CRITICAL EVALUATION OF MANNITOL DETERMINATION AND CLEARANCE

by

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After mannitol had been proposed by SMITH *et al.*[1] as a substance whose renal clearance is a measure of glomerular filtration rate, several methods of determination were introduced.

The original procedure requiring fermentation of the plasma samples was considered unreliable by SMITH himself. CORCORAN AND PAGE developed a direct method for the determination of mannitol [2], based on the MACFADYEN formaldehyde method [3]. At about the same time, HAMBURGER AND RIJCKEWAERT described a similar method, based on the same principle [4]. In 1949 WEST AND RAPOPORT proposed some minor modifications of the CORCORAN AND PAGE method [5].

During our work we found mannitol clearance values that differed considerably from those published by the authors mentioned above. We therefore investigated various procedures critically.

1. *Comparison between the mannitol determination method of* CORCORAN AND PAGE *and that of* HAMBURGER

The main difference between these methods lies in the concentration of the sulfuric acid used during the oxidation of mannitol by periodic acid; CORCORAN AND PAGE prescribe 0.1 *N* and HAMBURGER 1.21 *N* sulfuric acid. For both methods the spectral absorption was measured (Fig. 1). The curves obtained agree well with the resulting colours, being red/violet with the CORCORAN AND PAGE method and purple with that of HAMBURGER. The absorption at 570 mμ was for both methods practically the same, using equivalent amounts of mannitol.

The standard deviation was determined for both methods.

TABLE I

Method	*Number of determinations*	*Standard deviation*
CORCORAN AND PAGE	25	2,3%
HAMBURGER AND RIJCKEWAERT	33	2,5%

2. *Influence of sodium fluoride on plasma concentration*

HAMBURGER advocates collection of the blood samples with fluoride in order to prevent glycolysis, which could influence the value of the plasma blank (personal communication). As mannitol is present in the plasma only[4, 6], we investigated the

References p. 168

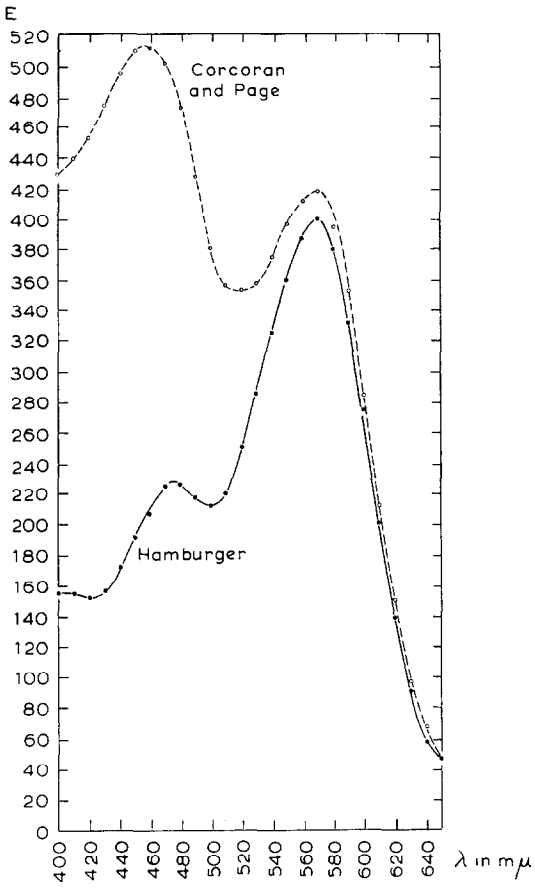

Fig. 1

influence of sodium fluoride addition on packed-cell-volume and, as a consequence, on plasma volume.

Mannitol-containing blood was collected with heparine. Portions of 4 ml were mixed with various quantities of sodium fluoride. In each mixture, haematocrit and

TABLE II

	mg NaF added per 4 ml blood	*Haematocrit value %*	*Relative plasma volume*	*Reciprocal of relative plasma volume*	*Mannitol conc. in mg*	*Mannitol conc. in % of (1)*
Series I	0	28.9	71.1	100	549 (1)	100
	10	22	78	91	509	93
	20	22	78	91	509	93
	40	18.9	81.1	87	467	85
Series II	0	42	58	100	666 (1)	100
	10	35	65	89.5	600	90
	20	32	68	85.5	573	86
	40	29	71	82	552	83
	80	30	70	83.5	500	75

References p. 168

plasma mannitol concentration were determined. The results of two series are given in Table II. The value for the relative plasma volume was taken as 100, and the results obtained with sodium fluoride mixtures were expressed in percents of this value.

It appears that fluoride gives an augmentation of the relative plasma volume by attracting fluid from the erythrocytes, resulting in a decrease of mannitol concentration. Both effects are quantitatively correlated, as may be seen from Fig. 2, where

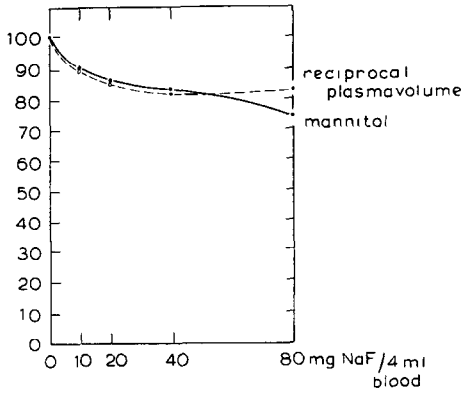

Fig. 2

mannitol concentration and the reciprocal value of the plasma volume are given for various quantities of sodium fluoride added to 4 ml blood samples.

3. *Clearance measurements*

Lower values for the mannitol clearance must be expected after omitting the NaF addition to the blood samples.

In 13 normal individuals we found a mean clearance value of 85 ml/min (extremes 76 and 103) per 1.73 m^2 body surface. The clearances were determined over at least four successive periods after a single mannitol dose. For the clearance calculations the plasma levels at three minutes before the middle of each period were used.

The mannitol dose was high (*ca.* 140 grams) in 8 persons, leading to initial plasma levels of 500–800 mg%. In 5 persons the dose was low (15 grams). There was no significant difference between these two groups as regards the mean mannitol clearance.

As can be seen in Table III, the normal values recorded by most investigators are substantially higher than ours, with the exception of BRODSKY *et al.*[12].

The reason for some of these discrepancies can be found in the use of NaF during blood collection, which may result in a 7 to 25% apparent increase in mannitol clearance. As most investigators make no reference to their method of blood collection, it is impossible to evaluate this factor in all instances.

Another point of difference might be sought in the use of single injection or constant infusion technique, but the data given in Table II lend no support to this hypothesis.

The possibility must be considered that the unusually high plasma concen-

References p. 168

TABLE III

Author	*Ref.*	*Method*	*Technique*	*Normal clearance value*
NEWMAN *et al.*	6	SMITH	single inj.	107
ELKINTON	7	SMITH	single inj.	95
BERGER *et al.*	8	SMITH		109
		CORCORAN AND PAGE		109
DOMINGUES *et al.*	9	CORCORAN AND PAGE	single inj.	109
SCHWARTZ *et al.*	10	CORCORAN AND PAGE	const. inf.	95
HAMBURGER *et al.*	4	HAMBURGER	single inj.	120
LIPS	11	HAMBURGER	single inj.	112
BRODSKY *et al.*	12	CORCORAN AND PAGE (modific.)	const. inf.	83.6

tration used by both BRODSKY and us may have caused a lower clearance value as a result of the higher concentration gradient between tubular urine and plasma and the consequent increase in back-diffusion. However, as mentioned above, we found the clearance independent of the mannitol plasma concentration this confirmed observations of NEWMAN [6]. In addition, we followed the clearance in some persons, from high to much lower plasma-concentrations, without observing any tendency for the speed of the clearance to increase.

SUMMARY

The mannitol clearance in normal persons was found to be lower than is indicated by most authors. The method of the blood collection appeared to have an unexpected influence on the clearance values obtained. In this manner at least some of the discrepancies can be explained.

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