

Disorders of Adhesions or Adhesion-Related Disorder: Monolithic Entities or Part of Something Bigger—CAPPS?

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ABSTRACT

The purpose of this article is to review progress in the field of abdominopelvic adhesions and the validity of its two underlying assumptions: (1) The formation of adhesions results in infertility, bowel obstruction, or other complications. Reducing or avoiding adhesions will curb these sequelae. (2) “Adhesions” is a monolithic entity to be tackled without regard to any other condition.

Evidence is discussed to validate the first assumption. We reviewed progress in the field by examining hospital data. We found a growing trend in the number and cost of discharges for just two adhesion-related diagnoses, and the low usage of adhesion barriers appears in at most 5% of appropriate procedures. Data from an Internet-based survey suggested that the problem may be partly due to ignorance among patients and physicians about adhesions and their prevention.

Two other surveys of patients visiting the adhesions.org Web site defined more fully *adhesion-related disorder* (ARD). The first survey ($N=466$) described a patient with chronic pain, gastrointestinal disturbances, an average of nine bowel obstructions, and an inability to work or maintain family or social relationships. The second survey (687 U.S. women) found a high (co-) prevalence of abdominal or pelvic adhesions (85%), chronic abdominal or pelvic pain (69%), irritable bowel syndrome (55%), recurrent bowel obstruction (44%), endometriosis (40%), and interstitial cystitis (29%).

This pattern suggests that although “adhesions” may start out as a monolithic entity, an adhesions patient may develop related conditions (ARD) until they merge into an independent entity where they are practically indistinguishable from patients with multiple symptoms originating from other abdominopelvic conditions such as pelvic or bladder pain. Rather than use terms that constrain the required multidisciplinary, biopsychosocial approach to these patients by the paradigms of the specialty related to the patient’s initial symptom set, the term *complex abdominopelvic and pain syndrome* (CAPPS) is proposed.

It is essential to understand not only the pathogenesis of the “initiating” conditions but also how they progress to CAPPS. In our ARD sample, not only was the frequency of women with hysterectomies (56%) higher than expected (21 to 33%), but also the rates of the “initiating” conditions was 40 to 400% higher in patients with hysterectomies than in those without. This may represent increased surgical trauma or the loss of protection against oxidative stress. Related was the higher frequency of ARD patients reporting hemochromatosis (HC; 5%) than expected (~0.5%) and the higher rates (20 to

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Postsurgical Adhesions; Guest Editor, Michael P. Diamond, M.D.

Semin Reprod Med 2008;26:356–368. Copyright © 2008 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.

DOI 10.1055/s-0028-1082394. ISSN 1526-8004.

700%) of initiating conditions in patients with HC than in those without HC. Together with findings related to the toxicity of Intergel, these findings raise the possibility that heterozygotes for genes regulating oxidative stress are at greater risk of developing surgical complications as well as more severe and progressive conditions such as CAPPs.

KEYWORDS: Adhesions, adhesion-related disorder, complex abdominopelvic and pain syndrome, chronic pelvic pain, hysterectomy, iron overload, hemochromatosis

The history of adhesion prevention has been analyzed in terms of six epochs¹ divided principally according to the level of sophistication of the approaches used. The period referred to as “The Industrial Revolution” starting around 1989 was marked by the introduction of Interceed (1989; Ethicon, Inc, Somerville, NJ),² Seprafilm (1996; Genzyme Corp; Cambridge, MA),^{3,4} Preclude (ca. 1990; WL Gore & Associates, Flagstaff, AZ)⁵ and Adept (2007; Baxter Healthcare Corporation, Deerfield, IL). Hyaluronic acid, Flogel (poloxamer; Alliance Pharmaceutical Corp., San Diego, CA), tolmetin, Focalgel (Focal, Inc., Lexington, MA), and tissue-type plasminogen activator were all evaluated for adhesion prevention, but did not reach the point of regulatory submission. Sepracoat (1997; Genzyme Corp, Cambridge, MA)⁶ was denied approval, and Intergel (2002; Ethicon, Inc., Somerville, NJ)⁷ was approved but withdrawn for safety reasons.⁸ Adcon-L (1998; Gliotech, Inc., Cleveland, OH) was approved for spinal surgery but later withdrawn. Seprafilm II was briefly available in Europe but discontinued, and SprayGel (Covidien, Mansfield, MA), and Hylagel (Fidia Advanced Biopolymers, s.r.l. Abano Terme, Italy) remain available only outside the United States.

This “Industrial Revolution” has fueled an explosion in our grasp of abdominopelvic adhesions and its etiology,^{9–11} epidemiology,^{12,13} cost,^{14–16} prevention in human¹⁷ and animal¹⁸ models, as well as its clinical manifestations of pain, infertility, and bowel obstruction.^{10,19–21} Two assumptions underlying the contemporary study of adhesions and their prevention are the following:

1. The formation of adhesions results in infertility, bowel obstruction, or other complications. Reducing or avoiding adhesions will curb these sequelae.
2. “Adhesions” is a monolithic entity to be tackled without regard to any other condition.

The purpose of this article is to review our progress in the field and its underlying assumptions.

DOES REMOVAL OR AVOIDANCE OF ADHESIONS IMPROVE PATIENT OUTCOMES?

It has long been argued that the collection of outcome-based data for regulatory purposes would be impractical

due to the multifactorial nature of pain and infertility or the prolonged follow-up required in large numbers of patients to evaluate bowel obstruction.²² Nonetheless, studies have emerged that permit us to test our hypotheses that the removal (i.e., adhesiolysis) or avoidance of adhesions (i.e., use of adhesion barriers) will result in clinical benefits.

Adhesion Reduction and Surgical Complications

That the reduction in adhesion formation would result in the overall reduction of surgical complications is obvious from the several epidemiologic studies finding that approximately one third of patients undergoing abdominal or pelvic surgery were admitted nearly twice in the next 10 years for a problem related to adhesions or that could be complicated by adhesions.^{13,23} The same argument is justified from the numerous studies showing the reduction in incidence, extent, or severity of adhesions using a variety of adhesion barriers. More direct evidence comes from a small retrospective study involving 52 patients undergoing a second cesarean section, which found that delivery times and operative times were reduced in patients having Seprafilm placed at a first cesarean section compared with those in patients where Seprafilm was not used. Blood loss was also reduced but did not reach significance.²⁴ Relaparotomy time was also reduced in children treated with Seprafilm ($N=67$) undergoing abdominal surgery compared with that of control patients.²⁵ A prospective randomized study failed in 191 patients to demonstrate any significant differences in the time to close a loop ileostomy if Seprafilm had been used at the time of ileostomy creation. This failure was attributed to the variability in techniques used by the large number of surgeons (29) participating in the study.²⁶

Adhesion Reduction and Infertility

The American Fertility Society (AFS) classification of adnexal adhesions²⁷ inherently acknowledges an inverse relationship between adhesions and fertility²⁸ and has been confirmed in two ways. First, pregnancy rates have correlated with AFS scores (before adhesiolysis) in prospective settings by both laparotomy²⁹ and laparoscopy.³⁰ Second, the pregnancy rates among infertile

women treated by salpingo-ovariolysis was higher (45%) than that among matched untreated patients (16%).³¹ Although the hypothesis that fertility can be improved using an adhesion barrier remains untested prospectively, 78% (18 of 23) of patients undergoing reconstructive pelvic surgery treated with Interceed barrier became pregnant compared with only 47% (7 of 15) of control patients.³²

Adhesion Reduction and Bowel Obstruction

The relationship between bowel obstruction and adhesions is well-known^{19,21,33} and the management of bowel obstruction well described.^{19,34,35} Recently, Seprafilm was shown to reduce the rate of adhesive small bowel obstruction (SBO) requiring operation from 3.4% to 1.8% in 1701 patients undergoing small bowel resection with a follow-up of 2 to 5 years.³⁶ In two smaller retrospective series, Seprafilm reduced early SBO after surgery from 14% (26 of 183) to 6.5% (12 of 184) in patients undergoing gastrointestinal surgery³⁷ and from 20% (6 of 30) to 0% (0 of 21) in patients undergoing surgery for transabdominal aortic aneurysm.³⁸ A meta-analysis failed to detect a benefit of Seprafilm in terms of postoperative intestinal obstruction.³⁹

Adhesion Reduction and Pain

The relationship between adhesions and chronic abdominal or pelvic pain is more controversial.^{21,40,41} Adhesions may cause pelvic pain by tethering tissues, causing nerve traction, or by entrapping nerves. Indeed, nerve endings have been found within adhesions.⁴²

Not all adhesions cause pain, and not all pain is caused by adhesions. Part of the problem appears to be in the complex way pain is referred within the abdominal cavity as evidenced from studies involving conscious pain mapping. Furthermore, the conventional view that dense vascular adhesions are “worse” than filmy adhesions is challenged by observations that higher pain scores are associated more with filmy adhesions between movable structures rather than fixed or dense adhesions.⁴³ Twenty-five percent to 57% of patients with chronic pelvic pain (CPP) are estimated to have adhesions, with or without endometriosis.⁴⁴ In 75% of patients with a physical source of pain, emotional factors contribute greatly to the perception of pain and the ability to cope with it.

Despite the uncertain relationship between adhesions and pain, adhesiolysis does provide some relief. In a German study⁴⁵ involving laparoscopic adhesiolysis in female and male patients with chronic abdominal pain, there was a complete remission of pain in 45% of the patients, with 35% of patients reporting a substantial improvement up to 30 months. Other improve-

ments were reported in the United States^{46,47} and The Netherlands.⁴⁸ That these effects may be rooted in a “therapeutic” effect of laparoscopy itself alone is not clear as patients without obvious pathology undergoing diagnostic laparoscopy also reported a reduction or cessation of pain.⁴⁹

To test this further, 100 patients undergoing diagnostic laparoscopy for chronic abdominal pain were randomized to adhesiolysis or no treatment.⁵⁰ Patients and assessors were blinded. Forty-two percent of patients undergoing diagnostic laparoscopy reported improvement or remission at 12 months compared with 57% with adhesiolysis. The authors’ conclusion that although laparoscopic adhesiolysis relieved pain, it was no better than diagnostic laparoscopy, may reflect a type II error. Further, the apparent benefit of laparoscopy alone suggests that the source of pain in these patients may originate less from pathologic (i.e., adhesions) foci in the abdomen and more from higher levels in the nervous system. Whether this “placebo” effect is related to that reported in arthroscopy⁵¹ is unclear, although a more recent prospective and randomized study in endometriosis patients undergoing laparoscopy also suggests a positive effect of “sham” surgery.⁵² Lastly, the likely reformation of adhesions in at least 75% of surgical sites⁵³ may have abrogated any positive effect of adhesiolysis. In fact, the difference in pain reduction between the adhesiolysis and control groups would be consistent with the expected degree of improvement from adhesiolysis. Perhaps with a reduction of 25 to 30% in the incidence of adhesions (by site) that could be achieved with adhesion barriers, an effect of adhesiolysis on pain may have been more apparent. Indeed, in an uncontrolled series of 19 patients undergoing laparoscopic adhesiolysis with placement of Seprafilm for chronic intractable abdominal pain, 14 (74%) patients had discontinued pain medications at follow-up of up to 32 months.⁵⁴

REMOVAL OR AVOIDANCE OF ADHESIONS MAY IMPROVE PATIENT OUTCOMES—NOW WHAT?

The emerging evidence does support the notion that curbing adhesions improves outcomes for patients. But it is clear that there is a long way to go to eliminate the problems of adhesions

Our own analysis of discharge data from the Nationwide Inpatient Sample for the period 2001–2005 reveals a growing trend in the numbers of discharges for just two ICD-9-CM diagnosis codes (Table 1). A somewhat steady 2100 to 2400 patients a year have died with a principal diagnosis of Intestinal Adhesions with Obstruction (560.81), which produced in 2005 73,881 discharges and some \$3.45 billion of charges. But this is just the tip of the iceberg. When

Table 1 Hospital Discharge Data for Two Adhesion-Related Codes and Use of Barriers

	Year				
	2001	2002	2003	2004	2005
ICD-9-CM Diagnosis Code 568.0 Peritoneal Adhesions					
<i>All Diagnoses—Discharges</i>					
All discharges	156,621	168,154	172,935	180,806	186,387
Female percent of total (%)	74	73	72	73	72
ICD-9-CM Diagnosis Code 560.81, Intestinal Adhesions with Obstruction					
<i>All Diagnoses—Discharges</i>					
All discharges	89,048	91,664	88,965	94,708	99,075
Female percent of total (%)	63	62	62	62	62
<i>Principal Diagnosis Only—Deaths</i>					
All	2219	2366	2311	2140	2118
Female	1396	1404	1418	1264	1285
Female deaths as percent of female discharges (%)	3.25	3.19	3.36	2.81	2.78
99.77 Application of Adhesion Barrier		—	—	23,813	30,105

Source: Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality.

other inpatient diagnoses of peritoneal and pelvic adhesions are added, the financial cost of adhesions easily exceeds \$5 billion, and that is before outpatient costs and loss of work are considered.

The use of adhesion barriers as evidenced from code 99.77 is also very low. This is almost certainly an underestimate. Based on estimated sales of adhesion barriers of \$100 million, an average price per unit of \$200, and an average usage of 1 unit per procedure, adhesion barriers are only used, conservatively, in 500,000 procedures annually. To estimate their potential usage, assuming that obstruction due to adhesions represents 1% of general surgical admissions in 1 year,⁵⁵ then the figure of 99,075 discharges for intestinal adhesions with obstruction represents some 9.9 million procedures where barriers might be used. The percentage of procedures in which adhesion barriers are used is at best a little over 5%.

Solving the problem of adhesions may be broken down into four main tasks:

1. Develop more effective antiadhesion agents for a variety of indications both by laparotomy and laparoscopy.
2. Expand basic research beyond that currently conducted by a handful of laboratories.
3. Increase physician and patient awareness about adhesions and their prevention to improve the use of adhesion barriers and other techniques, leading to more chances for improved outcomes.
4. Challenge the paradigms on which are based contemporary efforts in adhesion prevention. Is it time for a different look?

The development of more advanced antiadhesion agents has been discussed elsewhere,^{1,56} and other contributions in this issue of *Seminars in Reproductive*

Medicine provide a glimpse of the excellent basic research being conducted in the field. The last two items will be discussed further here.

IMPROVING PHYSICIAN AND PATIENT AWARENESS ABOUT ADHESIONS

The ramifications of physician and patient ignorance about adhesions has long been the subject of debate in the boardrooms of medical product companies and the barrooms of conferences on adhesions. Corporate advertising as well as sponsorship of several excellent studies such as those analyzing data from the Scottish National Health Service^{12,13} has greatly increased awareness of adhesions. Revolutionizing patients' access and use of medical information, the Internet has spawned the proliferation of Web sites promoting research and awareness and providing information and support to families and patients affected with all manner of conditions, particularly those heretofore relegated to obscurity in medical textbooks. Accordingly, in 1996 we formed The International Adhesions Society, and its adhesions.org Web site now receives more than 100,000 visitors monthly. Ignorance about adhesions among patients and physicians is frequently reported to us, arguably delaying diagnosis and treatment and inflicting additional suffering on patients shunned by their physicians, employers, and families as malingerers.

To characterize the causes of this ignorance, patients who had abdominal or pelvic surgeries were surveyed via the Internet⁵⁷ about information given them prior to surgery regarding adhesions and adhesion barriers. Five hundred seventy (43 male, 527 female) patients responded concerning 952 procedures. Patients reported being informed about adhesions prior to 27% of the procedures they underwent. In only 122 (12.8%) of these were adhesions mentioned as part of the informed

consent, and in another 132 (13.9%) adhesions were discussed. Information was imparted about adhesions in 55% of adhesiolysis procedures and in 9.3% of non-adhesiolysis procedures. Patients reported being provided with information about adhesion barriers in 46% and 6% of adhesiolysis and non-adhesiolysis procedures, respectively. Where adhesions were mentioned, barriers were mentioned in 46% of adhesiolysis procedures and in 22% of non-adhesiolysis procedures. Despite several obvious caveats involved in interpreting a study of this kind, it suggests the preoperative consultation and consent procedures may offer the ideal opportunity to educate patients about adhesions. Beyond medicolegal reasons for discussing adhesions,⁵⁸ patients do want to know about their treatment and its risks.⁵⁹ Even if they do not fully understand the information provided,⁶⁰ training (or even requiring) physicians to discuss adhesions with patients forces them to consider a strategy for their reduction.

CHALLENGING THE PARADIGMS OF ADHESIONS RESEARCH: IS IT TIME FOR A DIFFERENT LOOK?

Viewing the Problem as Adhesion-Related Disorder

Despite the increasing volume of work conducted, adhesions research has been practically compartmentalized, as if “adhesions” was an independent entity. Accordingly, the approach to “adhesions” patients was much like any monolithic disease but was clearly not meeting the needs of thousands of “adhesions” patients seeking referrals or other information. Why? Because we lacked effective antiadhesion agents? Because we did not fully understand the pathogenesis of adhesions? Because of ignorance about adhesions and their prevention? Perhaps it was because we wrongly assumed that “adhesions” is an independent and monolithic problem.

To determine the best approach to the “adhesions” patient, we first tried to describe more fully the condition of the “adhesions” patient. From hundreds of e-mails and telephone interviews, a typical picture of an “adhesions” patient emerged of a 30- to 50-year-old woman with several abdominal surgeries, including a hysterectomy and several bowel obstructions. She had chronic pain, could not eat properly, and had already seen several physicians who had told her that there was little to be done. The patient was desperate and frustrated and her family, social, and employment relationships were deteriorating.

An Internet-based survey was conducted to quantify what we had learned from our anecdotal library.⁶¹ Four hundred sixty-six patients (51 male, 415 female) reported having a diagnosis of adhesions for 7.0 ± 0.3 years. Sixty-eight percent of patients reported an average of 9.5 ± 0.7 full or partial obstructions. Most of

these respondents seem to represent a severe form of “adhesions” perhaps a notch or two below the 2100 or so patients dying annually with a primary diagnosis of intestinal adhesions with obstruction (Table 1). These data are consistent with descriptions of a living hell in which each of the sometimes > 25 adhesiolysis procedures offers only a temporary respite of less than a year from obstruction and debilitating pain. Indeed, 81% of respondents reported chronic pain of whom 68% took medication. In 68% of those patients, the medication worsened their bowel symptoms. Seventy-one percent of patients reported gastrointestinal disturbances, including 52% with chronic or severe constipation, 30% with chronic or severe diarrhea, and 24% with malabsorption problems. The totality of these patients’ suffering could not adequately be described by the monolithic term “adhesions” and so was coined the term *adhesion-related disorder* (ARD).

Our anecdotal impression that ARD compromises a patient’s ability to work was verified by 42% of respondents, 47% of whom could not obtain disability benefits. As a result of their condition, patients reported that either their relationships had suffered (57%) or their friends and family were not supportive (44%), or both (27%), with only 26% reporting intact relationships and supportive friends and family.

Commonly reported feelings of isolation and “craziness” are illustrated in the following excerpts from e-mails we received (without correction of spelling or grammar):

- have had 15 srgys. Each time the doctors go in they say I had so much ashesions. I had a hsty 4 years ago because of endo. Now the pain is back in full force. At first I thought I was crazy. . . . I do not no how long I can deal with this pain. Its so bad. Is there anyone who has gone though this before. I could really use some encouragement right now. I thought the pain was gone after the hsty. I guess I was wrong (9/9/2002).
- I have been suffering with endometriosis, adhesions, and IC [interstitial cystitis] for the past 13 years. I have had 24 surgeries and still live in constant pain from adhesions. . . . Without pain meds I cannot take care of my children or my husband. I cannot work anymore. . . . The adhesion site has been a savior to me at a time in my life when I thought I was all alone. Now I know I am not alone and there are other alternatives to just living in pain the rest of my life (5/10/2004).
- I thought I was the only one. I have had 12 surgeries to control the adhesions. . . . I thought I was going to beat this one, but now the symptoms have returned and all my hope has gone. . . . Thanks for posting this Website where I can know i’m not the only one.(4/17/2006).

In the extreme, some patients reported considering or attempting suicide:

- i really don't know what to do anymore... ii am to scared to ask for help but i really want it... I am so ready to just commit suicide but i never succeed (10/9/2003).
- I... feel suicidal trying to cope with ARD (3/6/2006).
- I lost another ARD patient this past weekend to suicide. Her family and friends were no support for her. He[r husband] was told her only problem was addiction to pain meds. That was the last straw,... (from an ARD volunteer 10/2/2006).
- I had a full hysterectomy... I am in constant pelvic/abdominal pain... had... additional surgeries for adhesions... I am still in constant pain 24-7... I am so depressed with thoughts of suicide, however, my deep faith will always prevent me from doing this (12/24/2004).

Based on anecdotal reports, patients were also asked about their use of physical therapy. In the 26% of patients using it, 29% benefited. Such therapy has been widely reported to benefit patients with a diagnosis of chronic pelvic pain.⁶² Forty percent of patients reported that their physician was able to help their condition somewhat, with another 51% reporting that their physicians acknowledged their problem but were unable to help. Contrary to earlier impressions, only 9% of patients reported that their physicians denied their problem and were unwilling to help.

Viewing ARD in the Context of Complex Abdominopelvic and Pain Syndrome (CAPPS)

The term *ARD* still leaves the same frustrated and desperate patient traversing continents and oceans in the hope of finding that one physician with "the secret" to their suffering. Continuing to puzzle us are observations that severe ARD patients are temporarily relieved of pain after adhesiolysis, and when pain recurs they are adhesion-free (and free of other pathology) at laparoscopy. Equally puzzling is the improvement in pain after diagnostic laparoscopy alone in patients with adhesions.⁵⁰ If by using the term *ARD* we have succeeded in acknowledging the existence of ARD patients' numerous symptoms, we continue to fail practically by assuming that they are all related by the common denominator of adhesions. As will be explained, a more successful approach may be derived by examining the problem of ARD in the context of a much larger problem of what we have termed *complex abdominopelvic and pain syndrome* (CAPPS) defined operationally as:

a syndrome of nonmalignant origin consisting of a complex of symptoms of the abdomen or pelvis that includes pain, bowel, or bladder dysfunction of at least 6 months duration.

Both sides of the debate about whether adhesions cause pain have failed to consider neurologic changes that occur in chronic pain. Although acute or subchronic pain may be due to surgically correctible pathology (i.e., adhesions, endometriosis, etc.), once pain has become chronic (e.g., 6 months), changes in the spinal cord and dorsal root ganglia⁶³⁻⁶⁵ result in the transmission of unsolicited, inappropriate, and uncontrolled impulses to the pain centers of the brain. Pain itself becomes the disease state rather than a local cause. Although pain can be temporarily arrested by the removal of triggers such as endometriosis and adhesions, pain may inevitably return because the neural changes themselves have not been addressed, akin to the phenomenon of phantom limb pain.⁶⁶ Indeed, phantom bladder pain has been reported in patients after cystectomy.^{67,68}

But the story continues. The complex neuroanatomy of sacral, lumbar, hypogastric, and pelvic plexi^{69,70} affords many opportunities for cross-talk between the nerves of abdominal and pelvic tissues.⁷¹ Impulses once appropriate from one organ may trigger impulses in a nearby pathway, deceiving the brain into believing that they have originated elsewhere. Further, pathology in one organ (e.g., uterus, bladder, bowel) may induce pathology⁷² or hypersensitivity⁷³⁻⁷⁵ in another. Thus, a patient in whom only one organ was affected initially may develop a problem in another.

Many studies attest to the coprevalence between various abdominal and pelvic disorders^{76,77} including adhesions.⁷⁸ A similar pattern of organ involvement appears to exist from our preliminary analysis of 687 female ARD patients from the United States responding to our Internet-based survey (Table 2). Focusing on adhesions and calculating the cumulative coprevalence of the five most frequent diagnoses or

Table 2 Conditions and Diagnoses Reported by U.S. Women Visiting an Adhesions-Oriented Web Site

Condition or Diagnosis	N	Percent of Total (%)
All U.S. women	687	100
Adhesions: abdominal	532	77
Adhesions: pelvic	433	63
Adhesions: abdominal or pelvic	582	85
Chronic abdominal (not pelvic) pain	383	56
Chronic pelvic (not abdominal) pain	383	56
Chronic pain: abdominal or pelvic	471	69
Irritable bowel syndrome	376	55
Recurrent bowel obstruction	299	44
Endometriosis	270	40
Interstitial cystitis	197	29
Fibroids	183	27
Pelvic Inflammatory Disease (PID)	98	14
Hemochromatosis or iron overload disorder	47	7
Previous hysterectomy	387	56

Table 3 Coprevalence of Conditions and Diagnoses Reported by U.S. Women Visiting adhesions.org Relative to Adhesions

	n	Percent (%)	n	Percent (%)	n	Percent (%)	n	Percent (%)	n	Percent (%)
Total (N = 687)		100								
Adhesions: abdominal or pelvic	582	85	Adhesions+							
Chronic pain (CP): abdominal or pelvic	471	69	452	66	Adhesions + CP +					
IBS	376	55	360	52	314	46	Adhesions + CP + IBS +			
Recurrent bowel obstruction	299	44	287	42	237	35	186	27	Adhesions + CP + IBS + Recurrent +	
Endometriosis	270	39	261	38	228	33	178	26	112	16
					174	25	149	22	96	14
IC	197	29	193	28					65	9.5

% is percentage of total number of U.S. women responding to survey.

conditions, in descending order of prevalence (Table 3), the data reveal a high degree of overlap between abdominal or pelvic adhesions, chronic abdominal or pelvic pain, irritable bowel syndrome (IBS), recurrent bowel obstruction, endometriosis, and interstitial cystitis.

These data suggest that the severe “ARD” patient suffers from a similar multifaceted, multiorgan phenomenon as the “chronic pelvic” or the “chronic bladder” pain patient. Even if patients from each of these groups started with just one condition, as each condition progressed, it began to overlap and coalesced with the other into the entity we have termed *CAPPS*. Although ~15 million women alone suffer from chronic pelvic pain, we have conservatively estimated that there are 150,000 to 250,000 women with the most severe form of the disease (as *CAPPS*), a high proportion of who will most likely have adhesions.

Without the perspective of *CAPPS*, a patient is at the mercy of compartmentalized medical practice. Although the severe *CPP/IC/ARD* patient is likely to display several seemingly unrelated symptoms, the most dominant one will determine the specialty to which the patient is initially referred. Unexplained dysmenorrhea or dyspareunia will no doubt receive a gynecologic diagnosis of adhesions, pelvic inflammatory disease (PID), or endometriosis. Unexplained bowel disturbances will be given a diagnosis of IBS from a gastroenterologist, and mysterious voiding issues will be given a diagnosis of IC by a urologist. A neurologist may well view the problem as one of pudendal neuralgia. Once locked into a diagnostic paradigm, the patient will be treated accordingly and usually in terms of end-organ rather than systematic pathology.

TREATING THE CAPPS PATIENT

Given the multifaceted nature of *CAPPS*, it seems appropriate that the patient be approached by an integrated multidisciplinary team including representatives from surgery, pharmacy, nursing, pain medicine, nutrition, psychology, physiotherapy, neurology, gastroenterology, gynecology, urogynecology, urology, psychiatry, and social work. Such a “biopsychosocial” approach⁷⁹ has been introduced, advocated, and to some degree validated in a number of areas of pain medicine, including pelvic pain.⁸⁰⁻⁸⁶

In adopting a multidisciplinary approach, it is essential to avoid the constraints imposed by the paradigms of any one element of the multifaceted condition (e.g., pain, adhesions). Accordingly, the term *CAPPS* is preferred over *ARD* as well as other superficially similar terms such as “chronic visceral pain syndrome.”⁸⁰ Perhaps this is what was meant by the recently expressed view that the “*multidisciplinary approach dealing with the pain is far more important than finding an organic cause and cure for the pain.*”⁸¹ Although for the treatment of a

patient who has entered the world of CAPPs, it may matter little that they entered through the door of IC, IBS, endometriosis, or ARD, a new opportunity exists to learn from CAPPs patients by:

1. Adapting therapies used in one variant of CAPPs in patients with a different variant. For example, sacral nerve stimulation has been shown to be effective in treating IC and is also useful in treating other CAPPs components such as chronic pelvic pain.^{87,88}
2. Learning how to prevent patients suffering from the “monolithic” varieties of individual diseases from progressing to the multifactorial condition.

IDENTIFYING RISK FACTORS FOR PROGRESSION TO CAPPs FROM THE PERSPECTIVE OF ARD

Genetic Factors

There has long been speculation about genetic factors in ARD. The relative inability to lyse fibrin may predispose a patient to adhesions. Hypofibrinolysis, associated with an allele of the plasminogen activator inhibitor-1 (PAI-1) gene, was found more often in women with endometriosis than in controls.⁸⁹ More directly related to adhesions, carriers of the IL-1RN*2 allele are at greater risk for adhesion formation.⁹⁰

Multiple Surgeries

A primary occurrence of adhesive small bowel obstruction (ASBO) is itself a risk factor for future obstruction. The rate of recurrence after a first ASBO was calculated⁹¹ as 16% after 41 months (range, 1 to 75 months), 18% at 10 years, and 29% at 30 years.⁹² The risk of

recurrent ASBO increased with increasing number of prior SBO episodes and reached 81% for patients with 4 or more admissions due to ASBO. Age < 40 years, type of adhesion, and presence of postoperative complications were also identified as risk factors for ASBO.⁹¹ The effect of multiple surgeries has been noted in other CAPPs-related areas. Women with IC had significantly more pelvic surgeries than did controls, often performed before IC was diagnosed and possibly for pain related to undiagnosed IC.⁹³ One overlooked consequence of multiple surgery is the accumulation of scar tissue within peritoneal tissue (as opposed to between peritoneal tissue, i.e., adhesions) and the effect this may have in entrapping sensory nerves, giving rise to pain and related sequelae. Perhaps one effect of repeated surgeries is to increase the population of fibroblasts of the “adhesion phenotype,”⁹⁴ making the recurrence of adhesions ever more likely.

Hysterectomy

Hysterectomy is associated with several CAPPs-related conditions.⁹⁵ Women with IC ($N=215$) had a higher (42%) prevalence of hysterectomies than did controls (21%).⁹³ A diagnosis of IC was made 1 to 5 years after hysterectomy in most of the 68% of the possible cases.⁹³ Hysterectomy is also associated with a high rate of SBO.⁹⁶ Sixty-seven percent of patients admitted for SBO had had a hysterectomy.⁹⁷ The rate of adhesion-related obstruction after gynecologic surgery for benign conditions without hysterectomy has been estimated at ~0.3%. With hysterectomy, this rate may be 2 to 3% and with radical hysterectomy as high as 5%.⁹⁸

Some 56% of our own sample of 687 U.S. women had had hysterectomies (Table 2), much higher^{93,99} ($p < 0.01$) than the reported frequencies of 21 to

Table 4 Fraction of Patients Reporting Various Conditions with or without Hysterectomy or Hemochromatosis/Iron-Overload Disorder

	+ Hyst	-Hyst	+ Hyst/-Hyst	+ H-I	-H-I	+ H-I/-H-I
<i>N</i>	387	300		47	640	
Condition						
+ Adhesions: abdominal or pelvic	0.97	0.69	1.40	1.00	0.84	1.20
+ Chronic pelvic or abdominal pain	0.84	0.48	1.76	0.98	0.66	1.47
+ Endometriosis	0.53	0.21	2.55	0.85	0.36	2.37
+ Interstitial cystitis	0.41	0.12	3.35	0.83	0.25	3.36
+ IBS	0.71	0.34	2.08	0.98	0.52	1.90
+ Recurrent obstruction	0.55	0.29	1.86	0.89	0.40	2.23
+ Fibroids	0.38	0.12	3.28	0.87	0.22	3.93
+ PID	0.22	0.04	5.07	0.81	0.09	8.62
+ Hemochromatosis/ iron-overload disorder	0.11	0.013	8.33			
Hysterectomy				0.91	0.54	1.70
Geometric mean of fractions/ratios	0.44	0.16	2.82	0.90	0.36	2.47

Hyst, hysterectomy; H-I, hemochromatosis or iron-overload disorder.

33%¹⁰⁰ in control populations. The rates of the various CAPPs-related conditions in this population was higher ($p < 0.001$) for each of the conditions in patients with a hysterectomy than in those without (Table 4).

Whether this effect of hysterectomy is reflective of collaterally damaged pelvic structures or a common pathology predisposing a patient to CAPPs is unclear. Alternatively, hysterectomy may place a woman at risk for oxidative stress related to iron overload as iron is no longer eliminated through menstruation.^{101,102} The protective estrogenic effect against oxidative stress may also have been a factor.^{103,104} Oxidative stress and its amelioration has been discussed in the context of adhesions^{105,106} or endometriosis¹⁰⁷ but not in regard to hysterectomy and adhesions.

Susceptibility to Oxidative Stress: Hemochromatosis and Iron-Overload Disorder

The frequency of a diagnosis of hemochromatosis or iron-overload disorder in patients with a hysterectomy was more than 8 times that in patients without (Table 4). The most common form in the United States is hereditary hemochromatosis (HHC), a recessive disorder resulting mainly from one of several HFE gene mutations. HHC affects ~0.5% of the population¹⁰⁸ and is characterized by iron deposition in multiple organs, liver disease, heart disease, joint disease, diabetes, and early death. Its symptoms include fatigue and joint and abdominal pain.¹⁰⁹ HHC may be a cause of infertility.¹¹⁰ Accumulated iron participates in redox reactions and the generation of reactive oxygen species leading to tissue damage via the peroxidation of lipids, proteins, and nucleic acid.^{111,112} A role for iron has been suggested in the pathogenesis of endometriosis.¹¹³⁻¹¹⁵

Of our sample of U.S. CAPPs-ARD patients, 6.8% (47 of 687) reported a diagnosis of hemochromatosis (HC) (5.1%) or iron-overload disorder (IOD) (5.7%) with substantial overlap. The frequency of HC patients is well above that expected (0.5%) in the general population ($p < 0.001$). The rates of various CAPPs-related conditions in this population was higher ($p < 0.001$) for each of the conditions in patients with HC/IOD than in those without (Table 4).

HHC heterozygotes, though not displaying a history of HHC, carry risks of iron overload¹¹⁶⁻¹¹⁹ and an altered pattern of fibrosis or inflammation.^{120,121} Because inflammation alters iron homeostasis,^{122,123} HHC heterozygotes (~25% in the United States) undergoing surgery may be at increased risk of adhesions or other complications and may suffer from more severe forms of other CAPPs-related conditions and may be less responsive to prophylaxis or treatment.

Support for this hypothesis comes from our preliminary work concerning possible Intergel Reac-

tion Syndrome (pIRS).¹²⁴ Intergel (ferric hyaluronate [FeHA]) was a gel of ferric hyaluronate used for adhesion prevention but withdrawn due to reports of late-onset pain, unexplained fever, infection, peritoneal reactions, and several deaths.^{8,125} Based on the possibility that the difference between the production of a granulomatous peritonitis in immature and mature rats in response to Intergel¹²⁶ could be accounted for by developmental differences in the expression of hepcidin, a regulator of iron transport,¹²⁷ we hypothesized that a similar subclinical deficiency in iron regulation, such as HHC heterozygosity, may contribute to pIRS. Compared with ~25% of the population, 3 of 7 (43%) patients reporting a reaction to Intergel had one of the three HFE main mutations. These patients, along with two others, were of Irish/Scottish ancestry, known to have a high prevalence of HHC. Three of the HFE-normozygotes and one of the HFE heterozygotes had had a prior hysterectomy, a finding that approached ($p = 0.08$) or exceeded ($p = 0.03$) significance depending whether a figure of 33%¹⁰⁰ or 21%^{93,99} is taken as the control prevalence of hysterectomy. Thus, the combination of surgery (disturbing iron homeostasis), the propensity to iron overload (either because of a HFE mutation or prior hysterectomy), and the administration of a bolus dose of iron into a single physiologic compartment (as Intergel, delivered intraperitoneally) may have led to the development of pIRS.

This finding has implications beyond pIRS. Because the differences in population frequencies of HFE mutations may account for intercontinental differences in adverse event rates to Intergel,¹²⁸ those same differences may influence the relative propensity of populations to form adhesions, to respond to antiadhesion measures, to succumb to other conditions, and for those conditions to progress to a multifaceted condition such as CAPPs. Other examples of genes that regulate oxidation for which this argument could be advanced include those for catechol-*O*-methyltransferase (COMT)¹²⁹ and GTP cyclohydrolase (GCH1),¹³⁰ polymorphisms that influence sensitivity to pain. Lastly, these findings have implications for the use of antioxidants and modulators of iron metabolism in the prophylaxis and treatment of CAPPs-related conditions.

CONCLUSIONS

Although great strides have been made in understanding adhesions, preventing them, and curbing adhesion-related sequelae, "adhesions" can no longer be considered a monolithic entity. Although "adhesions" may start out as a monolithic entity, a patient with "adhesions" may develop related conditions (ARD) until they are practically indistinguishable from patients with multiple symptoms stemming from other pelvic or abdominal pathologies to the point that they coalesce into a new

pathologic entity. Rather than use terms that constrain the approach to these patients by the paradigms of the specialty related to the patient's initial symptom set, it is proposed that a term such as *complex abdominopelvic and pain syndrome* (CAPPS) be used to allow the unencumbered development of a multidisciplinary biopsychosocial approach.

It is essential to understand not only the pathogenesis of the "initiating" conditions but also how they progress to CAPPS. In the case of adhesions, we have some understanding of how adhesions form and the breadth of problems experienced by the severe adhesions patient. But we have little understanding of how adhesions become ARD and how ARD becomes CAPPS. On the positive side, we can begin to apply what we have learned about the treatment of CAPPS stemming from other pathologies to the treatment of CAPPS stemming from adhesions.

ACKNOWLEDGMENTS

The author gratefully acknowledges the many thousands of patients whose personal communications have given a face to the suffering of adhesions and a sense of urgency in our quest to solve the problem. The author also thanks the numerous medical and patient volunteers around the world who have provided help and assistance to the adhesions.org Web site, especially Roberta and Bruce Speyer of OBGYN.net for making the work of adhesions.org possible.

ABBREVIATIONS

AFS	American Fertility Society
ARD	adhesion- related disorder
ASBO	adhesive small bowel obstruction
CAPPS	complex abdominopelvic and pain syndrome
COMT	catechol- <i>O</i> -methyltransferase
CPP	chronic pelvic pain
GCH1	GTP cyclohydrolase
HC	hemochromatosis
HHC	hereditary hemochromatosis
IBS	irritable bowel syndrome
IC	interstitial cystitis
IOD	iron-overload disorder
PAI-1	plasminogen activator inhibitor-1
PID	pelvic inflammatory disease
pIRS	possible Intergel reaction syndrome
SBO	small bowel obstruction

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