The Regional Acceleratory Phenomenon: A Review

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The regional acceleratory phenomenon (RAP) is a complex reaction of mammalian tissues to diverse noxious stimuli. The phenomenon occurs regionally in the anatomical sense, involves both soft and hard tissues, and is characterized by an acceleration and domination of most ongoing normal vital tissue processes. It may represent an "SOS" mechanism which evolved to potentiate tissue healing and local tissue defensive reactions. When a RAP is obtunded, retarded healing and lowered resistance to infection and mechanical abuse may ensue.

When ignored in experimental design, the phenomenon can seriously perturb studies of metabolic bone disease and of the effects of mechanical, endocrinologic, and biochemical factors on skeletal physiology.

This review concerns an entity which affects both skeletal and soft tissues and may explain certain features of some diseases. It can also perturb experimental studies of metabolic bone disease and of mechanical and other effects on skeletal physiology; if unrecognized, its features may be assigned to other causes. While physicians have long known many of its manifestations, it was first recognized and proposed as a general entity by the author. Of necessity, this review reflects his experience, biases, and limitations (1-4).

Characteristics of the Regional Acceleratory Phenomenon (RAP)

Causes
In a normal body any regional noxious stimulus of sufficient magnitude seems to evoke a RAP. It appears that the size of the affected region and the intensity of its response varies directly with the magnitude of that stimulus, although to different degrees in different individuals.

The effective noxious stimuli include crushing injury, fracture (5,6), bone operations of any kind (7-9), arthrotomy, arteriotomy, burns, acute denervation, acute paralysis (10,11), infarcts, soft tissue and bone infections (12-15), and most noninfectious inflammatory joint processes including rheumatoid arthritis, rheumatic fever, pseudogout and Reiter’s disease (10,16).

Nature
Once evoked, many ongoing regional soft and hard tissue vital processes accelerate above normal values. Collectively, those accelerated processes represent the RAP, and they include: perfusion (17); growth of skin, bone, cartilage, and hair (6,18-20); turnover of bone, cartilage, synovial fluid, connective and fibrous tissue (18,21,22); chondral and bone modeling including correction of malunions in children; skin epithelialization; cicatrization; soft tissue and bone healing (23); and cellular metabolism.

Consequently, an affected region develops erythema and edema and becomes warm on thermography as well as to touch. The accelerated local bone turnover increases the uptake by bone-seeking isotopic agents, which causes the hot regions often found in acute and chronic osteomyelitis, in actively healing fractures, in the presence of joint inflammation of any cause, in Sudeck’s atrophy, and in the presence of some bone metastases (24). Photon absorption studies and routine x-rays can reveal decreased regional bone density due to an increased remodeling space. A joint contracture, which was previously too rigid to respond to wedging casts or traction, can respond more readily during the three months or so following a major local bone operation, a phenomenon which suggests that the RAP rendered the capsular and related tissues more plastic for a time.

Clinically, as well as histologically, the particular cause of a RAP can imprint its own features on the concomitant general features of the RAP, so that their combination can appear characteristic or even diagnostic. Such char-
acteristic imprints (such as necrosis, pus, eosinophilia, Langhan's giant cells, hemosiderin, or scar) usually allow one to distinguish between trauma, acute pyogenic infection, immune reactions, chronic infections, necrosis, and metastasis as examples.

Among the above clinical manifestations, physicians will recognize some of the classical signs of inflammation (26,27), which this writer suggests represent an early recognized manifestation of a stereotyped, more general phenomenon.

Anatomical distribution

The RAP involves the region where its stimulus arose, such as a knee, wrist, leg, foot or hip, including soft and hard tissue components. Following an acute paraplegia, hemiplegia, or monoplegia, whether due to trauma, poliomyelitis or other acute disease, or whether due to lower motor neuron or central lesions, the RAP can affect the whole paralyzed part of the body (28,29). The transition from involved to uninvolved regions seems gradual, rather than abrupt, and the distribution of the RAP seems to reflect regional vascular anatomy and innervation. Given severe stimuli, abscopic involvement can occur, meaning that accelerations of ongoing tissue turnover and perfusion can occur in the contralateral regions of the body.

Duration

In healthy humans, and following a single stimulus such as a Colles' fracture, pyarthrosis or gunshot wound, clinical evidence of the RAP typically lasts about four months in bone, somewhat less in soft tissues, and longer for severe than for mild stimuli. But following acute paralysis as from a brachial plexus injury, or after a severe burn, the RAP can last from six months to over two years. Thus, for commensurate periods, it can accelerate the bone loss caused separately by mechanical deloading, and thereby can predispose to hypercalcemia and genitourinary tract lithiasis (25,30). When the causal stimulus persists for prolonged periods, as it can in active rheumatoid arthritis, osteomyelitis, Paget's disease of bone or in the presence of an osteoid osteoma, the RAP persists similarly without any known evidence of a natural limit to its duration.

The "SOS" Role of the RAP

The RAP may have evolved to accelerate healing of injuries and tissue defense reactions to local infection, infarction, mechanical abuse, and other noxious processes. Such a role suggests an "SOS" type phenomenon which would potentiate the survival of a species during evolution in a physically competitive environment. Once begun, it tends to dominate other ongoing processes and those endocrine, drug, and mechanical effects which tend to depress or potentiate those activities in healthy subjects.

Two different groups of clinical situations illustrate the postulated "SOS" role for the RAP. One reflects its positive effects, the second its impairment.

Clinical Examples of RAP Effects

Potentiated bone healing

In the type of fracture nonunion, termed a "biological failure" (31) or an atrophic or oligotrophic nonunion (32), fracture callus arises too slowly and too scantily for satisfactory union but not from any known flaw in treatment. Dr. Robert Schenk and a group of Swiss orthopedists, who developed a highly efficient system of internal fixation of fractures that has come into wide use in developed nations, taught the orthopaedic community that such nonunions can heal, given intimate apposition fixed rigidly enough to allow less than about 50 microns of interfraction motion (23). Such union occurs not by callus production but by BMU-based remodeling, which knits the fragments together with numerous secondary osteons crossing the fracture interface (23,33). BMU-based remodeling refers to the quantized or pocket-type turnover of adult human lamellar bone. It occurs in discrete units and involves an activating stimulus that causes an initial focal resorption process followed by a bone formation process. That A-R-F sequence normally consumes about three months (1,21,23,30,33), and the secondary haversian system represents one of its well-known products.

Normally, such remodeling turns over less than 5% of the adult human tibial compacta annually (34,35). If no other factor acts after such fixation, less than 5% of a tibial fracture interface would bridge in the first year. About twenty years would be required for complete bridging. Yet union typically occurs within six months because the operation itself (whether intermedullary nailing, compression plating, or a securely fixed sliding bone graft) accelerates the local bone turnover ten to fifty-fold above normal for more than a year. That reaction accelerates the healing process (23) in the soft tissues as well as in the bone.

Such observations suggest that normal fracture healing may routinely require an accompanying RAP. If so, a delayed union not due to inadequate treatment could reflect an obtunded RAP, and the often beneficial effects of bone grafting or electrical stimulation could, in part at least, result from a newly evoked RAP. Signifi-
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cantly, studies by Takahashi, et al have shown exactly such effects of electrical bone stimulation (36).

The pathological RAP

Two clinical entities seem to illustrate pathological or “runaway” RAPs. In Sudeck’s atrophy, an acute injury originally evokes a typical RAP, but the local accelerations characteristic of that RAP persist long after the original injury has healed. Sympathetic nerve blocks often cure this condition, but corticosteroids and related agents may not. The other entity, regional migratory osteoporosis, also may follow a local injury, although it can occur spontaneously. When due to injury, this disorder also persists long after the injury has healed; and it is intriguing that sympathetic blocks are not beneficial, but corticosteroids and some other prostaglandin inhibitors often help (37,38).

Arthrofibrosis

Joint stiffening due to diffuse fibrosis can follow regional surgery, trauma, infection, noninfectious inflammation as in rheumatoid arthritis, and the development of a regional osteoid osteoma. All of these can evoke a RAP which, among other effects, increases collagen production in the regional connective, fascial, capsular, and ligamentous tissues. Lacking frequent range-of-motion exercises, that fibrosis binds the regional gliding mechanisms together.

The next examples illustrate proposed clinical examples of obtunded or absent RAPs.

Neuropathic soft tissue problems

In diabetics with significant peripheral neuropathy but good perfusion, and in nondiabetic patients with denervated limbs or severe peripheral neuropathy of other origin (biochemical, mechanical, post-frostbite, nutritional), the affected tissues respond poorly to wounds, mechanical abuse, and/or infections (27). In healthy tissues, such lesions promptly evoke a RAP (which includes the classical signs of inflammation plus accelerated turnover and metabolism of local skin and underlying soft tissues). Local healing is thus accelerated. But in these neuropathic affections, those accelerations are either obtunded or absent, while erythema, increased perfusion, or edema develop slowly, healing is prolonged, and local resistance to infection, mechanical abrasion, and pressure declines. Proof of the regional rather than systemic origin of those phenomena lies in the fact that in the same individual no such problems arise in uninvolved body parts.

The Charcot joint

Whether due to diabetes, lues, syrinx, other central nervous system disease or traumatic lesions, typical Charcot joint signs include considerable local bone and joint destruction and gross instability (3) but relatively mild edema, heat, swelling, and discomfort. Static histologic examination of Charcot joints reveals typical kinds of tissue responses to those stimuli, including fibrosis, dilatation of capillaries, production of new woven bone, low grade inflammation, resorption of debris, and edema (12,26,40).

However, the static histology misses an important but quite consistent dynamic feature. That is, given equal destruction, daily usage, and instability, the Charcot joint tissues develop far less tissue response per week than would normal joints, in which equivalent abuse would promptly evoke pronounced swelling, edema, and erythema, greatly increased local perfusion, fibrosis, and reactive bone formation.

This observation suggests that an obtunded RAP plays a major role in the pathophysiology of Charcot joints. In addition, the associated impairment of deep pain sensation (41,42) allows daily activity to cause new damage faster than the lethargic, obtunded repair processes can react to and heal it, so destruction is progressive. Similar phenomena can occur in subjects with congenital absence of pain (43).

Clinically, an obtunded RAP accompanies local sensory but not motor denervation; it was rarely observed in victims of anterior poliomyelitis. Sensory impairment may be due to central or peripheral trauma, to central nervous system disease or peripheral neuropathy. Varied observations and experimental data support the concept. For example, in patients with paralysis due to spinal cord injury at the cervical or thoracic levels, in whom lower limb innervation remains intact, lower limb wounds and fractures heal normally and infection responds satisfactorily to treatment (44). In contrast, after regional peripheral denervation, reduced periosteal and longitudinal overgrowth occur in amputation stumps (45), and impaired healing in denervated tissues is well known.

Rheumatoid phenomena

The tendency of excessive local collagen production, postulated to be a positive RAP effect, to cause joint stiffness typically occurs early and during active and severe rheumatoid arthritis inflammation. However, in late cases of rheumatoid arthritis and in some of its variants, opposite effects can occur: ligaments and capsules stretch, joints become lax and subluxated, and microscopic tendon damage accumulates, so poorly repaired that spontaneous rupture finally occurs. Never-
theless, the classical external evidence of inflammation and other RAP manifestations is often unimpressive. Considerable internal damage may occur with minimal external signs of local tissue reaction, a state interpreted to indicate an impaired RAP. In addition to the disease process, therapeutic agents may play a role in that impairment. Paradoxically, in these same patients, skin and bone lesions may heal properly, and a ruptured rheumatoid tendon usually heals normally after surgical repair.

The RAP in Research

Histomorphometric bone studies

I first suspected that the RAP was a general entity about 1960 when the sixth and seventh ribs were removed at autopsy from a patient who had undergone a thoracotomy seven years earlier. Histomorphometric measurements of the originally resected sixth rib disclosed much higher bone turnover than was present in the uninjured adjacent rib. Numerous subsequent observations in human subjects have shown that any type of significant injury to a bone usually accelerates its turnover for a year or more.

This phenomenon suggests that repeated biopsy of the same bone before and after some treatment may produce effects on bone remodeling which yield profoundly perturbed data (25, 30, 46-49). The techniques of serial rib biopsies (50-53) and of obtaining a biopsy first from one and then from the opposite ilium (33, 54-57) have been developed to minimize that error. Most histomorphometrists now realize that serial biopsies of the same bone cannot provide useful pre- to post-treatment bone turnover parameters (1). These potentially perturbing effects of the RAP on experimental data are often overlooked by investigators interested in other kinds of skeletal problems, as indicated below.

Longitudinal bone growth

In children, bone growth often accelerates for some time after a major fracture or surgical procedure (58). With variable success surgeons have also tried to stimulate bone growth by periosteal stripping, or by implanting beef bone or ivory pegs (8, 19). The ensuing growth accelerations represent typical positive RAP effects.

Growth acceleration may also follow acute paralysis, whether due to trauma, poliomyelitis (11, 28, 29) or other affections, as well as local irritants such as chronic osteomyelitis, an osteoid osteoma, juvenile rheumatoid arthritis, or an irritating foreign body (12, 19). Some observers have attributed the unpredictable growth increases which can follow such affections to an effect of mechanical deloading. However, the invariable result of deloading without any complicating RAP, which appears in children paralyzed early in life [e.g., myelomeningocele (11)] is a short limb (2, 3, 59). On the other hand, acute paralysis can produce the bony and soft tissue phenomena of a RAP in both laboratory animals and humans. In those situations, I suggest that the RAP transiently stimulated growth, i.e., for about a year, which dominated the concurrent growth depression caused by mechanical deloading. When the transient dominating RAP subsided, the persisting depressive effect became apparent.

Similar opposing forces may explain the confusing results observed when experimental forces are applied across growing epiphyseal plates (2, 3). The surgical implantation of the hardware applying those forces evoked a RAP which tended to accelerate growth, while the mechanical forces exerted their own effects (2, 3), and investigators observed the variable net results (60, 61).

Bone loading experiments

The interest of the orthopaedic community in mechanical effects on bone architecture has made "Wolff's law" a password (62). In the last two decades of the 19th century Julius Wolff proposed in essence that living bone can occasionally change its internal architecture in response to a change in the mechanical loads it carries, and that such changes made it better equipped mechanically to support those altered loads. Accordingly, he proposed that the mechanical usage of a bone can influence its architecture. A representative experiment involves surgically implanting to each end of a bone hardware which is connected by restraints in order to compress the bone uniaxially. Some investigators attributed the resulting increased outside bone diameter and porosity to increased mechanical compression. However, they usually omitted the necessary control: i.e., identical devices implanted identically in the opposite limb but with the restraint disconnected. Such surgical procedures certainly cause a RAP, and the reported bone reactions are typical RAP manifestations (3, 7). Such experiments combine compression effects with unrecognized RAP effects.

The same problems occur in studies of mechanically deloading long bones by plate fixation (63, 64). To distinguish RAP from stress-strain effects, it is necessary to implant identical screw-plate devices on each femur, one of which has loosened screws. However, investigators have usually omitted this control. Although comparison of the effects of rigid to flexible plates involves the use of different materials, many investigators have not
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compared the effects of the materials independently for either the RAP or the mechanical bones (65,66), so conclusions based on such experiments are difficult to defend (67).

Discussion

Experimental studies of the RAP

High, et al have provided the only published experimental data specifically applicable to RAP effects (51-53). Evoked in adult canine rib by periosteal stripping, dynamic histomorphometric analyses (47,56,68) of the stripped as well as of the uninjured ribs revealed significantly accelerated turnover in the stripped ribs six weeks later, apparently unmodified by concurrent treatment with other agents. The design of those experiments eliminates mechanical deloading as a significant factor in the results, indicating that bone RAP effects need not necessarily reflect mechanical effects. On the other hand, other experiments reveal that a RAP can also result from acute deloading and, furthermore, can differ in kind and anatomical location according to the subject's age (14,22,69).

Mechanisms underlying the RAP

Although understanding is far from complete, the causes of the RAP are many and depend on the anatomy and competence and autonomic innervation of the regional blood supply, regional sensory innervation and mechanical loading, as well as the gamut of local biochemical and biological factors already known to be associated with injury, repair, metastasis, and inflammation, e.g., prostaglandins, leukotrienes, lysozymes, and other leukocyte activities. Takahashi, et al produced typical bone RAPs by electrical stimulation of bone with commercial equipment used to treat fractures, and control studies revealed that surgical implantation alone also caused unequivocal but less severe RAPs (36). Basic differences in some causative factors, both in kind and magnitude, may characterize soft and hard tissue RAPs, accounting for the differences in their microscopic features.

Similar to the features of the lower motor neuron or BMU-based bone remodeling (1), the RAP may represent a final common pathway for an appropriate physiologic expression of diverse stimuli. Its particular clinical, biochemical, and histologic features may accompany the specific features of the causative stimulus, such as trauma, infection, an immune reaction, or necrosis. The RAP is a process of the intermediary organization of tissues and organs and is not revealed in the properties of isolated cells, so effective study cannot utilize ex vivo systems but will require the use of intact subjects.

References


