From:	Holste, Dr. Joerg [ETHDE]
To:	Engel, Dr. Dieter [ETHDE]; Manley, Quentin [ETHUS]; Storch, Mark L. [ETHUS]
CC:	Batke, Boris [ETHDE]; Hellhammer, Dr. Brigitte [ETHDE]; Koehler, Petra [ETHDE]; Barbolt, Thomas [ETHUS]
Sent:	3/13/2006 9:39:30 AM
Subject:	AW: Mesh and Tissue Contraction in Animal
Attachments:	PPM_REV_0105094.pdf; PPM_REV_0105095.pdf

Quentin,

this was our scientific statement on mesh shrinkage:

Basically small pores, heavy weight meshes induce more fibrotic, bridging tissue reaction causing more mesh shrinkage during maturing of the collagenous tissue. See my presentation about biocompatibility.

Best regards,

Joerg

Dr.Joerg L.Holste

Research Fellow
Preclinical Safety Evaluation
Corporate Product Characterization
ETHICON R&D EUROPE
Phone: +49-40-5297-5248
Mobile: +49-(0)172-4525754
Fax: +49-40-5297-5761
e-mail: DHOLSTE@ETHDE.JNJ.COM

-----UrsprÃ¼ngliche Nachricht-----
Von: Engel, Dr. Dieter [ETHDE]
Gesendet: Montag, 13. MÃ¤rz 2006 09:11
An: Manley, Quentin [ETHUS]
Cc: Holste, Dr. Joerg [ETHDE]
Betreff: AW: Mesh and Tissue Contraction in Animal

Dear Quentin,

there are numerous articles published on shrinkage and we have also done some work internally. Joerg Holste is the most knowledgable person in that question. Joerg, can you answer Quentin?

Regards
Dieter

-----UrsprÃ¼ngliche Nachricht-----
Von: Manley, Quentin [ETHUS]
Gesendet: Dienstag, 7. MÃ¤rz 2006 00:50
An: Engel, Dr. Dieter [ETHDE]
Betreff: FW: Mesh and Tissue Contraction in Animal

Dear Dieter,

Plaintiff's Exhibit
PX 71

Could you pass this on to the person on your team who might best answer my question:

In this study by Ramshaw, polyesther mess contracted less than PP, maybe due to larger pore sizes: What other work has been done in this field and how does it point us in the direction of designing mesh for lower contraction? Is Ramshaw right in supposing that lower contraction is caused by higher tissue ingrowth? It does not seem obvious to me - they may be correlated as he has shown but it need not be causal. Am I mistaken in this assumption?

Thanks for helping me to learn.

Q

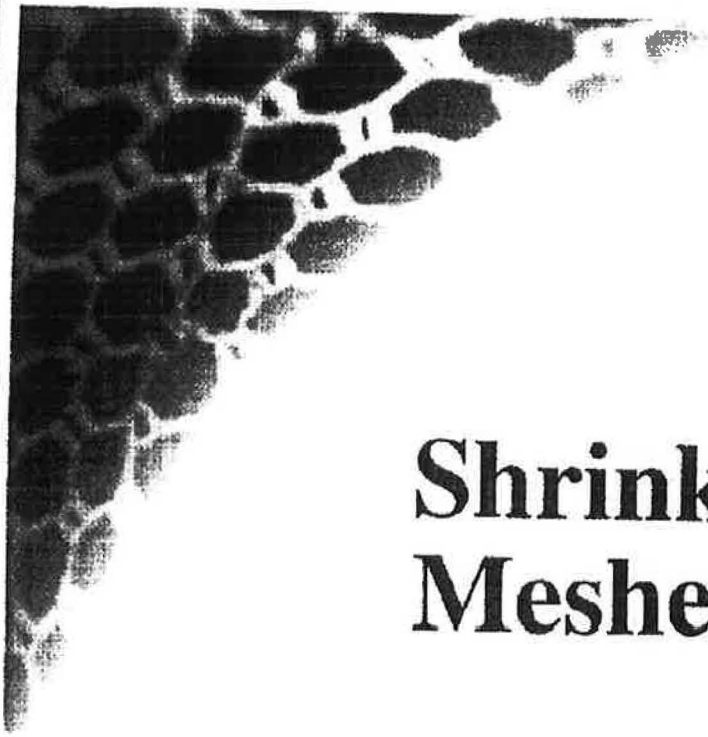
-----Original Message-----
From: Gosiewska, Anna [ETHUS]
Sent: Wednesday, March 01, 2006 10:25 PM
To: Manley, Quentin [ETHUS]
Cc: Dhanaraj, Sridevi [ETHUS]
Subject: Mesh and Tissue Contraction in Animal

Quentin,

I have attached below for your review a very interesting publication from Dr. Ramshaw's lab, in case you have not seen it yet. The swine model described in this paper might be very useful to us for testing prototype scaffolds for hernia repair.

Just to let you know that Sridevi and I have connected, and we will be working together on the tissue fascia repair project.

<< Datei: Hernia Contraction Ramshaw.pdf >>
Kind regards,
Anna



26205

Shrinking Meshes?

Scientific Statement
ETHICON GmbH
Research & Development Europe

Dr. med. B. Hellhammer
Dr. med. P. Köhler
Dr. med. vet. J. Holste

Ethicon Products
WORLDWIDE

Shrinking Meshes?

Alloplastic meshes of man-made materials can no longer be ignored in hernia surgery. The use of non-absorbable meshes has been able to drastically lower the rate of recurrence of incisional and of recurring inguinal hernia, and in most cases restoration of the abdominal wall function and the corresponding physiological tension-bearing capacity are possible (book extract 1).

For decades, meshes of mainly polypropylene (Marlex®, Prolene®) and polyester (Mersilene®) have been used for hernia repair.

The task of the mesh is the permanent reinforcement of the abdominal wall in order to prevent a hernia from occurring or recurring. The stability of the mesh must be matched to the physiological forces that are exerted on the abdominal wall under maximum strain (20923, 19514).

As far as stability and elasticity are concerned, the heavyweight polyester and polypropylene meshes currently on the market are overdimensioned or not flexible enough for their intended use.

As also described by the team of Prof. Schumpelick in Aachen, the amount and structure of the implanted material is critical for the frequency and intensity of local wound complications and the extent of scar formation, which can be as severe as adverse abdominal covering stiffness (23429).

Against the background of these hitherto over-dimensioned meshes, a large pore size, lightweight polypropylene mesh for the care of incisional hernias, called VYPRO® mesh, was therefore developed. This mesh comprises approximately equal amounts of non-absorbable polypropylene (Prolene®) and absorbable polyglactine (Vicryl®). Following absorption of the polyglactine fraction, markedly less material remains permanently in the body than before (< 30 % in comparison to Marlex®).

In addition, the non-absorbable framework for the first time shows an elasticity adapted to the abdominal wall. The considerably enlarged pores of 3–5 mm do not just increase the elasticity but also, as a result of the comparatively large foreign-body-free zones, reduce the unavoidable connective tissue foreign body reaction.

In order to optimise its handling properties in hernia repairs using the laparoscopic technique and the Lichtenstein technique, the VYPRO® mesh was strengthened in a diamond shape with additional absorbable polyglactine filaments and non-absorbable polypropylene filaments. This was called the VYPRO® II mesh.

Experiments on the tissue integration of both VYPRO® and VYPRO® II mesh show that, as a result of its coarse mesh construction and the elasticity similar to the abdominal wall, this implant is integrated into the abdominal wall largely without problems. The initially modest foreign body reaction is caused by absorption of the polyglactine fraction and is thus transient, and after 90 days persists only in a very weak form. A tension-bearing three dimensional collagen mesh forms, and as a result excessive connective tissue formation and disturbed scarring do not occur.

It is known that in physiological wound healing, wound contraction with an approximately 50 to 99 % reduction in area occurs as a result of collagen maturation and the contraction forces of the myofibroblasts. This effect is greater with the more mobile and flexible tissues. In addition to the early contraction between days 3 and 5 and to the following secondary phase from day 4 to day 20, further contraction may then still occur by collagen maturation within the scar. The initial cellular and vascular abundance of the connective tissue decreases over time, and at the same time the newly formed collagen fibrils mature to fully developed collagen fibres, which redeploy and align according to their functional demands (book extract 2).

During incorporation of the mesh into the tissue, the physiological wound contraction is accompanied by a reduction in the implant area. This reduction depends on the amount of implanted foreign material and the resulting inflammatory activity caused. In a comparative experimental study on dogs, Klinge et al. (22422) implanted a single-thread heavyweight polypropylene mesh (Marlex®) and a multi-thread reduced polypropylene mesh combined with polyglactine 910 (VYPRO®). After 4 weeks, the mesh size had reduced to 54 % of the initial area in the Marlex® group and to 66 % of the initial area in the VYPRO® group. Large pore size meshes tend to less fold formation and show a better biocompatibility.

As part of revision operations after mesh implantation, a total of 17 non-absorbable meshes were explanted at the Surgical University Clinic of the RWTH Aachen. Here also, area reductions of up to 40 % of the original size were observed (22427).

Similar compression rates of 30–50 % are observed even with PTFE not integrated into the tissue (unpublished data, Klinge, RWTH Aachen, 2000).

In our own experiments on hybrid pigs, prototypes of the VYPRO® II mesh were implanted and then measured after removal of the implant 90 days post-op. The remaining mesh area with VYPRO® II was on average 70 %. This reduction in implant area

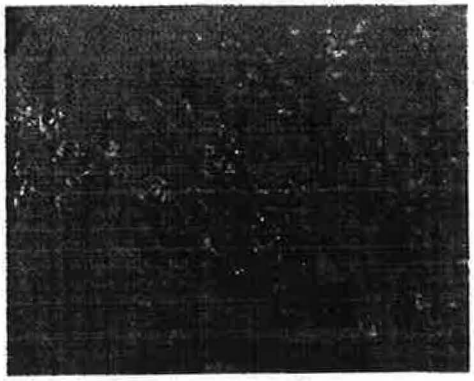
of 30% is comparable to that achieved with VYPRO®, as described by Klinge et al. (22422). The reduction is markedly less than with the heavyweight polypropylene meshes, which were reported to be of the order of 40% by Amid (21357) and the Prof. Schumpelick's team in Aachen (22422, book extract 1).

In a comparative investigation on rats, VYPRO® II mesh and a polypropylene mesh were implanted. After 28 and 56 days, the remaining mesh area was determined by outline measurement in situ before removal. The remaining areas were found to be 96% for the VYPRO® II mesh and 84% for the heavyweight polypropylene mesh.

The experiments on the tissue integration of the VYPRO® II mesh show that, as a result of its coarse-mesh construction and its elasticity being similar to that of the abdominal wall, this implant is incorporated into the abdominal wall with very little foreign body reaction. It grows a tension-bearing three dimensional collagen mesh, whilst excessive connective tissue formation and interfering scar formation do not occur.

Consequentially, the compression of the VYPRO® II mesh due to physiological wound contraction is tolerated markedly better, and in particular occurs without folds developing. This is in contrast with the heavy duty polypropylene meshes with which pronounced crumpling with the formation of sharp edges due to the mesh structure is observed (book extract 1).

Heavyweight PP mesh, 90 days post-implantation.
Fold development (implantation study TEP pigs).



Lightweight VYPRO® II mesh, 90 days post implantation.
Fold free incorporation (implantation study TEP pigs).

In summary, we can say that:

Mesh implants do not actively shrink, they are passively compressed (21357)!

As part of wound healing and the associated wound contraction, there is a reduction in the area of the implanted mesh. This reduction in area is a passive process and occurs only to the extent to which the tissue contracts. This phenomenon has been known for a long time and is already reported in surgical textbooks (book extract 1). One consequence of this is that with all meshes (21132) it should always be ensured that the mesh is an adequate size and a suitable shape for the anatomical conditions to ensure sufficient defect coverage even after the aforementioned physiological processes and thus to prevent a recurrence.

Dr. med. Brigitte Hellhammer
Dr. med. Petra Köhler
Dr. med. vet. Jörg Holste

ETHICON GmbH
Research & Development Europe

Literature:

23429

Minimierte Polypropylen-Netze zur praeperitonealen Netzplastik (PNP) der Narbenhernie.
Eine prospektive randomisierte klinische Studie

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Classification of Biomaterials and their related Complications in Abdominal Wall Hernia Surgery

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Book extract 1

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Ethicon Products
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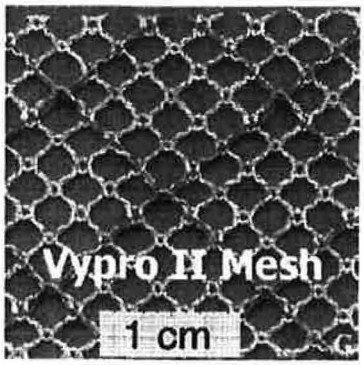
ETHICON Limited, PO Box 408, Bankhead Avenue, Edinburgh EH11 4HB, United Kingdom

Biocompatibility of Meshes

Small Pores and Standard Weight Mesh PROLENE

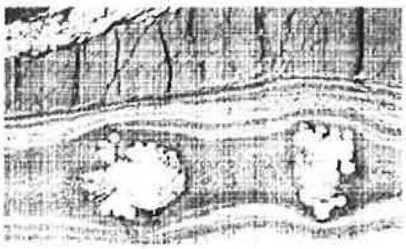
Large Pores and Leight Weight Meshes VYPRO



December 01

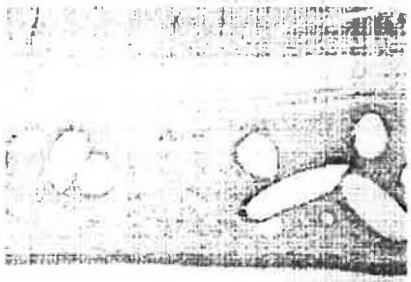
Dr.J.Holste R&D EUROPE
ETHICON GmbH Germany

Biocompatibility of Meshes

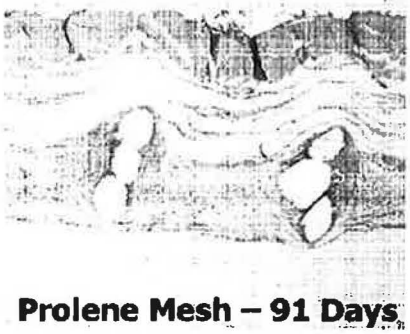


VYPRO Mesh - 7 Days

VYPRO Mesh - 91 Days



Prolene Mesh – 7 Days



Prolene Mesh – 91 Days

Biocompatibility of Meshes

Biocompatibility of Polypropylene Mesh

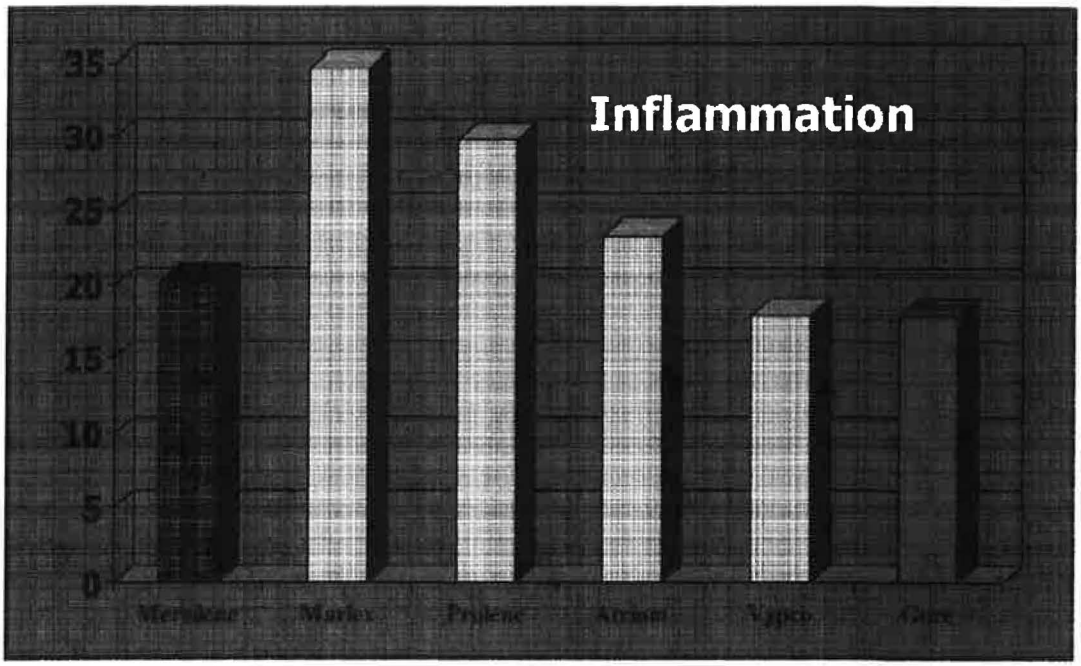
- Generally Mild Inflammatory Reaction
- Qualitative Differences to Mesh Construction
- All Constructions are Biocompatible

Biocompatibility of Meshes

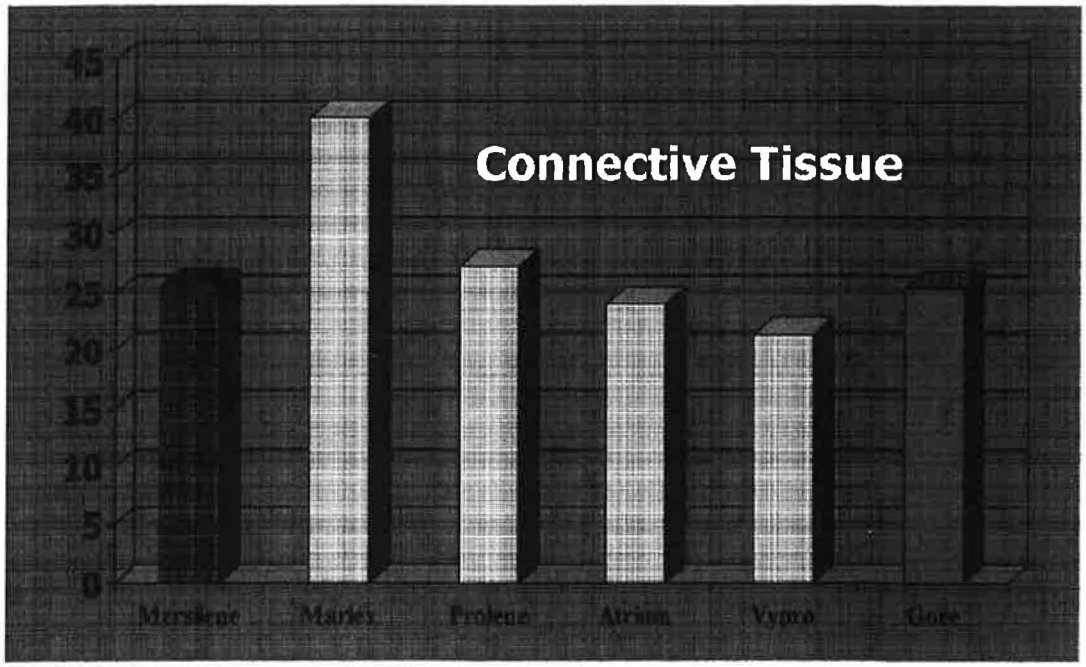
Tissue Reaction:

Chronic inflammatory process with increased cell turnover and connective tissue formation depending on the textile construction and physico-chemical properties of the meshes

Biocompatibility of Meshes



Biocompatibility of Meshes



Biocompatibility of Meshes

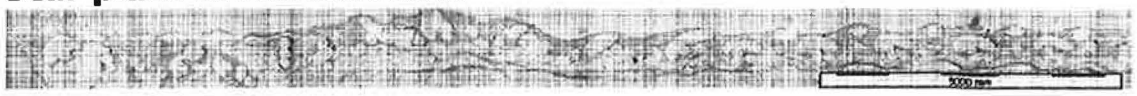
Fibrosis and Scar Formation

Mild Fibrosis in Vypro Mesh

Pore size:

Vypro = 5000 µm

Scar plate in Marlex Mesh



Marlex = 600 µm

Mild Fibrosis in Vypro II Mesh

Vypro II= 2000 µm