# Fracture healing: Fracture Healing Understood as the Result of a Fascinating Cascade of Physical and Biological Interactions. Part II

## Hojení zlomenin: kostni hojení jako výsledek fascinující kaskády fyzikálních a biologických interakcí. Část II

**S. M. PERREN**

AO Research Institute Davos, Switzerland

**SUMMARY**

Based on our own observations an explanation of the different factors influencing bone reaction is proposed. Special attention is given to the aspect of tissue deformation (strain). We propose thinking in terms of strain rather than of instability when contemplating tissue reaction. Considering the observed bone behavior should help improving the treatment of fractures and their complications

## THE "DARK SIDE" OF IMPLANT CONTACT

### a) Contact necrosis

The following documentation shows the effect of implant contact on blood supply

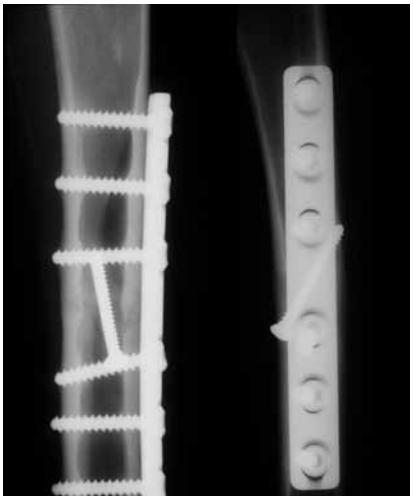


*Fig. 28. DCPlate with snug contact between the plate undersurface and bone. (Courtesy S. Tepic). See Fig. 29.*

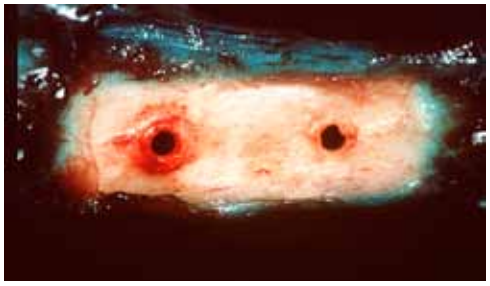


*Fig. 29. Transparent plate demonstrating the contact damage to blood supply by a snugly fitting plate. (Courtesy of U. Lüthi).*

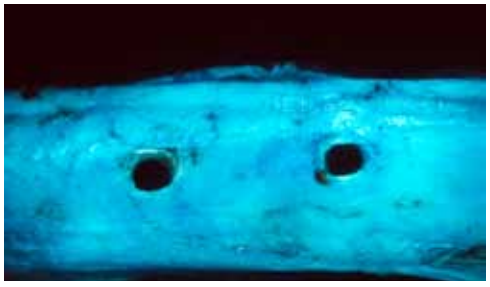


*Fig. 30. Blood supply to bone visualized using disulfine blue. The elevated plate allows for undisturbed blood supply.*

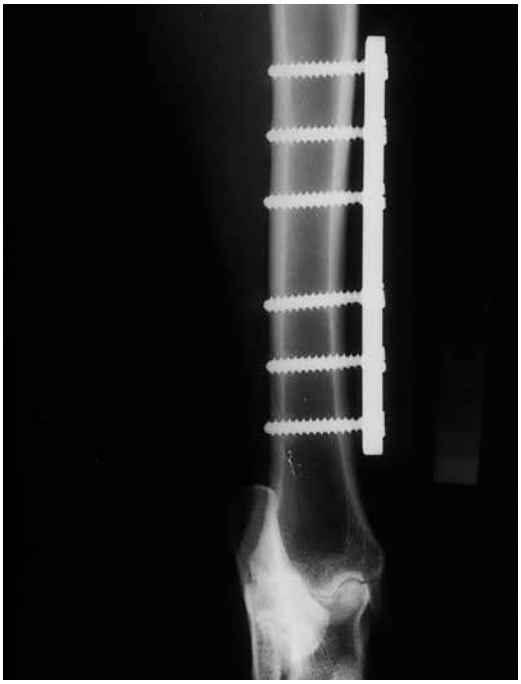


*Fig. 31. Elevated plate. Stable elevation is enabled by the use of locked screws.*

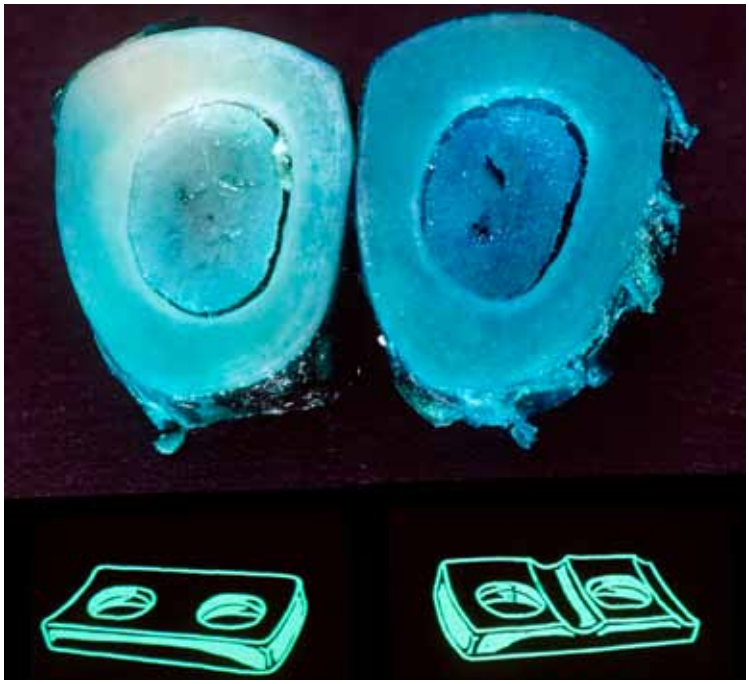
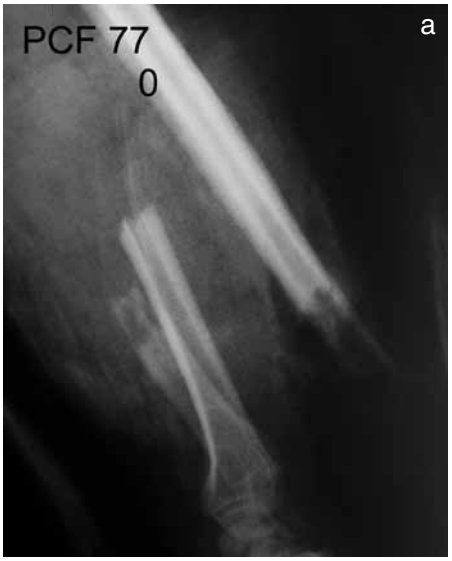


*Fig. 32. Cross sections demonstrating the internal blood supply: left: snugly fitting plate (Fig. 28) right elevated plate (Fig. 31) no damage to the blood supply.*



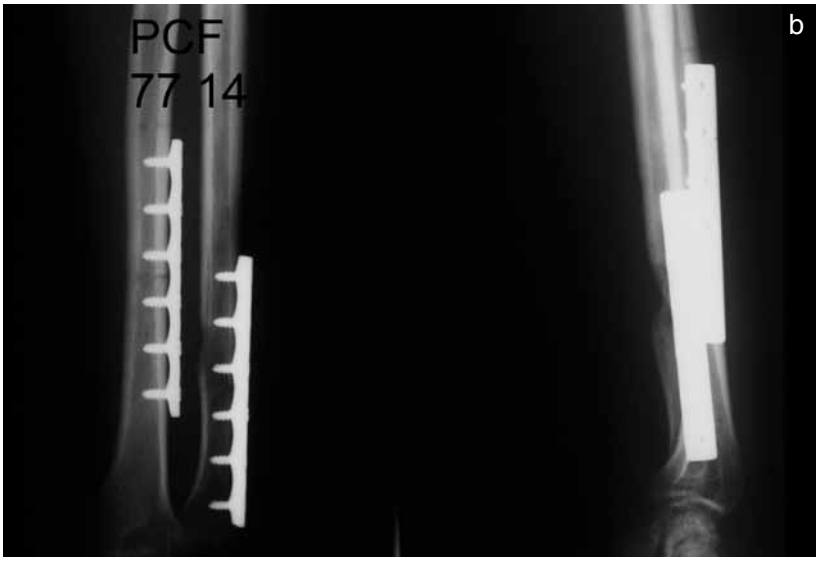




*Fig. 33. The PCFix is a classic example of an internal fixator brought to successful clinical testing (12). The screws are locked within the c.p. titanium plate. Early and solid healing in a compound forearm fracture. The PCFix with its advanced concept was not made available commercially. Later, the principle of locking screws was integrated into the LCP in combination with the conventional DCP construct (LC--DCP).*

*Fig. 34. Internal remodeling after nailing. Same process here shown as the front of remodeling and the advance of the porous zone towards the implant; but with the nail it is a centripetal movement. When this remodeling intensifies due to infection, for example, a ring sequester may form see Fig. 46.*

## Producing stress risers leading to refracture

For instance, a plate that snugly contacts the outer bone surface at the fracture site produces an avascular and, consequently, a necrotic zone of bone immediately deep to the plate contact (Figs 28 & 29).

The impaired or absent blood supply does not allow or retard the internal remodeling of the fracture site at this place. It produces what is called in technical terms a stress riser. When the plate is removed such a stress riser may give rise to a refracture (Fig. 35–Fig. 39 Courtesy of S. Kessler)

## Preventing stress risers

Implant contact may be avoided by using undercut plate undersurfaces or by elevating the plate from the bone as is achieved by the use of locked screws. Using such technology (17) it was shown that strong healing can be achieved within ten weeks while conventional contact plates cannot be safely removed until at least two years after implantation.

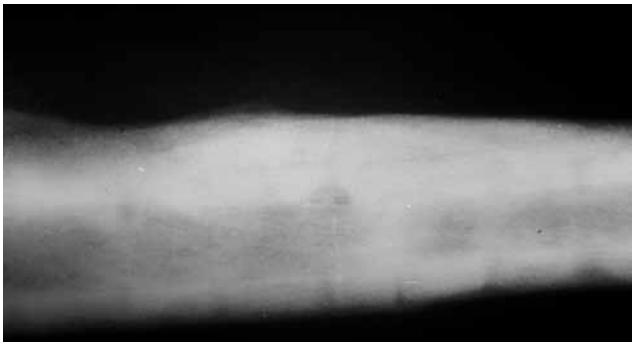


*Fig. 35. Situation months after removal of a plate. The small arrows indicate the position of the removed screws, the larger arrow indicates the lack of healing immediately deep to a snugly fitting plate (stress riser).*

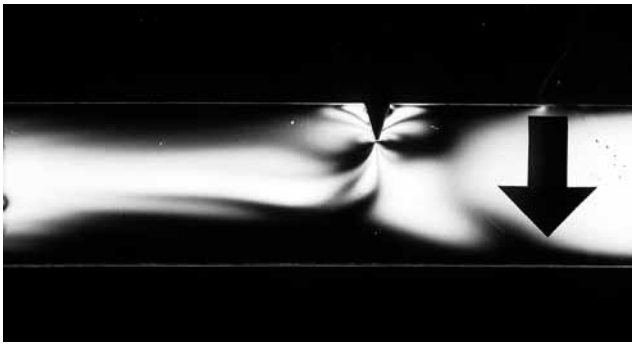


*Fig. 36. The effect of a stress riser in photo-elastic display. Strong concentration of stress/strain near the notch as a result of lack of healing in an area that is without blood supply.*

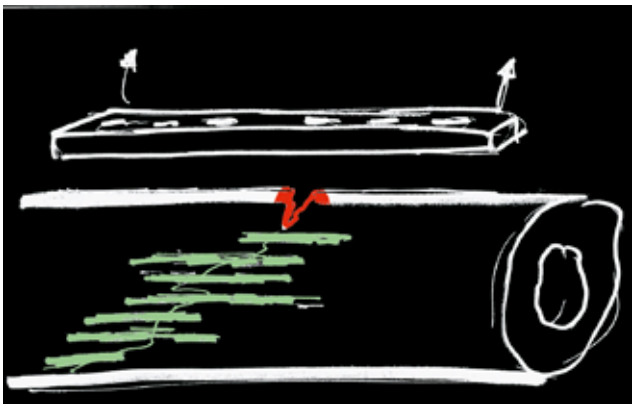


*Fig. 37. The contact of a snugly fitting plate produces an area of damaged blood supply. The result is the lack of solid bridging producing a mechanical notch with much increased stress.*

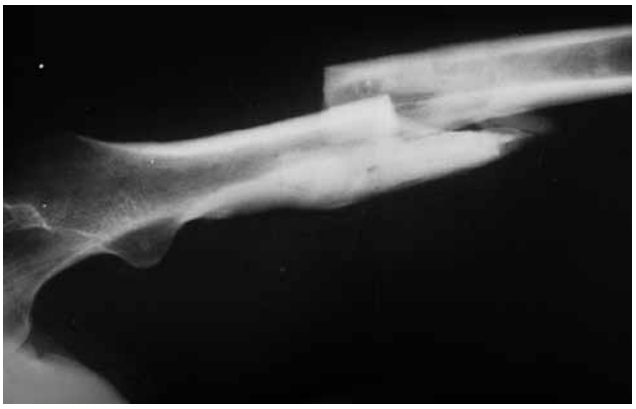


*Fig. 38. The refracture originates at the notch see Fig. 36.*

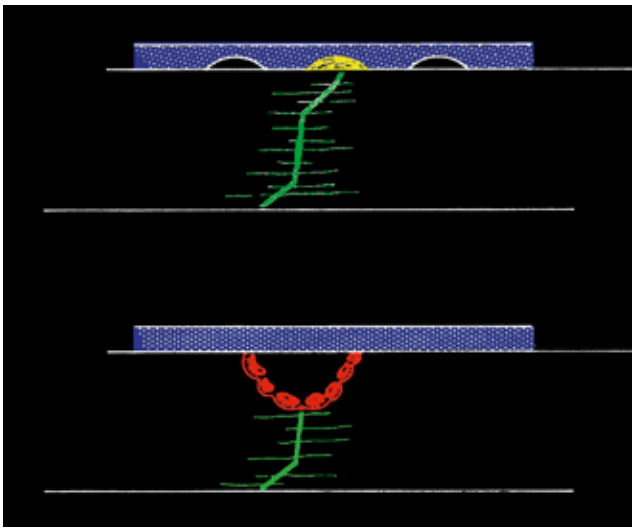


*Fig. 39. The same situation but with an undercut or elevated plate that permits blood supply avoiding notch formation and additionally allowing a callus bridge formation.*

## TOLERANCE TO INSTABILITY OF SIMPLE VERSUS MULTI-FRAGMENTARY FRACTURES

In a simple fracture the full displacement of the main fracture fragments is active within a single gap. In a multi-fragmentary fracture several serially lined up fracture gaps share the displacement of the main fragments and therefore in each of the gaps only a fraction of the main displacement is active (Fig. 40). At the beginning of fracture healing the tissue deformation in each gap is lower than in a single gap as mentioned above. Therefore, the multi-fragmentary fractures tolerate more instability than single ones[1]. Later on with unequal stiffening at the different fracture levels some gaps will solidify and the remaining non bridged gap will be exposed to larger tissue deformation. Rarely the multi-fragmentary fractures can behave like a single fracture, that is, they may be less tolerant to instability with time.

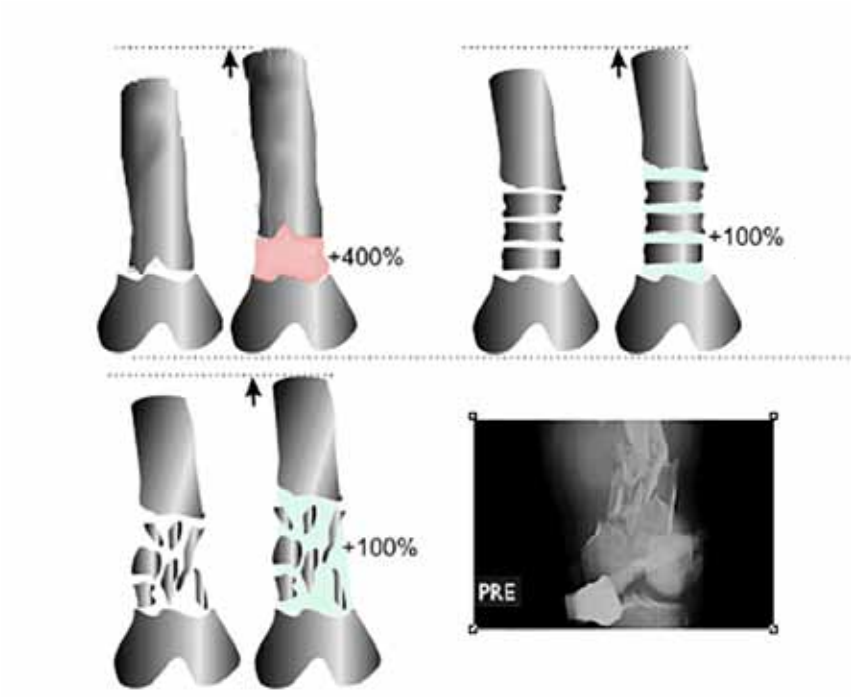



*Fig. 40. Different tolerance to mobility in the fracture gap for simple fractures and multi-fragmentary fractures. Given the same movement the simple fracture (upper left) undergoes 400% strain. The four fractures (upper right) share the movement and undergo only 100% strain. The lower pictures show a real situation (lower left) and schematic display (lower right).*

## BIOLOGICAL ASPECTS

We understand fracture healing as a biological process that is induced and modulated by existing physical conditions. The initiator is the change of physical conditions like onset of mobility while the effector is the biological reaction. The latter in turn changes physical conditions by reducing mobility and such like, which in turn modulates biology. The repair process changes the mechanical conditions, for instance by increasing structural (diameter of callus) and material stiffness (stiffness of callus elements).

### Duration of positive impact of the mechanical trigger of fracture repair

The fracture implies an initial displacement of fracture fragments with trauma and physical irritation of the tissues. The effect of a single displacement tapers off with time. The duration of the trigger effect is not well established. Still, recent observations indicate that repetition of the initial trauma after a few hours maintains its effect. Unexpectedly too, frequent triggers do not stimulate callus formation and probably pave the way for a new understanding of fracture healing (Hente R. and Perren S.M. unpublished data from the ARI)

### Biology at tissue level

The following aspects determine the possible contribution of tissues to fracture repair

[1] This may explain why simple transverse fractures are difficult to treat.

**Availability of cells**

In most situations of fresh fractures we can safely assume that enough cells are available, be it that they originate from cell division that is a contribution of the surrounding tissues, or be it that they stem from blood cells as mobile cell reserves of the body.

**Capability of cell differentiation**

As the cellular population will need to differentiate into granulation tissue, connective tissue, cartilage and bone the pool of repair cells needs to command an adequate population of cells able to differentiate into repair tissues.

**Blood supply**

The obvious element enabling repair is blood supply. The blood supply is damaged through accident, transport and surgery. The latter is the element that depends on tissue handling. In the early days the surgeon often acted with the aim of exposing and cleaning the fracture site. To allow perfect reduction and stabilization the soft tissues were often displaced and squeezed by application of retractors applied without care.

*Surgical approach*

Two elements deserve attention namely ligature of blood vessels during approach and stripping soft tissues which carry the blood vessels that provide blood supply to bone. In this context the assessment of surgical trauma is an important tool for improvement of surgical procedures (1).

*Implant contact*

Any contact of the implant with bone surfaces that carry blood vessels to and from bone results in ischemia and necrosis of the underlying bone. The resulting "contact necrosis" induces internal creeping substitution through internal remodeling (remodeling of the osteonal elements (5). This moves like a front from living bone into dead bone, that is, from living bone towards the contacting implant. When an osteon advances it opens the necrotic bone and produces a temporary porosis (stage t2 in Fig. 41). The advancing front of the osteonal remodeling similarly perambulates zones of dense dead bone, porotic opening and consecutive refilling (Fig. 42)

The process involves temporary porosis which was misinterpreted earlier on as bone loss due to unloading and referred to as "stress protection porosis" (Fig. 42). While under undisturbed conditions the bone maintains its load bearing structure (Fig. 43), under conditions of irritation such as infection the intensified remodeling may result in a front of intensive porosis where the pores may flow together. The result is formation of a sequester which impairs resistance to infection (Fig. 44). The same occurs after infected nailing (Fig. 46).

**Infection as an inhibitor of repair**

As a reaction to irritation patchy callus may be formed but its structure is not optimal to provide efficient repair. From a clinical standpoint the extent of soft tissue trauma with or without perforation of the skin determines much of the outcome of fracture treatment. The main aspect is reduction of resistance to infection. According to general opinion infection resistance is impaired in the presence of foreign bodies like implants. It is less probable that the mere presence of the implant is the culprit for what is called foreign body reaction. Two aspects of the implant deserve consideration – the material of the implant in respect to toxicity and – its surface in respect to adherence of tissues.

With best selection of each one of the two elements, material and surface structure, the implant loses its foreign quality.

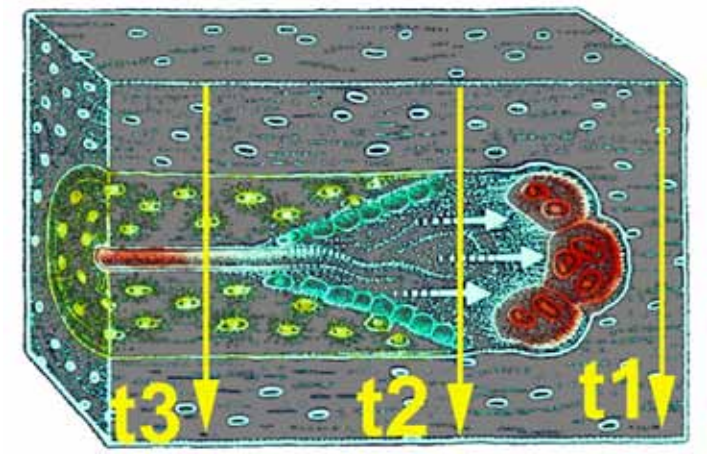



*Fig. 41. Advancing osteon at three different times.*
*t1: in front of the advancing dense dead bone t2: behind the drill head there is an open pore t3: the result of internal remodeling is removal of dead bone and formation of new living bone. This process goes through a phase of porosis.*


*Fig. 42. Cross-section of a plated bone, left: early temporary porosis right: later the pores are refilled. (Courtesy T. Dueland).*

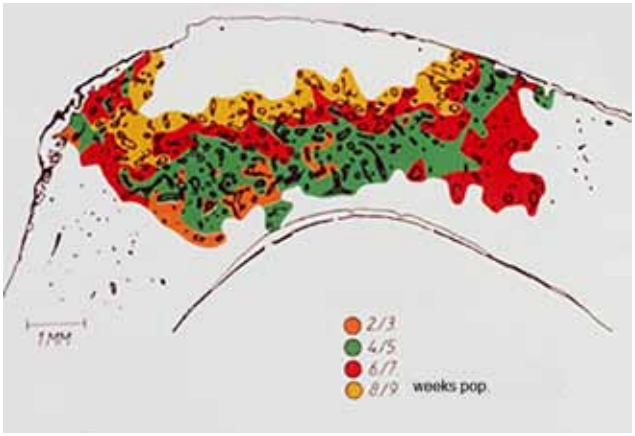



*Fig. 43. Internal creeping substitution of necrotic bone. The polychrome sequential marking shows the progress of the advancing front of osteonal remodeling. (Courtesy B. A. Rahn).*

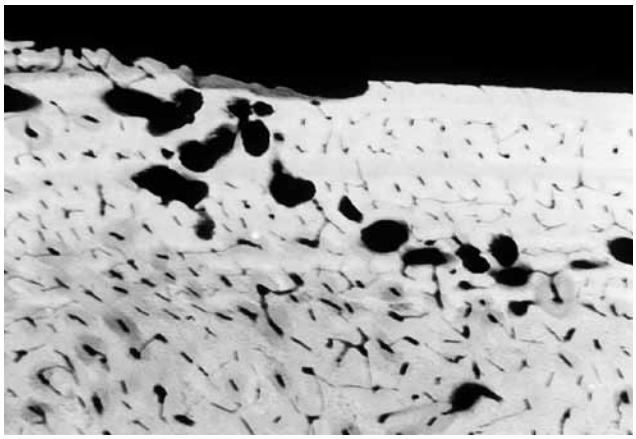


*Fig. 44. When the process or internal remodeling is intensified, e.g. due to infection, the pores may flow together and a sequester will detach. Formation of a sequester prolongs infection.*

**Special biological aspects of implant material**

As far as internal fixation of fracture is concerned there are two competing materials one of which is stainless steel which is strong and can sustain plastic deformation over a large range. Steel exhibits low corrosion as a bulk material. But steel is subject to fretting and with it pitting corrosion.

Pitting may markedly (~100x) increase local corrosion and release of corrosion products (Fig. 47). Because steel is an alloy it contains nickel which lacks tissue tolerance and is a frequent allergen. Furthermore, the surface of steel as used today does not favor the adherence of tissue. Therefore, as a rule, steel is encapsulated and there is formation of a dead space that impedes defense and promotes expansion of bacterial growth. On the other hand, titanium and its alloys with the exception of those containing vanadium contain only well tolerated elements and have a very low corrosion rate. In addition, titanium as used today provides surface conditions that favor adherence and thus minimize the incidence of dead space problems as mention above. Under conditions of fretting titanium produces wear particles with minimal corrosion. Furthermore, due to its very low solubility the body environment is saturated, which explains the exceptional tissue tolerance of titanium as an implant material. In combination with other implant metals the fact that the passive layer around titanium is electrically nonconductive allows titanium to be combined with steel without galvanic corrosion. Under such conditions the tissue tolerance of the combination of steel and titanium has been observed to be similar to the tolerance of steel. Allergic reactions to steel because of its alloy components nickel and chromium have not been observed with pure titanium. C.p. titanium tolerates less deformation than steel. This has resulted in less pre-warning of impending breakage when tightening screws. With today's locked screw technique unexpected screw failure is less of a problem. Still, jamming of the screw head at removal is a disadvantage that requires research to improve the locking mechanism. It is impressive to realize how even experts do not consider these special differences between implant materials.

*Fig. 45. Clinical case of a sequester immediately deep to a plate. (Courtesy T. Ruedi).*

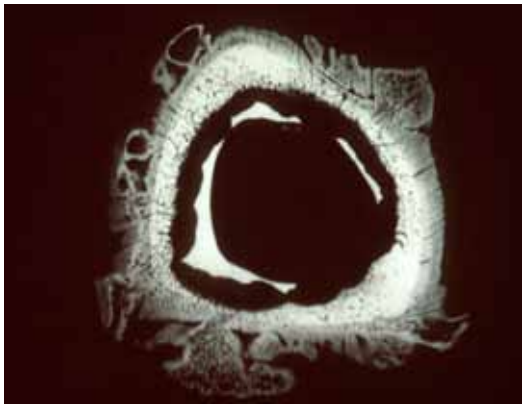


*Fig. 46. Around a medullary nail an identical sequestration like the one immediately deep to the plate and also around an infected fixator pin may form under conditions of infection. See Fig. 34 (Courtesy K. Wenda and M. Runkel).*

## MECHANO-BIOLOGICAL[2] CONDITIONS FOR SOLID BRIDGING OF FRACTURES

Simply put: fracture healing

– under flexible conditions needs induction and enabling of callus to restore stiffness and strength after a few weeks
– under absolute stability needs internal remodeling to restore stiffness and strength after several months.

### a) Induction

The importance attached to induction for fracture healing derives from the observation that a fracture gap kept rigidly open and stabilized in a way that does not allow any mobility (extremely low strain conditions) of the fracture does not produce callus for several months. The same situation but with a minimum strain level induces callus promptly.

### b) Enabling

As outlined earlier a tissue cannot bridge a mobile fracture gap point to point where more than 2% strain prevails. The woven structure of callus allows bridging along an elongated pathway but even woven bone cannot form a bridge where there is about 10% overall strain. The basic assumption of the strain theory[3] is that a tissue cannot be formed under strain conditions that exceed the elongation of the tissue (9).

## INSTALLING PROPER CONDITIONS FOR FRACTURE HEALING

At onset of fracture tissue deformation as a consequence of fracture mobility seems to be the critical element for induction of fracture healing. It is obvious that there is a lower limit of strain as zero strain does not induce repair. Still, data on exact amount of deformation for induction of healing is absent. More is known about the timing parameters of induction. Recent observations by Hente indicate that the spacing of single mechanical displacement is critical. He observed that short time delays (less than a minute) between single displacement does not induce bone formation. The consequence of

[2] We use the term "mechano-biology" for the interaction of mechanical and biological conditions or activities to replace the commonly used term biomechanics. The latter term in its strict sense describes the mechanics of the biological system such as the forces during locomotion.

[3] The strain theory primarily addresses a mode of thinking and observing that should pave the way to further insight. The application of strain in the individual fracture situation with high variance of conditions requires experience gained by observing fracture healing in terms of strain rather than instability.

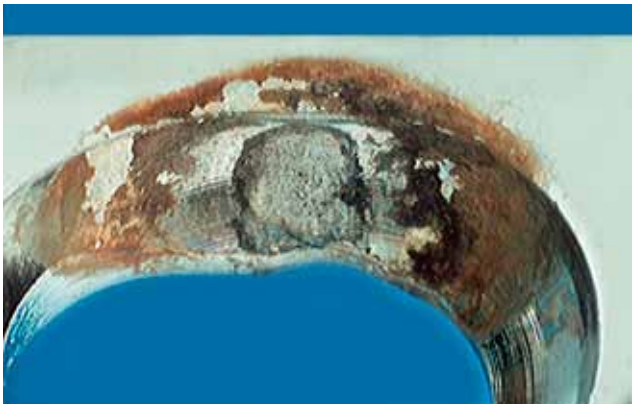


*Fig. 47. Screw hole of a steel plate under conditions of fretting (small displacements) even good quality steel may undergo pitting corrosion with local release of corrosion products. A situation that is accepted but improvable (modified).*

such an observation is that repeated tissue trauma seems to be an essential criterion of maintained formation of repair tissue.

### a) Mechanical conditions enabling solid bridging

When the strain is larger than the elongation at rupture of the tissue under consideration the tissue cannot be formed as it would not tolerate the deformation imposed. For the element of bone the critical strain tolerance is 2% (17). This means that if the bone element would be deformed by more than 2% (elongation at rupture) the bone element would be disrupted or cannot be formed. Fortunately, the three-dimensional structure of callus (woven bone) allows bone bridging to take place at up to about 10% strain. Under such conditions the element of bone is strained less than 2%. The bandwidth between the two essential conditions induction and enabling that are prerequisites for healing is fairly large.

### b) Physical and biological aspects of undisturbed healing

Based on the above-mentioned observations and conclusion we propose the following working hypothesis for spontaneous healing. The fracture disrupts bone and some soft tissues. The soft tissues have a good blood supply early on and may soon be repaired; surrounding tissues provide pluripotent cells. A highly mobile fracture situation is common and fracture repair is physically induced by tissue deformation (strain). The general experience is that the potential for healing of fresh fractures is astonishingly good and stimulation whether physical or chemical is not a priority at this moment. The first repair tissues are highly tolerant to strain but are unable to contribute much to reduction of mobility. The non-linear increase of stiffness helps to keep mobility within limits. At this point in time the opposing surfaces of the fracture undergo resorption, thus increasing gap width and decreasing strain. The next step in tissue differentiation is connective tissue which is less tolerant to strain but contributes to further reduction of mobility as a soft cuff of callus. Depending on the mechanical and biological conditions fibrocartilage is now formed. At the same time the callus cuff increases in diameter. This contributes to a further increase in stiffness whereby the stiffness increases markedly to the power of three or the diameter. The now low strain in the gap allows woven bone to bridge the fracture. The final internal and external remodeling of the callus restores the original shape and structure of cortical bone. This is the last phase and takes years. For the patient the fracture loses its impact when painless function (for instance, weight bearing) is achieved. In the presence of stabilizing implants the speed of healing is mostly of scientific interest.

### c) Physical and biological aspects of disturbed healing

When, under certain conditions, healing comes to a standstill the first question is generally in regard to the biological conditions. Unfortunately, proper technology to assess the biological situation is missing. Chipping the bone to observe whether cutting the bone surface will produce a small amount of bleeding at various locations is a crude tool. A technology that allows for prognosis of bone healing needs to provide an overview of soft tissue and bone blood supply and healing potential. Such a technology may be applied to an open fracture site. If it could be done before surgery it would be an ideal tool to determine prognosis and plan the intervention. The Doppler method might help if combined with sonic technology whereas results obtained with it as a single tool were disappointing. The next question is whether tissue deformation is not induced due to low strain conditions, or whether callus is induced but cannot bridge the gap because strain is too high. In the former case what is often a large gap keeps strain low. In the latter case we would expect formation of non-bridging callus. In a late phase of frustrated healing, callus may no longer be the main symptom. Let us assume that we cannot increase or decrease strain by exchanging the implant and the construct it forms with the bone. We then still have the opportunity within limits to increase or decrease functional load such as weight bearing.

Often the only way to save a situation with too high strain, especially when biology is ready but is no longer contributing to repair by callus formation, then rigid double plating, for instance, the addition of a helical plate is a solution. One would expect that after a very rigid fixation, especially with a fairly large gap, a strain condition would result with strain far below the minimum for induction. In such cases one can observe that after a year or longer the gap starts to fill up. We suspect that this behavior is not a reaction to the fracture but is bone formation unrelated to the fracture but probably related to the prevailing defect conditions. Thus, apart from healing under flexible conditions and internal remodeling under absolute fixation we would have a third pattern of repair without mechanical induction and with bony bridging occurring very late.

Under such conditions the implants would function like prostheses, and clinically the situation would be painless and allow function. Because of maintained painless function for the patient it would certainly not be critical and might possibly be irrelevant how late solid bridging occurs.

Earlier on double plating was condemned because of the risk of refracture. Contact necrosis immediately deep to the closely fitting implants was the culprit of this shortcoming of double plating. Since the new generation of implants has an undercut undersurface and especially since the locked screw technique allows application of elevated plates functioning like internal fixators double plating now offers a solution whereby the absence of contact necrosis avoids any shortcomings.

## HOW CAN WE ENSURE PROGRESS IN CLINICAL DAILY LIFE?

Two aspects stand out:

- Documentation of clinical failures needs our full attention to overcome complacency based on yesterday's success. Open documentation of surgical procedures allows for improved learning. Furthermore,
- Proper decision-making ensuring that the patient profits from progress in research avoiding business impedance.

### a) Improving learning of surgical procedures: the ICUC approach

Today a new technology of water tight documentation of surgical procedures has been developed by ICUC (www.icuc.net). Its Integrated, Complete, Unchanged and Continuous recording of surgical procedure (Surgicorder technology) provides anonymized and therefore uninhibited reporting and commenting of failures. Learning from visual clues and especially learning from failures supersedes indoctrination by teaching of so called "best procedures. Solid knowledge of what needs to be avoided, that is, knowledge that has been worked hard for should replace volatile hearsay.

### b) Improving decision making to ensure real medical progress

In the following we quote an example of a flawed decision relating to a burning issue of progress and decision making in medical technology: An internal fixator (see Fig. 30) (PC-Fix) (16) that made available the two conditions mentioned earlier, an optimal blood supply and an optimally tolerated material (pure titanium) together with handy application (based on point contact) was clinically tested in two exceptionally tough studies with a follow up rate of more than 97%. Such follow up rates do not allow for „documental phthisis" i.e. disappearance of failed cases, and is a precondition to assess low infection rates. The studies (3, 6) demonstrated a record low infection rate but it lost against business arguments. This demonstrates a weakness in decision making. The problem of innovation based on basic and clinical research is that decisions regarding its acceptance require a profound understanding that is unfamiliar to commercial management. This shortcoming, for instance, explains why polling so-called opinion leaders does not take into account disruptive progress. A valid answer requires preinformation about goals, technology and results that are not found on the business horizon. Without such information a new technology is generally labeled as a gadget.

The interaction of medical and industrial decision making has recently gained increasing attention (6, 14). The patient needs solid, reliable, safe and crucial medical progress. The issue of what makes the most money for industry or what reduces cost in the short-term for the hospital does not help the patient in the long run. Therefore, the power to decide what best treatment technology is must remain in the hands of the medical professionals. The cost saved by diminished complication rates far outweighs the cost spared by application of cheap implants. Furthermore, real progress precedes and does not scuttle behind problems. Asking "what problem can we solve" is a necessity but by no means paves the way to real basic progress. The latter is not measured by income but by improvement. The fact that administrative management should serve and enable and refrain from incompetent controlling power in unfamiliar areas is all too often disregarded today in favor of enhanced controlling power.

It is worth mentioning that at the same time that a statement was made at a congress that we have reached the top of a ladder meaning that we need no further research and clinical improvement a basic change was being initiated in the lab (17). At this time the locked plate was developed to allow for flexible fixation and to trigger callus formation, thereby overcoming decades of rigid brains and rigid fixations. The locked elevated plates also allowed for a radical improvement of bone blood supply. Improved infection resistance addressing not only material but also the structure of the implants and their application provided new solutions at a time when managers questioned the value of research. Complacency kills progress.

## CONCLUSIONS

Fractures that are not treated (spontaneous healing) or that are flexibly stabilized exhibit a healing mode with a stepwise differentiation of repair tissues. The physical conditions play an important role in triggering and modulating the biological healing process. Clinical fracture treatment and especially treatment complications has to consider the mechano-biological interplay in order to act and react properly. Improved learning and also progress in decision making regarding acceptance of progress offered by research are addressed as priority items for innovation and with it leadership.

## References[4]

1. DEL PRETE, F., NIZEGORODCEW, T., REGAZZONI, P.: Quantification of surgical trauma: comparison of conventional and minimally invasive surgical techniques for pertrochanteric fracture surgery based on markers of inflammation (interleukins). J. Orthop. Traumatol., 13: 125–130, 2012.
2. DUBS, L. (Ed.): Orthopädie an der Schwelle. Bern, Hans Huber Verlag 2000.
3. FERNANDEZ DELL'OCA, A. A., TEPIC, S., FRIGG, R., MEISSER, A., HAAS, N., PERREN, S. M.: Treating forearm fractures using an internal fixator: a prospective study. Clin. Orthop., 389: 196–205, 2001.
4. GANZ, R., PERREN, S. M., RUETER, A.: Mechanische Induktion der Knochenresorption. Fortschr. Kiefer Gesichtschir., 19: 45–49, 1975.
5. GAUTIER, E., PERREN, S. M.: Die Reaktion der Kortikalis nach Verplattung – eine Folge der Belastungsveraenderung des Knochens oder Vaskularitaetsprobleme? In: WOTLER, D., ZIMMER, E.: Die Plattenosteosynthese und ihre Konkurrenzverfahren. Berlin, Heidelberg, New York, Springer Verlag 1991, 21–37.
6. HAAS, N., HAUKE, C., SCHÜTZ, M., KÄÄB, M., PERREN, S. M.: Treatment of diaphyseal fractures of the forearm using the Point Contact Fixator (PC-Fix): Results of 387 fractures of a prospective multicentric study (PC-Fix II). Injury (Suppl.), 32: 51–62, 2001.
7. KLEIST, P.: Pharmazeutische Medizin: Humanforschungsgesetz – ein Spagat zwischen Persönlichkeitsrechten und Forschungsinteressen. Schweiz Med. Forum, 13: 1051–1052, 2013.
8. MÜLLER, M. E., ALLGOEWER, M., WILLENEGGER, H.: Technik der operativen Frakturenbehandlung. New York, Springer Verlag 1963.
9. PERREN, S. M., BOITZY, A.: Cellular differentiation and bone biomechanics during the consolidation of a fracture. Anatomia Clinica, 1: 13–28, 1978.
10. PERREN, S. M.: Physical and biological aspects of fracture healing with special reference to internal fixation. Clin. Orthop., 138: 175–196, 1979.
11. PERREN, S. M.: Evolution of the internal fixation of long bone fractures: the scientific basis of biological internal fixation: choosing a new balance between stability and biology J. Bone Jt Surg., 84-B: 1093–1110, 2002.
12. PERREN, S. M.: Optimizing the degree of fixation stability based on the strain. Orthopäde, 39: 132–138, 2010.
13. PERREN, S. M., REGAZZONI, P., FERNANDEZ, A. A.: Biomechanical and biological aspects of defect treatment in fractures using helical plates. Acta Chir. orthop. Traum. čech., 81: 267–271, 2014.
14. RAHN, B. A., GALLINARO, P., BALTENSPERGER, A., PERREN, S. M.: Primary bone healing. An experimental study in the rabbit. J. Bone Jt Surg., 53-A: 783–786, 1971.
15. REGAZZONI, P., FERNANDEZ, A., PERREN, S. M.: Qualitätskontrolle und Transparenz: langfristig zählen nur konkrete Aktionen. Schweizerische Ärztezeitung, 94: 29–30, 2013.
16. TEPIC, S., REMIGER, A. R., MORIKAWA, K., PREDIERI, M., PERREN, S. M.: Strength recovery in fractured sheep tibia treated with a plate or an internal fixator: an experimental study with a two-year follow-up. J. Orthop. Trauma, 11: 14–23, 1997.
17. YAMADA, H.: Strength of biological materials. Gaynor Evans, F., (Ed.), Baltimore, Williams & Wilkins Company 1970.

**Corresponding author:**
Prof. Stephan M. Perren, M.D.
AO Research Institute Davos
Clavadelerstrasse 8
7270 Davos, Switzerland
E-mail: sperren@bluewin.ch

[4] These references mainly concern the activity at the AO Research Institute. For an extensive List of Literature see Perren 2002