0.2 ml of 1% starch solution (bicarphen) or distilled water (phencarol and dimedrol).

Immunologic reactivity was determined as the number of AFC in the mouse spleen, revealed by the method of local hemolysis in gel [7] in response to intraperitoneal injection of the test antigen ($5 \cdot 10^8$ sheep's red blood cells), and the number of immune RFC in the spleen,

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TABLE 1. Effect of Antihistamine Drugs on HDT Reaction

Drug	Mice*		Guinea pigs †	
	dose (in mg/kg × number of injections)	intensity of reaction, mm	dose (in mg/kg × number of injections)	intensity of reaction, points
Phencarol	50×1	0,18±0,015	50×4	2,4±0,29
P		<0,01		<0,02
Bicarphen	50×1	0,24±0,019	50×4	1,9±0,24
P		>0,01		<0,01
Dimedrol	50×1	0,32±0,018	50×4	3,2±0,30
P		>0,05		>0,05
Control (physiological saline)		0,38±0,019		3,6±0,29

*Drugs injected immediately before immunization.
†Drugs injected 4 times from first day of sensitization.

TABLE 2. Effect of Antihistamine Drugs on Number of RFC in Immunocompetent Organs of Mice

Drug (dose 50 mg/kg)	Time of injection of drug relative to test antigen	Number of RFC per 10^3 nucleated cells					
		spleen	P	thymus	P	lymph nodes	P
Phencarol	Simultaneously	56,3±4,0	<0,01	42,6±6,2	<0,02	37,3±3,2	<0,01
	10 days previously	86,3±5,6	>0,05	56,3±2,9	>0,05	84,3±9,0	>0,05
Bicarphen	Simultaneously	46,7±4,3	<0,01	51,7±5,7	>0,05	65,0±5,7	<0,01
	10 days previously	90,0±3,2	>0,05	66,7±3,8	>0,05	94,7±5,6	>0,05
Dimedrol	Simultaneously	87,3±5,0	>0,05	56,7±2,4	>0,05	96,7±6,1	>0,05
	10 days previously	98,3±3.0	>0,05	60,3±4,3	>0,05	101,0±10,6	>0,05
Control (immunization)	—	97,3±2,7	—	61,3±1,2	—	102,0±3,1	—

thymus, and lymph nodes [6], counted per 10^3 lymphoid cells, and also as the intensity of the HDT reaction.

In experiments on mice the intensity of the HDT reaction was judged by the increase in diameter of the foot (in mm) 24 h after subplantar injection of the reacting dose of sheep's red blood cells [8].

The effect of the drugs on the HDT reaction to a skin allergen, namely dinitrochlorobenzene (DNCB) was tested in guinea pigs. The animals were sensitized by application of a 1% solution of DNCB on a shaved part of the trunk daily for 8 days. The intensity of the reaction was assessed in points, depending on the intensity of the inflammatory response on an area on the opposite side of the animal's trunk 24 h after application of the reacting dose of DNCB.

EXPERIMENTAL RESULTS

The experiments showed that phencarol and bicarphen reduced the intensity of the HDT reaction in mice to sheep's red blood cells and in guinea pigs to DNCB (Table 1).

Data on the effect of the antihistamine drugs on the immune RFC level are given in Table 2. They show that phencarol, if injected simultaneously with the test antigen, caused a decrease in the number of RFC in the spleen, thymus, and lymph nodes of the mice. Bicarphen under these experimental conditions caused a statistically significant decrease in the number

TABLE 3. Effect of Antihistamine Drugs on Number of AFC in Spleen of Mice

Drug	Dose (in mg/kg) × number of injections	Time of injection of drug relative to test antigen	Number of AFC per 10^6 nucleated cells		
			absolute	p	% of control
Phencarol	50×1	Simultaneously	195,8±3,8	<0,01	55.5
Bicarphen	50×1	"	210,0±13,5	<0,01	59,6
Dimedrol	50×1	"	209,0±7,5	<0,01	59,3
Control (immunization)	—	—	352,6±13,8	—	100
Phencarol	50×4	3 days previously	251,0±10,5	>0,01	67.5
Bicarphen	50×4	"	275,4±13,3	>0,01	74.0
Dimedrol	50×4	"	258,88±10,6	>0,01	69.6
Control (immunization)	—	—	372,1±4,2	—	100
Phencarol	50×1	10 days previously	298,0±7,5	<0,05	94
Bicarphen	50×1	"	296,4±5,5	<0,02	93,6
Dimedrol	50×1	"	292,6±7,4	<0,02	92,4
Control (immunization)	—	—	316,6±2,4	—	100

of RFC in the spleen and lymph nodes; after injection of dimedrol there was only a tendency for the number of RFC in the immunocompetent organs to decrease.

If injected 10 days before immunization the antihistamine drugs had virtually no effect on the RFC level.

Determination of the number of AFC after simultaneous injection of the antihistamine drugs and test antigen (Table 3) showed a decrease in the hemolysin level (to 55.5% after phencarol, to 59.6% after bicarphen, to 59.3% after dimedrol). These drugs had a less marked inhibitory effect on immunogenesis when injected before immunization of the animals. For instance, despite a fourfold increase in the total dose of the drugs, their administration 3 days before immunization had a weaker action on hemolysin production. When the antihistamine drugs were given 10 days before immunization the AFC level in the spleen of the experimental animals was not significantly different from the corresponding control. To judge from the results, phencarol, bicarphen, and dimedrol had an inhibitory effect on the primary immune response. This effect was about equally strong for each drug and was reversible in character.

It can be concluded from this investigation that the new antihistamine drugs phencarol and bicarphen depress allergic reactions of delayed type to a greater degree than does dimedrol.

If injected simultaneously with a test antigen, phencarol and bicarphen, unlike dimedrol, cause a marked decrease in the number of rosette-forming lymphocytes in immunocompetent organs.

Phencarol and bicarphen, while significantly differing from each other in the spectrum and duration of their pharmacological action, have virtually the same effect on immunologic reactivity of the recipient.

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