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Gonadal Influences on Erythrocyte Reducing Capacity in the Adult Male. (26217)

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Proper function of the normal mammalian erythrocyte is largely dependent on intracellular concentration of reduced glutathione, which permits metabolic reduction reactions to proceed at a normal rate. Because of its low redox potential, reduced glutathione is easily oxidized(1,2), thereby acting as a potent reducing substance. Consequently, any diminution in capacity of the erythrocyte to perform its usual reduction reactions suggests a defect, or deficiency, in reduced glutathione content.

The reducing capacity of the human red blood cell *in vivo* has been determined by Schwartz, Landau, and Soffer by measuring the extent to which an intravenous infusion of sodium thiosulfate altered ability of the erythrocyte to reduce iodine to iodide(3). In a group of normal adults of both sexes, sodium thiosulfate administration consistently

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produced a greater increase in erythrocyte reducing capacity in the adult female than in the adult male. The results were expressed in terms of a "reductivity index," which bears an inverse relationship to changes in red blood cell reducing activity, and relates these changes to amount of sodium thiosulfate infused. One castrated male was also studied, who exhibited a reductivity index within the range for normal females. Administration of testosterone to this patient, as well as to 3 normal female subjects, resulted in a significant fall in reductivity index toward normal male levels. Stilbestrol administration to 2 normal males produced a rise in reductivity index, to approach the normal female range. These phenomena suggested a relationship between gonadal secretions and erythrocyte reducing capacity(3).

The present study of a group of untreated adult male subjects with evidence of gonadal dysfunction is directed toward correlating the reductivity index with levels of urinary gonadotrophins, to evaluate further the influence of gonadal function on erythrocyte metabolism.

Materials and methods. Eight adult male subjects with disturbances in gonadal function were studied. Two patients had hypopituitary hypogonadism, one hypogonadotrophic hypogonadism, one disseminated carcinoma originating in the lung, and one subject had carcinoma of the pancreas. All 5 patients exhibited reduced quantities of urinary gonadotrophins, as measured in 24-hour specimens by the kaolin adsorption method of Bradbury *et al.*(4), as applied to the mouse bioassay technic(5). Of the remaining patients one had pancreatic carcinoma, associated with elevated gonadotrophin excretion. Another had slight bilateral testicular atrophy, without other clinical evidence of hypogonadism, but with striking excesses of urinary gonadotrophins. The third patient had clinical evidence of hypogonadism with small testes, but with normal urinary gonadotrophin levels. The ages varied from 20 to 77 years. All patients had previously undergone normal, spontaneous puberty, except for the 20-year-old male with hypogonadotrophic hypogonadism in whom puberty had not yet occurred (Table I). No patient had received gonadal hormonal treatment for at least 3 years prior to observation.

Studies were performed in the fasting state, prior to and after an intravenous infusion of 100 ml of 10% sodium thiosulfate (Kirk), following the procedure outlined by Schwartz, Landau, and Soffer(3). Except for occasional nausea and one episode of mild vomiting, no untoward effects were observed in any of the patients studied. Normal values for the reductivity index in this laboratory are reported elsewhere(3) to be from 28 to 42 (with a standard deviation of 5) for normal adult males, and from 68 to 127 (with a standard deviation of 17) for normal adult females.

Results. A significant elevation of reductivity index was observed in 5 of the 8 male patients (Table I), all of whom had reduced urinary gonadotrophin titers. The highest reductivity index was 72.8, which fell within the normal female range. This occurred in the young adult patient (No. 1) with hypogonadotrophic hypogonadism, thus suggesting that prepubertal male values may be of comparable magnitude. Two patients (Nos. 6 and 7), one with slightly elevated, and the other with normal urinary gonadotrophins, showed a modest increase in reductivity index to 45.8 and 42.2, respectively, both values just exceeding the highest level previously obtained in normal male subjects. These latter 2 values were not statistically distinct from normal, and suggested that only a partial androgen deficiency may have existed. One patient (No. 8), with markedly elevated urinary gonadotrophin titers, but no clinical evidence of hypogonadism, possessed a normal reductivity index of 29.0. No correlation was observed between adult age, body size, or erythrocyte sedimentation rate and reductivity index.

Discussion. The above results suggest that a normal erythrocyte reducing capacity in the human male depends, at least in part, on presence of adequate amounts of circulating androgens. When gonadal secretion is impaired, as indicated by either insufficient or excessive urinary gonadotrophin titers, a decrease in red blood cell reducing

TABLE I. Relationship of Reductivity Index to Gonadal Function in Adult Males.

Subject	Age, yr	Race	Reductivity index	Urinary gonadotrophins, muu/24 hr*	Hematocrit, %	Erythrocyte sedimentation rate, mm/hr	Clinical condition
1	20	N	72.8	Neg. at 5	44.5		Hypogonadotrophic hypogonadism Negative cell chromatin pattern Normal sella turcica
2	32	W	59.4	*Idem*	37	32	Carcinoma of pancreas Normal sella turcica
3	77	N	54.4	"	42	46	Carcinoma of lung with metastases Normal sella turcica
4	56	W	49.1	"	36	107	Chromophobe adenoma with secondary hypogonadism and myxedema Diabetes mellitus Idiopathic hyperlipemia
5	58	W	48.6	"	48		Chromophobe adenoma with secondary hypogonadism
6	68	W	45.8	Pos. at 50	35	45	Carcinoma of pancreas
7	32	W	42.2	Pos. at 10 Neg. at 50	43		Primary hypogonadism with azospermia and testicular immaturity Negative cell chromatin pattern Normal sella turcica
8	32	W	29.0	Pos. at 400	42.5	27	Slight bilateral testicular atrophy Spermiogenesis present (biopsy) No clinical hypogonadism Negative cell chromatin pattern Normal sella turcica Very high protein-bound iodine without hyperthyroidism

* Mouse uterine units/24-hr urine volume.

capacity occurs, reflected by a rise in reductivity index toward the normal female range. Since the reducing capacity of the erythrocyte probably mirrors the intracellular concentration of reduced glutathione, the presence of hypogonadism in the male is presumably related to an interference with the activity of reduced glutathione, probably by shifting the erythrocyte glutathione equilibrium in favor of the oxidized form.

Summary. The effect of an intravenous infusion of sodium thiosulfate on erythrocyte reducing capacity was determined in 8 male patients with disturbances of gonadal function. A reductivity index was then determined for each patient which is inversely proportional to the erythrocyte reducing capacity. In 5 patients with reduced urinary gonadotrophin titers, the reductivity index was significantly higher than that of normal males. In the 3 remaining patients with normal or elevated urinary gonadotrophins, there was a normal or equivocally elevated reductivity index. These results indicate that hypogonadism in the human male may be associated with a decrease in reducing capacity of the red blood cell. This probably reflects an inadequate activity of reduced glutathione in the erythrocyte.

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