Postoperative adhesions and their prevention

Philippe Robert Konincx, Maria Mercedes Bindia, Roberta Corona, and Carlos Roger Molinas

INTRODUCTION

The fact that adhesions can form following abdominal surgery has been known since the beginning of surgery. Yet during the early years of surgery, adhesion formation received little attention, the focus being on infection and survival. In the seventies clinical endocrinology developed explosively, driven by the introduction of oral contraceptives and by the introduction of radioimmunoassays—a technique that permitted for the first time the assay of reproductive hormones—and reproductive medicine and infertility became a subspecialty. Simultaneously, reproductive surgery developed and the prevention of postoperative adhesion formation became important. Microsurgery was introduced (1) first as a magnification tool permitting tubal reanastomosis and developing subsequently as a principle of surgery emphasizing the prevention of desiccation and gentle tissue handling (Fig. 1). Prevention of adhesion formation was mainly based upon careful observational medicine and common sense, and most of the principles became only much later experimentally confirmed. Some mistakes, however, were also introduced such as the free peritoneal graft to cover denuded peritoneal areas, a technique shown later to be strongly adhesigenic (2).

The history of surgery and adhesion prevention cannot be viewed separately from the development of endometriosis and endometriosis surgery because cystic ovarian endometriosis is strongly associated with adhesion formation and also because endometriosis surgery is the most frequently performed fertility surgery. Diagnosis of infertility and of endometriosis and their treatment has driven the development of diagnostic laparoscopy complemented with minor laparoscopic surgical interventions and by microsurgery. When lightweight endoscopic cameras were introduced in the mid-eighties, endoscopic surgery developed explosively replacing microsurgery and also laparotomy not only in gynecology but also in abdominal surgery and urology. This had important consequences for fertility and endometriosis surgery and for our awareness of adhesion formation. Until the early nineties, fertility surgery with prevention of adhesion formation had remained centralized in highly specialized fertility centers (3,4). We then witnessed in parallel the increasing use and success of IVF and the development of more advanced endoscopic surgery such as deep endometriosis and bowel, pelvic floor, and oncologic surgeries. With laparoscopic reproductive surgery becoming mainstream surgery, the microsurgical focus on the prevention of adhesion formation got lost. Indeed outside reproductive surgery, adhesion formation was widely considered as an unavoidable by-product of surgery, which could largely be prevented by good quality surgery. In retrospect, it is astonishing how fast the principles of microsurgery became by and large forgotten, with the overall belief that laparoscopic surgery was “minimal invasive” surgery and thus even better than microsurgery and that adhesion formation would rapidly become a minor problem (5,6).

With the realization that laparoscopic surgery was not the solution to prevent adhesion formation (7,8), laboratory research on and clinical interest in adhesion formation revived and new products were developed. Only in the last decade, we have become aware of the clinical importance of adhesion formation, mainly though the SCAR studies (9-11). These studies clearly demonstrated that the incidences of bowel obstruction and of reoperation due to postoperative adhesions keep increasing linearly for at least 10 years and are much higher than anticipated. In addition, the awareness of postoperative adhesions as a cause of infertility and pain grew. With the awareness of the clinical importance, we realized the associated costs, the market potential, and the necessity of randomized clinical trials for new products. “Quality of surgery” obviously being a key element in these trials, we realized that quality control of the individual surgical procedure was close to nonexistent (12), and video registration was introduced as a monitoring aid for these trials. And simultaneously also came the awareness that quality of surgery might be variable—that good quality surgery cannot be considered as universal with obvious consequences for the interpretation of adhesion formation statistics.

In conclusion, postoperative adhesion formation has never received the attention it deserves as evidenced by the absence of adequate keywords to search the literature. Only very recently the clinical importance has been acknowledged (13-17), stimulating research and the foundation of a dedicated society, the PAX society, today called the Peritoneum and Surgery Society (P&8), spanning gynecology and surgery.

PATHOPHYSIOLOGY OF ADHESION FORMATION

The Mesothelial Cell and the Peritoneal Cavity

Mesothelial cells form a monolayer resting on a basal membrane and an underlying connective tissue lining the organs and the wall of the abdominal cavity, the pleura, and the pericardium. Mesothelial cells have been considered to be of mesothelial origin, but recent evidence has shown that both mesothelial cells and endothelial and hematopoietic cells are derived from a common progenitor cell originating embryologically in the splanchnic mesothelium (18). More recently mesothelial stem cells, which are able to differentiate to mesothelial cells, endothelial cells, smooth muscle cells, myoepithelial cells, adipocytes, chondrocytes, and osteoblasts, have been described. In culture these mesothelial cells behave as epithelial cells, expressing mainly cytokeratin, but under the influence of TGF-β, HGF, or EGF, they transform into spindle-shaped mesenchymal cells expressing mainly vimentin. The relationship between mesothelial stem cells and peritoneal repair following injury remains unclear.
Indeed it remains debated whether these cells derive from the peritoneal fluid, from the mesothelium, from the submesothelial connective tissue, from the vascular endothelium, or from blood cells. In any case, the concept of mesothelial stem cells is bound to be important for our understanding of peritoneal repair and of adhesion formation (19–21).

The roles of mesothelial cells in maintaining normal serosal membrane integrity and function is still only partially understood. They secrete glycosaminoglycans and surfactant to allow the parietal and visceral serosa to slide over each other. They actively transport fluids, cells, and particulates across the serosal membrane. They actively modulate gas resorption as CO$_2$ from the pneumoperitoneum (22,23). They synthesize and secrete mediators, which play important roles in regulating inflammatory, immune, and tissue repair responses. But we do not understand yet how these mesothelial cells communicate with each other and with surrounding cells as well as what the role of progenitor cells is (24).

In the absence of ovarian activity, peritoneal fluid is scanty. During the menstrual cycle, peritoneal fluid is mainly formed as an ovarian transudate arising mainly from the developing follicle or corpus luteum. Hence peritoneal fluid contains concentrations in steroid hormones that are much higher than in plasma. Mesothelial cells are highly specialized cells regulating the transport of fluid and proteins, especially those larger than 20 kDa, between the peritoneal cavity and the bloodstream. For small molecules exchange is rapid by simple diffusion, but for larger molecules transfer is much slower. Thus concentrations of blood proteins such as albumin, LH, and FSH are more than 40% lower than in plasma, whereas locally secreted macromolecules as CA125 and glycolipids accumulate in peritoneal fluid with concentrations that are much higher than in plasma (25–31). Peritoneal fluid contains high amounts of macrophages, which secrete, especially when activated, such as in endometriosis, a large variety of cytokines and growth factors. Peritoneal fluid thus is a specific microenvironment with protein and hormone concentrations that are much different from plasma (32,33).

When the mesothelial cell becomes traumatized (Fig. 3), as demonstrated for hypoxia during CO$_2$ pneumoperitoneum, the large flat mesothelial cell retracts, known as “bulging of cells,” and the highly specialized layer of contiguous peritoneal cells is transformed into a layer of individual cells and between these cells large areas of basal membrane is directly exposed (34–39). Similar effects are believed to occur in response to all types of trauma such as desiccation, mechanical, or chemical trauma. The repair of this mesothelial cell trauma is rapid, and the peritoneal lining becomes normal again within two to three days. The consequence of this effect is largely unknown. Disruption of this highly specialized membrane is bound to affect all those substances transport of which is actively regulated by the mesothelium layer. The resorption of CO$_2$ from a pneumoperitoneum increases (22,23), whereas diffusion of larger molecules probably is greatly enhanced. It remains unclear to what extend this is associated with an inflammatory reaction and what the role is of attraction and activation of macrophages and their secretion products as cytokines and growth factors.

The Classic Model of Adhesion Formation: A Local Phenomenon

A trauma of the peritoneum, involving besides the mesothelial cells also the basal membrane and the submesothelial connective tissue, is followed by a local inflammatory reaction, exudation, and fibrin deposition (Fig. 2). This fibrin is normally...
Pneumoperitoneum, or for desiccation, one fibrin deposition—The updated model of adhesion formation. Flat mesothelial cells × the classic model of adhesion formation as a local process with pneumoperitoneum–induced mesothelial hypoxia. Whether adhesions will be velamentous, thick, and vascu-
larized and what factors determine innervations (43–45). Also adhesion remodeling is something that is poorly understood. The Updated Model: The Peritoneal Cavity as a Cofactor—Studies published since mid-nineties have shown that the entire peritoneal cavity can be a cofactor in adhesion formation (5,7,22,23,46–60). Identified so far in laparoscopic rabbit and mouse models for adhesion formation are desiccation, hypoxia, reactive oxygen species (ROS), and manipulation (60), which increase adhesion formation at an injured area. Since CO2 pneumoperitoneum–induced mesothelial hypoxia results in the entire exposed peritoneal area in retraction of mesothelial cells exposing directly the extracellular matrix (34–39), it is postulated that this results in the attraction into peritoneal fluid of substances of cellular elements and thus enhances adhesion formation and/or decreases repair without causing adhesion formation outside the injured area. For hypoxia by CO2 pneumoperitoneum, or for desiccation, one might argue that they also affect the injured site. The observation, however, of a similar dose-dependent effect following manipulation of the omentum and organs outside the injured area supports the concept that the entire peritoneal cavity can be a cofactor in adhesion formation (Fig. 3). It seems logical to postulate that any trauma to the large and flat mesothelial cells will induce them to retract as a defense mechanism and that this effect is more pronounced when trauma is more severe. However, we do not know what the exact mechanisms are through which adhesion formation is further modulated. We only can speculate that macrophages and their secretion products, blood constituents, or other inflammatory products affect directly the repair process or the differentiation of stem cells at the injured area. Any postulated mechanism should explain that desiccation enhances...
adhesion formation and that the effect is dose dependent. CO₂ pneumoperitoneum also enhances adhesion formation and the longer the procedure, the higher the effect. The effect upon adhesions seems mediated through mesothelial hypoxia since the mesothelial layer stains hypoxic and since the increase in adhesions is prevented by the addition of 3% to 4% of oxygen (restoring the physiologic intraperitoneal partial oxygen pressure of 30–40 mm Hg) and is absent in mice partially deficient for hypoxia-inducible factor-1α and 2α (HIF1α and HIF2α) being the first to be activated by hypoxia. Similar effects are observed when partial oxygen pressures exceed 80 mm Hg, thus increasing ROS, and this effect can be prevented by ROS scavengers.

Pathophysiology of Adhesion Formation: Conclusions

The classic model, which views adhesion formation as a local phenomenon (Fig. 2), and the effect of the entire peritoneal cavity (Fig. 3) and its constituents should be considered as complementary. The importance of each effect might vary with the localization and the type of injury. Following severe traumas, large areas, e.g., the pelvic cavity, can become completely occluded by fibrous adhesions and these areas probably escape from the influence of peritoneal fluid. In these circumstances, adhesion formation may follow mainly the classic model. For minor lesions, especially nonapposed lesions, such as those frequently occurring during fertility surgery, the effect of the peritoneal cavity probably is dominant.

Both models are also important for our understanding of adhesions prevention agents. A flotation agent will also dilute peritoneal fluid and any factor secreted locally by the denuded areas as well as will hamper the access of macrophages, which cannot swim. Barriers on the other hand might, in addition to keeping tissues separated, shield the injured area from the peritoneal fluid and its constituents, something that might be beneficial or detrimental according to circumstances.

To understand the role of the mesothelial cells in peritoneal repair, both models have to be considered simultaneously. Obviously, peritoneal repair and adhesion formation between injured areas is a local process. The repair cells, however, are at least partially derived from incorporation of free-floating mesothelial cells in the peritoneal fluid, which today could be considered partially differentiated stem or progenitor cells. Since repair can be accelerated and adhesion formation decreased, by intraperitoneal injection and transplantation of autologous mesothelial cells, any deleterious effect to the peritoneal cavity is bound to affect these free-floating cells. Today we can only speculate about endocrine or other factors affecting the function of these cells and even about the sheer number of cells available for repair. It is unclear whether, as a response to trauma of the peritoneal cavity by hypoxia or desiccation, the number of free-floating mesothelial cells/stem cells are expected to be increased by attraction or to be decreased because free-floating cells could attach to cover the denuded areas in between retracted mesothelial cells. The importance of mesothelial cell and their differentiation is also highlighted by the observation that the fibroblast cultured from adhesions are permanently differentiated from other mesothelial fibroblasts (61–63) and by the observation that recurrence rates after adhesiolysis are much higher than expected.

Clinically, some individuals form adhesions more easily after surgery than others—an observation supported by the fact that some mice strains form much more adhesions than others—while variability of adhesion formation is much lower in inbred strains (53). We also do not know why some adhesions are filmy and thin while other adhesions are dense; why some adhesions are vascular or avascular, or innervated or not.

PREVALENCE AND CLINICAL CONSEQUENCES OF POSTOPERATIVE ADHESION FORMATION

Following abdominal surgery, adhesions are formed in over 70% of women, and they have been considered as a cause of infertility, pain, and bowel obstructions (Fig. 4). The clinical importance of adhesion formation has been emphasized by the SCAR study (9–11) demonstrating in a 10-year follow-up of abdominal surgery in Scotland that the incidence of postoperative adhesion formation and of bowel obstruction kept rising almost linearly for a period of at least 10 years. Moreover, reinterventions occurred in some 50%, in many persons more than once, and at least 6% could be linked directly to adhesion formation. Repeat surgery was more difficult, more tedious, and associated with more complications because of adhesions. From these findings, models have been constructed, calculating cost of adhesions formation for society, and conversely the savings that could be realized by adhesion prevention assuming that reduction in adhesion formation could linearly be extrapolated to a reduction in pain, in infertility, and in repeat surgery or bowel obstructions.

The real clinical picture, however, is not so clear. The first confounding factor is quality of surgery, which is variable. Duration of surgery and complication rates decrease by training as demonstrated in a series of learning curves in both humans and animal models. Both the duration of endoscopic surgery and the extent of manipulation have been demonstrated to directly affect adhesion formation. It must be recognized that in contrast with medical therapy for which quality control is strictly organized, there is no quality control for surgery (12). Further, there are no data available permitting to judge the importance of adhesion formation for fertility, not even after fertility-promoting surgery. The clinical importance of adhesion formation has been emphasized by the SCAR study (9–11) demonstrating in a 10-year follow-up of abdominal surgery in Scotland that the incidence of postoperative adhesion formation and of bowel obstruction kept rising almost linearly for a period of at least 10 years. Moreover, reinterventions occurred in some 50%, in many persons more than once, and at least 6% could be linked directly to adhesion formation. Repeat surgery was more difficult, more tedious, and associated with more complications because of adhesions. From these findings, models have been constructed, calculating cost of adhesions formation for society, and conversely the savings that could be realized by adhesion prevention assuming that reduction in adhesion formation could linearly be extrapolated to a reduction in pain, in infertility, and in repeat surgery or bowel obstructions.

The real clinical picture, however, is not so clear. The first confounding factor is quality of surgery, which is variable. Duration of surgery and complication rates decrease by training as demonstrated in a series of learning curves in both humans and animal models. Both the duration of endoscopic surgery and the extent of manipulation have been demonstrated to directly affect adhesion formation. It must be recognized that in contrast with medical therapy for which quality control is strictly organized, there is no quality control for surgery (12). Further, there are no data available permitting to judge the importance of adhesion formation for fertility, not even after fertility-promoting surgery.

The real clinical picture, however, is not so clear. The first confounding factor is quality of surgery, which is variable. Duration of surgery and complication rates decrease by training as demonstrated in a series of learning curves in both humans and animal models. Both the duration of endoscopic surgery and the extent of manipulation have been demonstrated to directly affect adhesion formation. It must be recognized that in contrast with medical therapy for which quality control is strictly organized, there is no quality control for surgery (12). Further, there are no data available permitting to judge the importance of adhesion formation for fertility, not even after fertility-promoting surgery.

The real clinical picture, however, is not so clear. The first confounding factor is quality of surgery, which is variable. Duration of surgery and complication rates decrease by training as demonstrated in a series of learning curves in both humans and animal models. Both the duration of endoscopic surgery and the extent of manipulation have been demonstrated to directly affect adhesion formation. It must be recognized that in contrast with medical therapy for which quality control is strictly organized, there is no quality control for surgery (12). Further, there are no data available permitting to judge the importance of adhesion formation for fertility, not even after fertility-promoting surgery.
Figure 4 Adhesions vary from short but strong bands (1), causing eventually bowel obstruction, to filmy adhesions between omentum and the appendectomy scar (2) to dense vascularised adhesions between uterus and abdominal wall (3) to dense adhesions as seen in endometriosis (4).

whereas the only randomized control trials did not demonstrate a clear effect upon pain (66).

PREVENTION OF POSTOPERATIVE ADHESION FORMATION

Adhesion formation between opposing injured peritoneal surfaces are acknowledged to be different from adhesion reforma-
tion following lysis of adhesions and from de novo adhesion formation outside the areas of surgery. Since adhesion preven-
tion has been investigated adequately only for the former, the following paragraphs will not discuss de novo adhesions and adhesion reformation.

Good Surgical Practice and Conditioning of the Peritoneal Cavity

Good surgical practice and gentle tissue handling have been introduced as an important tenet by the pioneers of micro-
surgery. This includes moistening of tissues by continuous irri-
gation, moistening of abdominal packs, glass or plastic rods for mobilization of tissues, and precise microinstruments. Reduc-
tion in adhesion formation was anticipated. However, it is only recently that the importance of prevention of desiccation and of gentle tissue handling have been proven, emphasizing how important and accurate clinical observation can be.

Key to good surgical practice today is whether the animal data can be extrapolated to humans. These data probably can be extrapolated because the effect of CO\textsubscript{2} pneumoperitoneum, the duration-dependent increased CO\textsubscript{2} resorption, observed in mice and in rabbits also occurs in women. Taking into account the findings in animal models, good surgical practice today should include the following. First, the insufflation gas should be conditioned in order to minimize hypoxia and desiccation; this requires humidification of the gas and the addition of 3% to 4% of oxygen to the CO\textsubscript{2}. Moreover, cooling of the peri-
toneal cavity is important since it decreases both the effects of hypoxia and of desiccation, cells being more resistant to
metabolic damage at lower temperatures. Cooling of the peritoneal cavity makes it possible for the humidified and saturated insufflation gas to condense upon entrance to the pelvic cavity, thus preventing desiccation. Secondly, the duration of surgery should be kept to a minimum as well as the amount of bleeding and the extent of tissue manipulation. In summary, the surgeon should be experienced and well trained.

Observation of strict sterility remains mandatory to prevent any kind of infection. This simple statement should be balanced against the observation that it is difficult to completely disinfect the umbilicus and that each time the vagina is opened, at least some risk of infection occurs. This is even more likely with entry into the bowel. Good surgical practice therefore should begin by observing strict sterile conditions. This might sound obvious but it is not so evident, since in endoscopic surgery many surgeons no longer wear masks (endoscopic surgery being considered a semisterile intervention). Looking carefully at endoscopic interventions many minor mistakes are noticed if judged by the standards of open surgery. Whether extensive lavage following surgery might reduce adhesion formation or the risk of some minor infection is unknown. Following deep endometriosis surgery with full thickness resection and a bowel suture, extensive lavage with 8 L clearly decreased the postoperative inflammation as judged by CRP concentrations while preventing late bowel perforations (De Cicco C, unpublished observations). This has stimulated us to extend the use of extensive lavage to all surgical interventions with an increased risk of infection such as following hysterectomy or salpingostomy for hydrosalpinx. Interestingly, microsurgery also emphasized lavage for removing clots, foreign substances, and fibrin.

Taken together these measures of good surgical practice along with conditioning of the pneumoperitoneum, cooling and prevention of inflammation, should reduce adhesion formation by more than 60%.

**Adhesion Prevention in Animal Models**

A wide range of products have been shown to be effective in animal models. Efficacy of all products described so far has been extensively investigated in our laparoscopic mouse model. It should be realized that in this model all criteria of good surgical practice as described are fulfilled, with standardized lesions, controlled duration of surgery, strict control of temperature, and absence of desiccation (Fig. 5). It should also be realized that the laparoscopic mouse model is a model for three distinct pneumoperitoneum conditions: normoxia, hypoxia, and hyperoxia. The first model intends to minimize any peritoneal damage except for the lesions inflicted to induce adhesions. Thus, adhesions will form according to the classic model, with little or no effect of the peritoneal cavity. In this model, 4% of oxygen was added to the CO$_2$ pneumoperitoneum to prevent mesothelial hypoxia. The second model is the “hypoxia model” since adhesions are enhanced by CO$_2$ pneumoperitoneum–induced mesothelial hypoxia. In this model, pure CO$_2$ was used. In the third model, called hyperoxia model, 12% of oxygen was added to the CO$_2$ pneumoperitoneum, a concentration known to enhance adhesions probably by cell damage by ROS.

Dexamethasone decrease adhesions by some 30% in the hypoxia model (47), by 60% in the hyperoxia model (67), and, especially, by some 76% in the normoxia model when it is combined with low temperature (68). ROS scavengers decrease adhesions by 10% to 15% in both the hypoxia and hyperoxia models, an effect too small to be demonstrated in the normoxia model, with much less adhesions to start with. Calcium channel blockers decrease adhesion formation by some 35% of inhibition in both the hypoxia model (47) and hyperoxia model, whereas less inhibition, around 17%, was
observed in the hyperoxia model. Ringers lactate as a flotation agent is marginally but significantly effective (51). The effect of other solutions, e.g., agents such as carboxymethylcellulose (CMC) and Hyskon are marginal (46) and surfactants such as phospholipids give some 35% of inhibition in the hypoxia and hyperoxia models and 58% in the normoxia model when it is combined with low temperature. Icodextrin (Adpekt, 4% α-(1–4) glucose polymer) unfortunately could not be evaluated since it is degraded enzymatically in mice. Barriers such as Hyalo- barrier gel, Spraygel, and Intercoat are highly effective in all models with a reduction of 58% to 90% in adhesion formation. Prevention of angiogenesis also reduces adhesion for- mation, as demonstrated in PGF knockout mice and by the administration of anti-VEGF and anti-PIGF monoclonal anti- bodies (55,61,63,70,71).

The transplantation of cultured mesothelial cells into the peritoneal cavity also is effective in decreasing adhesion formation (72,73) and in remodeling the area of mesothelial denudation. More recently, mesothelial cells were used as transplantable tissue-engineered artificial peritoneum and research is focusing on the use of mesothelial progenitor cells (74).

**Adhesion Prevention in Humans**

Adhesion prevention in humans has been limited to barri- ers and flotation agents with a reduction of adhesion forma- tion that ranges, for all products, between 40% and 50%. Most important is that for none of these products efficacy has been proven for endpoints that really matter, i.e., pain, infertility, bowel obstruction, or reoperation rates. We should also realize that large randomized controlled trials were needed because of the high intradividual variability and that in these trials the surgical interventions were limited to rather simple and straightforward interventions as cystectomy and myomec- tomy. In addition, these trials have been performed during interventions performed by laparotomy or by laparoscopy under conditions of CO2 pneumoperitoneum—enhanced adhe- sion formation and slight desiccation. It, therefore, is still unclear to what extend the available results of efficacy can be extrapolated to more severe or other types of surgery, and whether in the human the effect will be additive to good surgical practice and conditioning of the peritoneal cavity (46).

Sheet barriers such as Sepafilm (hyaluronic acid- carboxymethylcellulose) (75–77), Intereced (oxidized regener- ated cellulose), (78,79) and Gore-Tex (expanded polytetrafluoro- ethylene) (80) are proven effective but did not become very popular for various reasons. Sepafilm is difficult to use dur- ing laparoscopy. Intereced requires the removal of any remain- ing bleeding to be efficacious, whereas Gore-Tex, being non- degradable, must be removed from the applied site during a second surgery.

Since Intergel (0.5% ferric hyaluronate gel) has been withdrawn from the market, only Hyalobarrier gel (auto-cross- linked hyaluronic acid gel (81)), Spraygel (polyethylene gly- col), and Intercoat/Oxiplex (82,83) remain available for clin- ical use. Overall efficacy appears to be similar for all three products. A comparison between these three gels can unfortu- nately not be made since comparative trials do not exist. Also the strength of the available evidence varies and a Cochrane review of hyaluronic acid and Spraygel concluded that only for hyaluronic acid the evidence was solid (84).

While in humans the efficacy of Ringers lactate as a floata- tion agent has not been proven, Adpekt (Icodextrin) (85–87), a macromolecular sugar with a higher retention time in the peritoneal cavity, was expected and shown to be efficacious in adhesion reduction. A major advantage is the traditional absence of side effects, which were well established since this has been extensively used for peritoneal dialysis. The strength of the available evidence demonstrating efficacy was in a Cochrane review not considered very solid (84).

Strong arguments can be found in the literature to use LHRR agonist prior to surgery as adhesion prevention (88), but specific clinical trials are lacking.

**DISCUSSION AND A LOOK INTO THE FUTURE**

The concept of mesothelial cells as stem cells, which can be transplanted to peritoneal trauma areas to modulate repair and decrease adhesion formation in animal models, is actu- ally stimulating research aimed at collecting large amounts of autologous mesothelial stem cells and at manipulating them in culture prior to transplantation. Simultaneously, the addi- tion to the peritoneal fluid of factors known to stimulate res- ident mesothelial proliferation or mobilization or differentia- tion are investigated in order to decrease adhesion formation (89). Both the activation and multiplication of mesothelial cells is expected to be developed into new strategies to reduce post- operative adhesion formation (24,90,91). Also, the potential of using mesothelial stem cells derived from muscle is actively been investigated (92).

Immense progress has been made over the last 15 years in our understanding of the pathophysiology of adhesion for- mation and the mechanisms behind it. A major advance is the traditional concept viewing adhesion formation as a local inflammation with fibrin deposition and removal, the peritoneal cavity has been demonstrated to have an important role. Hence good surgical practice, gentle tissue handling, prevention of desic- cation, hypoxia and ROS production, and conditioning of the peritoneal cavity by cooling have become the first key aspects in prevention of adhesion formation. Since the mechanisms by which the peritoneal cavity influences adhesion formation remains unexplored we may reasonably expect that in the near future we will be able to decrease adhesion formation even further.

Inhibition of fibroblast proliferation obviously is an objective in adhesion prevention. The use of dexamethasone to reduce adhesion formation has been around since a long time but the efficacy has been debated and questioned. In our laparoscopic mouse model especially under conditions of minimal trauma to the peritoneal cavity the effectiveness was very pronounced. This was surprising, since other anti- inflammatory agents such as COX1 and COX2 inhibitors were not effective. Therefore, dexamethasone is suggested to be effective, and that not because it is an anti-inflammatory agent but because it inhibits mesothelial proliferation. This is also consistent with the observations that dexametha- sone reduces cell proliferation, collagen deposition, and lung fibrosis (93). The hormonal factors modulating fibroblast prolif- eration are being extensively investigated and hepatocyte- derived growth factor (HGF) has been demonstrated to pre- vent peritoneal fibrosis. (94,95). That HGF is also effective in reducing adhesion formation was demonstrated by “painting” with adenovirus containing the HGF gene directly onto sur- face of the injured area (96).

Since we understand that during adhesion formation different mechanisms are sequentially involved, adhesion prevention strategies should aim no longer at only one
mechanism but consider sequentially all different mechanisms. By doing so, we can decrease adhesion formation by more than 90% in animal models. Prevention of adhesions will start with good surgical practice, conditioning of the peritoneal cavity through cooling, and prevention of desiccation and of hypoxia by adding 3% to 4% of oxygen. This will reduce adhesion formation by over 50%. If all the last strategies are associated with products as ROS scavengers and desmethylsone, adhesion formation in mice drops by an additional 30% this means to an 80% to 85% of total adhesion reduction. If at the end of surgery, barriers are added, which by themselves are more than 50% effective, the cumulative adhesion formation reduction has been proven today to be more than 90%. Since the mechanisms through which the following products decrease adhesion formation are different from those listed before, we may expect that the effects will be additive. Indeed, effectiveness between 30% and 40% was demonstrated for phospholipids and calcium channel blockers, whereas drugs preventing angiogenesis, by blocking Flk1 of VEGF, are even more effective. This has not been demonstrated yet since in models in which adhesion formation is already reduced by more than 90%, it becomes statistically difficult to prove additional effects. In conclusion, it seems reasonable to expect virtually adhesion-free surgery in not too distant future.

**SUMMARY**

We have been aware for a long time that adhesions occur almost systematically in at least over 80% of women undergoing abdominal surgery. The widely held belief has been that adhesion formation increases with the severity of surgery and with infection but that this could largely be prevented by good quality surgery. Thus, postoperative adhesion formation has for many years been emotionally ignored by the “good surgeons.” Only in the last decade, we have become aware of the clinical importance of adhesion formation, mainly though the SCAR studies, which have clearly demonstrated that the incidences of bowel obstruction and of reoperation due to postoperative adhesions keep increasing linearly for at least 10 years and are much higher than anticipated. That postoperative adhesions can cause infertility and pain is well known, although quantitative data are missing.

Adhesions formation between traumatized areas has traditionally been considered as a local process, i.e., an inflammatory reaction, exudation, and fibrin deposition followed by fibroblast proliferation together with angiogenesis. In the last decade, we have become aware of the importance of the peritoneal cavity in the healing process. The concept emphasizing the importance of the peritoneal cavity affects adhesion formation. Although today the focus is on prevention of deleterious factors, we must also focus on increasing favorable factors and recognize the importance of peritoneal stem cells in the repair process.

**ACKNOWLEDGMENTS**

PRK wishes to thank his current collaborators, Jasper Verguts, Carlo De Cicco, Ron Schornan, Roberta Corona, and Adriana Bastidas, and his past collaborators, Jose Ordonez, Narter Yesidaglar, Osama Elkelani, Ospan Mynbaev, and Karina Mailova, for contributing actively to the concepts described. The authors also thank Marleen Craessaerts and Diane Wolput for their help.

**REFERENCES**

16 RECONSTRUCTIVE AND REPRODUCTIVE SURGERY IN GYNECOLOGY


10. Lower AM, Hawthorn RJ, Ellis H, et al. The impact of adhesions on hospital readmissions over ten years after 8949 open gynaeco-


13. Practice Committee of the American Society for Reproductive Medicine. Society of Reproductive Surgeons. Pathogenesis, con-
sequences, and control of peritoneal adhesions in gynecologic sur-


18. Mynbaev Chapuli R, Perez-Pomares JM, Macias D, et al. Different-


21. Mutsaers SE, Prele CM, Lansley SM, et al. The origin of regen-


30. Koninckx PR, Ritiotton L, Seppala M, et al. CA-125 and placent-


38. Obnudovic MM, Stojimirovic BB, Tripinac DP, et al. Ultrastruc-


42. Herrick SE, Mutsaers SE, Ozau P, et al. Human peritoneal adhe-


44. Sulaiana H, Gabela G, Davis MC, et al. Presence and distribu-

45. Birda MM, Molinas CR, Bastidas A, et al. Efficacy of barriers and hypoxia-inducible factor inhibitors to prevent CO2 pneumoperitoneum-enhanced adhesions in a laparo-


49. Mynbaev OA, Koninckx PR, Bracke M. A possible mechanism of peritoneal pH changes during carbon dioxide pneumop-

50. Elkelani OA, Molinas CR, Mynbaev O, et al. Prevention of adhe-


53. Molinas CR, Tjea M, Vanacker B, et al. Role of CO2 pneumo-

54. Molinas CR, Birda MM, Carminetti P, et al. Role of vascular endothelial growth factor receptor 1 in basal adhesion formation and in carbon dioxide pneumoperitoneum-enhanced adhesion...


87. Schindler AE. Gonadotropin-releasing hormone agonists for use in contraception and the related anoxemia as a cofactor in adhesion formation. In: Combined Meeting of the International Congress on Peritoneal Repair and Adhesions (PAX, Fifth Meeting) and International Mesothelioma Interest Group (IMIG, Fifth Meeting). October 5–8, 1999; Stoke Rochford, Grantham, Lincolnshire, UK.


89. Schindler AE. Gonadotropin-releasing hormone agonists for use in contraception and the related anoxemia as a cofactor in adhesion formation. In: Combined Meeting of the International Congress on Peritoneal Repair and Adhesions (PAX, Fifth Meeting) and International Mesothelioma Interest Group (IMIG, Fifth Meeting). October 5–8, 1999; Stoke Rochford, Grantham, Lincolnshire, UK.


