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The fracture cascade

managing individuals who continue to fracture on antiosteoporotic therapies

The effective management of individuals with osteoporosis should include not only the prescribing of an antiosteoporotic agent but also regular encouragement to ensure drug persistence and adherence.

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Fractures in people with osteoporosis can occur with minimal trauma such as falls or even spontaneously while coughing, sneezing or just turning in bed. The less the force involved in the injury, the greater the 'brittleness' of the individual's bone, reflecting the severity of his or her osteoporosis. Following a single fracture, the risk of further fracture is increased, resulting in the 'fracture cascade'. Recurrent fractures can be devastating, leading to loss of confidence, despair and physical, psychological and social decline.[1,2]

In women, fractures of the wrist (Colles fracture) and ankle occur within five to 10 years after the onset of menopause. Spinal, hip and pelvic fractures increase in incidence in men and women into their eighties and beyond.[3] The number of individuals suffering from the consequences of osteoporotic fractures in the year 2000 was

IN SUMMARY

- **Following a single fracture in an individual with osteoporosis, the risk of further fracture is increased, resulting in the 'fracture cascade'.**
- **The effective management of individuals with osteoporosis should include not only the prescribing of an antiosteoporotic agent but also regular encouragement to ensure persistence and adherence with taking their medications.**
- **Antiosteoporotic agents reduce the risk of subsequent fractures rather than prevent them. Unfortunately, this means that there will be a number of individuals who comply with therapy and continue to fracture.**
- **Factors influencing recurrent fracturing while on antiosteoporotic therapy include the antiosteoporotic agent being used and compliance with taking it, calcium and vitamin D status, smoking, alcohol consumption, secondary causes of osteoporosis, trauma due to falls and abnormal bone remodelling due to long-term (more than five years) use of antiresorptive osteoporotic agents.**
- **People who fracture recurrently usually require detailed evaluation and appropriate treatment, and specialist referral is recommended.**
- **Resistance and balance training exercise programs improve reflexes and muscle strength and reduce the risk of falls.**
- **The atypical peripheral fractures reported to be associated with long-term bisphosphonate therapy should not detract from prescribing bisphosphonates. However, caution and avoidance of indefinite long-term exposure to these medications must be considered in all patients.**

Table 1. Potential reasons for refracturing on antiosteoporotic agents

- Severity of osteoporosis
- Limited antifracture efficacy of antiosteoporotic agent being used
- Poor drug adherence or persistence
- Suboptimal calcium and/or vitamin D serum levels
- Lifestyle factors (smoking and alcohol excess)
- Undiagnosed secondary causes of osteoporosis
- Recurrent falls
- Antiosteoporotic agent-related abnormalities in bone remodelling

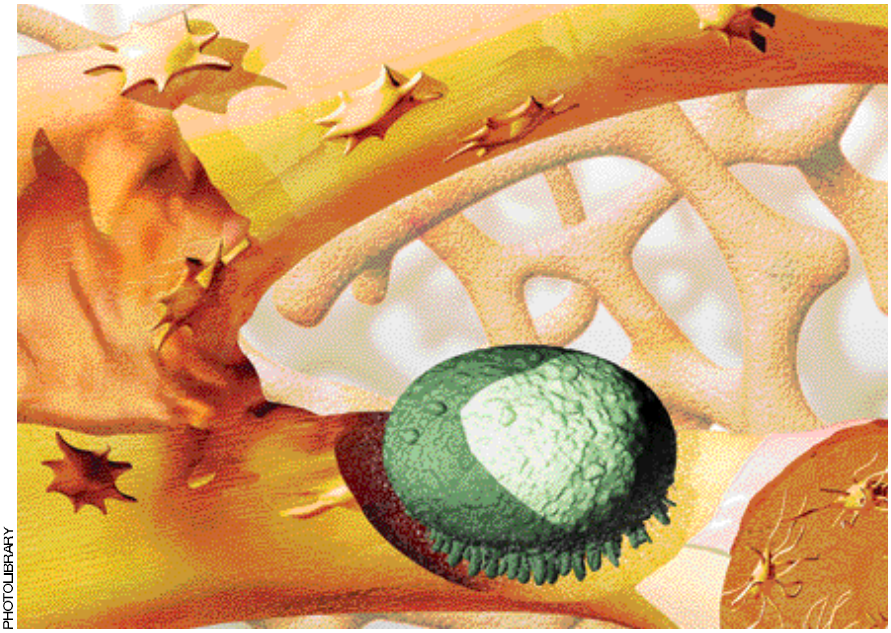


Figure 1. An osteoclast destroying bone trabeculae. Antiresorptive agents act by inhibiting osteoclast bone resorption

conservatively estimated to be 50 million worldwide.

There are many reasons why individuals sustain fractures. As patients generally believe that treatment with effective antiosteoporotic agents will stop recurrent fractures, it is no wonder that many start panicking when they continue to fracture while they are taking these drugs.

Reasons for recurrent fracture on treatment

Some of the reasons why individuals continue to fracture while on antiosteoporotic therapy are discussed below and summarised in Table 1.

Efficacy of antiosteoporotic agents

All individuals who sustain a minimal trauma or osteoporotic fracture should receive antiosteoporotic therapies. The risk of suffering a further fracture is at least doubled, irrespective of the type of fracture, and may even be higher if the individual is older than 70 years or has an underlying medical illness that predisposes to osteoporosis.[4,5]

Antiosteoporotic therapies can be classified as antiresorptive or anticatabolic (those agents that inhibit or slow the bone resorption phase of the bone remodelling cycle – Figure 1) and anabolic (those agents that stimulate new bone formation). The antiresorptive agents include the bisphosphonates, oestrogens and progestogens used as hormone therapies and the selective oestrogen receptor modulator raloxifene.

The bisphosphonates have differential effects on hip and other nonvertebral fracture reduction according to their potency (Table 2). Strontium ranelate is an antiosteoporotic agent with a dual mechanism of action: it has been shown to stimulate new bone formation, probably by recruiting osteoblast precursors, as well as to decrease bone resorption.

All antiosteoporotic agents are effective. In randomised clinical trials, they have been shown to reduce the risk of subsequent fractures by 25 to 70%, rather than by 100%.[6] Unfortunately, this means that there will be a number of individuals who comply with therapy and continue to fracture.

Optimal calcium and vitamin D supplementation

The efficacy of antiosteoporotic agents is dependent on individuals having optimal levels of calcium and vitamin D and optimal lifestyles.

Most randomised trials have been performed with calcium and vitamin D as additives to antiosteoporotic agents. A daily intake of 1500 to 2000 mg of calcium (dietary and/or supplemental) is recommended when prescribing antiosteoporotic agents to optimise skeletal efficacy.[6,7]

Table 2. Bisphosphonates: potencies and osteoporosis treatment regimens*

Bisphosphonate	Relative potency	Route	Regimen for osteoporosis and cancer-induced bone disease	PBS listing and availability†
Etidronate	1x	Oral	Osteoporosis: 400 mg daily for two weeks of every three-month cycle; calcium carbonate 1.25 g daily for other 76 days	Listed on PBS for established osteoporosis in patients with fracture due to minimal trauma
Clodronate	10x	Oral	Osteolytic lesions (breast cancer metastases, multiple myeloma): 800 mg twice daily	Listed on PBS for bone metastases from breast cancer Not TGA approved for osteoporosis
Pamidronate	100x	Intravenous	Osteolytic lesions (breast cancer metastases, advanced multiple myeloma): 90 mg infusion every three to four weeks, administered over two hours Osteoporosis (off-label use): 30 to 90 mg infusion every four to six months, administered over two to three hours	Listed on PBS for bone metastases from breast cancer Not TGA approved for osteoporosis
Alendronate	1000x	Oral	Osteoporosis: 70 mg once weekly	Listed on PBS for osteoporosis in patients aged 70 years and older with confirmed osteoporosis and in patients with fracture due to minimal trauma
Ibandronic acid	5000x	Oral	Metastatic bone disease from breast cancer: 50 mg daily (also 6 mg intravenous infusion every four weeks, but private hospital authority required) Osteoporosis (off-label use): 150 mg once monthly	Listed on PBS for bone metastases from breast cancer Not TGA approved for osteoporosis Once-monthly 150 mg oral dose is registered overseas for osteoporosis treatment and prevention in postmenopausal women Infusion 3 mg/3 mL every three months is TGA approved for use in the treatment of postmenopausal osteoporosis but is not available
Risedronate	5000x	Oral	Osteoporosis: 35 mg once weekly or 150 mg once monthly (also 5 mg daily)	Listed on PBS for osteoporosis in patients aged 70 years and older with confirmed osteoporosis and in patients with fracture due to minimal trauma, and for corticosteroid-induced osteoporosis
Zoledronic acid	10,000x	Intravenous	Osteoporosis: 5 mg infusion once yearly, administered over 15 to 30 minutes, maximum of three doses	Listed on PBS for osteoporosis in patients aged 70 years and older with confirmed osteoporosis and in patients with fracture due to minimal trauma, and for corticosteroid-induced osteoporosis

ABBREVIATIONS: PBS = Pharmaceutical Benefits Schedule; TGA = Therapeutic Goods Administration.
* As of 1 April 2010. † Various authorities are required for the prescription of bisphosphonates on the PBS.

This may need to be balanced against gastrointestinal side effects (e.g. constipation) and possible cardiovascular risks, which are still debated. Vitamin D deficiency is common in patients with osteoporosis and contributes to the fracture risk. Cholecalciferol should be added if individuals have a serum 25-hydroxyvitamin D (25-OHD) level of less than 75 nmol/L.[8,9]

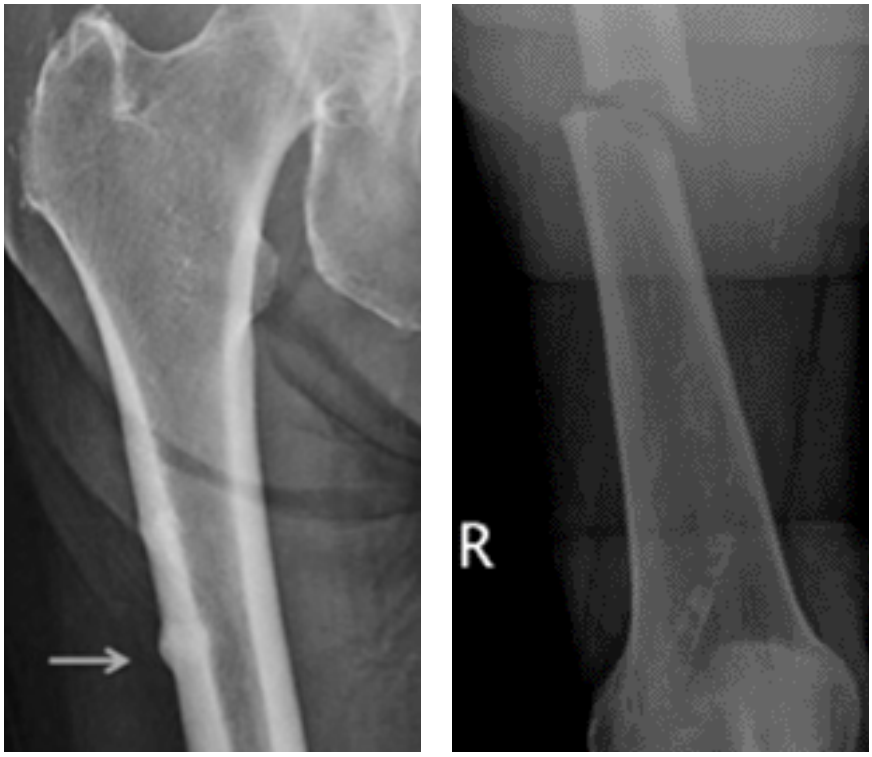
Individuals should be encouraged to modify lifestyle factors such as smoking and excessive alcohol intake because stopping smoking and reducing alcohol consumption may add to fracture risk reduction.

Drug persistence and adherence

Less than 40% of women persevere with long-term therapy with bisphosphonates for osteoporosis. Published studies demonstrate that the antifracture efficacies of bisphosphonates are reduced by at least 50% in women who comply poorly with their medications.[10,11] Men have been poorly researched in this respect, and data are not available.

Bisphosphonate side effects such as heartburn, gastrointestinal upset, bone pains and skin rashes often lead to poor compliance and reduced long-term adherence.[12] Many of the oral bisphosphonates are very poorly absorbed from the gut; alendronate and risedronate, for example, need to be taken on an empty stomach, in an erect position and at least 30 minutes prior to ingestion of a meal so as to allow for adequate gut absorption. Incorrect dosing may lead to suboptimal drug absorption and lack of efficacy.[12] Individuals must comply with the 'how to take' pharmaceutical instructions when administering their antiosteoporotic medications. Ingestion of any foods or liquids other than water may result in suboptimal absorption and reduced efficacy.

Changing to newer drug regimens – once-weekly (alendronate and risedronate) and once-monthly (risedronate) oral preparations or the once-yearly parenteral infusion (zoledronic acid) – have been shown to improve drug compliance.[13] Strict dosing instructions may lessen drug-related side effects, improve persistence and adherence and result in reduced risk of recurrent fractures.[12,14]



Figures 2a and b. Atypical femoral diaphyseal fractures in two individuals treated with long-term alendronate. a (left). Stress fracture with callus formation on the outer cortex of the femoral shaft. b (right). Complete transverse fracture through a previous stress fracture.

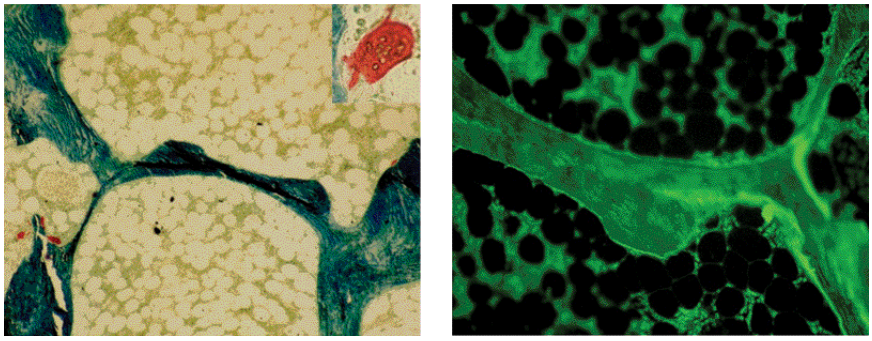
Secondary causes of osteoporosis

Recurrent fractures may occur in individuals with secondary causes of osteoporosis who receive antiosteoporotic agents and in whom their underlying disorder has been overlooked. Secondary causes of osteoporosis should be suspected in women aged over 40 years who suffer low trauma osteofragility fractures and those with a bone mineral density (BMD) Z-score of less than -2.0. Medical illnesses such as coeliac disease, blood dyscrasias (e.g. myeloma), hyperthyroidism, hyperparathyroidism, anorexia and vitamin D deficiency and medications such as corticosteroids may result in accelerated bone loss and an increased fracture risk.[15] Some of these disorders may not only cause a dramatic decline in BMD and alteration in bone quality but may also result in proximal muscle weakness and propensity to falling.

The premature onset of menopause, whether spontaneous or following chemotherapy, results in an increased lifetime fracture risk because these women live longer with a decreased bone density than do women who have natural menopause. Women with breast cancer treated with aromatase inhibitors can experience rapid rates of bone loss (since these medications cause profound oestrogen deficiency and resultant high bone turnover and net bone loss).[16] Similarly, men receiving androgen deprivation therapy for prostate cancer and those with 'silent' male testosterone deficiency are at increased risk (through

Table 3. Managing recurrent osteoporotic fracturing

- Investigate for causes of recurrent falls and severity of osteoporosis
- Check compliance with antiosteoporotic medication
- Check intake of calcium and vitamin D
- Encourage stopping smoking and limiting excessive alcohol intake
- Evaluate and treat possible secondary causes of osteoporosis
- Encourage participation in resistance and balance training exercise programs
- Optimise testosterone replacement in men with hypogonadism
- Assess bone turnover by measuring markers of bone resorption
- Treat severe osteoporosis more aggressively with an anabolic agent



Figures 3a and b. Histomorphometric changes of bone turnover suppression in a bone biopsy specimen taken from an individual with adynamic bone disease treated with long-term alendronate. a (left). Static bone histomorphometry showing minimal osteoid matrix synthesis on the surfaces of cancellous bone due to reduced osteoblast activity and large inactive osteoclasts with multiple nuclei lying dormant on the bone surface (see insert of a magnified view of an osteoclast) due to suppression of osteoclast activity by bisphosphonates. b (right). Low bone turnover demonstrated by the absence of tetracycline labels.

the low sex steroid levels of hypogonadism resulting in high bone turnover).[17]

Investigating for and treating the underlying cause may significantly reduce the risk of recurrent fractures. Detailed discussion relating to secondary causes of osteoporosis in women and men have previously been published in *Medicine Today*.[15,18]

Recurrent falls and repetitive trauma

Trauma remains the most common cause of recurrent fractures. Individuals who fall because of balance disorders due to oversedation, overtreatment with antihypertensive drugs or middle ear disease (vertigo), or because of poor vision (cataracts and age-related macular degeneration) or recurrent mini-strokes (microvascular cerebral disease) are susceptible to recurrent fractures.[19,20] Antiosteoporotic agents will not reduce their risk of falling and hence it is important to investigate and manage the specific causes of falling.

General practitioners have a critical role in assessing and managing the contributions of balance, vision and medications associated with falling. Although many patients fall, it is those who need assistance to regain their feet who are most at risk of fracture. Review by a geriatrician and an occupational therapist, enrolment in falls prevention and balance programs and the use of hip protectors are important strategies to minimise the risk of fracture.[21]

Abnormal bone remodelling and adynamic bone disease

Approximately 10% of the human skeleton is remodelled each year. Osteoblast activity (bone formation) and osteoclast activity (bone resorption) coupling and microdamage repair is crucial to maintaining a healthy skeleton.[22] Bone coupling is a mechanism whereby old bone is removed and replaced with new viable bone and stress risers (microfractures occurring along trabecular plates) are repaired. Normal bone turnover allows for microfracture repair and maintains optimal bone elasticity.

Antiresorptive agents act by inhibiting the bone remodelling cycle, inhibiting osteoclast bone resorption and allowing osteoblast bone formation to continue, with adequate bone formation to fill in the resorption pits. The antifracture efficacies of bisphosphonates relate to their avid binding affinity to hydroxyapatite crystals in bone, resulting in long-term skeletal retention. When given for protracted periods, large stores of the bisphosphonates are recycled in bone and may result in marked suppression of bone turnover. This can lead to adynamic bone disease in which the bone is homogenously hypermineralised, brittle and more susceptible to minimal trauma or spontaneous fracture.[23]

Atypical peripheral fractures were reported in the late 1980s when etidronate (a first-generation bisphosphonate) was used for treating various metabolic bone disorders.[24,25] It was administered as an oral continuous daily dosage and often for a protracted time. This regimen was shown to cause bone mineralisation defects and focal osteomalacia. Later developments led to the use of a cyclical regimen (a 400 mg daily dose administered for two weeks of a three-monthly cycle) designed to mimic the normal bone remodelling cycle without causing prolonged suppression of bone turnover. This regimen resulted in effective fracture risk reduction without untoward effects on bone.

More recently, isolated reports have emerged in the literature of atypical femoral diaphyseal and sacroiliac fractures occurring in individuals receiving long-term aminobisphosphonates (Figures 2a and b).[26-30] These newer agents – alendronate, risedronate and zoledronic acid – are many times more potent than etidronate because of their avid uptake, low desorption, higher reattachment and less diffusion in bone (high bone affinity). Bone biopsies taken from individuals receiving these agents have shown severe suppression of bone turnover (Figures 3a and b).[26]

Although the number of reports in the literature is growing, the incidence density (the person–time incidence rate) for a patient on a bisphosphonate sustaining atypical fractures is calculated to be as low as 1/1000 per year (95% confidence interval, 0.3–2).[29] Moreover, a review of 284 records for hip or femur fractures among 14,195 women in three trials – the Fracture Intervention Trial (FIT), the FIT Long-Term Extension (FLEX) trial and the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial (HORIZON-PFT) – found a total of only 12 fractures in 10 patients that were classified as occurring in the subtrochanteric or diaphyseal femur, a combined rate of 2.3 per 10,000 patient-years.[30]

Antiosteoporotic agents that significantly suppress bone turnover as part of their mechanistic effect to treat osteoporosis may, therefore, potentially cause harm with long-term use.[12,26-30] A fine balance is required to allow for 'optimal' inhibition of bone resorption yet allow sufficient turnover to repair microdamage. Individuals who sustain recurrent or atypical fractures and who have been treated with antiresorptive agents for more than five years require specialist referral and evaluation. However, it is often difficult to elucidate the cause for their recurrent fractures. Many have coexisting severe osteoporosis with BMD T-scores of less than -3.5 and remain at high risk of osteoporotic fractures. The decision to continue, suspend or change the treatment is a significant challenge that may warrant expert opinion.

Managing individuals with recurrent fractures

People who fracture recurrently usually require detailed evaluation and appropriate treatment, as described below and summarised in Table 3. Specialist referral is recommended.

Reducing falls

Patients should be investigated for the causes of recurrent falls and the severity of osteoporosis. GPs have a critical role in identifying individuals at risk of falling

and sustaining recurrent fractures. Resistance and balance training exercise programs have been shown to improve reflexes and muscle strength and reduce falls risk.[31]

Improving medication compliance and calcium/vitamin D status

Compliance with antiosteoporotic medication should be checked, as should also intake of calcium and vitamin D.

Repeat BMD monitoring and regular patient review may enhance patient compliance with antiosteoporotic medications. If there are problems with compliance, then an annual intravenous infusion of a potent bisphosphonate such as zoledronic acid may be preferred to daily, weekly or monthly tablets.

High-dose vitamin D supplements (3000 to 5000 IU daily) are required to correct severe vitamin D deficiency.[9]

Modifying smoking and alcohol consumption

Lifestyle modification regarding stopping smoking and limiting excessive alcohol consumption should be encouraged.

Treating secondary osteoporosis

Any secondary causes of osteoporosis should be evaluated and treated.[15]

Optimising testosterone replacement

Testosterone replacement therapy in men with hypogonadism in whom testosterone is not contraindicated should be optimised. There is no role for anabolic steroids in women who continue to fracture.

Assessing bone turnover

Bone turnover can be assessed by measuring the markers of bone resorption. These include the degradation products of type 1 collagen such as amino or C-terminal ends of carboxytelopeptides (NTX or CTX) or urinary deoxypyridinoline excretion rates.[32]

Elevated resorption markers in an individual treated with an antiresorptive agent such as a bisphosphonate may suggest poor compliance, suboptimal drug absorption or an underlying secondary cause.[33] In contrast, individuals treated with long-term bisphosphonates who are found to have suppression in bone resorption markers may be at risk for adynamic bone disease.

Treating severe osteoporosis

Severe osteoporosis may be treated more aggressively with an anabolic antiosteoporotic agent. There is no role for combining different classes of antiresorptive agents (e.g. a bisphosphonate with raloxifene or strontium ranelate).

Individuals with multiple spinal fractures (two or more) who continue to fracture despite 12 months of therapy with antiresorptive agents such as alendronate, risedronate, raloxifene and strontium ranelate may be considered for daily subcutaneous injections of the parathyroid hormone (1–34) fragment, teriparatide. This potent anabolic agent has been shown to reduce fracture risk by up to 70%.[34] Antiresorptive agents are ceased during the 18-month course of teriparatide therapy, but calcium and vitamin D supplements must be continued. Antiresorptive agents should be recommenced after the course is completed. Treatment with teriparatide requires specialist supervision and monitoring of serum calcium levels.

Summary

The effective management of individuals with osteoporosis should include not only the prescribing of an antiosteoporotic agent but also regular encouragement to ensure persistence and adherence with medication. Repeat bone densitometry and the use of bone resorption markers may be useful for confirming both compliance and efficacy. Resistance and balance training exercise programs improve reflexes and muscle strength and reduce the risk of a patient falling. Reports of atypical femoral fractures should not detract from prescribing appropriate therapies. However, caution and avoidance of indefinite long-term exposure to bisphosphonates must be considered in all patients.

General practitioners are well placed to identify individuals at risk for falling and sustaining recurrent fractures and a recently released NHMRC-approved guideline from the Royal Australian College of General Practitioners provides evidence-based recommendations to help them manage postmenopausal women and older men (over 60 years of age) with osteoporosis.[35] MT

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A list of references is available on request to the editorial office.

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