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Postoperative Cognitive Dysfunction (POCD) and Markers of Brain Damage After Big Joints Arthroplasty

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1. Introduction

Brain dysfunction can manifest itself either as focal lesions or mental impairment (Roach et al., 1996). In orthopedic patients, in comparison to any other group of hospitalized people, cognitive dysfunction was present more often. It included a deterioration of perception, memory, information analysis, attentional focus as well as of concentration and decreased patients' response (L. S. Rasmussen, 1998). When occurring after a surgery, the symptoms were defined as Postoperative Cognitive Dysfunction (POCD) (Newman, Stygall, Hirani, Shaefi, & Maze, 2007) and were nonspecific signs of brain disorders resulting from cellular abnormalities. Very often the dysfunction's nature was subclinical and no changes in diagnostic imaging were present (Wu, Hsu, Richman, & Raja, 2004). As a consequence, the hospitalization time was longer, the outcome and quality of life were worsened as well as prolonged medical and social assistance were necessary (Gao et al., 2005; Veering, 1999). The problem concerned up to 26% of elderly patients during the first week after a non-cardiac surgery (Rohan et al., 2005). Amongst 60-year-old patients who underwent major surgical procedures under general anesthesia lasting over 2 hours, 10% suffered from memory impairment and concentration problems for more than 3 months after the surgery. The disorder occurs twice more often in 70 – 80-year-old people in comparison to 60 – 70-year-olds (Harwood, 2000). According to statistic data, about 70% of the patients with POCD die within 5 years compared to about 35% of the patients without postoperative delirium (Fodale, Santamaria, Schifilliti, & Mandal, 2010).

All above data were alarming, but the problem seemed to be more complex. The diagnosis of POCD depends on performing a proper assessment of the cognitive function before and after the surgery through a battery of neuropsychological tests, so the incidence of POCD varies. According to the work of Blaise et al., the variability can result from nonstandardization of neuropsychological tests performed at different times of the day, lack of a control group, differences in significance levels between studies as well as from the so-called "learning effect", as when the same test is applied to the same person many times (Blaise, Taha, & Qi, 2007). Another question concerns the time at which the diagnosis of POCD was made. Different drugs administered in the perioperative period can affect patients' cognition. Thus some authors believe that the diagnosis of POCD should be made not earlier than 2 weeks after the surgery (Blaise, et al., 2007).

2. Surgery induced stress response and risk factors of POCD

Surgery induced stress response leads to [1] the activation of the sympathetic nervous system, [2] increased secretion of pituitary hormones, and [3] immunological as well as hematological changes (Desborough, 2000).

Activation of the sympathetic nervous system leads to an increased secretion of catecholamines from the adrenal medulla and of norepinephrine from presynaptic nerve terminals. It results in such cardiovascular effects as tachycardia and hypertension (Desborough, 2000).

The secretion of adrenocorticotrophic hormone (corticotrophin, ACTH), growth hormone (GH) and arginine vasopressin (AVP) increases; the secretion of thyroid-stimulating hormone (TSH) as well as of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) may increase or decrease. As a result, the secretion of cortisol and aldosterone increases; that of insulin often decreases, while that of glucagone usually decreases; and, finally, decreases, and the secretion of thyroxine and tri-iodothyronine decreases. All those changes influence the metabolism of carbohydrates, proteins and fat as well as that of salt and water (Desborough, 2000).

Immunological and hematological changes include cytokine production, acute phase reaction, neutrophil leucocytosis and lymphocyte proliferation (Desborough, 2000). Cytokines - mainly interleukin-1 (IL-1), tumor necrosis factor- α (TNF- α) and IL-6, released from activated leukocytes, fibroblasts and endothelial cells - play an important role in the systemic inflammatory reaction (Desborough, 2000). Some authors (Blaise, et al., 2007; Singh & Antognini, 2010; Van Munster et al., 2009) suggest that inflammation plays a substantial role in the pathogenesis of POCD. Their claim was supported by the observation that cyclooxygenase-2 (COX-2) inhibitors protect the amyloid β -induced memory disturbances in mice (Blaise, et al., 2007). The animal studies also showed that the development of POCD in rats was associated with glial activation and the expression of proinflammatory cytokines within the hippocampal region (Blaise, et al., 2007). Some studies revealed the role of interleukin-18 (IL-18) in the neuroinflammation and neurodegeneration of the central nervous system. Patients with a defect in the IL-18 cytokine promoter gene had a higher concentration of serum amyloid peptides (Fodale, et al., 2010). The amyloid β peptide concentration was related to learning and memory deficiencies as well as to neurodegeneration. Continuous infusion of amyloid β peptide in rats resulted in learning and memory impairments. Higher levels of amyloid β peptide in the hippocampus were observed in older rats when compared to those in younger ones (Fodale, et al., 2010). Some anesthetic agents can influence the amyloid β production. Isoflurane increases the amyloid β production through an alteration in the processing of amyloid precursor protein; desflurane also causes an increase, but only in the presence of hypoxia. Propofol and thiopental do not significantly change the amyloid precursor protein (Fodale, et al., 2010).

The following were counted as risk factors of POCD in an early postoperative period: advanced age, a general anesthesia rather than a regional one, an increasing duration of anesthesia, poor education, re-operation, postoperative infections, postoperative respiratory complications, lower preoperative level of consciousness, and treatment with cholinergic drugs and benzodiazepines, but also sleep deprivation, isolation, noise, bright light and such physiologic disturbances as hyponatremia or hypoalbuminemia as well as male sex, depression or reduced activity in daily life (Blaise, et al., 2007; Canet et al., 2003; Fines & Severn, 2006; Kyziridis, 2006; Singh & Antognini, 2010; Veering, 1999). Oddly enough, there

was no evidence that hypoxemia is associated with the development of POCD (Fines & Severn, 2006). Some studies found that hypotension was the only intraoperative risk factor responsible for postoperative delirium (Kyziridis, 2006). However, other authors did not support that observation (Fines & Severn, 2006).

Some authors discussed the role of genetic factors in the pathogenesis of neurodegenerative disorders. They found an association between the apolipoprotein $\epsilon 4$ (APO- $\epsilon 4$) allele and Alzheimer's disease (Blaise, et al., 2007), so the APO- $\epsilon 4$ gene could be a predictor of postoperative cognitive disorders (Fodale, et al., 2010).

3. Etiology of POCD

The high incidence of cognitive dysfunction in orthopedic patients can result (apart from the above mentioned risk factors) from long bone fractures, prolonged immobilization, and partially from perioperative stress (Wu, et al., 2004) or a surgery technique. Colonna et al. concluded that the incidence of cerebral embolization after lower extremities arthroplasties was up to 40 – 60% (Colonna et al., 2002). Thromboembolic events played an important etiological role. There were described fatal cerebral embolizations that constituted complications accompanying long bones fractures (Riding et al., 2004), total knee replacements (Jenkins, Chung, Wennberg, Etchells, & Davey), hip arthroplasties (Fallon, Fuller, & Morley-Forster, 2001), and vertebroplasties (Scroop, Eskridge, & Britz, 2002) in which the embolic material passed into the brain through an open foramen ovale (Sukernik, Mets, & Bennett-Guerrero, 2001), although postmortem examinations did not reveal it (Colonna, et al., 2002).

3.1 Biomarkers of brain damage

Biochemical tests are useful diagnostic tools in the examinations of functional brain disorders. Elevated serum concentrations of the markers of brain damage indicate that there has been a neuronal and/or glial injury. The biomarkers are released as a consequence of either transient ischemia or ultimate cell degradation, and their serum concentration depends on the localization of pathological changes, the degree of tissue damage and the time that has passed since the onset of changes.

The ideal marker of brain damage should be: [1] highly specific, [2] highly sensitive, [3] released in cases of an irreversible damage to cerebral neurons only, [4] possible to detect in the blood and/or cerebrospinal fluid within a short period of time after the injury, and [5] released in well-known time sequences after the injury; furthermore, it ought to be [6] age- or sex-independent, [7] easily detectable in the blood since frequent drawing of cerebrospinal fluid samples is impractical, and [8] its concentration should be easily measureable in laboratory tests (Ingebrigtsen T). Many compounds were investigated for this purpose of founding such a marker. In the '70s, it was lactic dehydrogenase (LDH) and aspartate aminotransferase (AspAT); in the '80s, creatine kinase BB isoenzyme (CK-BB); and later, the S100B protein and neuron-specific enolase (NSE). Nowadays, glial fibrillary acidic protein (GFAP) seems most promising (Ingebrigtsen & Romner, 2003). The latter three (the S100B protein, NSE and GFAP) were the best known biomarkers of brain damage (Ingebrigtsen & Romner, 2003; L. E. Pelinka, 2004). Of these the S100B protein is thought to correspond the best to the optimal indicator of a neuronal injury (Ingebrigtsen & Romner, 2003).

3.2 S100B protein

In 1965, Moore isolated from the bovine brain a fraction containing brain specific proteins (Kleindienst & Ross Bullock, 2006). Since then, our knowledge about the above mentioned compounds has increased. Currently, the S100B proteins family consist of 24 members, with similar structures and like functions (Marenholz, Heizmann, & Fritz, 2004).

They play different roles in the human body and are present in many types of cells and tissues (Eckert et al., 2003). Some members of the S100 protein family are specific for certain localizations (Heizmann, 2004). High S100B protein concentrations were present inside the brain, mainly in astroglial and Schwann cells (Ali, Harmer, & Vaughan, 2000; L. E. Pelinka, 2004) as well as in adipocytes, chondrocytes and melanocytes (L. E. Pelinka, 2004; Raabe et al., 2003). The S100B protein can be either actively released into the extracellular space or passively excreted after cell death (L. E. Pelinka, 2004). An animal study revealed high S100B concentrations in cerebral regions injured by chronic ischemia (Ohtani et al., 2007).

In 2003, there was published a review of 18 clinical studies (involving 1085 patients) of the S100B protein as a marker of brain damage (Kleindienst & Ross Bullock, 2006). In 2004 and 2005, another 6 papers appeared (involving more than 600 adults) on the correlations between an elevated concentration of the S100B protein and poor outcome after brain injury (Kleindienst & Ross Bullock, 2006). The highest S100B protein serum level was observed just after an injury (Ingebrigtsen & Romner, 2003), then normalized within 24 hours, even in patients with poor outcome (Kleindienst & Ross Bullock, 2006). The study of Raabe and Seifert showed an increased concentration of the S100B protein on the 6th day after head trauma, probably as a result of a secondary injury (Kleindienst & Ross Bullock, 2006). The elevated posttraumatic S100B protein concentration was also demonstrated in an animal model (Kleindienst & Ross Bullock, 2006).

The increased concentration of the S100B protein can be a result of an increased permeability of the blood-brain barrier, regardless of cerebral damage (Kleindienst & Ross Bullock, 2006). The results of animal studies suggested that S100B protein levels correlated with the degree of shock: in moderate shock they were higher than in a severe one (L. E. Pelinka, 2004). The S100B protein concentration was increased just after bilateral long bones fractures as well as after local ischemia and the reperfusion of the liver, gut and kidneys (L. E. Pelinka, 2004). Elevated levels of S100B protein were shown in basketball and hockey players after competitions as well as in runners, boxers (Stalnacke, Tegner, & Sojka, 2003), swimmers and soccer players; although in the latter there was a correlation between an increased protein concentration and the frequency of head injury (Stalnacke, Ohlsson, Tegner, & Sojka, 2006). There was a possibility that some amounts of the S100B protein were released from red cells, melanocytes and steatocytes. The protein's origin – whether it was extra- or intracerebral – remains unclear. If it was of cerebral origin, the question is whether it was released due to an astroglial injury or activation, or as an effect of the blood-brain barrier impairment (Stalnacke, et al., 2003). Stress and physical effort can lead to an increased permeability of the blood-brain barrier (Stalnacke, et al., 2006). In some cases, a raised plasma level of the S100B protein was an effect of long bones fractures, multiple traumas and surgical procedures. It also occurred in melanoma patients (Salama, Malone, Mihaimeed, & Jones, 2008) and in sepsis-associated encephalopathy (Piazza, Russo, Cotena, Esposito, & Tufano, 2007).

The possibility that the S100B protein could be released from extracerebral localizations as well confines its utility as a marker of brain damage, which, nonetheless, still ranges from 70 to 80% (Raabe, et al., 2003). The S100B protein was a very useful biochemical tool

because of its short (below 30 minutes) half-life (Ingebrigtsen & Romner, 2003; Raabe, et al., 2003) as well as sex and age non-dependent serum concentrations (Ingebrigtsen & Romner, 2003). Neither alcohol overdose nor hemolysis altered its concentration (Raabe, et al., 2003). The S100B protein was stable in solution, there was no need to centrifuge and freeze its samples (Raabe, et al., 2003). Contemporary biochemical tests measure either S100B or S100A1B and S100BB serum levels. Because S100BB is considered to be the most brain-specific unit, its determination could eliminate the influence of the extracerebrally released S100B protein (Raabe, et al., 2003).

3.3 S100B protein in orthopedic patients

There were a few papers on the S100B protein in orthopedics only.

Kinoshita et al. (Kinoshita et al., 2003) examined 14 patients; half of them underwent total knee arthroplasty (TKA) with bone cement, the other half underwent intramedullary nail stabilization of the tibia. All the procedures were performed with tourniquet and ischemia. In the TKA group, in blood samples withdrawn 15 minutes after tourniquet release, there was a statistically significant elevation of the S100B serum level in comparison to the group where tibial fracture was stabilized with an intramedullary nail. The authors suggested that the increase was due to a transient injury of brain tissues caused by bone cement (Kinoshita, et al., 2003).

An increased serum concentration of the S100B protein was observed after injuries which did not include brain damage. The highest levels were noted in patients with long bones fractures (Anderson, Hansson, Nilsson, Djlai-Merzoug, & Settergren, 2001). Studies on people with isolated bone fractures without brain injury revealed that patients with hip, radius or tibia fractures had significantly higher concentrations of the S100B protein, but those with phalanges, hand or foot fractures did not (Undén et al., 2005). In animal studies there were increased S100B serum levels after bilateral femur fractures in rats (L. Pelinka et al., 2003). These results indicated that bone marrow could be a potential source of the S100B protein.

During orthopedic cement was used for fixing the elements of the prosthesis to the bone basis. The use of cement can lead to hemodynamic instability, a decrease in cardiac output, heart contractility, systemic vascular resistance and blood pressure, i.e. to the so-called bone cement implantation syndrome (Donaldson, Thomson, Harper, & Kenny, 2009). Hemodynamic changes have an impact upon cerebral perfusion, as in the relation between the S100B concentration and the degree of shock that has been discussed above (L. E. Pelinka, 2004). Although the presence of bone cement inside the medullar cavity itself did not produce hypotension, hemodynamic instability is often observed when hammering the prosthesis stem into the bone (Sharrock, Beckman, Inda, & Savarese) - the pressure inside the marrow cavity increases. The higher the pressure, the better the penetration of the cement into the bone and the greater the strength of osteosynthesis. But due to the increased pressure, the translocation of the cellular material originating at the site of the surgery into the systemic circulation was facilitated, and the said material could reach the lungs via the bloodstream. The diameter of the lung capillaries is about 8 μm . In 1956, Niden and Aviado showed that there was a possibility of transferring glass spheres up to 420 μm in diameter through the pulmonary vessels (Nunn, 1981). The second way of going round the pulmonary filter was via the foramen ovale. In 1/3 of the population it is closed only functionally. Thus, it is a way for transferring the embolic material into the brain. The presence of cellular material from the site of the surgery in the circulation can be shown with an ultrasound examination as a "snow flurry." In the work of Hayakawa et al.

(Hayakawa, Fujioka, Morimoto, Okamura, & Kemmotsu, 2001), the “snow flurry” was observed from the beginning of the reaming of the femoral canal until the end of the surgery and it intensified especially while the cemented prosthesis stem was being inserted into the bone. This was not noted during procedures without bone cement use. A histological examination of the elements forming the “snow flurry” revealed the presence of amorphous eosinophilic particles with fibrin attached to their surface. The same was noted in patients who had undergone cemented hip arthroplasty during the whole procedure, either before or after bone cement use. In none of the samples were fat particles or bone marrow detected; the authors thought that they had examined “bone dust” particles with attached fibrin fibers (Hayakawa, et al., 2001). The work was limited to a relatively small group: only 7 patients were examined. In the study of Kim et al., the histological examination of samples from the right atrium revealed the presence of fat particles in 34 and 44% as well as of bone marrow cells in 13 and 11% of the procedures, with and without bone cement use, respectively (Kim, Oh, & Kim, 2002). The contribution of bone cement to the etiology of thromboembolic events was suggested (Scroop, et al., 2002). Clark and al. showed a transient, but statistically significant, decrease of cardiac output, by 33%, and of stroke volume, by 44%, during procedures with bone cement use; before the use of bone cement there were no changes between the two (the cemented and the cementless) groups. Because embolic material was released either before or after bone cement use, the decrease in cardiac output and stroke volume might have been followed by the embolic material originating from bone marrow or a vasodilatation caused by a monomer (Clark, Ahmed, Baxendale, & Moran, 2001). Dog studies showed that an intravenous injection of the acrylic acid monomer does not affect the partial pressures of oxygen and carbon dioxide in the arterial blood. Mild and transient hypotension was observed while monomer concentration in the pulmonary artery was much higher than that noted in usual clinical situations (Concepcion, 1998).

The author of the present chapter examined changes in S100B protein levels in patients who underwent total hip arthroplasty, with or without bone cement use. In both groups of patients the mean preoperative concentration of the S100B protein was comparable to that in healthy subjects and reached its maximum just after the operation. In the cemented group its level was significantly higher than in the cementless one and normalization was slower. The operation technique in both types of hip arthroplasty was similar. The elevated serum S100B protein levels may be a result of the S100B protein release from bone marrow as well as of the transfer of cellular materials from the site of the surgery with the bloodstream into the brain (Edmonds, Barbut, Hager, & Sharrock, 2000; Ozelsel et al., 1998; Sukernik, et al., 2001). Because all patients with intraoperative mean blood pressure dropping below 50 mmHg were excluded from the study, it ruled out hypotension as a possible cause of the elevation of the S100B concentration. We concluded that the most probable cause of an increased S100B protein was bone cement use (Kinoshita, et al., 2003; Scroop, et al., 2002). The exothermic polymerization reaction is not always complete because the monomer particles' mobility decreases with the progression of this process. After its completion, 2 to 6% of the monomer remains; it yields to late polymerization to a limited degree, partially transferring into the circulation (Kuhn, 2005). Due to which, the normalization of the elevated S100B protein level in the cemented group was slower.

3.4 POCD and anesthesia

There were discussions on the influence of different types of anesthesia (general vs. regional) on elderly patients. Neither had advantages for the recovery of cognitive functions

in geriatric patients during the first three days after the surgery (Dahn et al., 1999). Randomized clinical studies did not show a prevalence of any special kind of anesthesia in POCD prevention (Wu, et al., 2004). Moreover, in 2009, Avidan et al. (Avidan et al., 2009), in his retrospective cohort study including 575 patients, did not find a long-term cognitive impairment due to surgery and illness. But in the ISPOCD study a higher incidence of postoperative cognitive dysfunction was observed after total hip and knee arthroplasties. In both these groups the serum level of the S100B protein was significantly higher, regardless of the diagnosis of POCD in the postoperative period (Linstedt et al., 2002).

Such was the conclusion from both statistic and bibliographic data. However, the central cholinergic system has been identified as the basic system of neurotransmitters taking part in the regulation of the level of conscience, memory and learning (Fodale, et al., 2010), and the interactions between anesthetic drugs and this system may be important in the pathogenesis and development of POCD. There are two main classes of cholinergic receptors: nicotinic and muscarinic. Nicotinic acetylcholine receptors (nAChRs) are ligand-gated cation channels and muscarinic acetylcholine receptors (mAChRs) are ligand-gated K^+ channels, divided into five subtypes (M1 – M5). The agonists of central mAChRs and nAChRs may improve, while the antagonists might impair performance in cognition, learning and memory (Fodale, et al., 2010). Volatile anesthetics and ketamine are potent inhibitors of nAChRs. Desflurane selectively binds the M1 subtype, sevoflurane depresses the M1 and M2 subtypes, whereas isoflurane interferes with the M3 subtype only. All barbiturates are competitive antagonists of mAChRs. Propofol acts on mAChRs and nAChRs, but in concentrations higher than those used clinically. Fentanyl and morphine inhibit signals mediated by both types of receptors and remifentanyl does not change the release of acetylcholine from cholinergic nerves. Furthermore, for example neuromuscular blocking agents or neostigmine administered during general anesthesia can influence cholinergic transmission. The interactions between anesthetics and amyloid β peptide have been discussed above. Thus, it is possible that general anesthesia could be a factor in the pathogenesis of POCD (Fodale, et al., 2010). However, in his study, Hudetz et al. (J. Hudetz et al., 2009; J. A. Hudetz et al., 2009) found that a single administration of ketamine, 0.5 mg/kg, during the induction of anesthesia reduced the incidence of POCD to one week after a cardiac surgery. The authors concluded that it was due to the anti-inflammatory properties of ketamine.

In some cases, an increased concentration of the S100B protein was an effect of an increased permeability of the blood-brain barrier (Kleindienst & Ross Bullock, 2006). In such cases regional anesthesia with intravenous sedation can be effective in limiting surgery-induced stress and the inflammatory reaction of the human organism. In reducing stress it diminished a possible cause of the elevated S100B protein concentration. Regional anesthesia decreased mortality and the incidence of POCD in the early postoperative period (L. Rasmussen et al., 2003; Williams-Russo, Sharrock, Mattis, Szatrowski, & Charlson, 1995). That was confirmed by the observations made by patients under general anesthesia; those with lower values of the Bispectral Index (BIS) had lesser disturbances in cognitive functions, especially in information processing, between the 4th and 6th weeks after the surgery (Farag, Chelune, Schubert, & Mascha, 2006). But there still remained the question concerning the influence of anesthesia and sedation - particularly of anticholinergic therapy (1st generation of antihistaminics) and long-lasting benzodiazepines - on postoperative cognitive functions. An increased S100B protein serum level was observed during a therapy with β -adrenergic agonists and phosphodiesterase inhibitors (Linstedt, et al., 2002).

According to Sharrock et al. (Sharrock et al., 2005), there occurred a worsening of test-evaluated cognitive functions occurred during the first hour after the surgery, with significant improvement during the second hour. However, in patients aged over 70 years the problem can last longer (Sharrock, et al., 2005), probably due to the influence of centrally acting analgesics administered after the operation. Insufficient postoperative analgesia, hypoglycemia, hypotension and hypoxaemia may all be important.

There were studies (Herrmann et al., 2001; Kilminster, Treasure, McMillan, & Holt, 1999; Snyder-Ramos et al., 2004) showing that an elevated serum S100B protein correlated with a worsening of the results of neuropsychological tests, while in some papers those correlations (Anderson, 2002) were not observed. Patients after cardiac surgery with an increased serum S100B concentration who showed any signs of brain injury had a shorter time of survival (Johnsson, 2000); thus, an elevated level of the S100B protein may reflect subclinical brain damage. Linstedt et al. (Linstedt, et al., 2002) did not observe any differences in S100B protein serum concentrations in urological patients, irrespective of the presence (or absence) of signs of POCD, but in all the patients after hip or knee arthroplasty an increased serum level of the S100B protein was noted, regardless of the presence (or absence) of POCD. An elevated concentration of the S100B protein may partially reflect a release of the protein from an extracerebral localizations, e.g. from bone marrow. During bone cement use, however, one of the reasons of an increased S100B protein level may be a thermal bone marrow injury, or an injury to the brain or red blood cells.

4. Summary

Cognitive dysfunctions in hospitalized patients were important clinically and socially, but difficult to analyze methodologically. Disturbances at the cellular level can manifest themselves as mood disorders and lead to a deterioration in the patients' functioning and their social assessment. It is very difficult to define either the normal state or the pathology of cognitive functions.

Although there was no agreement as to the correlation between an increased serum concentration of the S100B protein and the results of neuropsychological tests, we know that the measurement of the S100B protein as a single parameter was not sufficient to anticipate the occurrence of POCD in the postoperative period following orthopedic procedures.

The identification of patients with preexisting risk factors of POCD, shortening the period of time preceding the surgery and a proper technique of the procedure as well as physical and intellectual exercises, nutrition and medication (Blaise, et al., 2007) play an important role in decreasing the incidence of neurocognitive deficits in the elderly.

5. References

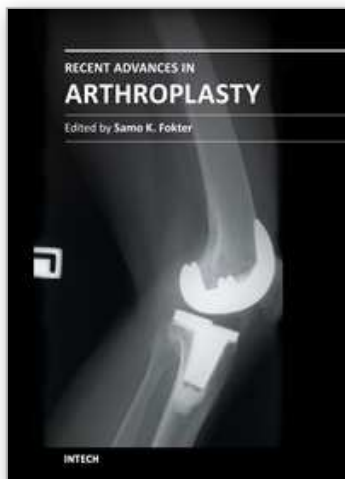
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The purpose of this book was to offer an overview of recent insights into the current state of arthroplasty. The tremendous long term success of Sir Charnley's total hip arthroplasty has encouraged many researchers to treat pain, improve function and create solutions for higher quality of life. Indeed and as described in a special chapter of this book, arthroplasty is an emerging field in the joints of upper extremity and spine. However, there are inborn complications in any foreign design brought to the human body. First, in the chapter on infections we endeavor to provide a comprehensive, up-to-date analysis and description of the management of this difficult problem. Second, the immune system is faced with a strange material coming in huge amounts of micro-particles from the tribology code. Therefore, great attention to the problem of aseptic loosening has been addressed in special chapters on loosening and on materials currently available for arthroplasty.

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