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Laparoscopic Surgery and the Systemic Immune Response

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Objective
The authors review studies relating to the immune responses evoked by laparoscopic surgery.

Summary Background Data
Laparoscopic surgery has gained rapid acceptance based on clinical grounds. Patients benefit from faster recovery, decreased pain, and quicker return to normal activities. Only more recently have attempts been made to identify the metabolic and immune responses that may underlie this clinical success. The immune responses to laparoscopy are now being evaluated in relation to the present knowledge of immune responses to traditional laparotomy and surgery in general.

Methods
A review of the published literature of the immune and metabolic responses to laparoscopy was performed. Laparoscopic surgery is compared with the traditional laparotomy on the basis of local and systemic immune responses and patterns of tumor growth. The impact of pneumoperitoneum and insufflation gases on the immune response is also reviewed.

Conclusions
The systemic immune responses for surgery in general may not apply to laparoscopic surgery. The body's response to laparoscopy is one of lesser immune activation as opposed to immunosuppression.

Laparoscopic surgery provides tremendous benefits to patients, including faster recovery, shorter hospital stay, and prompt return to normal activities. Additionally, laparoscopic procedures provide better cosmesis, greater patient satisfaction, and result in greater demand for new procedures.[1,2]

While laparoscopy is "minimally invasive," systemic immune responses are still invariably activated. Overall, responses to surgery in general are reflected in terms of cytokine function and cellular messenger systems. While cytokine levels do not directly reflect immune status, they give us a framework to understand systemic immunity in terms of underlying immune activation. This knowledge provides a background to understand how laparoscopic surgery affects systemic metabolism and immunity. Many studies have recently become available in both humans and animals (Table 1). In most cases, however, owing to the rapid acceptance of laparoscopic surgery, clinical trials have not been randomized. On the other hand, animal models may not be directly applicable to clinical situations. In this review, the systemic, metabolic, and immune responses to laparoscopic surgery studied to date are summarized in the context of established responses to surgery and injury in general.

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INJURY TO THE HUMAN BODY ALTERS NORMAL PHYSIOLOGY ACROSS SEVERAL SYSTEMS

Because alterations are proportional to the extent of injury, the physiologic response to minimally invasive surgery may, intuitively, be different than those for traditional open surgery. The acute-phase protein response appears to be one example.[3] The cytokines interleukin-1 (IL-1), tumor necrosis factor (TNF), and interleukin-6 (IL-6) are known to be major mediators of the acute-phase response.[4] Interleukin-6 primarily regulates the hepatic component of the acute-phase response resulting in the production of acute-phase proteins.[4–7] The generation of acute-phase proteins is a well recognized response to tissue injury.[3] The C-reactive protein is a key marker acute-phase protein that has a consistent response and provides a dependable screening test overall for acute-phase reactants. The C-reactive proteins rise approximately 4 to 12 hours after surgery and peak at 24 to 72 hours. Subsequently, C-reactive proteins remain elevated for approximately 2 weeks.[8]

Several investigators have examined how laparoscopic surgery affects the acute-phase response by measuring C-

Table 1. IMMUNE RESPONSE MEDIATORS PREVIOUSLY EVALUATED DURING LAPAROSCOPIC SURGERY

Peripheral blood
Interleukin-6
C-reactive proteins
Tumor necrosis factor
Interleukin-1
Histamine response
Total leukocyte counts
T-lymphocyte populations
Delayed-type hypersensitivity
Neutrophil activation and function
Peritoneal host defenses
Macrophage activation
Leukocyte function

reactive proteins (Table 2). The C-reactive proteins have been found to be reduced in laparoscopic procedures compared with more traditional laparotomy.[9–13] The C-reactive protein remained significantly elevated at 24 and 48 hours in patients with open cholecystectomy compared with those undergoing a laparoscopic procedure.[10] Alterations in C-reactive proteins also have been associated with postoperative differences in C-reactive protein and erythrocyte sedimentation rates and C-3 complement levels at both 24 and 48 hours after open cholecystectomy but not laparoscopic cholecystectomy.[11] The degree of alteration of C-reactive proteins was noted to be 20 fold after open cholecystectomy but only a 5 fold increase after laparoscopic cholecystectomy.[12] In summary, the acute-phase response as measured by C-reactive proteins is significantly less when cholecystectomy is performed laparoscopically.

Other studies examining cholecystectomy have found no significant differences in C-reactive proteins between laparoscopic and open groups.[14,15] In one of these studies, McMahon failed to detect any difference in acute-phase protein responses between "mini" open cholecystectomy and laparoscopic cholecystectomy.[15] These results do not correlate to other studies that evaluate open cholecystectomy. The question arises whether the smaller incision and less surgical injury of mini-cholecystectomy underlies the tempered acute-phase protein response.

Examination of C-reactive proteins in laparoscopic *versus* traditional inguinal herniorrhaphy also have not shown significant differences. One randomized prospective study showed no significant difference in C-reactive proteins between laparoscopic inguinal hernia repair patients and open hernia repair.[16] The selection criteria for this study was that patients undergo a primary unilateral hernia repair, which is not always an accepted indication today for laparoscopic hernia repair. This is consistent with the findings of Bolufer, who reported that inguinal hernioplasty had the smallest effect on C-reactive protein responses of all laparoscopic groups studied.[17]

INTERLEUKIN-6

The cytokine response to injury under normal surgical conditions has been extensively investigated.[8,18,19] As previously mentioned, injury provokes an acute-phase protein response that is detectable in peripheral blood. The primary mediator of these responses is thought to be IL-6.[5] Serum IL-6 levels are early and sensitive markers of tissue damage because they rise in proportion to the surgical trauma and associated injury.[6] Additionally, elevations in IL-6 levels have been correlated with the subsequent clinical development of major complications.[18] Furthermore, Il-6 alterations have been directly correlated with length of operation and blood loss during surgery.[8] The tumor necrosis factor (TNF) and IL-1β also contribute to the acute-phase response, but are primarily responsible for the nonhepatic manifestations of the acute-phase response, which include fever and tachycardia.[5] Other proteins such as transferrin and eicosanoids and leukotrienes and prostaglandin E_2 also contribute but to lesser extents.

The acute-phase response after laparoscopic surgery has been studied in several clinical trials measuring IL-6 levels after laparoscopic cholecystectomy (Table 3). Interleukin-6 levels have been noted to be reduced in patients undergoing laparoscopic procedures compared to traditional laparotomy.[12,13,20-23] Additionally, a linear correlation between peak concentrations of IL-6 and C-reactive proteins has been noted.[12,21] Interestingly, the reduction of IL-6 levels was not seen in a group of laparoscopic patients that had undergone endoscopic retrograde cholangiopancreatography (ERCP) before removal of the gallbladder.[13] Even though IL-6 levels in the ERCP group were similar before gallbladder removal, the ERCP group had the highest IL-6 response. This suggests that ERCP before cholecystectomy might prime the response in such a way that the benefit of reducing IL-6 response gained by performing the procedure laparoscopically may be nullified.

Table 2. PEAK C-REACTIVE PROTEIN LEVELS AFTER CHOLECYSTECTOMY

Author (year)	Laparoscopic (mg/L)	Open (mg/L)	p
Cho (1994)	24	104	<0.05
Halevy (1995)	26.8	128.6	<0.001
Bolufer (1995)	49*	95*	0.005
Joris (1992)	39	87	<0.05
Mealy (1992)	20.6	106.9	<0.04
Roumen (1992)	48	203	<0.01
McMahon (1993)	48†	84†,‡	0.13
Redmond (1994)	69	53	NS

NS = not significant.

* Various open and laparoscopic procedures were performed in this study. The majority of the laparoscopic procedures were cholecystectomy.

† Expressed as area under the curve.

‡ Open procedures were performed as "mini" cholecystectomy using a 5–7-cm incision.

Table 3. PEAK IL-6 LEVELS AFTER CHOLECYSTECTOMY

Author (year)	Laparoscopic (pg/mL)	Open (pg/mL)	p
Glaser (1995)	15	50	0.02
Maruzynski (1995)	12.5	48.8	<0.001
Joris (1992)	17	71	<0.05
Suzuki (1994)	21	186*	<0.01
Cho (1994)	51	124	<0.01
Vander Velpen (1994)	800%	580%†	NS
Roumen (1992)	<20	<20‡	
		34§	<0.05‖
McMahon (1993)	117¶	135¶,#	

NS = not significant.
* Included various types of major abdominal surgery.
† Compared with baseline levels.
‡ Patients less than 60 years old.
§ Patients greater than 60 years old.
‖ Significant only in the group of patients over 60 years of age. There was no significant difference between IL-6 levels in those patients under 60 who underwent either OC or LC.
¶ Total area under the curve.
# Open procedure was a "mini" cholecystectomy through 5–7-cm incision.

Other studies, however, have shown contrary findings. Roumen[10] reported that IL-6 levels only were detected in patients after the age of 60 undergoing laparotomy. Furthermore, they found no relative correlation between plasma concentrations of IL-6 and C-reactive proteins. McMahon[15] showed no significant difference between laparoscopic cholecystectomy and mini-laparotomy cholecystectomy groups. That study found that IL-6 levels in both laparoscopic and mini-cholecystectomy groups were similar to historical reports of standard cholecystectomy levels. The IL-6 levels did correlate with those for C-reactive proteins and so were thought to suitably reflect the acute-phase response.[15]

In a randomized prospective study of primary inguinal hernia repair, no significant differences in postoperative IL-6 levels were detected between laparoscopic or open herniorrhaphy groups.[16] As with C-reactive protein studies, it may be that overall tissue damage for these procedures is significantly less than during formal open surgery. Additionally, the effects of general anesthesia given in all operative groups in these studies may be a greater determinant of the overall metabolic response in hernia repair.[16]

Some studies have evaluated IL-6 after laparoscopic and open colon resections. Harmon[24] found that patients undergoing laparoscopic colon resection had a significant blunting of peripheral blood IL-6 responses. This study, however, noted no significant rise in IL-1 levels at any time. In contrast, Kuntz[25] examined the colon resection in rats and found that IL-1β levels increased after the open operation to significantly greater levels than after the laparoscopic procedure. The IL-6 was not measured. Other investigators have found that IL-6 is actually increased in laparoscopic colectomy. Douglas[26] examined mongrel dogs who underwent either a segmental resection of the left colon through a 10-cm midline abdominal incision or a laparoscopic assisted approach. The IL-6 was elevated in all groups, but was statistically greater in the laparoscopically resected group than in any other group. Bessler[27] later substantiated this study by finding that IL-6 was elevated in pigs undergoing laparoscopic colon resection as compared with open laparotomy. They also found associated acidosis and hypercarbia, which they felt induced an important temporary stress-like state. Colon resections involve small incisions when assisted laparoscopically. It is difficult to stratify how a smaller incision alone or combined with pneumoperitoneum, acidosis, and hypercarbia may affect systemic, metabolic, and immune responses in laparoscopically assisted colectomy.

In summary, although several studies that examine IL-6 in laparoscopic surgery are available, no consensus has been reached as to its metabolic or immunologic role. The IL-6 response may or may not accurately reflect an acute-phase response as C-reactive protein responses appear to do. As discussed, inherent difficulties with randomizing patient sample groups has contributed to difficulties in obtaining reliable and reproducible data amongst clinical studies published to date. However, further research into this area is warranted because understanding IL-6 responses could have implications on the types of surgery and anesthesia undertaken.[28]

PERIPHERAL HISTAMINE RESPONSE

Histamine is produced by mast cells upon stimulation by various extracellular ligands. It exerts well recognized systemic affects on allergic, cardiovascular, pulmonary, and inflammatory responses. Histamine alters the function of granulocytes, macrophages, and T-lymphocytes. Nies[29] has examined plasma histamine levels in 40 patients with acute cholecystitis during and immediately after laparoscopic and open cholecystectomy. The authors demonstrated significantly greater intraoperative and postoperative histamine levels in those patients undergoing laparoscopic cholecystectomy. Histamine levels rose to their highest levels during the establishment of pneumoperitoneum and laparoscopic access. There were no significant differences in overall outcome between the two groups. Additional studies will be required to determine a clear impact of peripheral histamine responses during laparoscopic surgery.

PERIPHERAL LEUKOCYTE POPULATIONS

Immunosuppression is an established consequence of surgical stress and injury.[30–32]

This has been defined not only in terms of cytokine, but perhaps more importantly, in the cellular components of the systemic immune response.[30,33] Several recent studies have

examined how laparoscopic surgery affects various cellular components of the immune system.

Laparoscopic surgery may attenuate the cellular immunosuppression created by the stress of surgery.[34] A number of studies have evaluated this in terms of total leukocyte counts, specific leukocyte populations, and leukocyte subpopulations. Some have demonstrated a significant increase in overall peripheral leukocyte numbers in open, but not patients with laparoscopic cholecystectomy.[9,14] For unclear reasons, however, there were no significant correlations between elevated white blood cell count and C-reactive protein concentration in these studies. This may not be surprising, however, as Aronson[35] has demonstrated amplified acute-phase responses in patients with agranulocytosis. Peripheral leukocyte populations may not be the principal determinant of an acute-phase response as much as an hepatic response to stress and injury. Kloosterman[36] has demonstrated a transient increase in granulocyte numbers after open cholecystectomy but not after laparoscopic cholecystectomy. No other significant change was obvious amongst total peripheral leukocyte counts, which suggests a potential, selective role for granulocytes between the groups studied. Vallina and Valesco[34] examined peripheral lymphocyte subpopulations in 11 patients undergoing laparoscopic cholecystectomy. They demonstrated that the ratio of T-helper to T-suppressor cells on the first day postoperatively was significantly decreased to 13% below preoperative levels. After 1 week, there were no significant changes because the T-lymphocyte populations returned to their preoperative status. The authors found no statistical difference in absolute CD-4 and CD-8 cell counts. Hansborough[33] had previously studied patients with open cholecystectomy and showed that there was a significant drop in the individuals' CD-4 and CD-8 levels. While collectively the significance of these studies remains to be determined, it does appear as though laparoscopic surgery may impact on the cellular components of the immune response less than open laparotomy.

How does laparoscopic surgery affect immune cell *function*? T-cell function has been examined using delayed type hypersensitivity (DTH) models. Delayed type hypersensitivity has been shown to be significantly depressed after laparotomy.[37] Trokel[38,39] evaluated delayed type hypersensitivity in rats undergoing laparoscopic insufflation or midline laparotomy incision. Animals undergoing laparotomy had significantly diminished delayed type hypersensitivity responses when challenged with keyhole limpet hemocyanin antigen or phytohemmaglutanin (PTH) postoperatively. Rats undergoing insufflation and laparoscopy had unchanged DTH responses from preoperative responses which were generated 10 days after the initial sensitization with keyhole limpet hemocyanin. Bessler[40] also examined the response of pigs to sow Bac-e antigen after either laparoscopic or open colectomy. Pigs undergoing laparoscopic resection had a 20% greater response in the postoperative period in this model. Phytohemagglutinin skin tests were also performed in patients undergoing laparoscopic cholecystectomy, and a significant reduction in PTH response (67% *versus* 0%) was noted in the open cholecystectomy group skin phytohemagglutinin DTH responses compared with the laparoscopic group on the day after surgery.[36] On the sixth day after surgery, the response in both groups had returned to normal.

Classically, DTH responses are associated with T-cell related immunologic function. It is thought that this would indicate any attenuated related response in this lymphocyte population for patients or animals undergoing laparoscopic procedures. However, it must be appreciated that DTH responsiveness is a complex immune system that involves multiple interactions amongst both lymphocytes and lymphocyte subpopulations. Any disturbance at any aspect of this immunologic cascade could affect the response. Although all of the above studies have shown that laparoscopic groups maintain their DTH response better than laparotomy groups, it is unknown at this time which specific component of the DTH pathway is responsible for the preserved cellular immunologic function response.

Several investigators have evaluated whether neutrophil function is altered in laparoscopic surgery. Carey[41] investigated the affects of laparoscopic surgery on the activation of neutrophils. As their endpoint of study, the authors measured the generation of hypochloric acid, the most potent of neutrophil antimicrobial oxidants. Peak hypochloric acid production was similar preoperatively in both groups. While hypochloric acid production fell significantly on the first day after open laparotomy surgery, there was no similar depressed response found in patients undergoing laparoscopic surgery. Hypochloric acid kinetics returned to preoperative levels in both groups by the sixth day after surgery. Of note, patients undergoing laparoscopic procedures included strictly laparoscopic and laparoscopic-assisted operations in nearly equal numbers. A cellular mechanism for decreased neutrophil hypochloric acid production after laparotomy remains to be determined.

Neutrophil function has also been examined by measuring neutrophil elastase (PMN-elastase). Neutrophil-elastase is one of the major enzymes present in neutrophils and upregulated during activation.[42] Gal[43] examined laparoscopic cholecystectomy patients with chronic cholecystitis. Neutrophil-elastase elevation was found in both patients who underwent open laparotomy and laparoscopic cholecystectomy on the first postoperative day. However, by the third day, there were marked differences because PMN-elastase levels returned to normal in patients who underwent laparoscopic cholecystectomy, but remained substantially elevated for patients who had undergone open cholecystectomy. By the fourth day after surgery, only laparoscopic cholecystectomy groups had returned to baseline levels. Similarly, Suzuki[23] examined patients undergoing laparoscopic cholecystectomy compared with those undergoing major abdominal operations. They found a significant difference in granulocytic PMN-elastase levels. No correlation

was found between elastase and IL-6 levels. McMahon also examined elastase levels and did find a significant correlation with alterations in IL-6 and C-reactive proteins amongst their laparoscopic and open cholecystectomy groups which were studied.[15] However, no significant difference between mini-laparotomy cholecystectomy and laparoscopy group were shown. Alternatively, Redmond[14] found significant increases in neutrophil superoxide anion release and chemotaxis in open cholecystectomy groups compared with laparoscopy in a randomized prospective study. When compared to open laparotomy, peripheral leukocyte function may indeed be better preserved after laparoscopic surgery. The importance of this in the systemic immune response after laparoscopic surgery is only partially understood.

Other markers of peripheral leukocyte function have been monitored. Monocyte superoxide anion and TNF production in patients who undergo open cholecystectomy are increased compared with those patients who undergo laparoscopic cholecystectomy.[14] In a rat model, natural killer cell cytotoxicity (NKCC) has been shown to be decreased significantly in both laparoscopy and laparotomy groups compared with control and pneumoperitoneum groups.[44] No significant difference in NKCC was found between laparoscopic and open groups.

BACTEREMIA AND ENDOTOXEMIA

Laparoscopy is increasingly used in situations complicated by peritonitis.[45–48] Investigators are evaluating the potential hazard of exacerbating hematogenous spread of bacteria from intraperitoneal sepsis. Some have found no adverse effects. Gurtner[49] found that no significant difference in bacteremia, endotoxemia, or physiological parameters of sepsis between pneumoperitoneum and laparotomy groups in a rabbit model of sepsis. The comparison laparotomy group underwent a 10-minute procedure rather than 1 hour of insufflation in the pneumoperitoneum group. Similarly, in a rat sepsis model, Dugue[50] found no increase in bacteremia in the pneumoperitoneum group. In this model, sepsis was induced by opening the terminal ileum 24 hours before insufflation, and the control group was noninsufflated. However, Bloechle[51] found significantly greater percentages of positive blood and abdominal cultures and greater peritonitis severity scores (based on histologic analysis of organs) in a laparoscopic model of perforated gastric ulcer in rats at 12 hours after the procedure compared with animals undergoing abdominal puncture. While none of these studies conclusively answer whether pneumoperitoneum exacerbates bacteremia, they certainly do suggest the need for further experimental studies in this area.

PERITONEAL HOST DEFENSES AND MACROPHAGE ACTIVATION

The local environment of the peritoneal cavity is a logical place to study the immune stress response invoked by laparoscopic surgery. Indeed, local peritoneal immune response may prove to be important in susceptibility to infections and spread of tumors.

Postoperative immunosuppression can result in increased susceptibility to bacterial invasion after traditional open laparotomy. Recent investigations have focused on how minimal access to the abdomen using laparoscopic techniques and incisions alters the intraperitoneal immune response.

Many speculate that laparoscopic incisions and pneumoperitoneum may produce less physiological stress locally in the abdomen and thereby preserve this regional anatomic component of the systemic immune response. Collett[52] examined the immune response in pigs undergoing Nissen fundoplication by both open laparotomy and laparoscopic techniques. This study investigated peritoneal clearance of *E coli* by instilling this bacteria into the abdominal cavity of some animals at the time of operation. Bacterial counts of peritoneal fluid were significantly greater at 8 hours after surgery in animals undergoing open laparotomy. This was not found in laparoscopic surgical procedures. The authors speculated that a depressed immune response contributed to a decreased peritoneal clearance in the open laparotomy group. Next, the effects of open *versus* laparoscopic surgery on neutrophil phagocytosis were examined. Despite a tendency toward greater value in bacterial contaminated animals undergoing laparoscopy, there were no significant differences in neutrophil function compared with open laparotomy. In addition, there were no significant differences in superoxide production by neutrophils in either group.[52] In summary, the authors speculated that laparoscopically challenged animals had a maintained peritoneal immune response as indicated by an ability to clear and respond to a peritoneal septic challenge.

While only limited clinical experimentation has been performed, peritoneal lymphocyte function has been evaluated. Eyrard[53] examined peritoneal lymphocyte populations in humans undergoing laparoscopic cholecystectomy. These patients' peritoneal lymphocytes showed no impairment of function after surgery.

Based on this limited data, peritoneal leukocyte function appears to be better maintained after laparoscopic surgery. Certainly, the molecular and cellular mechanisms responsible for this remain to be elusive.

TUMOR GROWTH

There is a heightened awareness recently that laparoscopic surgery may have an impact on the spread of intraperitoneal malignant disease. Laparoscopic surgery for malignancy must maintain the principles of surgical oncology: sufficient resection margins and adequate excision of node bearing tissue. Several series indicate this is possible.[54] However, reports of abdominal wall and peritoneal tumor recurrences after a laparoscopic resection for malignancy has led to speculation that pneumoperitoneum may detri-

Table 4. TUMOR SPREAD AND LAPAROSCOPY

Author (year)	Model	Results
Jones (1995)	GW-39 Human Colon Cancer Cells injected into abdominal cavity of hamsters. Animals then underwent either laparotomy or pneumoperitoneum.	Increased recurrence of tumor at abdominal wall and intraperitoneally in pneumoperitoneum compared with laparotomy group.
Bessler (1994)	Mouse mammary carcinoma or B-16 melanoma injected in dorsal skin. Animals then underwent pneumoperitoneum, laparoscopy, or no procedure.	Laparotomy group had larger and more easily established tumors compared with laparoscopic or control groups.
Jacobi (1996)	Colon adenocarcinoma DHD/K12/TRb in a rat model. Animals then underwent laparotomy, laparoscopy with either air or CO_2, or without insufflation. Tumor growth was then evaluated *in vitro* or *in vivo*.	Trend toward more intraperitoneal tumor growth in laparotomy and air laparoscopy groups.
Mutter (1996)	Single intrapancreatic innoculation of ductal cell carcinoma in rats. They then underwent laparoscopy or laparotomy. Additionally, the procedure groups were divided into those undergoing tumor manipulation or no tumor manipulation.	No differences were detected between laparoscopy and laparotomy when no tumor manipulation was performed. Tumor manipulation during laparoscopy caused less tumor growth and spread compared with laparotomy.
Allendorf (1995)	Mice had intradermal innoculation of murine mammary carcinoma cells. Animals were then subjected to insufflation, midline incision, or anesthesia only.	Tumors were more easily established and grew more aggressively after laparotomy than after insufflation.
Bouvy (1996)	CC-531 tumor cells were placed intraperitoneally in rats. Animals underwent laparotomy, CO_2 laparoscopy, or gasless laparoscopy.	Peritoneal tumor growth was greatest in the laparotomy group. The gasless group had the smallest tumor growth in the laparoscopy group.

mentally affect tumor growth.[55–63] The question of whether pneumoperitoneum alone or combined with removal of malignancy may lead to local or disseminated tumor implantation remains unanswered. This may have implications as the popularity of minimally invasive staging procedures of intraabdominal malignancies continues to grow.[64–66]

While numerous prospective clinical trials are ongoing, investigators are now examining whether laparoscopic surgery differ affects tumor growth compared with more traditional therapies in animal models (Table 4). Jones[67] found that intraabdominal tumor growth was increased significantly in hamsters subjected to pneumoperitoneum. These animals had increased implantation of free intraabdominal cancer cells at the wound sites or within the abdominal cavity compared with laparotomy. They noted no increase in the liver, lung, or jejunum compared with laparotomy groups. However, other investigators have found that laparoscopy may actually limit tumor spread compared with laparotomy.[68–73] In a model of pancreatic tumor growth in rats, Mutter[69] has found tumor growth, measured in terms of amount of tumor and regional spread and metastases, to be comparable in both laparoscopy and laparotomy groups when manipulation of the tumor was not performed. Manipulations of the tumor during laparotomy significantly increased tumor growth and spread compared with laparoscopy.[69] However, removal of tumor through a port site has been shown to enhance local tumor growth in an animal model.[73] Alteration of TNF levels has been found to be associated with this alteration of tumor growth in one study.[71] Initially, TNF levels were elevated in both laparotomy and insufflation groups. At 16 hours after surgery, TNF levels remained elevated in the insufflation group, while TNF levels decreased significantly in the laparotomy group. While it is not possible to postulate a causal relationship from this data, it does suggest that further investigation into mediators of tumor growth in laparoscopy is warranted.

As will be discussed, it is possible that tumor growth and immune functions may be affected by the type of gas used during pneumoperitoneum insufflation. Jacobi[74] examined tumor growth in a colon adenocarcinoma rat model after insufflation with carbon dioxide, helium, or gasless suspension. Tumor cells increased after insufflation with carbon dioxide compared with controls, but helium could not stimulate tumor cell growth *in vitro*. *In vivo*, subcutaneous tumor growth was promoted by carbon dioxide compared with helium and the control groups to a statistically significant level. Total intraperitoneal tumor was greater in the carbon dioxide group, however, this did not reach statistical significance. Jacobi further examined insufflation with air carbon dioxide as compared with laparotomy in the rat colon cancer model. They found that the intraperitoneal tumor was lower in CO_2 insufflated groups compared with laparotomy animals.[72] The intraperitoneal tumor was similar after laparoscopy with air insufflation compared with the

laparotomy group, although not to statistically significant levels. It is not clear whether the component gas for pneumoperitoneum alters tumor growth in animals.

CARBON DIOXIDE PNEUMOPERITONEUM

A pneumoperitoneum is usually required for laparoscopic surgery and never for open laparotomy. The physiology of the pneumoperitoneum is complex with local and systemic effects of a gas instilled under pressure.[75] Different gases such as helium, argon, and nitrous oxide have been evaluated as alternatives to the most commonly used gas — carbon dioxide. The question has naturally arisen to whether the carbon dioxide pneumoperitoneum influences the systemic metabolic and immune response to laparoscopic surgery.

There are new studies recently published that suggest it may. West[76] investigated the production of cytokines in peritoneal macrophages incubated in carbon dioxide. Macrophage TNF and IL-1 responses to bacterial endotoxin were lower for macrophages incubated in carbon dioxide than in either air or helium. A proposed mechanism for this difference was that carbon dioxide affected the intracellular medium by creating a more acidic environment. Macrophage function is known to be impaired by drops in extracellular pH.[77,78] West speculates that the impairment in peritoneal macrophage cytokine production may contribute to an apparent lack of inflammatory systemic response during laparoscopic surgery rather than the physiologic stress of the surgery itself. This provides a potential molecular mechanism to explain peritoneal macrophage immunosuppression.

Subsequently, West provided additional experiments to study the kinetics of carbon dioxide induced alteration in cytokine secretion. A significant reversible inhibition of TNF and IL-1 was demonstrated in macrophages incubated in carbon dioxide but not with helium or air.[79] They also demonstrated that inhibition of IL-1 occurred within 15 minutes of carbon dioxide exposure. The IL-1 mRNA production similarly decreased at this time. This difference in IL-1 production was rapidly abrogated after incubation in a controlled atmosphere. In contrast, TNF levels and macrophages exposed to carbon dioxide were inhibited only after a longer incubation. Additionally, normal levels of TNF m RNA were found despite the inhibition in TNF production. Inhibition of TNF persisted after the removal of carbon dioxide for 30 to 60 minutes after incubation in a controlled atmosphere. These experiments suggest that the effect on IL-1 and TNF responsiveness in peritoneal macrophages exposed to carbon dioxide may occur through different and independent cellular mechanisms.

An alternative hypothesis was provided by Watson[80] in a study of mice subjected to laparoscopy with both air and carbon dioxide. The control group of animals underwent open laparotomy. In this study, peritoneal tissue macrophage release of superoxide and tumor necrosis factor after both laparotomy and air laparoscopy were significantly increased compared with the control procedure and carbon dioxide laparoscopy. However, in these studies peritoneal macrophage phagocytosis was significantly decreased in air laparoscopy and laparotomy compared with carbon dioxide insufflation. Furthermore, a decrease in CD11β expression and an increase in bacterial translocation were found in both laparotomy and air laparoscopy groups. The authors speculated that some factor in air, perhaps a low level contaminant such as airborn endotoxin, rather than carbon dioxide itself, was responsible for the alterations measured in macrophage function. Puttick[81] examined the effects of warm carbon dioxide pneumoperitoneum to a physiologic temperature. These investigators examined patients undergoing laparoscopic cholecystectomy with either room temperature or ambient body temperature pneumoperitoneum. Greater levels of cytokines were detected in the intraperitoneal fluid harvested at operation from the room temperature carbon dioxide pneumoperitoneum group. Tumor necrosis factor and IL-1 were both statistically significantly increased in this group. The IL-6 increased only marginally. The intraperitoneal source of cytokine production may be resident peritoneal macrophages in such a model. It would appear that carbon dioxide pneumoperitoneum, by unclear mechanisms, does seem to attenuate peritoneal macrophage immune response.

Without doubt, the clinical efficacy of laparoscopic surgery has been established. It is becoming apparent that systemic immune and metabolic responses of surgery in general may not apply to laparoscopic surgery. Luckily, the pace of investigation in this exciting area is increasing. The most recent studies attack hypotheses from the cellular and molecular levels with careful attention to controls. As these efforts multiply, the systemic, metabolic and immune consequences of laparoscopic surgery will be better understood and hopefully patients will be the beneficiaries.

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