Surgery-Induced Alterations in Plasma Recognition Factor Activity in Normal Renal Donors and Renal Recipients (37398)

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Donovan (1) has reported that functional impairment of the reticuloendothelial system (RES) occurred as a result of surgery. Depression of the reticuloendothelial (RE) function was observed during early phases of the postoperative period and gradually returned to normal values. The restoration in RE function varied in various populations ranging from first postoperative day to the tenth. Donovan also reported that the degree of impairment may have been related to the duration of operative procedure and the presence of hypotensive episodes. Subsequently, Saba and Di Luzio (2) demonstrated that surgical stress in rats induced impairment in phagocytosis which occurred within 30 min. Recovery was observed 3 hr later denoting the reversibility of the phagocytic impairment.

In view of the role of the RES as a major component of host defense mechanisms, impairment of RE function following surgery may well have significant implications in the postoperative period in relationship to ability of the host to respond to bacterial, viral and neoplastic challenges.

Impairment of RE function may exist at both cellular and humoral levels. It has been amply demonstrated that circulating factors exist in plasma which have been demonstrated as phagocytic promoting factors, or opsonins (3–5) which reside in the alpha-globulin component of plasma (6). Reticuloendothelial impairment induced by the administration of colloidal and particulate materials resulted in depletion of circulating phagocytic promoting factors which was associated with impairment of intravascular clearance (7). In agreement with the observation of Donovan (1) and Saba and Di Luzio (2), it was observed that surgery in experimental animals produced impaired phagocytosis as well as depletion in the activity of plasma recognition factors which are essential for optimal phagocytosis to occur (8).

The relationship of the findings of opsonin depletion in rodents following surgery (8) to the human situation has not been defined. A unique opportunity to evaluate the influence of surgical stress on normal human subjects becomes possible in the renal transplantation program where normal donor subjects were undergoing unilateral nephrectomy to provide a kidney for a subject being maintained by renal dialysis while awaiting renal grafts. Recognition factor activity was evaluated in renal donors and renal recipients at various phases of their clinical state to ascertain the nature and degree of opsonin alterations.

Materials and Methods. Venous blood was obtained in heparinized syringes from healthy normal subjects which served as renal donors as well as patients undergoing renal transplantation. The plasma was immediately assayed for humoral recognition factor activity levels in accordance with the procedures developed in this laboratory (9–11). Briefly, rat liver slices approximately 200 mg of weight were prepared with a Stadie–Riggs tissue slicer and placed in incubation flasks which contained Krebs–Ringer phosphate buffer to which equal volumes of plasma were added. Heparin (100 units) was added to each flask as was 2 mg of the RE test lipid emulsion which was labeled with ^{131}I-labeled triolein. The uptake of the lipid particulates by Kupffer cells was determined by means of a Nuclear Chicago Auto-Gamma Scintillation Counter. The data are expressed as percent of added radioactivity which was phagocy-

TABLE I. Plasma Recognition Factor Depletion and Recovery Following Unilateral Nephrectomy in Normal Subjects and Renal Transplantation in Subjects in Renal Failure.[a]

	Normal group	Renal failure
Pretherapy values, % uptake	9.8 ± 1.7	7.8 ± 1.9
Preoperative, % uptake	9.8 ± 1.7	7.2 ± 1.0
Maximum degree of postsurgery recognition factor depletion, %	77 ± 6	63 ± 10
Time of maximum depletion, days	3.3 ± 1.0	3.2 ± 1.2
Time of restoration of normal recognition factor activity, days	9.6 ± 1.0	8.1 ± 1.1

[a] Values expressed as means ± standard error and derived from 8 subjects per group. Plasma recognition factor levels are expressed as percent of the ^{131}I-labeled RE test lipid emulsion phagocytized by rat liver slices. In nonplasma containing incubation media, the uptake ranges from 0.4 to 0.6%.

tized per 100 mg of liver tissue. All human plasma samples were analyzed in duplicate for recognition factor activity. At the time of assay, no knowledge of the clinical state of the subject was made available to individuals conducting the assay.

The normal group, serving as renal donors, consisted of 4 males and 4 females ranging in age from 29 to 40 while the individuals undergoing renal transplantation, consisting of 5 males and 3 females had a range from 13 to 37. Blood samples were obtained prior to surgery and at frequent intervals thereafter during the postoperative period for humoral recognition factor activity determinations.

Results. Preoperative and/or immunosuppression procedures which were administered the day prior to surgery in the renal recipient group did not materially influence recognition factor activity of plasma (Table I). The initial value for recognition factor activity, as reflected in ability of plasma to promote a phagocytic event, was 8.1%/100 in the recipient group and 9.6 in the control. In the subjects in renal failure, depletion of recognition factor activity followed surgery. However, the time of depletion and the degree of depletion varied somewhat. When compared to control values, the degree of depletion in the kidney-recipient group ranged from 33 to 94 with a mean of 63%. The temporal relationships revealed that maximum depletion occurred at postoperative Days 1–7 with the mean postoperative day of maximum depletion being 3. In all instances, recovery of recognition factor activity occurred within 3–16 days following surgery.

In the renal donor group it was observed that essentially similar responses of recognition factor depletion occurred following surgery. The maximal depletion of recognition factor activity in the renal donor group likewise occurred on Days 1–7 with the mean being 3 days. The degree of depletion in the donors ranged from 45 to 90 with a mean value of 77%. Thus, it appears that the response to surgery in the group which in the preoperative period have been maintained on renal dialysis was not distinctly different from the normal population. Two representative responses of recognition factor activity following surgery are presented in Fig. 1 to reflect the variations observed in time of depletion and degree of recovery.

Discussion. The present studies, in conjunction with previous observations that impairment of the functional activity of the RES occurred as a result of surgery both in man (1) and experimental animals (2, 8), is suggestive that the surgically induced impairment in functional expression of macrophage cells is due to depletion of plasma recognition factors or opsonins rather than a direct influence of surgery *per se* on the macrophage cell population. It is possible that one of the mechanisms involved in recognition factor depletion is the entrance of subcellular components of tissue into the circulation as a result of surgery. These subcellular elements would be anticipated to interact with

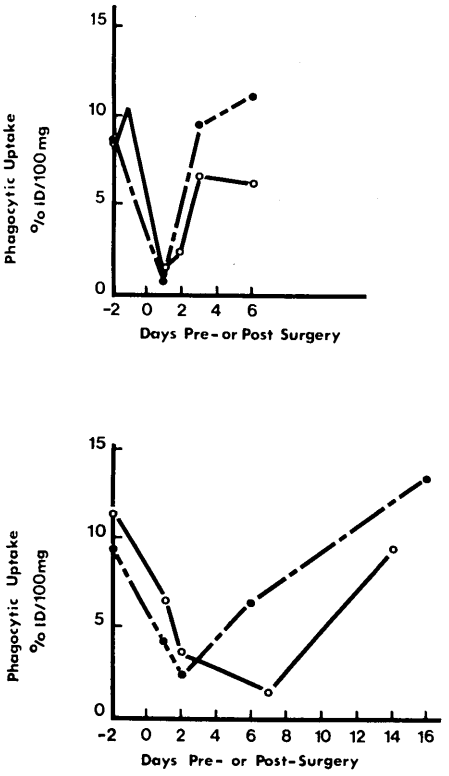

FIG. 1. Alterations in recognition factor activity as reflected by phagocytic uptake following surgery in two renal donors (—●—) and two renal recipients (—○—). The depletion and recovery phases typify the response seen in the population studied. Day zero is considered as the day of surgery.

recognition factors which would permit their clearance from the vascular compartment.

Previous consideration of the states which are associated with alterations in humoral recognition activity of plasma revealed that neoplasia was associated with profound depletion of recognition factor activity (9–11). This alteration occurred when a variety of particles such as the ^{131}I-RE test lipid emulsion, colloidal gold or technecium sulfide were employed (10). It was not observed when bacterial species were utilized as a test particulate showing some degree of specificity (11). Additionally, it was observed that severe, that is greater than 40% surface area, burn in children also induced depletion of recognition factor activity (12). Additionally, in the burn episode, the imposition of bacterial infections was associated with profound depletion of recognition factor activity (12). Whether a common denominator exists in all of these clinical states as well as in surgery to produce significant depletion of recognition factor activity remains to be ascertained.

Likewise, whether the alteration of recognition factor activity following surgery or that which occurs in other disease states in any manner comprises the response of the host to foreign agents remains to be ascertained, as does the relationship of opsonin depletion to the observations of Lewis and Cole (13) that operative surgery will increase the incidence of metastases in experimental animals. The findings of Fisher and Fisher (14) that RE blockade, an event associated with depletion of recognition factor activity in plasma (7) produces increased acceptance of tumors also provides a possible link between recognition factor alterations and acceptance of tumors in surgically stressed animals.

The demonstration that the opsonic fraction can be isolated in the alpha component of plasma (6) and is capable of promoting phagocytosis when injected into experimental animals (6) provides a ready method of treatment in the event the clinical consequences of postsurgery recognition factor depletion are identified.

Summary. Depression of the phagocytic activity of the reticuloendothelial system has been demonstrated to occur following surgery in rodents and in man. Since optimal expression of macrophage cells generally requires the presence of phagocytic-promoting factors, studies were undertaken to evaluate alterations in plasma recognition factor activity in normal subjects undergoing unilateral nephrectomy to provide a kidney for a person in renal failure. Additionally, plasma recognition factor activity was measured at varying intervals in patients maintained on renal dialysis and undergoing renal transplantation. Recognition factor activity was evaluated by the ability of plasma to enhance the phagocytosis of ^{131}I-triolein labeled RE test lipid emulsion by macrophage cells incubated *in vitro*. In both surgical populations studied, significant depletion of plasma recognition

factor activity occurred at 1–7 days post-surgery. Restoration of opsonic activity occurred in all cases. Surgery induced phagocytic depression may reflect recognition factor depletion.

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