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Прорывы, провалы и вызовы в исследованиях спаек
Advances, Retreats and Challenges in Adhesions Research

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Keywords

Adhesions, Adhesiolysis, Adhesion Related Disorder, Complex Abdomino-Pelvic and Pain Syndrome, CAPPS, ARD, chronic pelvic pain, bowel obstruction, therapeutic ultrasound.

Abbreviations

ARD	Adhesion Related Disorder
ASBO	Adhesive small bowel obstruction
ASRM	American Society for Reproductive Medicine
CAP	Chronic Abdominal Pain
CAPPS	Complex Abdomino-Pelvic and Pain Syndrome
CPP	Chronic Pelvic Pain
CRPS	Complex Regional Pain Syndrome
FC	«Full Conditioning» Method
FDA	Food & Drug Administration (United States)
HA	Hyaluronic Acid
IBS	Irritable Bowel Syndrome
IC-BPS	Interstitial Cystitis-bladder Pain Syndrome
IUD	Intrauterine Device
SBO	Small Bowel Obstruction

Summary

The purpose of this paper is to review the progress being made to tackle adhesions, both in terms of advances and «retreats» and to list some of the challenges for the future.

1.1 Are adhesions still an extensive and costly problem?

Advances: Several pharmacoeconomic analyses highlight the cost and burden of adhesions. While certain adhesion barriers reduce adhesion formation, there is evidence that adhesion barriers may improve other surgical outcomes only in some reports.

Retreats: The cost of in-patient procedures for adhesions in the USA outpaced that of other inpatient hospital services by 27% from 1997 to 2013.

Challenges: There were over 350,000 in-patient procedures related to abdominopelvic adhesions in 2013 (USA) with aggregate direct costs between $6.2 and $12 billion, equivalent to 20%-40% of the entire budget of the US National Institutes of Health (NIH). These costs do not include outpatient care, work losses, family disruptions, pain management or adhesion-related infertility. While we have achieved some success, the adhesions «community» must emulate the success that groups advocating for other medical conditions have achieved by educating the public that adhesion related complications can happen to anyone undergoing surgery. We still lack reliable data that address whether adhesion barriers improve surgical outcomes. Much of the data on the cost and burden of adhesions comes from the USA and also Europe. More data are needed to assess the extent of the problem around the world.

1.2 Is adhesion-related bowel obstruction still a problem?

Advances: Recently issued professional guidelines for the management of obstruction may reflect an increased awareness about adhesions and willingness and ability to tackle them. Mortality associated with adhesion-related bowel obstruction has declined in the USA from a high of 2421 in 2000 to 1545 in 2013. There is some evidence that adhesion barriers may influence SBO-related measures, but more data are required.

Retreats: Although adhesions research in general has declined, research related to adhesive bowel obstruction is scant.

Challenges: Adhesion related bowel obstruction remains a significant and costly problem with 97,945 (all) and 76,805 (principal) discharges in the US in 2013. These accounted for 95% of the costs of all abdominopelvic adhesions discharges. We must develop better prevention strategies for patients most at risk of obstruction and for those who have already obstructed.

1.3 Is adhesion-related infertility still a problem?

Advances: We are beginning to understand the economic impact of treating adhesion-related infertility secondary to other procedures.

Retreats: Because of advances in assisted reproductive technologies, little progress has been made in improving adhesion-dependent fertility outcomes after surgery.

Challenges: Due to cost and ethical issues of assisted reproductive technologies, adnexal adhesiolysis may be making a resurgence in popularity.

1.4 Is adhesion-related pain still a problem?

Advances: We are now clarifying the relationship between adhesions and pain. There is enough of an association between adhesions and pain to justify their prevention initially, but due to central sensitization, neural cross-talk and the development of CAPPS (Complex Abdomino-Pelvic and Pain Syndrome), adhesiolysis may not be as successful as would be expected if the only reason for pain was a direct, local irritant effect of adhesions. Wearable therapeutic ultrasound appears helpful for pain in adhesions patients.

Retreats: Lack of good quality data and misinterpretation of some existing data has added to the confusion about the use of adhesiolysis for pain.

Challenges: We must understand better the complex relationship between adhesions and pain. Non-surgical approaches should certainly be used before resorting to surgery but since the therapeutic effect of laparoscopy combined with adhesiolysis may be great enough to justify its performance, adhesiolysis should

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nonetheless remain an option for ARD patients. We must address the fibrosis that occurs at the «base» of the adhesion to address nerve entrapment which may account for adhesion pain.

1.5 Have adhesion barriers achieved their potential?

Advances: Creation of ICD9-CM code 99.77 has allowed tracking of adhesion barrier usage, but shows a slow rate of their adoption, reaching only about 12% for some procedures in the USA.

Retreats: Little progress has been made developing effective adhesion barriers that can eliminate adhesion-related bowel obstruction, infertility and pain, as well as reduce costs. Regulatory, legal, integrity or safety issues with Intergel, Seprafilm and Adcon have added to the hurdles of the regulatory climate that impede investment in development of anti-adhesions products in the USA. This has had global repercussions.

Challenges: Adhesion barriers have not achieved their potential. Government and private investment in adhesions research must be encouraged to ensure the smooth development of these sorely needed products. Regulatory pathways must be redefined to meet the challenges of approving the barrier use in the context of simultaneous measures such as conditioning.

1.6 Progress in developing anti-adhesion products

Advances: Despite the adverse effect of the US business and regulatory climate on the development of anti-adhesion products, companies around the world have taken on the challenge of developing anti-adhesion products. Advances have been made with improved formulations of hyaluronic acid or PEG-based products. Advances have been made in understanding the interaction between hypoxia, inflammation, fibrinolysis, genetic factors, oxidative stress and adhesions. There are some promising clinical data regarding «peritoneal conditioning» which uses a modified insufflation gas, heparin lavage, an adhesion barrier and peri-operative steroids.

Challenges: We must develop anti-adhesion barriers that can be placed around the bowel without fear of ileus, abscess, infection or dehiscence. Barriers must be capable of laparoscopic delivery and function in the presence of bleeding. Barriers must not potentiate tumor growth. Drug-device combinations, or biologically based products will likely break the limit of efficacy seen with the current generation of barriers. We must develop drug-polymer products that can both act as adhesion barriers and provide pharmacological modulation of adhesions or fibrosis. We must look to gene therapy, cell therapy and tissue engineering approaches to preventing adhesions. We must develop a good method of imaging adhesions non-invasively and quantitatively. We must strive to reduce the absolute incidence of adhesions rather than reduce the extent or severity of adhesions based on an abstract scoring system.

1.7 Non-Barrier reduction of adhesions and their consequences

Advances: Whether laparoscopy improves adhesions-related outcomes remains unclear. More widespread use of warm and humid insufflation gases, or modification of gases in other ways may be needed to settle this question. The banning of powdered gloves which provides a source of peritoneal irritation is an advance. We are beginning to understand the role of manual techniques to treat or prevent adhesions.

Retreats: Hysterectomy is still performed for pain in large numbers despite the lack of evidence to support its use. Treating these patients non-surgically would remove a large number of patients from the pool of people at-risk from adhesions and other sequelae. While great efforts are being made to limit the use of opioids for chronic pain, little progress has been made on expediting development and regulatory and reimbursement approval for non-opioid alternatives.

Challenges: We need to understand how lifestyle and medical factors affect conditions related to adhesions. Smoking, overweight status and exercise are associated with gynecological adhesions, although the causal relationship is not known. Pre-operative modification of a patient's inflammatory state can help to improve surgical outcomes. This would include smoking cessation, dietary modification, use of anti-oxidants and use of anti-inflammatory drugs. Prediction of a patient's adhesion propensity may permit preventative approaches to be tailored to the patient. We must develop a multidisciplinary approach to treating the wide range of problems experienced by adhesions patients – pain, obstruction, bowel, urinary, genital and musculoskeletal issues.

1.8 Treating and Preventing ARD as a subset of CAPPS

Advances: Perhaps the biggest advance that has been made is in the understanding the holistic nature of the problem of adhesions in terms of Adhesion Related Disorder (ARD) and Complex Abdomino-Pelvic & Pain Syndrome (CAPPS), and how many symptoms experienced by adhesions patients may be a manifestation of central sensitization or functional somatization. This has lead to the development of

a wearable therapeutic ultrasound device to treat many painful symptoms which can obviate the need for surgery for pain in the absence of defined pathology. Although adhesiolysis should remain an option for adhesions patients in pain, non-surgical alternatives such as wearable ultrasound and manipulative techniques should be attempted first.

1.9 What do adhesions patients want us to know?

Patients were asked through social media «What is the single most important thing you would like to say to doctors and scientists working on adhesions?» Their answers fell into the following categories:

1. Please understand how this has affected my life.
2. Please understand that I really hurt and that I sometimes feel all alone.
3. Please learn and teach about adhesions and their consequences.
4. My most important symptoms are pain and constipation.
5. Please improve diagnostic methods for adhesions.
6. Learn how to prevent adhesions and treat patients.

1.10 Conclusion

We have come a long way in understanding the etiology and pathogenesis of adhesions. We see signs that adhesion barriers may provide clinical benefit and we have started to understand the nature of pain and related conditions. We have better strategies for dealing with obstruction and for treating adhesion-related pain but we still have much to do.

1. Introduction

I am honored to contribute this paper for the special edition of the INNOVA journal, based on the proceedings of the International Scientific and Practical Conference «Medical Implants» held in Kursk, Russia, March 18-19 2016.

The existence of adhesions has been appreciated for centuries, but their significance came to the fore with the revolution in antisepsis, anesthesia and invasive surgery in the nineteenth century [1]. By the time of one of the earliest reviews of the subject in 1911 [2], a number of approaches to treating or preventing adhesions had been recorded. The first commercial product appears to be «fibrolysin», a preparation of «liquor thiosinamine (allyl thiourea) with sodium salicylate», introduced in 1892. Outliving a number of short-lived products (reviewed in [1]) was Cargile Membrane, derived from the peritoneum of the Danish Ox, which was commercialized in the USA by Johnson & Johnson from approximately 1904 to 1992.

With the introduction in 1989 by Johnson & Johnson of their second anti-adhesion product, Interceed® (TC7) Absorbable Adhesion Barrier, interest flourished in not only products to prevent adhesions but also their etiology, epidemiology, economics and clinical manifestations [3]. The purpose of this paper is to review progress made by international efforts to tackle adhesions, in terms of advances, «retreats» and challenges for the future.

2. Are adhesions still an extensive and costly problem?

Several well conducted analyses of the Scottish database found that about one third of patients undergoing abdominal or pelvic surgery will be hospitalized nearly twice in the 10 years after an initial surgical procedure for a problem related to adhesions, or for a procedure that could be complicated by adhesions [4], for example by increased operative time, bladder injury, unintended enterotomy and infection [5, 6]. A series of Dutch studies confirms these estimates [7] and identifies risk factors for difficult adhesiolysis in re-operations [8-10]. The risk of obstruction is estimated at 2%, the average increased operative time due to adhesions is 15 minutes, and there is a 6% risk of bowel injury at adhesiolysis [11]. The same group has provided data from the Dutch Surgical Colorectal Audit that suggest that presence of adhesions from a prior abdominal procedure compromises the effectiveness of a subsequent colorectal resection for cancer [12].

The extent of the problem can be appreciated from estimates of in-patient adhesion-related discharges or procedures in the USA. 383,840 discharges occurred in 2013. The reduction from the 1997 figure (Table 1) was dominated by a large reduction in discharges for female peritoneal adhesions. This decrease may be due to:

- A larger number of women are having out-patient surgery.

Table 1: In-patient discharges for pelvic-abdominal adhesion-related ICD9-CM Codes (USA)

ICD9-CM Code		1997	2005	2013
568.0 - Peritoneal Adhesions	All diagnosis discharges	145,182	180,470	199,770
	All diagnosis M:F	27:73	28:72	35:65
	Principal diagnosis discharges	10,300	8,523	4,345
	Principal diagnosis M:F	14:86	16:84	22:78
560.81 - Intestinal Adhesions with Obstruction	All diagnosis discharges	89,829	95,967	97,945
	All diagnosis M:F	38:62	38:62	39:61
	Principal diagnosis discharges	67,308	71,581	76,805
	Principal diagnosis M:F	38:62	37:63	39:61
614.6 - Female Pelvic Peritoneal Adhesions	All diagnosis discharges	181,674	169,089	86,125
	Principal diagnosis discharges	16,011	9,515	2,425
TOTAL	All diagnosis	416,685	445,526	383,840
	Principal diagnosis	93,619	86,619	83,575
	Aggregate cost, millions	$1,872	$3,706	$5,338
	Relative to 1997 $cost, population and procedures*	1.00	1.08	1.03

Source: Healthcare Cost and Utilization Project, (US) Agency for Healthcare Research and Quality (http://www.hcup-us.ahrq.gov)
***** Cost adjusted using population data obtained from the US Census Bureau. Prices adjusted for inflation using data (Series CUUR0000SS5702, Inpatient hospital services) obtained from the US Bureau of Labor Statistics (www.bls.gov/data).
M:F – Male : Female ratio

Table 2: In-patient Pelvic-Abdominal Adhesion-Related Procedures

	1997	2005	2013
All procedures	396,062	431,077	356,465
Principal procedures	75,341	88,159	76,380
Aggregate cost (principal procedure only)	$1,625MM	$3,841MM	$6,282MM
Relative to 1997 $cost, population and procedures*	1.00	1.18	1.27

Source: Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality (http://www.hcup-us.ahrq.gov)
The following ICD9-CM codes were used: 54.5, 56.81, 54.51, 54.59, 57.12, 57.41, 58.5, 59.01, 59.02, 59.03, 59.11, 59.12, 65.8, 65.81, 65.89
* Cost adjusted using population data obtained from the US Census Bureau. Prices adjusted for inflation using data (Series CUUR0000SS5702, Inpatient hospital services) obtained from the US Bureau of Labor Statistics (http://www.bls.gov/data/).

· A reduced desire by surgeons to operate solely for pelvic adhesions (see section 5) consistent with the reduction in discharges with a primary diagnosis of peritoneal adhesions (568.0) despite an increase in discharges with that as a secondary diagnosis.

A similar picture is obtained when in-patient procedures involving abdominal or pelvic adhesiolysis are considered (Table 2). These findings are consistent with those of others [13] for the period 1988 to 2007.

There is a difference in the pattern of change in the aggregate costs over time between the discharge and the procedure data. When adjusted for population changes, consumer prices and numbers of procedures, the discharge data shows a small fluctuation in cost relative (8% increase – 2005; 3% increase -2013) to the 1997 data, whereas the procedure data both shows larger increases (18% - 2005; 27% - 2013). The difference may reflect higher increases in surgical care than for non-surgical care.

The aggregate cost of these procedures in 2013 was $6.2 billion. This does not account for out-patient procedures, adhesions outside of the abdomen or pelvis, the loss of work and the disruptions in the lives of patients and their families afflicted. It does not include the cost of pain management, treatment of infertility due to adhesions [5], or treatment of urinary frequency due to adhesions [14]. More importantly this figure is based only on the cost of these procedures when listed as a principal procedure. It does not consider the contribution of adhesions (e.g. by prolonging or complicating a procedure [11, 15]) to the cost of the event where the adhesion-related code was listed as a secondary code. Assuming that the adhesion-related secondary procedure contributes only 25% to the cost of the principal procedure, the cost of the 356,465 in-patient procedures for abdominopelvic adhesions is $12.0 billion.

In perspective, adhesions-related abdominopelvic discharges or procedures rival those for heart bypass, appendix and other well known operations. This «cost of adhesions» represents 20-40% of the $30.86 billion annual budget request for the US National Institutes of Health in 2013. Our estimates are higher than those given elsewhere [16], which omitted several codes in their analysis. Estimates of the burden of adhesions have also been reported for Sweden [17] The Netherlands [18] and The United Kingdom [19].

Do barriers improve surgical outcomes?

There is ample evidence that adhesion barriers reduce the development of adhesions [20]. Both Interceed® [21] and Seprafilm® [22] reduce the development of adhesions but Adept® has shown only a small benefit over and above lactated Ringer's solution in one study [23] and no benefit in another [24] Although our meta-analysis showed no benefit of crystalloids in reducing adhesions [25], the included studies involved the use of small volumes (~200ml) of crystalloid. The much larger volumes of crystalloid employed as a control for Adept may well have had an effect.

A retrospective study of myomectomy or hysterectomy for myoma in the USA from 2003 to 2011 found that barriers were associated with an increased incidence of postoperative adverse outcomes such as fever, ileus, early obstruction, pain and length of stay [26]. These increases depended on whether the surgery was performed by laparoscopy, laparotomy or robotic surgery. Length of stay was reduced with barriers in open myomectomy and closed hysterectomy. No data were available to determine which of the approved barriers (Interceed, Seprafilm, Adept[a] and Intergel – 2003 only) were associated with these events and in which kinds of surgery.

One small retrospective study showed a reduction in delivery and operative times at cesarean section after Seprafilm was used in a prior cesarean section. A small reduction in blood loss was also noted, but did not reach significance [27]. A randomized study involving 753 patients failed to demonstrate any reduction of adhesions or delivery time at a repeat cesarean section after Seprafilm was used in a previous section [28]. Almost twice the number of patients treated with Seprafilm had severe adhesions compared with the control patients. For Interceed, one retrospective review of 262 primary cesarean sections found that there was a higher adhesion-free outcome (74%) associated with the use of the barrier than when no barrier (22%) was used [29]. Economic analyses of the benefits of adhesion barriers such as Interceed in cesarean section [30] and other procedures [31] remain largely theoretical.

A prospective study in children found that the re-laparotomy operative time was significantly shorter when Seprafilm had been used previously [32]. A prospective study failed to demonstrate any significant differences in the time to close a loop ileostomy after Seprafilm use at the ileostomy creation. This failure was attributed to the variability in techniques used by the large number of surgeons [33]. In a small study, nausea, and constipation were reduced in patients undergoing colorectal surgery and receiving Seprafilm [34].

A retrospective analysis of 267,368 patients who underwent colectomy found increases in the numbers of patients with postoperative abscess, wound complications, bowel obstruction, ileus, re-operation and peritonitis when Seprafilm was used. From a cohort of 382,355 patients who underwent hysterectomy, increases in wound complications, bowel obstruction and ileus were found with Seprafilm [35]. Whether there was any bias introduced by surgeons selecting more difficult cases in which to apply the barrier, is unknown. Other studies involving adverse events after the use of Seprafilm have been cited in a citizen petition to FDA regarding its withdrawal [36]. These reports require detailed review to ascertain their significance. Our meta-analysis [21] of the safety and efficacy of Interceed found very few adverse events, but the patients in the included studies were mainly those undergoing elective reproductive fertility surgery. A small underpowered study showed a reduction in time to reverse a Hartmann's pouch using Adept [37].

The effect of adhesion barriers on bowel obstruction, infertility and pain are discussed below.

3. Is adhesion-related bowel obstruction still a problem?

Adhesions are the most common cause of post-surgical bowel obstruction [11, 38] and account for, or are associated with, 56% [39, 40] to 74% [41, 42] of all cases of obstruction. The incidence of adhesive bowel obstruction after abdominal surgery ranges from 0.5% to 10% [11, 43, 44] depending on the type of surgery. As much as 37% of obstruction cases are treated surgically [42].

Having one ASBO is a risk factor for future obstruction with a

[a] It is unclear whether the ICD9 tracking code 99.77 for application of an adhesion barrier would be used for Adept® Adhesion Reduction Solution.

Table 3: Trends in the Number of Deaths and Length of Stay related to Obstruction, USA

	1993	1997	2000	2005	2010	2011	2012	2013
Total number of discharges	63,547	67,308	65,735	71,581	79,224	78,707	75,025	76,805
LOS (length of stay), days (mean)	11.527	9.785	9.648	9.498	8.739	8.430	8.354	8.269
In-hospital deaths	2,391 (3.76%)	2,301 (3.42%)	2,421 (3.68%)	2,053 (2.87%)	1,948 (2.46%)	1,809 (2.30%)	1,670 (2.23%)	1,545 (2.01%)

16% rate of recurrence after 41 months [45]. This risk increases with increasing number of prior obstructive episodes reaching 81% for patients with 4 or more admissions due to ASBO. Age, type of adhesions and postoperative complications are also risk factors for ASBO [46].

Table 1 shows a 9% increase in the number of all discharges for adhesions with obstruction from 1997 to 2013 (14% increase in number of principal discharges with this diagnosis) despite an 18% increase in population over the same period. This is consistent with other findings for the period 1988 to 2007 [13].

The UK's Royal College of Surgeons published an analysis of care given to patients undergoing emergency bowel surgery [40]. Given the high one-month mortality rate (~15%, 7% in patients undergoing emergency adhesiolysis) associated with emergency laparotomy, the recommendations included: prompt access to experienced senior surgical and anesthesiology staff; prompt access to antibiotics and surgery; critical postoperative care; and the conservative management of intestinal obstruction secondary to adhesions for up to 72 hours in the absence of ischemia, presumably to allow to full evaluation by senior staff. The findings of other studies vary in their consistency with this last recommendation [42, 47].

That these and other [44, 48] guidelines are being published is a welcome advance and may reflect an increased awareness about adhesions and willingness and ability to address the problem. Possibly related may be a downward trend (Table 3) in the number of obstruction-related deaths and length of stay despite a modest increase from 1993 to 2013 in the number of in-patient discharges with a diagnosis of intestinal adhesions with obstruction (560.81). This decline in the death rate has sharpened from 2010 to 2013 when there were only 1545 deaths.

Use of Gastrografin in the diagnosis of SBO may also exert a therapeutic effect in accelerating resolution in some patients [49], although the mechanisms is unclear [50].

Use of barriers to reduce adhesions-related bowel obstruction

Several studies involving Seprafilm have reported beneficial effects on ASBO but their conclusions have been challenged [36]. The rate of ASBO requiring operation was reduced by Seprafilm from 3.4% to 1.8% in 1701 patients undergoing small bowel resection [51]. Seprafilm reduced early SBO from 14% to 6.5% [52] in one retrospective study and from 20% to 0% in another [53]. A reduction in intestinal obstruction with Seprafilm could not be detected in a meta-analysis [54]. An underpowered study showed a small non-significant reduction in SBO after colorectal surgery when Seprafilm was used [34].

In a prospective study involving 181 patients, the recurrence of ASBO was reduced from 11.1% to 2.2% when Adept was used [55]. This effect may be the result of the large volume of liquid (1 litre) used, as suggested by the considerable effect of the lactated Ringer's solution used in the control arm in the two principal efficacy studies of icodextrin in gynecological surgery [23, 24]. There do not appear to be increased complications with Adept [56].

4. Is adhesion-related infertility still a problem?

Adhesions are found in 20-40% of infertility cases [5]. The adverse effect of adnexal adhesions on fertility is well known [38]. Pregnancy rates correlate inversely [57] with the ASRM classification [58, 59] of adnexal adhesions and improve with adnexal adhesiolysis [60]. Surgery for inflammatory bowel disease has been suggested to reduce pregnancy rates by as much as 50% although it is unclear how much of this was contributed by adhesions [11]. With the efficacy of assisted reproductive technologies, adnexal adhesiolysis to treat infertility has declined and was predicted to become obsolete [61]. However against the background of cost, ethical and moral questions around these technologies and advances in surgical technique, a resurgence of adnexal adhesiolysis has been advocated [5] and predicted [62]. The costs of adhesion-related infertility as a consequence of a prior surgery are significant and have been estimated at $875 and $350 per woman undergoing laparotomy or laparoscopy respectively [5].

Use of barriers to reduce adhesions-related infertility

Only one small retrospective study showed an improvement in fertility with the use of Interseed adhesion barrier in patients undergoing reconstructive pelvic surgery [63].

5. Is adhesion-related pain still a problem?

Although 25-57% of patients with chronic pelvic pain are said to have adhesions, alone or with endometriosis [64-66], the role of adhesions in abdominal or pelvic pain remains confusing and controversial [67, 68, 69]. Much of this confusion is derived from observing the effects of adhesiolysis on pelvic or abdominal pain. The non-specific effects of surgery are said to be particularly evident in pain-related conditions, where well-designed studies are most needed [70]. Adhesiolysis was reported to relieve pain in German [71], Swiss [72], American [73-75], British [76], and Dutch [77] studies. A recent analysis concluded that the evidence for laparoscopic adhesiolysis as a treatment for pain is insufficient to draw definitive conclusions [69].

An interestingly designed Dutch study [78] has added to the confusion due to its questionable interpretation and citation in a government report. Patients undergoing diagnostic laparoscopy for chronic abdominal pain were blinded and randomized to adhesiolysis or no treatment [78] and pain blindly assessed after 12 months. Forty-two percent of patients undergoing laparoscopy only reported improvement or remission compared with 57% of those with adhesiolysis. Despite this numerical (but not statistical) advantage of adhesiolysis, the authors concluded that «although laparoscopic adhesiolysis relieves chronic abdominal pain, it is not more beneficial than diagnostic laparoscopy alone. Therefore, laparoscopic adhesiolysis cannot be recommended as a treatment for adhesions in patients with chronic abdominal pain». These conclusions were relied upon by a US government report on noncyclic chronic pelvic pain in women [79] which stated that there is «no evidence of benefit of lysis of adhesions».

These conclusions are based on several flaws, including a type II error [80, 81] and a failure to account for adhesion reformation in determining effect size. Reports of this type carry considerable weight. Despite tempering statements within the body of the report, its inaccurate conclusions may leave a policy-maker, payor, patient or surgeon with the mistaken

impression that adhesiolysis does not benefit chronic pelvic pain and should not be performed at all. After correspondence with the report's authors, they agreed to amend their conclusions to reflect the limitations of the report's conclusions [80]. This discussion highlights our poor understanding of the many facets of pelvic and abdominal pain. There are two main questions that arise:

Does an only modest effect of adhesiolysis prove that pain is unrelated to adhesions?

The unclear correspondence between adhesiolysis and pain relief may be due to several factors:

- When adhesions are lysed, nothing is done to modify the underlying scar which can still trap or irritate nerves.
- The contribution of underlying pathology such as endometriosis must be considered. Inflammatory processes within deep endometriotic foci can serve as a source of nociceptive stimulation [82] independent of any contribution of adhesions.
- Failure to treat, recurrence or worsening of a co-morbid pathology such as endometriosis may account for some of the «failure» of adhesiolysis to treat pain.
- A 75% rate of adhesion reformation [83] along with the 42% effect of laparoscopy alone could account for the improvement in pain of 15% observed in the Dutch study [78].
- The conventional wisdom 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 [84].
- There are complex pain referral patterns in the abdomen which account for the lack of anatomic correspondence between the site of an adhesion and the site of pain [85].
- Psychological factors contribute significantly to a patient's perception of pain and their ability to cope with it in possibly 75% of patients with an identifiable physical explanation for the pain [66].
- In conventional wisdom, adhesions cause pain by tethering tissues, causing nerve traction, or by entrapping nerves. Nerve endings have been found within adhesions [86]. In patients with long-standing pain, it may no longer be productive to focus on the location of an adhesion as the «source» of pain, as central sensitization [87], the development of a functional somatic syndrome [88] or CAPPS (Complex Abdomino-Pelvic and Pain Syndrome) [3] may have occurred. The initiation of pelvic «cross-talk» by an «irritation» [89] such as an adhesion may explain our observation of the co-prevalence of pelvic, urological, musculoskeletal and gastrointestinal symptoms in adhesions patients and may explain why any pain that was directly related to adhesions would account for only a part of the patient's overall pelvic or abdominal pain, relievable by adhesiolysis. This is consistent with the reduction of pain in adhesions patients in a small study involving pregabalin, a drug primarily affecting neuropathic pain [90], and with the notion that a type of "phantom" pain may occur in pelvic conditions [91].

What can we learn about the nature of «adhesion-related» pain and how to treat it?

There appears to be a high background therapeutic effect of surgery alone [70] which may obfuscate any effect of adhesiolysis. Patients without obvious pathology undergoing diagnostic laparoscopy also reported a reduction or cessation of pain [92], as did endometriosis patients undergoing laparoscopy with biopsy [93]. A possible related phenomenon has been reported for arthroscopy [94].

I encounter many refractory patients who report transient (3-9 months) reductions of pain after adhesiolysis with no recurrence of adhesions or other pathology. Speculatively, this may be explained by a medium (3-9 months) term therapeutic effect of general anesthesia on down-regulating central sensitization [95], or resetting sensitized nociceptive circuits [96] in a manner analogous to mechanisms proposed for the effect of anesthetic doses of ketamine [97] in patients with Complex Regional Pain Syndrome (CRPS). Chronic pelvic pain has been regarded as a form of CRPS [98].

While there is a sufficient nexus between adhesions and pain to warrant their prevention, the initial approach to adhesion-related pain should consider the nature of the pain and the mechanisms that may exist over and above the «conventional» wisdom as to how adhesions may contribute to pain. After non-surgical approaches [99] have failed (see section 9), the therapeutic effect of laparoscopy combined with adhesiolysis may be great enough to justify performing it.

Along with explosion in the use of opioids for chronic pain in the US there is an epidemic of abuse and misuse of prescription opioids. Many patients with pelvic pain, including those with adhesions, are stable users of these drugs. While it is preferable that these patients reduce or eliminate their opioid use, government efforts [100] to limit the availability of opioids need to be accompanied by policies that provide for expedited marketing approval of alternatives as well as approval for payment by health insurance companies [101]. One such alternative is PainShield® MD Wearable Therapeutic Ultrasound whose use we have pioneered for patients with pelvic and abdominal pain, including those with adhesions (see section 9).

Effect of adhesion barriers on pain

There are few data available to answer the question as to whether adhesion barriers help to reduce pain. In an uncontrolled series, 19 patients underwent laparoscopic adhesiolysis and placement of Seprafilm for chronic intractable abdominal pain. 14 (74%) patients had discontinued pain medications at follow-up of up to 32 months [102].

6. Have adhesion barriers achieved their potential?

The trend in barrier usage and factors influencing it

In 2002, the Centers for Medicare & Medicaid Services (USA) approved the creation of ICD-9-CM code 99.77 for the «Application of an Adhesion Barrier for Prevention of Adhesions» which has enabled the use of barriers to be tracked. The approval was based largely on public comment, most of which originated from the members of the International Adhesions Society[b]. Table 4 shows that the utilization of adhesion barriers, has grown since 2002 and peaked in 2011. Whether this represents a reduction in utilization or overall underreporting is unknown. It does not include outpatient use of adhesion barriers.

Based on estimated sales of adhesion barriers of $200 million, an average price per unit of $250 and an average usage of 1 unit per procedure, adhesion barriers are only used, in about 800,000 procedures yearly. Assuming that obstruction due

[b] http://adhesions.org/campaigns.htm.
Since 2015 ICD9 codes have been replaced with ICD10 codes which are:
3E0M05Z Introduction of Adhesion Barrier into Peritoneal Cavity, Open Approach
3E0P05Z Introduction of Adhesion Barrier into Female Reproductive, Open Approach

Table 4: Trends in the use of adhesion barriers or in-patient admissions (from ICD9-CM 99.77)

Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Admissions	2,281	11,766	23,122	29,243	30,726	37,710	53,564	46,130	63,270	65,571	62,255	59,700

to adhesions represents 1% of general surgical admissions in one year [103], then the figure of 97,945 discharges for intestinal adhesions with obstruction represents some 9.8 million procedures where barriers might be used. The percentage of procedures in which adhesion barriers are used is at best a little over 8.2%, an encouraging increase from the figure of 5% previously calculated in 2005 [104]. These estimates are broadly consistent to those found for adhesion barrier usage in 2005 and 2011 respectively in hysterectomies (0.95%, 1.9%) and myomectomies (4.7%, 6.9%) [26]. They are also consistent with data found for Seprafilm usage in 2000 and 2010 respectively in hysterectomy (1.1%, 9.8%) or colectomy (6.2%, 12.4%) [35].

Nonetheless, the adoption of adhesion barriers is disappointingly low. Advances have been made in improving awareness among surgeons about the medico-legal aspects of adhesions [105] as well as advocating for better information to be provided to patients as part of the consent process [106, 107]. Both of these aspects would likely increase adoption of barriers, but there is still much to be done as evidenced by reports from Germany [108], The Netherlands [109] and the UK [110-112].

Arguably, the most significant factor in the low adoption of adhesion barriers is the slow progress in developing barriers that can eliminate adhesion-related bowel obstruction, infertility and pain. This is all the more disappointing since it is already 27 years after the introduction of Interceed in 1989, the first barrier produced in the «modern» era [1].

This disappointment bears some resemblance to that expressed by Richardson in 1911 [2] some 25 years after the first reports of anti-adhesions materials in 1886: «It is very evident from the reports that none of these substances can be relied upon to furnish more than a small percentage of successful results, and on this account, cannot be recommended for general use». Richardson suggested why these anti-adhesion materials would not be successful: «It is futile to search for some agent that will banish adhesions from the realm of abdominal surgery, inasmuch as the processes involved in their formation are identical with those involved in peritoneal repair». Is it futile to search for an anti-adhesion material that will reduce obstruction, pain or infertility or are there other reasons why barriers that will do these things have not been developed?

The regulatory environment on the development of outcomes-based endpoints

Since the US market has historically been the most lucrative market for anti-adhesions products, US regulatory requirements have played a significant part in determining the design of clinical studies that would be used to support sales of adhesion barriers around the world.

All anti-adhesion products approved in the USA (Interceed, Seprafilm, Adcon, Intergel, Adept) have been Class III devices for which preclinical and clinical studies are needed to demonstrate the safety and efficacy of the product. For clinical efficacy it has been sufficient to demonstrate the reduction of incidence, extent and/or severity of adhesions. There have been attempts by FDA to officially require clinically meaningful endpoints such as bowel obstruction, pain or infertility. These have been opposed by industry on the grounds that these endpoints are governed by many factors that would make studies so burdensome, costly and time consuming that it would be uneconomical to develop an anti-adhesion barrier. Furthermore, due to the complications resulting from adhesions at a re-operation (bleeding, operating time, risk of damaging organs etc.), the incidence, extent and severity endpoints are themselves clinically meaningful. I was one of the industry representatives who presented this argument at a public hearing on this matter [113] which resulted in the issuance of a guidance document by FDA [114].

This situation allows a company to minimize costs by performing well defined studies. After approval it can fund larger, less expensive post-marketing outcomes-based studies which are essential to convince surgeons that the product provides clinical value in a variety of situations. Further complicating FDA approval in the USA is the requirement that separate data be provided for laparoscopy and laparotomy surgery. Economic endpoints are not needed for FDA approval, but a company is well-advised to incorporate them to facilitate appropriate reimbursement from insurance companies or government agencies.

Clearance of a Class II device requires more limited data in a more rapid and less expensive process called the 510k pathway. Such devices include: Preclude® Pericardial Membrane (WL Gore & Associates, AZ); Sepramesh® Bioresorbable Permanent Mesh (CR Bard, RI); Proceed® Surgical Mesh (Ethicon, NJ); Parietex™ Optimized Composite Mesh (Medtronic, MN), and SurgiWrap® Bioresorbable Sheet (Mast Biosurgery, CA). These devices are primarily used for tissue reconstruction or reinforcement. A claim that they minimize «tissue attachments» to the material itself is permitted, but claims that they reduce «adhesions» as for the Class III devices, are not permitted. There is only a semantic distinction between an «attachment» and an «adhesion» as outside of United States the Mast Biosurgery product is called «SurgiWrap® Bioresorbable Adhesion Barrier Film» and some of their non-US product literature is identical to their US version, except that the word «adhesions» is used in place of «attachments».

How have business matters affected development of anti-adhesion products?

The slow progress in the adoption of adhesion barriers may be less related to scientific limitations and more related to the consequences of business decisions made by US companies which deterred global investment in anti-adhesion products.

When Johnson & Johnson launched Interceed Barrier in 1989, FDA called it a «significant advance in medical device technology» [115]. Interceed's success in open gynecological surgery was replicated several times [21] and there were plans to introduce a version which overcame the compromise in efficacy when hemostasis was less than meticulous [116, 117]. By 1991 the revolution in laparoscopic surgery was in full swing and FDA required a separate clinical study for approval for laparoscopic use. Despite two small successful independent studies in endometriosis [118] or myomectomy [119] surgery, a company-conducted study found that Interceed increased adhesions in laparoscopic gynecological surgery [120] possibly because Interceed had been wrapped around the ovary and Fallopian tube, holding them in approximation. Interceed was not developed for laparoscopy or for general surgery, but continued to be used in laparoscopy outside the USA (where separate approvals were not required) and off-label in the USA.

Johnson & Johnson was also developing a (non-cross-linked) hyaluronic acid (HA) solution (Tenalure) which could coat large peritoneal surfaces without needing to specifically place a solid barrier such as Interceed. The clinical studies were unsuccessful but given their large investment in the HA program, Johnson & Johnson expedited the development of Intergel, an iron cross-linked version of Tenalure.

My team at Ethicon (Johnson & Johnson) was responsible for the initial preclinical optimization studies for Intergel, published in part later [121]. Based on the correlations between the animal and clinical data for Interceed and Tenalure, we predicted that Intergel would have clinical efficacy [122]. Our preclinical studies also suggested that Intergel may evoke peritoneal reactions, potentiate infection and lose efficacy in the presence of bleeding. Despite launches in Europe and the USA in 1998 and 2002 respectively, these studies appear to have become part of

the public record [123] only after Intergel was withdrawn in 2003 due to reports of adverse events and deaths, and after a colorectal surgical study was terminated because of unacceptable morbidity, prolonged ileus, late postoperative peritonitis, anastomotic dehiscence and a death [124]. Other details of the Intergel case emerged when Ethicon's Chief Medical Officer alleged that he was fired for his role in withdrawing Intergel and other products [125-127].

Mechanistically, my independent studies suggested that free iron may be released from Intergel by the action of reactive oxygen species released in inflammation, or from trace amounts of peroxide entering the product in the sterilization process [128]. The effects of free iron would be more noticeable in patients prone to iron overload such as those with a prior hysterectomy or a genetic predisposition [129]. This would also explain the differences in the rate of adverse events found in the American [122] and European [130] Intergel clinical studies. Because of the known long-term toxicity of iron, and its role in granuloma, mesothelioma and carcinogenesis [128] as well as Alzheimer's Disease [131], i have advocated to for the implementation of a screening program for the approximately 80,000 patients exposed to Intergel, especially those who had had pre-menopausal hysterectomies [132] or an ethnic or genetic predisposition to iron overload [133].

The Intergel episode was a disaster for many of the patients that used it, and for the millions of patients who would have benefited from a renewed interest in adhesions research had Intergel been successful. Companies now halted their anti-adhesion programs, partly because they perceived Intergel's failure to be due to heightened requirements imposed by FDA, despite the approval of Adept® (4% Icodextrin) in 2006 and the issuance of a Guidance Document by FDA concerning adhesion barriers [114]. One offensive explanation of Intergel's demise that circulated was that the initially adverse decision of the FDA advisory panel reviewing Intergel had been dominated by the monthly mood swings of a distinguished female member! Whatever the motive or origin of this sort of comment, the effect of all this was to discourage other companies or investors to fund development of promising anti-adhesion candidates. Even Johnson & Johnson attenuated its interest in adhesions. When they acquired Omrix Pharmaceuticals in 2008, they also acquired a fibrin anti-adhesion product, Adhexil, with an excellent profile in preclinical [134] and pilot clinical [135, 136] studies, but declined to develop it further.

Also possibly playing on the mind of investors was the fate of Gliatech who had started to successfully market ADCON L for spinal adhesions. A failure to report adverse events, in addition to other issues resulted in actions by FDA which eventually forced Gliatech into bankruptcy in 2002. Although these issues were certainly serious [137], so were those in the Intergel case. The perceived disparity in the treatment of large and small companies may well have been a factor in the reticence to invest in anti-adhesion products. Nonetheless the irresponsible actions of a few executives at Gliatech doomed not only ADCON for spinal adhesions, but also other versions that were showing promise for abdominal and pelvic adhesions. On the basis of studies we conducted in 1996 for Gliatech with ADCON in a gynecological animal model, our prediction that it would be clinically successful came to fruition in a pilot study [138].

Meanwhile Genzyme was developing the concept of using a dilute solution of HA (Sepracoat®) during surgery to protect peritoneal surfaces from desiccation and abrasion. The 23% reduction in clinical de novo adhesions [139] was considered unimpressive and was not approved by FDA after a 1997 hearing. Possibly anticipating this, Genzyme had begun to develop a film of HA and carboxymethylcellulose (Seprafilm®) for both general surgery [140] and gynecological [141] laparotomy. Seprafilm was approved in the USA in 1996 and Genzyme sponsored a number post-marketing preclinical [142] and clinical [22] studies characterizing Seprafilm's effects, including its effects on outcomes such as ASBO. Genzyme also invested heavily in improving awareness about adhesions, initiated the lobbying for the creation of the ICD9-CM code 99.77, and acquired Biomatrix, another company with a platform of HA-based surgical products.

Genzyme were also interested in a solution approach like that of Intergel. They conducted animal models similar to those used for Intergel's development and found that not only their own product (Sepragel) but also one formulated similarly to Intergel, potentiated infection [143]. Accordingly, Genzyme took the appropriate and expensive decision to terminate the Sepragel project which had reached clinical trials. Further, when Genzyme found an increased occurrence of anastomotic leak, fistula, peritonitis, abscess, and sepsis after wrapping Seprafilm around a fresh bowel anastomosis [144], they added precautionary language to their product information.

Despite Genyzme's impressive investment in a range of adhesion-related products and programs, Seprafilm sales never reached the expectations set by stock analysts which were driven partly by information provided by the company. Sales projections in 1997/98 for Sepracoat and Seprafilm had been as high as $100 and $200 million respectively [145], but only after about 15 years of sales did annual Seprafilm sales reach approximately $150-180 million. One reason for the shortfall in expectations was that Seprafilm was never developed for laparoscopic use, despite Genzyme's access to a device that could deliver a 10 x 15cm sheet of Seprafilm [146]. Instead, Genzyme tested a powdered version of Seprafilm (Sepraspray) in a small gynecological clinical study and found only a slight reduction in adhesions [147]. A large study involving laparoscopic colorectal resection found a statistically higher rate of adverse events in patients treated with Sepraspray powder than in untreated patients [148].

With no product for laparoscopic use, some surgeons began to use an extemporaneous slurry of Seprafilm for application through a trocar [149, 150]. When Genzyme sales staff in the USA began sharing this information with other surgeons, Genzyme was fined $55 million by the US Department of Justice [151, 152] mainly for this unlawful product promotion. Against this background, a citizens' petition to FDA to have Seprafilm withdrawn from the US market has been filed [36] alleging that Seprafilm, even as approved, is unsafe. The petition appears to imply that ethical lapses occurred at Genzyme much before the incidents relating to «Sepraslurry». A full consideration of these allegations is beyond the scope of this article. It does appear that while some charges are without foundation, others require further investigation.

Regardless of the outcome of FDA's deliberations in this matter, the effect of this petition, the judgments against Genzyme, as well as the history of Intergel and Adcon, is to make both the US government and companies more cautious of anti-adhesion products. This may have a detrimental effect on investment in adhesions research not only in the US, but of course the rest of the world since companies have perceived that if the US market in adhesion barriers is not worthwhile, neither is it in the rest of the world. Recent expansion of markets outside of the US has however encouraged investment in adhesion products that do not rely on the US market.

Another reason why investment in adhesion barriers may have waned is because a number of product failures have only been evident at the clinical trial phase. Companies have failed to take advantage of the correlations we have observed between data generated in animals and data generated in humans and the selection of appropriate decision-making models [153]. Notable failures for which correlations were available before the conduct of the clinical trial include

Pumactant [154] and Flogel [155].

7. Progress in developing anti-adhesion products

Previously, the development of anti-adhesion products was focused on the US market with other markets a secondary objective. With the business and regulatory climate in the USA, this situation is reversed and we find many examples of products originating around the world, or US-based companies marketing their products solely elsewhere. This has lead to an injection of new concepts for treatments. The descriptions below of products that are marketed, or for which clinical data exist in abdominopelvic surgery, are illustrative of the global efforts in adhesion prevention.

Progress in barrier product development

Hyaluronic acid-based products

Hyaluronic acid-based medical products have an excellent record of safety and biocompatibility. Cross-linking is usually needed to provide sufficient viscosity and residence time for anti-adhesion efficacy. The type of cross-linker affects product efficacy as well safety, as exemplified by the cases of Sepragel and Intergel.

Hyalobarrier® Gel (Anika Therapeutics, MA, USA) is autocross-linked HA. Developed in Italy, it has been marketed in Europe since approximately 2000. A meta-analysis of five studies involving the use of small volumes (~10ml) in gynecologic laparoscopy and hysteroscopy indicates that the product is safe and effective [156].

HyaRegen® Gel (BioRegen Biomedical, Changzhou, China) uses an undisclosed method of cross-linking. Favorable results were recently reported using 160ml volumes in a trial involving 215 patients undergoing gynecologic laparoscopy [157].

Medicurtain® (Shin Poong Pharm, South Korea) is cross-linked with hydroxyethylstarch, a molecule with a well known safety profile. The product is marketed mainly in Asia [158].

Guardix® Sol (Genewel, South Korea) is a gel of hyaluronic acid and CMC used in several anti-adhesion applications [159]. Another formulation, Guardix SG contains a poloxamer and alginate.

C-qur® (Atrium Medical, NH, USA) is a HA-CMC film coated with Omega-3 fatty acid undergoing clinical evaluation [160].

Carbohydrate-based products

Interceed (oxidized regenerated cellulose), Adept (icodextrin) and the hyaluronic acid-based products are all carbohydrates. Seprafilm is composed of hyaluronic acid and another carbohydrate derivative, sodium carboxymethylcellulose (CMC). CMC is a non-degradable derivative of cellulose used widely for food, pharmaceutical and industrial applications. My group at Johnson & Johnson elected not to pursue development of a large volume of CMC for adhesion prevention due to the tendency of cellulosics like CMC to accumulate in vascular endothelial cells, Kupffer liver cells, renal glomeruli and spleen [161]. CMC in smaller volumes is the basis for Oxiplex® gel (also Intercoat or MediShield; Fziomed, CA, USA) which failed to receive FDA approval for prevention of spinal adhesions but which is marketed outside the USA. In two small studies Oxiplex reduced adhesion scores [162, 163] in gynecological laparoscopy, but did not reduce adhesions in patients with initially severe adhesion scores and stage IV endometriosis.

CMC is the main component of Mezogel (Lintex, St. Petersburg, Russia), reported to reduce adhesion formation [164, 165] ileus [166] and recurrence of ASBO [167]. Studies are underway to incorporate various drugs into the polymer [168].

CMC is also a component of A-Part® Gel (Aesculap AG, Tuttlingen, Germany) along with polyvinyl alcohol. No difference in rates of adhesion formation after A-Part or control treatment were found after median laparotomy in 62 patients, but a lower rate of wound impairment or peritonitis was seen with the A-Part gel [169].

4DryField® (PlantTec Medical, Bad Bevensen, Germany) is a starch derivative which controls bleeding, and reduced adhesions in two small gynecological laparoscopy studies [170,171]. A polysaccharide hydrogel in development by a partnership of Dutch and American companies (Actamax, DE, USA) has produced preliminary safety data in humans [172] and a HA-alginate material is under development (Alafair Biosciences, TX, USA) [173].

Sulphated polysaccharides may mimic heparin. ADCON (Gliatech, OH, USA) was composed of dextran sulphate and a solution of it showed early promise [138] in gynecologic surgery before the events described in section 6. Another sulphated polysaccharide is fucoidan (ARC Medical Devices, Vancouver, Canada), derived from algae and is currently marketed for use in horses [174].

Chitosan, a polysaccharide derivative of chitin obtained from the exoskeleton of crustaceans, was found to be as effective as a HA gel (Haohai Biological Technology Co, Shanghai, China) in a study involving 114 enterostomy patients [175]. A gel of N,O-carboxymethylchitosan (NOCC) (Kytogenics, NJ, USA), another chitin derivative, showed some promise in gynecologic laparoscopy [176] before funding was exhausted. Mediclore (Daewong Pharmaceutical, South Korea) is composed of chitosan, gelatin and poloxamer, a compound with reverse thermal gelation properties.

ADBLOCK (Terumo, Japan) is a dextrin based hydrogel polymer that has completed an initial clinical safety study [177].

Polyethylene glycol (PEG) based products

A number of hydrogels based on polyethylene glycol have been introduced for sealing vascular, lung, liver and other tissues at surgery. Related chemistries can be used to produce adhesion barriers that can be sprayed easily at laparoscopy. The first product in this category made by Focal [178] required photopolymerization which was retarded by the carbon dioxide used at laparoscopy. Out of the clinical failure of this product for adhesions came a new company, Confluent Surgical who developed SprayGel [179] which did not require photopolymerization. Limited success was achieved with SprayGel in clinical trials in gynecologic laparoscopy [180], but polymerization was still retarded by the pH drop caused by the carbon dioxide pneumoperitoneum. This was partly solved by evacuating the CO_2 prior to spraying and modifying the molecule to produce SprayShield®. There was marginal success in three small published studies [181-183] and the results of other unpublished studies are unknown [184]. The technology was passed in two consecutive acquisitions to its present owner, Integra LifeSciences (NJ, USA) who appear to have no plans to pursue further development.

The problem of incomplete gelation of the PEG in a CO_2 environment was solved by NeoMend (CA, USA) who had acquired technology from 3M (MN, USA) [185] to produce ProGel® AB. This was successful in a small pilot clinical trial in laparoscopic myomectomy [186]. ProGel AB was acquired by CR Bard who have no plans to pursue development.

CoSeal® Surgical Sealant (Baxter Healthcare Corp, CA, USA) is a PEG-based product, sold around the world as a sealant and for haemostasis. A version of this product formerly known as Adhibit was under investigation for adhesion prevention in gynecologic surgery [180]. Outside of the USA, Coseal is also marketed for adhesion prevention in both laparoscopy and laparotomy, but within the USA it is likely used «off-label» for adhesion prevention.

Fibrin

Fibrin products have been valuable adjuncts in surgery for many years [187]. The ability of fibrin sealants to reduce

adhesions [134] is greatly dependent on formulation and method of purification. Fibrin can also control bleeding and has few biocompatibility issues found with other polymers. Adhexil (Omrix, Israel, now part of Johnson & Johnson) showed excellent efficacy in preclinical [134] and pilot clinical [135,136] studies, but was not developed further. A number of commercial fibrin glue products are used «off-label» for adhesion prevention.

Adhesion barriers and bleeding

The efficacy of Interceed is compromised in the presence of bleeding for three reasons. Firstly, being a slightly acidic material, denaturation of blood in the interstices of the fabric prevents the closure of its pores during swelling and the formation of a continuous barrier. Secondly, the deposition of clot, or denatured blood may form a scaffold for adhesion formation between surfaces. Thirdly, the denatured blood may act as a nidus for increased phagocytic activity which could enhance fibrosis by the release of cytokines. The effect of blood on the performance of Interceed experimentally can be overcome by either controlling haemostasis meticulously, by adding heparin to the Interceed, or by neutralizing the surface of the Interceed [116].

Although the same mechanisms may not operate against other barriers, their efficacy in the presence of bleeding must be assessed. This is all the more important in laparoscopy where bleeding may reinitiate on removing the pneumoperitoneum that acts to tamponade small vessels. The lack of efficacy of Seprafilm in cesarean section [28] may be due in part to its sensitivity to blood as we found in published [134] and unpublished animal models[c]. Other workers found that Seprafilm was effective in a bleeding animal model, along with Hyalobarrier [188]. The tissue reactions found with Intergel may have been due in part to its dependency on haemostasis[123]. We also found the efficacy of SprayGel was compromised in a bleeding field [134]. but ProGel AB was still effective [189].A collagen-based membrane (Prevadh Film, Sofradim, Lyons, France) was also highly effective in a bleeding model [190] as well as after myomectomy by laparotomy [191]. Although the product was marketed around the world (except USA), it was discontinued due to the cost of obtaining US approval. Preliminary studies indicate that 4DryField (PlantTec Medical, Bad Bevensen, Germany), a starch derivative may act both as a haemostatic agent and an adhesion barrier (see above).

Drug approaches – clinical attempts

The extensively reviewed [38, 192, 193] pathophysiology of adhesions provides a number of opportunities for pharmacologic intervention. Many of these have shown promise in animal models [1, 194], but the few that have progressed to the clinical study stage will be discussed here.

In some cases multiple local or systemic dosing, slow-release dosing, or synergistic combination with a barrier may be preferable [194], which may explain the disappointing results from unpublished clinical studies widely known to have been performed in the 1980s and 1990s, using solutions of ibuprofen and tolmetin applied to the peritoneal cavity.

Evidence that modulation of inflammation in combination with an adhesion barrier may help to reduce adhesions comes from the pivotal Seprafilm study in patients with ulcerative colitis [140]. Lower rates of adhesion formation were found in patients receiving long term corticosteroids prior to surgery; this effect was best seen in patients also receiving Seprafilm.

[c] In a rabbit uterine model with bleeding comparing the effect of Interceed, Seprafilm, a fibrin glue preparation with untreated controls we found that extensive adhesions (Mean ± SEM, N=6 for all groups) formed in Control animals (54 ± 10%). Both INTERCEED (72 ± 9%) as well as Seprafilm (54 ± 9%) failed to reduce the extent of adhesions. A statistically significant reduction in the % extent of adhesion formation was observed for Fibrin Glue (18 ± 11%, p< 0.05) compared to Controls, under conditions where INTERCEED was shown to fail.

This observation supports the concept that adhesion formation can be influenced by modulating the pre-operative inflammatory state or by enhancing the pre-surgical population of macrophages that express fibrinolytic activity [1]. Supporting this further is a correlation between the preoperative plasma levels of C Reactive Protein (CRP), an inflammatory marker, and postoperative adhesions after myomectomy [195]. This same study found a further link between preoperative CRP levels, fibrinolysis inhibitory activity (PAI-1) and postoperative adhesions, supporting decades of work which has linked compromise of fibrinolysis to adhesion formation. A single treatment with recombinant plasminogen activator was not effective in reducing overall adhesion levels, either because the dose was too low, or the dose was not provided over a long enough period of time.

Many attempts have been made to use heparinoids to reduce adhesions by limiting fibrin deposition. Heparin has a small degree of clinical efficacy when applied as a single intraperitoneal dose [196]. However, it appears to act synergistically in combination with Interceed, possibly because of complexation with serum proteins. Clinically the combination of Interceed and heparin improved adhesion-free outcome in adnexal surgery from 35% with Interceed alone to 47.5%, in an underpowered study [197]. In animal studies the addition of heparin helped to protect against the reduction of Interceed's efficacy in a bleeding field. This product was not commercialized in the early 1990's mainly because the regulatory pathway for drug-device combinations in the USA was unclear at that time. More recently FDA has established an «Office of Combination Products» to facilitate approval of these sorts of products.

The efficacy of oral proteolytic enzymes (Wobenzyme) has been evaluated in three Russian studies [198, 199]. Another enzyme, serratiopeptidase [200] is widely marketed for the relief of a number of conditions including adhesions. I am unaware of data that supports its use for adhesions and a recent review concluded that «the existing scientific evidence for Serratiopeptidase is insufficient to support its use as an analgesic and health supplement» [201].

Promising directions

We now understand more clearly the interaction between inflammation and fibrinolysis [202], and the induction of an adhesion phenotype in peritoneal fibroblasts [203] by macrophages. This system is regulated by hypoxia [204, 205] and reactive oxygen species [193]. This work is consistent with our observations on the association between iron overload disorders, hysterectomy and adhesions (see section 8) and would suggest a role for the use of anti-oxidants such as lycopene [206].

Regarding adhesion barriers, «there is a limit to how much more efficacy can be squeezed out of a polymer by cross-linking, copolymerization, blending or derivatization» [1]. We must also consider lifestyle factors (see section 8) and adopt a multifaceted approach such as the «full conditioning» (FC) method developed in Belgium. Women undergoing deep endometriosis surgery were randomized to standard laparoscopy or FC consisting of a modified insufflation gas (86% CO_2, 10% N_2O, 4% O_2), peritoneal cooling, humidification, heparinized rinsing solution, 5 mg of dexamethasone (intramuscular, at the end of surgery) and the use of Hyalobarrier gel. At second-look laparoscopy, adhesions were completely absent in 12/16 women in the FC group compared with 0/11 women in the control group. Postoperative pain and CRP concentrations were lower in the FC group with faster clinical recovery [207]. In a small study in women undergoing robot assisted myomectomy, the effect on postoperative pain could be replicated when humidification and cooling were

omitted. A small, not statistically significant, reduction of adhesions was also found [208]. Although the success of this approach has been welcomed, further investigation of the safety of N_2O has been advocated [209].

We are beginning to understand the genetic factors involved in adhesion development [210, 211, 3, 193, 212] which has opened the possibility of gene therapy [213] as well as personalized medicine [214] where anti-adhesion approaches are tailored to a patient's genotype or phenotype.

Lastly, it must be noted that clinical data concerning the performance of adhesion barriers often use a scoring system that assesses the incidence or severity of the adhesions. Except for the surgeons most intimately involved in grading adhesions, these methods are somewhat abstract. Although a statistically significant outcome may be obtained which shows that agent X reduces adhesions, the system is open to misunderstanding and even manipulation. We are now at the stage where we should strive to reduce the absolute incidence of adhesions rather than reduce the extent or severity of adhesions based on an abstract scoring system.

8. Non-barrier reduction of adhesions and their consequences

Does laparoscopy result in better adhesions outcomes than laparotomy?

Laparoscopy has been widely believed to result in less adhesion formation by avoiding damage due to retractors and abrasion by sponges [215]. In 2003 we updated our meta-analysis of the rates of adhesion development after open or closed abdominopelvic surgery [25]. Adhesion development should be classified according to whether it is for the first or a subsequent time, or whether it is at a site of direct surgical intervention, or the result of indirect surgical trauma [216]:

> ***Type 1: De novo adhesions: Adhesions occurring at sites with no previous adhesion.***
>
> ***1a:*** De novo adhesions at sites where no surgical procedure was performed, e.g., adhesions caused by indirect trauma
>
> ***1b:*** De novo adhesions at sites of a surgical procedure other than adhesiolysis, e.g., adhesions caused by direct trauma.
>
> ***Type 2: Reformed adhesions: Adhesions reforming at sites of previous adhesiolysis.***
>
> ***2a:*** Adhesions occurring at sites of adhesiolysis only.
>
> ***2b:*** Adhesions occurring at sites of adhesiolysis, plus sites of another procedure, e.g., treatment of endometriosis.

Surprisingly we found slightly better adhesion-free outcomes in laparotomy than in laparoscopy for both type 1b (37% vs. 45%) and reformed (14% vs. 27%) adhesions. A recent meta-analysis has found that laparoscopic surgery reduced the rate of adhesion formation by 25% and decreased the adhesion severity score for gastrointestinal surgery [217]. In a large retrospective study, open and laparoscopic gynecological procedures were associated with comparable risks of adhesion-related readmissions, with the exception of laparoscopic sterilizations [6]. In a meta-analysis, the incidence of ASBO was significantly lower in laparoscopic than in open surgery cohorts (1.4% vs. 3.8%) and in ten studies that compared directly the two methods (odds ratio 0.38, 95% confidence interval 0.16 - 0.91) [11], no difference was found for re-operations for bowel obstruction or pregnancy rate [215].

The equivocal conclusions one draws from the above reports may be due to several factors [218]. Firstly, any advantage of laparoscopy may only be in type 1a adhesions. This distinction has not been considered in most analyses. Secondly, any advantage of laparoscopy may be countered by a reduced ability to handle tissues atraumatically, the effects of the products of combustion from laparoscopic cautery [219] or the flow of cold,arid gas (see below). Increased abdominal pressure may reduce tissue perfusion [220], which could result in anaerobic metabolism and oxidative stress which are associated with the development of an adhesion cellular phenotype [221].

Modified insufflation gases and gasless laparoscopy

The cold, arid carbon dioxide used for laparoscopic insufflation is known to damage the peritoneal mesothelium. This damage is greatly attenuated if the gas is warmed and humidified using the INSUFLOW® device (Lexion Medical, St. Paul, MN, USA) [222]. This device may also help to reduce recovery time, hypothermia and postoperative pain [223].

Other workers believe that while it is important to humidify the gas, adhesions can be reduced by cooling the gas [224], adding nitrous oxide [225] or oxygen [226]. Clinically, there was a numerical reduction in SBO after warmed, humidified gas has been used, in a small underpowered study [227].

Gasless laparoscopy has been proposed to avoid the problems of using fast flowing gases [228], although no controlled studies have been conducted to demonstrate any advantage of this method in terms of adhesions. In a meta-analysis, gasless laparoscopy was associated with a shorter recovery time, lower postoperative $PaCO_2$ and reduced nausea and vomiting while conventional CO_2 pneumoperitoneum was associated with a shorter surgical time [229].

Powder-free gloves and other surgical factors

Talc or corn starch powder used to lubricate surgical or examination gloves have long been known to induce adhesions and granulomatous peritonitis. Powder also potentiates infection and carries latex allergens [230] or endotoxin [231]. Although cornstarch powder was banned in the UK and Germany around 1999, only recently have the US FDA proposed such a ban [232].

Varying methods of cautery or peritoneal closure (or non-closure) have been perceived to influence the development of adhesions. Well designed clinical studies on this subject are sparse [215], but the principles of atraumatic technique and good haemostasis remain [233].

Manipulative techniques

Manipulative techniques to treat disease have been practiced since antiquity [234]. Techniques known by various names (e.g. visceral manipulation, myofascial physical therapy, Barral Method, Uplegder Technique, cranio-sacral therapy etc.) share many similarities but vary widely by individual practitioner and their school of training. Manual therapy has been used to treat infertility [235] and pelvic pain [236]. Akin to the continuous passive motion used in orthopedic surgery, early mobilization in an animal model has been shown to reduce adhesion formation [237].

We found in a survey that 29% of adhesions patients who had received some form of physical therapy, reported a benefit [238]. Despite the widespread use of these methods, little has been published in the peer reviewed literature [239]. Two uncontrolled studies reported a benefit of manual therapy to treat infertility (retrospectively) [240] and small bowel obstruction (prospectively) [241]. The therapy was provided over several consecutive days and aimed at «deforming or detaching adhesions». Whether adhesions are actually lysed or whether the therapy improves blood flow, stimulates peristalsis, or directs the remodeling of adhesions, is unclear. I suspect that many patients diagnosed with «chronic bowel obstruction» without a history of hospitalization for obstruction who respond

Table 5: Odds ratios for various lifestyle factors in adhesions and pelvic pain patients

Lifestyle Factor	GYN Adhesions	Recurrent Bowel Obstruction	CPP
Under weight	0.95	1.56	1.06
Overweight	1.69 *	1.01	1.00
Obese	1.75 *	1.13	1.49
Regular exercise	0.66 *	1.04	0.67 *
Yoga	0.95	1.43	1.12
Stress reduction	1.45 *	1.55 *	1.22
Meditate	1.25	1.48	1.70 *
Religious membership	0.86	0.90	0.77
Attend religious service	0.93	0.78	0.93
Married	1.08	0.84	0.96
Divorced	0.74	1.04	1.10
Smoke anytime	1.26	1.16	1.84 *
Currently + previously smoke	2.13	1.29	4.16 *
Currently smoke only	1.57	1.30	2.11 *
Previously smoke only	0.98	1.02	1.49
Smoke, no exercise, overweight/obese	3.59 *	1.45	1.93

* $p < 0.05$

to this sort of therapy, may in fact suffer from severe and chronic constipation precipitated by opioids, the stress of their chronic pain syndrome, or a phenomenon of central sensitization. The possibility that bowel adhesions may be lysed [237] without direct vision, raises safety concerns. More work is needed to standardize these methods and characterize their benefits.

A number of patients are using the «I LOVE YOU» method of self-massage in which the right fist traces the letters «I», «L», and «U» over the abdomen to stimulate peristalsis.

Lifestyle factors

By understanding the association between lifestyle and medical factors and conditions related to adhesions, we can begin to devise treatment and prevention strategies [193]. In a survey of 687 US women visiting the adhesions.org web site, the association between various medical or lifestyle factors was determined [3]. These patients reported diagnoses of abdominal or pelvic adhesions (85%), chronic abdominal (CAP) or pelvic pain (CPP) (69%) and recurrent bowel obstruction (44%). Patients with a prior hysterectomy had a higher risk (risk ratio) of adhesions (1.4), CAP or CPP(1.76) as well as other adhesions-related conditions. Similar findings were made for patients with an iron-overload disorder for adhesions (1.2) and CAP or CPP (1.47). Iron-overload may place a patient at higher risk of oxidative stress [3]. In addition to the surgical reasons why hysterectomy is associated with adhesions and chronic pain, hysterectomy may induce an iron overload-like condition as iron is no longer eliminated through menstruation. In the US, approximately 72,000 hysterectomies are performed annually with pain as the primary indication [242] despite there being insufficient evidence to provide any basis for comment as to its ability to treat pelvic pain [79]. Treating pain non-surgically in these patients would remove this pool of patients at risk of adhesions, as well as other sequelae of hysterectomy.

Odds ratios were calculated for other lifestyle factors in this cohort [104] to identify risk factors for adhesions, recurrent bowel obstruction and chronic pelvic pain (Table 5). The presence of a risk factor does not imply causality. Overweight status was a risk factor for pelvic adhesions and regular exercise appeared beneficial for adhesions and pelvic pain.

Long term or current smoking was a risk factor for CPP, possibly because of the effects of smoking on fibrinolysis [193]. Smoking, lack of exercise and overweight status, combined, was a risk factor for adhesions and borderline for CPP. Patients with recurrent bowel obstruction had a very different risk factor profile from those reporting adhesions or CPP.

Assessing a patient's lifestyle and genetic factors may help to predict their likely response to surgery and to customize
has been noted
us external signs
print patterns [244].
Fingerprint patterns have shown correlations in other diseases [245]. The same group has determined a number of risk factors of pelvic adhesion formation including type of surgery (adhesiolysis, laparotomy, repeated surgeries, peritoneal drainage, emergency status of previous surgery) and inflammation (history of sexually transmitted infections, IUD (Intrauterine devices) use, two or more abortions, complications of pregnancy related to pelvic inflammatory disease) [246].

9. Treating and preventing ARD as a subset of CAPPS

Adhesions have almost always been viewed merely as a surgical problem that could sometimes be prevented with barriers and could sometimes be treated with adhesiolysis. We attempted to understand the problem from the viewpoint of patients, their pattern of bowel obstruction and gastrointestinal disturbance, their nutrition, their use of analgesia, their ability to work and receive disability assistance, their social support structure, and the attitudes and abilities of their physicians [238]. To more adequately describe these patients and create a new treatment paradigm that would consider the spectrum of these problems, we coined the term «Adhesion Related Disorder» (ARD) in the late 1990's.

Adhesion Related Disorder (ARD): a constellation of recurrent bowel obstruction, chronic abdominal or pelvic pain, chronic diarrhea or constipation. Patients often develop a variety of psychosocial issues, and have undergone a number of procedures in an attempt to diagnose and/or correct a sometimes unidentifiable underlying problem.

The most severely affected ARD patient develops not only pain and bowel obstruction but often a set of overlapping and coalescing bowel, urinary, genital and musculoskeletal symptoms. These patients share much with patients with other chronic pelvic and abdominal conditions such as irritable bowel syndrome (IBS), interstitial cystitis – bladder pain syndrome (IC-BPS), pudendal neuralgia, sacroiliac joint pain, endometriosis and pelvic floor dysfunction. These patients account for 10-20 million of the 100 million or so US patients with chronic pain. ARD, like its relatives in the world of pelvic and bladder pain, may have effectively developed into a phenomenon of central sensitization [87] or a functional somatic syndrome [88]. To aid in the reframing of new diagnostic and treatment paradigms, we coined the term CAPPS [3].

Complex Abdomino-Pelvic & Pain Syndrome (CAPPS): a syndrome of non-malignant origin consisting of a complex of symptoms of the abdomen or pelvis that includes pain, bowel, bladder or genital dysfunction of at least 6 months duration.

Framing ARD as a subset of CAPPS reframes the way we think about the prevention of adhesions and treatment of their consequences. Acute obstruction requires immediate admission, assessment and treatment. Other patients with long-standing

symptoms of unexplained pain and/or chronic constipation, often after multiple examinations, have obtained a diagnosis of «adhesions» in one of five ways:

a) There is a history of clinically confirmed adhesive obstruction.

b) Adhesions have been clinically confirmed by direct observation, or in limited cases by non-invasive methods.

c) The patient has a history of prior surgery or trauma suggestive of adhesions.

d) The patient is given a diagnosis of adhesions after excluding other causes.

e) The patient was given no diagnosis, sometimes told there is nothing wrong after extensive testing, but has «self-diagnosed» after consulting the internet and social media.

For category (a) patients with an obvious risk of re-obstruction, an «obstruction plan» should be developed with the patient's local hospital and general surgeon to provide for rapid and early triage in event of obstruction. For all patients, pain and chronic constipation may not be directly related to any sub-clinical obstruction due to adhesions (even if present), but rather a result of opioid use, or a manifestation of central sensitization or functional somatization. Several elements should be considered in the treatment of these patients:

- The presence of other symptoms within the CAPPS family should be evaluated by relevant specialists (urology, gynecology, urogynecology, neurology, pain management, gastroenterology, physical therapy, psychotherapy, dietician etc.) preferably within the context of an integrated multidisciplinary program, such as the one we helped found at Celebration Health Hospital, Florida. ARD/CAPPS patients are often depressed and suffer sleep disturbances.
- A self-care plan should include modification of diet, smoking, exercise and massage.
- A pelvic floor/pelvic pain/abdominal pain physical therapist should treat muscle spasm and trigger point issues if present. Limited and expert visceral manipulation should be considered.
- Medications should be reviewed, particularly those affecting the bowel, such as opioids.
- Psychotherapy techniques may be used such as cognitive behavioral therapy and biofeedback to assist pain management. Attempt to determine if there is a history of physical or sexual abuse that may be contributing to the patient's condition.
- The patient and his/her family should be referred to counseling to facilitate their social support structure.

For the reasons described in section 5, operating on adhesions patients in the absence of obstruction may have limited and transient success. If adhesiolysis is attempted, adhesion barriers and conditioning should be employed where possible. Most surgeons will not operate on these patients, not because of some understanding about pain, but because of the risk of reformation after adhesiolysis. The only option for these patients is to endure further misery, restricting their diet and opioid use. For patients in category (a) there is the added torture of knowing that they will likely obstruct again.

We have found a wearable therapeutic ultrasound device (PainShield® MD) to be very effective in treating pain, painful constipation and related painful symptoms in patients with ARD and CAPPS [247]. In at least 80% of patients the following are reduced:

- Pelvic or abdominal pain.
- Bowel related pain – such as painful defecation and rectal spasm.
- Painful constipation.
- Urological symptoms such as pain, and painful frequency and urgency.
- Genital symptoms such as painful intercourse.
- Musculoskeletal symptoms such as sacroiliac joint pain.
- Opioid intake.

The device may act by:

1. Relaxing the muscles of the pelvic floor, as pelvic floor muscle spasm is a major contributor to pelvic and abdominal pain [236, 248].
2. Normalizing neural activity by stimulating repair of the myelin sheath which may be damaged in chronic pain conditions [249].
3. Relaxing intestinal smooth muscle.

For full disclosure, based on our initial results, I set up a company to market this device. It seems appropriate that any candidate for adhesiolysis, hysterectomy, neurectomy or neurostimulator implantation only for pain should first be treated with this device.

10. What do adhesions patients want us to know?

As scientists and medical professionals our «customers» are those patients we treat. It is important that we listen to our customers. Through social media I asked patients: "What is the single most important thing you would like to say to doctors and scientists working on adhesions?" I have excerpted verbatim and categorized the many replies below.

1. Please understand how this has affected my life

* I want my life back- to be pain-free.
* [adhesions] robbed me of a life. I not only have pain that has made me bedridden it's caused a lot of life threatening medical problems, not only multiple MRSA infections but now two strokes and a heart attack...I can't live my life I just exist. I'm just waiting to die.
* Adhesions ROB YOU OF A FULL life!
* Adhesions can affect every aspect of your life - social, financial, sexual, professional. From excruciating pain to basic bodily functions
* To think that this is not a problem is grotesque: Constipation, dyschezia, internal tightness, back pain, all increased 10 fold following hormonal treatment. It felt as if someone had sawn my organs together and nothing could flow, bend and move normally anymore.
* Loss of mobililty because of all this Pain and constant suffering, very very slow working stomach an bowels. This feels like I've literally just had surgery! Every day
* I live with adhesion pain daily and am in constant fear of obstruction. Doctors seem to be very fearful of adhesions - you get that look that says ' nothing we can do about adhesions '
* I've had a few adhesion related bowel obstructions, the pain of which I can honestly say is worse than giving birth.

2. Please understand that I really hurt and that I sometimes feel all alone

* The mistaken notion some providers have that adhesions 'don't hurt' or can otherwise cause significant symptoms is a travesty.
* The pain is real. It isn't something that you can just throw more pain medication at. Yes, there are adhesions that don't cause pain but even the smallest one has the capacity to be debilitating.
* Adhesions can be incredibly painful. Patients come to Dr's and express how debilitating they are and are treated like they should walk it off, just eat broth and take an anti depressant...The way we are treated causes more emotional distress on top of an already stressful situation.
* Terrified. Hopeless. Belittled. Alone. Less than human. Is how I feel when a doctor tells me my adhesion's can't cause pain.
* How debilitating this condition is for the sufferer and how being told it is purely IBS is frustrating when you are experiencing blockages and daily pain.

* Doctors who do not acknowledge Adhesions and their problems, do not understand how isolated a patient feels when no one seems to acknowledge their medical issues.

* When your own dr doesn't know what to do with you ,where do we turn? I feel isolated from the world, a let down to my parents ...And a let down to my child. I've lost all my friends over the yrs too. Therefore we.. have depression now struggling just to survive let alone Live.

* We are not drug seekers. Our pain is chronic.

* Never, ever dismiss a person from your medical care without trying to at least point them to other medical doctors or options.... No one wants to go to a doctor only to be pointed to the door as if they are worthless and hopeless.

* Not all of the medical professionals understand and have the knowledge about adhesions and the pain that goes with having them! Adhesions and the pain that goes along with them is a complicated issue to understand! What is adhesions and pain? Is it a true illness or just an issue bundled up with other illnesses or issues with ones health? Most doctors ignore that it exists because adhesions is not something that is seen on most test, scans and xrays until it causes a very serious complication of obstructions in "our" bodies! Managing the pain is very hard with the hype about opiate addiction in the news!

* I found more doctors who thought all I wanted was another pain pill. I didn't. I wanted it to go away.

* Please make sure doctors don't dismiss the pain they cause.

3. Please learn and teach about adhesions and their consequences

* The most important issue to me is acknowledgement... Many doctors and nurses do not have a clue concerning the "side effects" of adhesions.

* I wish all drs, knew about adhesions and not say to us that is in our minds.

* [adhesions] should be mentioned on consent forms

* No information given about adhesions, at all!

* [adhesions] should be a KEY part of surgical training!

* acknowledgement that adhesions have an impact on your quality of life, More awareness of adhesion disorders, it seems very patchy.

* I would like to ask that doctors not be so quick to dismiss our symptoms as IBS;

4. My most important symptom is...

* I can't have a proper bowel movement and everything I eat hurts. So then I barely eat anything.

* 1. pain control 2. constipation

* I really wish doctors would work on pain management

5. Please improve diagnostic methods for adhesions

* Please work on improving imaging techniques. After many discouraging physician visits, negative tests and misdiagnoses, it ultimately took surgery to discover and confirm that adhesions are the cause my debilitating pain. Many patients may never be properly diagnosed since currently there are no available options to accurately image and view adhesions.

* More investigation into ways of diagnosing / visualising them, without the need for further surgery;

* Please ...focus on less invasive diagnostic testing and treatment. Having a laparoscope and excision surgery isn't a simple procedure.

6. Learn how to prevent adhesions and treat patients

* DON'T put foreign material in an abdoman that's double timing already to fight against itself.

* More effort put into prevention and solution, and physical massage therapy - these should be par for the course post surgery, known to all medics, and available routinely on the NHS;

* talk with me realistically about the adhesions and multiple episodes of small bowel obstruction I have had. Make a plan for me in case another episode happens- so I can come straight into hospital, with things like pain relief which helps and plans for surgery if needed.

11. Conclusion and challenges

If Richardson were with us today, I would propose that he revise his statement of 1911 [2]: «It is futile to search for some agent that will banish adhesions from the realm of surgery...»

I would propose that he adopt a more optimistic outlook. We have come a long way in understanding the aetiology and pathogenesis of adhesions. We see signs that adhesion barriers may provide clinical benefit and we have started to understand the nature of pain and related conditions. We have better strategies for dealing with obstruction and for treating adhesion-related pain. It is true we have much work to do, and the following perhaps are our main challenges:

1. While there is no shortage of data detailing the extent of the problem of adhesions and their reduction by adhesion barriers, prospectively conducted randomized studies demonstrating the improvement of clinical outcomes are needed.

2. In addition to trying to prevent adhesions from attaching one tissue to another, we must also address what is happening at the «base» of the adhesion. Even if we can prevent the adhesion itself with adhesion barriers, we are doing nothing to control the fibrosis within the plane of the tissue that will entrap nerves and could cause pain, even if adhesions are prevented or removed.

3. We must develop drug-polymer products that can both act as adhesion barriers and provide pharmacological modulation of adhesions or fibrosis.

4. We must look to gene therapy, cell therapy and tissue engineering approaches to preventing adhesions.

5. We must develop a good method of imaging adhesions non-invasively and quantitatively [44]. Ultrasound and cine-MRI methods are showing some promise [250, 251].

6. We must develop anti-adhesion barriers that can be placed around the bowel without fear of ileus, abscess, infection or dehiscence. Barriers must be capable of laparoscopic delivery and function in the presence of bleeding. Barriers must not potentiate tumor growth.

7. We must develop government and industrial partnerships to ensure the development of these sorely needed products. Regulatory pathways must be redefined to meet the challenges of approving the barrier use in the context of simultaneous measures such as conditioning.

8. We must find alternatives to opioid analgesia for «adhesions» patients that do not compromise bowel function.

9. We must develop better prevention strategies for patients most at risk of obstruction and for those who have already obstructed.

10. We must understand better the complex relationship between adhesions and pain, and the pathology of pain in patients that have adhesions. We need to understand if some patients with adhesions are being given a diagnosis of obstruction because they have chronic constipation but without clinical confirmation.

11. We must develop a multidisciplinary approach to treating the range of problems of ARD patients – pain, obstruction, bowel, urinary, genital and musculoskeletal issues. The approaches should include, neuromodulation, physical therapy [234, 239, 241], psychotherapy, and therapeutic ultrasound in addition to use of drugs and surgery.

12. We must reduce the need for surgical procedures performed for pain by exhausting non-surgical treatments first. This would be true for procedures such as adhesiolysis and neurectomy and certainly for procedures whose benefits are

doubtful (hysterectomy performed only for pain [79], in the absence of other pathology).

13. More training must be given to medical students and surgeons on the causes and consequences of adhesions and ARD. Information given to patients as part of the consent process must be expanded.

14. We must listen to our patients and learn from them.

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13. Disclosures

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The content of this paper has not been influenced by any other entity. Synechion owns and funds the International Adhesions Society (IAS, adhesions.org, iscapps.org, pelvicpainology.com) which does not have not-for-profit status. The IAS may receive funds from other commercial entities. The author is also president of KevMed,LLC. which markets PainShield MD Wearable Therapeutic Ultrasound for the treatment of pelvic pain and related disorders.

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