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LETTERS TO THE EDITOR

Sir,

The bone growth chamber recently developed by Albrektsson et al. (1982) seems to be well suited for quantifying newly formed bone in cortical bone implants. Although expected, bone ingrowth into the marrow spaces was, however, absent. This is not surprising, as there was only small contact with the surrounding natural bone.

However, in our view, the newly developed chamber does not qualify as a model for testing the Fibrin Adhesive System (FAS) for its osteogenic potential, because the FAS comes to lie in a titanium tube which rules out biological degradation. Unless fibrin undergoes degradation by tissue plasminogen activators and cellular components like polymorphonuclear neutrophils (PMNs) and macrophages, it may persist locally for days and even weeks, forming a barrier to natural tissue ingrowth. We established the negative effects of too much fibrin on wound healing by implanting plastic rings into the dorsal fascia of rats.

The fibrin clots which were completely enclosed by the plastic rings prevented the ingrowth of granulation tissue.

The role of FAS in terms of supporting wound healing and enhancing the osteogenic potential lies in its stimulating action on the fibroblast system as precursor of cells with an osteogenic potential. But fibrin will only stimulate this system if it is applied as a thin film and is allowed to undergo physiological degradation.

Pflüger et al. (1979) showed ingrowth of newly formed bone to occur in porous cylindrical stainless steel implants with a porosity of > 100 µm. Of all the models published for evaluating the osteogenic potential of FAS, these implants, which have pores of different lengths and sizes, appear to come closest to the B.G.Ch. Using this model, implants treated with FAS were found to resist much higher pull-out forces than those of a control group without FAS (2.43 p versus 1.40 p). Fluorochrome labeling showed endosteal bone formation up to the rough cylinder surface at 1 week in FAS-treated implants, with resultant partial skeletal attachment of implants and resistance to higher pull-out forces.

In addition, polychrome labeling demonstrated osteoblastic activity in pores with FAS. However, the bore was larger in this model than the implant so that the FAS layer was interposed between the implant and metaphyseal bone, thus being exposed to natural degradation by the ingrowth of vessels and cellular elements. Local tissue plasminogen activators appear to be of secondary importance, unless they are transported to the site of the implant by periosteal capillary ingrowth. We applied low-dose antifibrinolytics (aprotinin, 500 KIU/ml of fibrin sealant) in bone in an attempt to prevent a further delay of fibrinolysis. But we found PMNs to play a major role in fibrin degradation in bone. This was also seen and aptly described as a strong inflammatory reaction by Albrektsson et al. (1982), to whom our comments are addressed. However, this inflammatory reaction is not due to infection. It rather reflects the natural response of the organism to exogenous fibrin, which undergoes cellular degradation.

The group A implants were consistently found to contain newly formed bone. This is easily explained by the species used, i.e. rabbits. Rabbits have a largely primary bone structure (Eitel et al. 1981) which is mainly supplied by the periosteal vascular network.

According to Albrektsson et al. (1982), there was no significant difference between the FAS and the control groups in terms of the amount of bone ingrowth in the cortical (proximal) canal, but "a tendency towards more bone ingrowth in the control group".

We feel that, in an experimental study, any method should be assessed on the basis of statistical significances.

Another aspect of the study which merits a comment is that, in the control group, the implant canals were filled with blood and medullary cells.

Obviously, this creates ideal conditions for new bone formation, because it provides for the local presence of cells involved in fibrin degradation (PMNs, macrophages) and for free spaces in the canal system. Fibroblast and capillary ingrowth is thus substantially facilitated. In contrast, by filling the canals with FAS barriers are produced.

It is well accepted that certain medullary cells are capable of differentiating to osteoblasts. New bone is known to be formed when red marrow is grafted to the anterior chamber of the eye (Simmons 1980). Burwell (1969) showed in rabbits that the osteogenic potential of bone bank material can be maximized by impregnation with autologous marrow. This would suggest that Albrektsson's control group is, in fact, no real control group.

All this goes to show that Albrektsson's chamber is not a model which is well suited testing, or establishing, the osteogenic potential of FAS, quite aside from the fact that an osteogenic potential of FAS was described in numerous experimental and clinical studies.

The FAS system appears to develop its action on the osteogenic potential in the early phase of bone healing, as was shown by Böhler et al. (1977) who found bone deposition and transformation to be significantly increased on osteography. This appears to suggest accelerated callus formation. Mineralization processes proper are, however, not affected by FAS.

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Sir,

Schlag & Redl regard our bone growth chamber method to be well suited for quantifying newly formed bone in an implant. However, the negative results we experienced when evaluating FAS in the bone healing situation could according to Schlag & Redl be explained by:

(1) The use of rabbits with "largely primary bone structure" which Schlag & Redl believe is the reason for the good bone ingrowth in our controls;
(2) Biological degradation of FAS did not occur;
(3) The dose of FAS was too large in our experiment;
(4) The use of medullary cells in our control group was not adequate.

We will first respond to these questions, then (5) try to analyse the implant paper by Pflüger et al. (1979) already discussed by us in our article and by Schlag & Redl, and finally, (6) make some comments on the quantifying methods in many publications about FAS and its said stimulatory effects on bone formation.

1. Our chamber has been applied in experimental studies in rabbits and dogs (Hallén et al. 1976) with equally good results in form of bone ingrowth. Furthermore, as mentioned in our article this chamber is a methodology that has been

evaluated clinically (Tjellström et al. 1978a, b) with a demonstrated good bone ingrowth in the tibia of adult man. In the clinical as well as in the experimental use of the BGC, more bone has been found to invade the chamber canal placed in the cortical bone compared to the canal of the marrow space. However, there is not an absence of bone in the marrow-located canal, as wrongly stated by Schlag & Redl.

2. We do not understand why a biological degradation of the FAS could not take place in our chamber. The plastic ring experiment, briefly described by Schlag & Redl is without a reference and to our knowledge not published. Therefore, we cannot evaluate the relevance of this research with respect to our bone chamber model.

3. The relevant dosage of FAS is not clear. In the literature, including the paper by Böhler et al. (1977) where Schlag is a co-author, there is very little, if any, recommendation for the proper dose of FAS. Avoiding "too much fibrin" or recommending "a small amount of fibrin" cannot be regarded as very precise recommendations as to the correct dose. However, in the light of experimental data by Zilch (1981), not available to us when we designed our experiment, the dose after all seems to be an important question and we feel the need of further experimental data to define the accurate dose of FAS.

4. In our paper we compared bone formation in FAS-environment with that of an environment with blood and medullary cells. The choice of a medullary cell control group was thoroughly described in our paper and no-one who read our contribution could be in any doubt as to our knowledge of blood and medullary cells as potential bone stimulators. In essence, we regard artificial, foreign FAS-treatment to be interesting to the orthopaedic surgeon only if FAS could be demonstrated to be a more effective bone stimulator than are autologous, easily accessible blood and medullary cells. The addition of blood and medullary cells as in our control group is, furthermore, providing a controlled experimental situation as "empty" controls may accidentally become impregnated with blood and medullary cells in the bone site thereby causing an inconsistency in the state of the control group.

5. Schlag & Redl claim the study by Pflüger et al. (1979), finding pull-out forces of FAS-treated metaphysary bone implants of 2425 p whereas pull-out forces of control implants were 1931 p, to present strong evidence for the bone stimulating effects of FAS. If they could be statistically verified, we agree that the experimental results presented by Pflüger et al. would indicate a more rapid bone anchorage with than without FAS when stainless steel implants are inserted in oversized ($\cong$ 10 per cent) holes. However, the paper by Pflüger et al. (1979) presents no evidence that FAS is to be recommended when implants are inserted in fitting defects which, of course, is the clinically interesting question. Furthermore, after excluding some animals for various reasons, it seems that Pflüger et al. (1979) have been comparing the pull-out forces in 4 or 5 animals where the implants were treated with FAS with the pull-out forces in 5 or 6 other animals where the implants were not treated with FAS. Knowing the great variability in bone forming capacity in different rabbits, Pflüger et al. would have had to use a considerably larger number of rabbits to compensate for this uncertainty if a statistical evaluation of their material is to be allowed. Also, the pull-out forces for the implants inserted in the diaphysary bone were 760 p in the FAS group and 850 p in the control group (Pflüger et al. 1979); this was not mentioned by Schlag & Redl but was probably the reason why Pflüger et al. (1979) themselves, quite correctly, only claimed that the use of FAS seemed to be advantageous for bone anchorage. They did not attempt to perform a statistical evaluation of their material.

6. Schlag & Redl are critical of the fact that we did not perform a statistical evaluation of the outcome of our experiment. We indicated some reasons for not treating the material statistically. However, if a statistical evaluation comparing the bone formation on the FAS-side with that of the medullary side is actually performed, we find a statistically significant ($P < 0.01$) lesser bone formation in the FAS-group. Examining the papers claiming the effectiveness of FAS-treatment on bone healing (Böhler et al. 1977, Bösch et al. 1977a, b, 1979, 1980, Passl et al. 1979, Pflüger et al. 1979, Neckel & Schergus 1982) we find only one, the paper by Böhler et al. (1977),

which was truly quantified and evaluated by statistical methods. The remaining publications are only qualitative or semiquantitative and would, looking through the same critical eyes as those of Schlag & Redl, present meagre evidence of any bone stimulating effect of FAS. In a recently published and statistically evaluated study by Zilch & Noffke (1981) no significant influence of FAS on bone healing was demonstrated.

To summarize, at present we fail to recognize any real and valid indication for FAS-treatment of bone injuries. This is not a contraindication for further experimental investigations with FAS, but only when more conclusive experimental data have been presented would we recommend the clinical use of FAS for bone stimulation.

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