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N-3 Polyunsaturated Fatty Acids in Health and Disease - Clinical and Molecular Aspects

Thesis for the degree of philosophiae doctor

Trondheim, June 2009

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Omega-3 Flerumettede Fettsyrer og Helse – Kliniske og Molekylære Aspekter

Omega-3 fettsyrer tilhører gruppen essensielle fettsyrer. Det betyr at vi ikke kan lage dem selv, men at de må tilføres gjennom kosten, hvor de bl.a. finnes i fet fisk, plantefrø, oljer og nøtter. I kroppen brukes de bl.a. som byggesteiner i hjernevev, øyet og cellemembraner, og til å lage en rekke forskjellige signalmolekyler. Studier tyder på at disse fettsyrene kan ha helsebringende effekter på mange områder, deriblant hjerte- og karsykdommer, betennelsestilstander og kreft. Et for lavt inntak av omega-3 fettsyrer er skadelig. Dagens metoder er ikke ideelle for å påvise for lavt omega-3 kostinntak. Vi har derfor undersøkt om måling av genuttrykket av Δ-6 og Δ-5 desaturaser, som er viktige i omdannelsen av fettsyrer, kan brukes som en markør på omega-3 ernæringsstatus. Vi fant at hvite blodceller i cellekultur oppregulerte genuttrykket av desaturasene når omega-3 fettsyrer manglet. Tilsvarende fant vi at genuttrykket av desaturasene var høyere hos friske forsøkspersoner som ikke spiste fiske enn hos dem som spiste fisk. Denne forskjellen forsvant etter to uker med omega-3 tilskudd. Dette indikerer at genuttrykket av desaturasene er regulert av kostinntaket av omega-3 fettsyrer, men det trengs ytterligere studier for å fastslå om dette kan benyttes diagnostisk til å påvise et for lavt kostinntak av disse essensielle fettsyrene.

Flere befolkningsstudier viser at et høyt inntak av omega-3 fettsyrer er assosiert med lav forekomst av visse typer kreft. Dette er best dokumentert for bryst-, prostata- og tykktarmskreft. I cellekultur hemmer omega-3 fettsyrer vekst av kreftceller og gir programmert celledød (apoptose). Imidlertid er de molekylære mekanismene involvert uklare. Studier av genuttrykket til humane leukemiceller (HL60) behandlet med omega-3 fettsyren EPA, viste aktivering av et signalspor kalt ufoldet protein respons (UPR). Dette er en normal stress- og forsvars respons som gir cellene en mulighet til å gjenopprette likevekten og reparere skader før de fortsetter normal cellesyklus. Dersom stresset er for stort kan cellen gå i apoptose. Endringer i kalsiumnivåer i cellen kan utløse UPR. E2R2 celler, en klon av HL60 celler, er motstandsdyktige mot visse endringer i kalsiumnivået. De var mindre følsomme for EPA, og fikk ikke aktivert UPR responsen. Det er derfor sannsynlig at den veksthemmende effekten til EPA skyldes endringer i kalsiumlikevekten, som igjen aktiverer UPR responsen. Vi undersøkte også hvordan fettsyren DHA hemmer vekst av ondartede tykktarmskreftceller (SW620). Analyser av gen- og proteinutrykk viste at flere målproteiner for cellegift i kreftbehandling ble påvirket gunstig. I motsetning til cellegift, er omega-3 ufarlig og uten bivirkninger. Resultatene indikerer at omega-3 kan ha en plass i kreftbehandling, for eksempel i kombinasjon med dagens terapimetoder. Flere studier er nødvendige for å fastslå om behandling med omega-3 kan redusere bruken og/eller øke effekten av konvensjonell kreftbehandling. De foreløpige resultatene synes imidlertid allerede nå å kunne gi grunnlag for å anbefale kreftpasienter omega-3 tilskudd.

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Veiledere:	**Svanhild A. Schønberg og Kristian S. Bjerve**

Finansieringskilder:	**Norges teknisk-naturvitenskapelige universitet, Kreftfondet ved St. Olavs Hospital og Norges Forskningsråd (FUGE, Småforsk)**

Overnevnte avhandling er funnet verdig til å forsvares offentlig
for graden PhD i molekylærmedisin
Disputas finner sted i Auditoriet LA21, Laboratoriesenteret, St Olavs Hospital, Trondheim
5. juni 2009, kl 12.15

Contents

Acknowledgments

This work has been carried out at the Department of Laboratory Medicine, Children's and Women's Health, the Norwegian University of Science and Technology (NTNU) and the Department of Medical Biochemistry, St. Olavs Hospital HF.

I would especially like to thank my supervisors Kristian S. Bjerve and Svanhild A. Schønberg and my co-workers for all help, encouragement and inspiration.
Thanks to Merete Mack for teaching me the basics of cell culturing. Thanks to Mona Kvitland for teaching me RNA-isolation and RT-PCR. Thanks to Ketil Thorstensen for all help with the desaturase project and manuscripts. Thanks to Gro Leite Størvold for useful discussions, help and advice on western blotting and the project in general. Thanks to Caroline Hild Jakobsen for teaching and helping me with the microarray experiments. Thanks to Professor Hans E. Krokan. Thanks to Turid Follestad at the Department of Mathematical Science (NTNU) for performing the statistical analysis of the microarray experiment. I would also like to thank to Hilde Bremseth and Anne Gøril Lundemo.

Finally, I would like to thank my friends and family for your help and support.

Jens Erik Slagsvold

Trondheim, March 2009

List of papers

Paper I:

Slagsvold JE, Thorstensen K, Kvitland M, Mack M and Bjerve KS. *Regulation of desaturase expression in HL60 cells.* Scand J Clin Lab Invest. 2007; 67(6): 632-42.

Paper II:

Slagsvold JE, Thorstensen K, Kvitland M, Erixon D, Knagenhjelm N, Mack M and Bjerve KS. *Fatty acid desaturase expression in human leukocytes correlates with plasma phopholipid fatty acid status*. Scand J Clin Lab Invest. 2009. In press.

Paper III:

Slagsvold JE, Pettersen CHH, Follestad T, Krokan HE and Schønberg SA. *The antiproliferative effect of EPA in HL60 cells is mediated by alterations in calcium homeostasis.* Lipids. 2009; 44(2): 103-13.

Paper IV:

Slagsvold JE, Pettersen CHH, Størvold GL, Follestad T, Krokan HE and Schønberg SA. *DHA alters expression of target proteins of cancer therapy in malignant colon cancer cell line.* Manuscript submitted.

Abbreviations

5-FU	5-fluorouracil
ALA	α-linolenic acid (18:3 n-3)
Apaf-1	apoptotic peptidase activating factor 1
ATF4	activation transcription factor 4
ATF6	activating transcription factor 6
Bcl-2	B-cell CLL/lymphoma 2
BiP/GRP78	immunoglobulin heavy chain-binding protein/glucose-regulated protein of 78 kDa
BHT	butylated hydroxytoulene
Cdc25c	cell division cycle 25 homolog c
CDK1/Cdc2	cyclin-dependent kinase 1
CDK2	cyclin-dependent kinase 2
CDK4	cyclin-dependent kinase 4
CDK6	cyclin-dependent kinase 6
CHOP/Gadd153	growth arrest- and DNA damage-inducible gene 153/C/EBP-homologous protein
CNS	central nerve system
D5D/FADS1	delta 5 desaturase
D6D/FADS2	delta 6 desaturase
D9D/SCD	delta 9 desaturase
DHA	docosahexaenoic acid (22:6 n-3)
Ec	econazole
EDEM	ER degradation-enhancing α-mannosidase-like protein
eIF2α	eukaryotic translation initiation factor 2, α subunit
EPA	eicosapentanoic acid (20:5 n-3)
ER	endoplasmic reticulum
ERAD	ER-associated degradation
FA	fatty acid
FBS	fetal bovine serum
FDR	false discovery rate
G6PDH	glucose-6-phosphate dehydrogenase
GADD34	growth arrest and DNA damage gene 34
GADD153/CHOP	growth arrest- and DNA damage-inducible gene 153/C/EBP-homologous protein
GC	gas chromotography
GCOS	GeneChip® Operating Software
GLA	gamma-linolenic acid (18:3 n-6)
GO	Gene onthology
HDAC3	histone deacetylase
HGLA	dihomogamma-linolenic acid (20:3 n-6)
IAP	inhibitors of apoptosis
IP3R	inositol 1,4,5-triphosphate receptor
IRE1	inositol-requiring enzyme 1
LA	linoleic acid (18:2 n-6)

MAPK	mitogen-activated protein kinase
MEAD	mead acid (20:3 n-9)
MM	mismatch
NF-κB	nuclear factor-kappaB
OA	oleic acid (18:1 n-9)
PA	palmitoleic acid (16:1 n-7)
PBMC	peripheral blood mononuclear cells
PBS	phosphate buffered saline
PBST	phosphate buffered saline with 1 % Tween-20
PCNA	proliferating cell nuclear antigen
PERK/PEK	PKR-like ER protein kinase/pancreatic eIF2α kinase
PL	phopsholipids
PPARs	peroxisome proliferators-activated receptors
PUFA	polyunsaturated fatty acid
RB	retinoblastoma protein
RyR	ryanodine receptor
RT-PCR	realtime polychainreaction
SA	stearic acid (18:0)
SERCA	Sarco/Endoplasmic-Reticulum- Ca^{2+}-ATPases
SOC	store-operated Ca^{2+} channels
SQSTM1	sequestosome-1
TBE	trisborate
TBST	Tris-buffered saline Tween-20
TGT	Target intensity value
tLivin	truncated livin
UPR	unfolded protein response
VEGF	vascular endothelial growth factor
XBP1	x-box binding protein 1

Introduction

N-3 and n-6 polyunsaturated fatty acids (PUFAs) are essential nutrients in man since the can not be synthesized *de novo*. The clinical symptoms of n-6 PUFA deficiency as well as their dietary requirements in man was described more than 50 years ago [1-3]. The possible important epidemiological, clinical and biochemical effects of n-3 PUFAs were reported nearly 20 years later by Dyerberg *et al.* [4], but it still remained several years before the first cases of n-3 PUFA deficiency were reported in man [5-7]. International dietary guidelines on n-6 and n-3 PUFA requirement are now generally adopted, and overt essential PUFA deficiency is therefore a rare clinical condition. Such guidelines are primarily given to ensure good health and well being in the population, also considering special needs in population groups such as the elderly, infants, pregnant women and the fetus. Essential PUFA deficiency will not occur as long as these dietary guidelines are followed.

During the last decades the focus on n-3 PUFAs has shifted from their role as essential nutrients to the ability of the long-chain n-3 PUFAs EPA and DHA to prevent, cure or reduce the risk of a wide range of diseases if the dietary intake is increased above the present dietary recommendations. Studies have reported beneficial effects of n-3 PUFAs on cardiovascular disease, metabolic syndrome and inflammatory conditions [8-13]. They have also been reported to affect central nerve system (CNS) function and development [14,15], as well as CNS diseases [16]. Furthermore, several studies indicate an inverse relationship between dietary intake of n-3 PUFAs and various types of cancer [17-21]. Reports show that they may inhibit growth of cancer cells [22-24], as well as enhance the cytotoxic effect of chemoradiotherapy in cancer [25].

However, a number of investigators have reported that n-3 PUFAs have no significant effect on several of these conditions, including cardiovascular [26], inflammatory [27] and CNS disease [28], as well as cancer [29]. One possible explanation for the discrepancies in these reported effects could be that the study populations are heterogeneous with respect to their prestudy functional n-3 PUFA status. It is less likely that a population having an adequate functional n-3 PUFA status will react beneficially to an increased intake of EPA and/or DHA, than a population having a

suboptimal dietary intake. Another possibility is that unknown molecular mechanisms account for the effects in some, but not all individuals. The present thesis addresses these two questions. We investigated whether desaturase mRNA expression may be exploited as a method to classify whether individuals have an adequate or a suboptimal dietary n-3 PUFA intake. Furthermore, we investigated molecular mechanisms behind n-3 PUFAs' inhibitory effect on cancer cell growth.

Unsaturated fatty acids

Unsaturated FAs contain one or more double bonds between the carbons in the FA chain. Monounsaturated FAs are FAs with one double bond, in contrast to PUFAs, which have more than one. The monounsaturated FAs palmitoleic acid (PA, 16:1 n-7) and oleic acid (OA, 18:1 n-9) are common constituents in the triacylglycerols of human adipose tissue, and serve as energy reserves [30]. Olive oil, meat and dairy products are the most important dietary sources of these FAs [31].

There are two major families of dietary PUFAs, the n-3 and the n-6 families. N-3 PUFAs are characterized by having a double bond between carbon 3 and 4 from the methyl end of the carbon chain. This end is also named n or ω. The n-6 PUFAs have a double bond between carbon 6 and 7 from the methyl end.

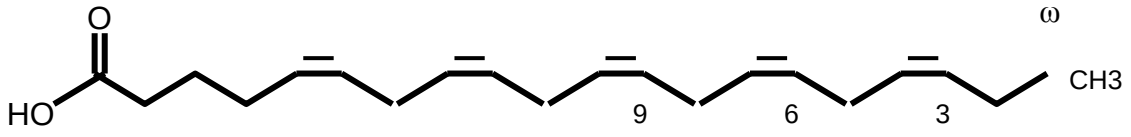

Figure 1. The omega-3 PUFA eicosapentaenoic acid (EPA, 20:5 n-3).

Mammalian cells can not synthesize n-3 and n-6 PUFAs from acetyl-CoA, but rely on the dietary essential precursor PUFAs α-linolenic acid (ALA, 18:3 n-3) and linoleic acid (LA, 18:2 n-6). These PUFAs are further synthesized into highly unsaturated FAs such as eicosapentaenoic acid (EPA, 20:5 n-3) and docosahexaenoic acid (DHA, 22:6 n-3), or arachidonic acid (20:4 n-6), respectively. N-3 PUFAs are incorporated

mainly into phospholipids (PL) where they also serve as substrates for the biosynthesis of eicosanoids of the prostaglandin, leukotriene and thromboxane families [32-34]. Plant-based foods, such as seeds, oils and nuts, are important sources of ALA, whereas fatty fish is the primary food source of EPA and DHA [35]. Dietary PUFA intake is one of the most critical factors affecting tissue PUFA availability. However, other factors like digestion, absorption, hormones, age, FA oxidation, as well as desaturase activity play a key role in this [36]. PUFAs are released from the PL by phospholipases [37]. They may further be recycled through remodelling of the PL via the deacylation-reacylation pathway (Land's pathway) [38].

The presently best established available tools for diagnosing essential FA deficiency are reliant on finding typical FA profile changes in the plasma PL, measured by gas chromatography (GC). These changes generally occur relatively late, when overt essential FA deficiency is present. Studies have also suggested that measurement of erythrocyte FA content may serve as a biomarker of long-term dietary FA intake [39]. However, a diagnostic tool to measure a nutritional essential FA deficit at an early stage, possibly even before nutritional deficiency has reached clinical significance would be useful.

Desaturases

Two groups of acyl-CoA desaturases are present in mammals. One group consists of the delta 6 desaturase (D6D, FADS2) and the delta 5 desaturase (D5D, FADS1), and the other comprises the stearoyl-CoA desaturase (SCD, delta 9 desaturase, D9D). Four isoforms of D9D have been identified in mice [40-43]. In humans, however, studies strongly suggest that a single gene encodes D9D, and that it generates two transcripts by use of alternative polyadenylation sites [44]. D9D catalyzes the conversion of palmitic acid (16:0) to palmitoleic acid (PA, 16:1) and stearic acid (SA, 18:0) to oleic acid (OA, 18:1).

D5D and D6D participate in the synthesis of PUFAs, such as arachidonic acid (AA, 20:4 n-6) and docosahexaenoic acid (DHA, 22:6 n-3), from linoleic acid (LA, 18:2 n-6) and α-linolenic acid (ALA, 18:3 n-3) respectively. In this process, the desaturation by D6D is the first and rate limiting step followed by elongation by elongase and desaturation by D5D (Figure 2) [45].

N-6 FAs	Enzymes	N-3 FAs
18:2 n-6 (LA)		18:3 n-3 (ALA)
↓	Δ6 Desaturase	↓
18:3 n-6 (GLA)		18:4 n-3
↓	Elongase	↓
20:3 n-6 (HGLA)		20:4 n-3
↓	Δ5 Desaturase	↓
20:4 n-6 (AA)		20:5 n-3 (EPA)
↓	Elongase	↓
22:4 n-6		22:5 n-3
↓	Elongase	↓
↓	Δ6 Desaturase	↓
↓	Peroxisomal β-oxidation	↓
22:5 n-6		22: 6 n-3 (DHA)

Figure 2. Synthesis of n-3 and n-6 PUFAs by desaturases and elongases.

The transcription factors sterol-regulatory element binding protein 1c (SREBP-1c) and peroxisome proliferator activated receptor-α (PPAR-α) are important in the regulation of the desaturases [46]. However, a number of factors such as insulin, dietary cholesterol [46], vitamin A [47], growth hormone [48], as well as iron [49] influence desaturase activity. The activity of D5D and D6D is one of the main determinants of tissue PUFA composition, which in turn is regulated by the amount of cellular PUFA present [50,51]. Measurement of desaturase mRNA expression may therefore reflect FA status. However, studies on desaturase expression in humans are scarce. One study reported that the expression of D5D and D6D in peripheral blood mononuclear cells (PBMC) correlated with the amount and type of dietary fat consumed [52]. This suggests that measurement of desaturase mRNA expression in a peripheral blood sample possibly could serve as a marker of FA status.

PUFAs are also implicated in regulation of the expression of a diversity of genes [53-55], including genes important for cell proliferation and differentiation [56]. It has been suggested that desaturase expression could serve as biological target(s) for the discovery and development of pharmaceuticals to treat atherosclerosis [57]. Altered

desaturase expression has also been linked to cancer development [58,59] as well as type 2 diabetes and obesity [60]. Recent studies indicate that altered D9D activity due to a high-carbohydrate diet may contribute to the obesity [61]. Thus, measuring changes in desaturase expression in human cells may be important for expanding our understanding of the molecular bases for a variety of conditions, as well as mechanisms behind the diverse biological effects of FAs.

N-3 PUFAs and cancer

Epidemiological studies indicate an inverse relationship between dietary intake of n-3 PUFAs and cancer, especially colon, prostate and breast cancer [17-21]. For example, Eskimo populations in Alaska who consume diets based almost exclusively on fish seem to have a very low incidence of these types of cancer. However, the incidence has increased with the "westernization" of their diet, including intake of less n-3 PUFAs [62-64]. Likewise, the decreased consumption of fish and increased intake of vegetable oils rich in n–6 PUFAs among Japanese women during the past decades have been accompanied by increased breast cancer rates [65]. Several studies indicate a health benefit on cancer as well as other diseases by decreasing the dietary omega-6/omega-3 PUFA ratio [66,67]. However, epidemiologic studies on n-3 PUFAs and cancer are not conclusive [29].

Substantial experimental work from *in vitro* and animal models are more consistent in showing that n-3 PUFAs inhibit cancer cell proliferation, promote cell differentiation, induce apoptosis and limit angiogenesis [22-24,68].

Cell cycle and cancer

Most cells in body tissue are maintained in a quiescent state called G0. However, they are regularly driven to re-enter the cell cycle by extracellular signals. One of the key characteristics of cancer cells is proliferation independently of extracellular signals. Cancer cells can re-enter the cell cycle regardless of positive or negative external stimuli. This often occurs due to alteration of the growth signaling due to modification or overexpression of growth factor receptors or to mutations of components of the intracellular pathway carrying the signal, like Ras [69]. Such genes that contribute to

converting normal cells into cancer cells are termed oncogenes, whereas genes that protect the cell from becoming cancer cells are termed tumor suppressor genes [70]. Another hallmark of cancer cells is resistance to apoptosis [71]. For example, altered expression of the inhibitors of apoptosis (IAP) family members are increasingly being acknowledged to play an important role in cancer development [72].

The cell cycle consists of four distinct phases; gap 1 (G1), synthesis (S), gap 2 (G2) and mitosis (M). The G1 phase is considered the most important step with respect to the control of cell proliferation and growth. During the G1 phase, the cell receives information from the extracellular environment and determines whether to proliferate or to adopt an alternate fate, like differentiation or apoptosis [73,74]. DNA is replicated during the S phase. The G2 phase is the second growth phase before cell division during the M phase [74]. Figure 3 gives an overview of the cell cycle and cell cycle regulators. Activation of each phase is dependent on proper progression and completion of the previous one. Cell cycle checkpoints are used to monitor this. The two main cell cycle checkpoints are the G1/S checkpoint and the G2/M checkpoint. The checkpoints enable the cell to delay the cell cycle progression in response to intra- or extracellular stress. The checkpoints are important quality control measures of the cell cycle and protect the cell from genomic instability, as they allow cells to respond to DNA damage [75,76]. Loss of cell cycle checkpoints is considered mandatory for the development of cancer [73,74].

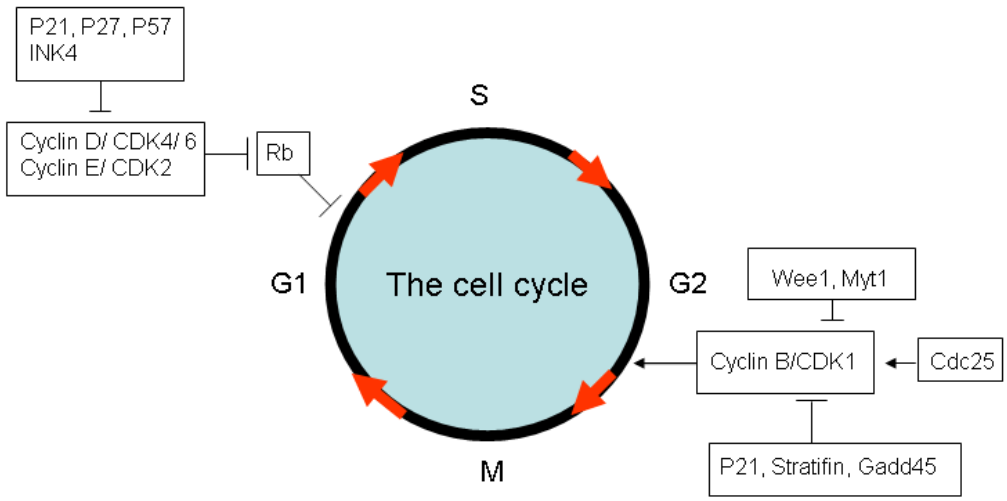

Figure 3. Overview of the cell cycle and main cell cycle checkpoints.

The G1/S checkpoint

The G1 phase cyclins consist of cyclin D and cyclin E. These cyclins associate with cyclin-dependent kinase 4/6 (CDK4/6) and cyclin-dependent kinase 2 (CDK2) respectively, to form active kinase complexes which play a key role in the G1/S checkpoint [77]. The activity of the CDKs is regulated by phosphorylation and dephosphorylation, and by interaction with CDK inhibitors like the Cip/ Kip family, composed of p21, p27 and p57, and the INK4 family of proteins, which inhibit cyclin D/ CDK4/ 6 and cyclin E/ CDK2 (Figure 3) [78,79]. Expression of p21 can be induced by the tumor suppressor p53 in response to DNA damage. However, it can also be induced independently of p53 [80]. Mutations in the p53 gene are the most commonly observed genetic lesions in cancer cells [81].

The so-called "pocket proteins" are the targets of the G1 cyclins. These consist of retinoblastoma protein (Rb) and its homologues p107 and p130. In quiescent cells, Rb is in a hypophosphorylated active form that represses gene transcription required for transition from G1 to S phase. After growth stimulation, it becomes inactivated by phosphorylation by the cyclin D/ CDK4 /6 and cyclin E/ CDK2 complexes (Figure 3). Maximum phosphorylation occurs in the late G1 phase, and results in release of S phase specific transcription factors that are bound to and sequestered by unphosphorylated Rb during the G1 phase [82,83]. Growth inhibitory signals exert their effect by direct downregulation of cyclin levels or by inducing cyclin dependent kinase inhibitors [79]. Overexpression of cyclin D and CDK4 as well as loss of Rb and alteration of CDK inhibitors have been found in different cancers [73].

The G2/M checkpoint

Similar to the cyclins in the G1 phase, the cyclin B/ CDK1 complex plays the key role in the G2/M checkpoint and induces mitosis. The activity of the complex is regulated by the balance between the inhibitory kinases Wee1 and Myt1, and the activating phosphatase Cdc25 (Figure 3) [84].

Transcriptional targets of p53 like p21, stratifin (14-3-3 sigma) and Gadd45 also play a key role in regulating the G2/M checkpoint. P21 and stratifin both inhibit CDK1, whereas Gadd45 dissociates CDK1 from cyclin B (Figure 3). P53-independent pathways may also cause G2 arrest by inhibiting CDK1 activity in response to DNA damage. For

example, DNA damage stimulates the kinases Atm and Atr, which activate the Chk1 and Chk2 kinases, which then phosphorylate Cdc25, causing it to be anchored in the cytoplasm where it cannot activate CDK1 [74,84].

Chemotherapeutic agents aim to inhibit the cell cycle or induce apoptosis in cancer cells. Hence, targets of these drugs are generally key cell cycle progression proteins, like cyclins, CDKs and CDK inhibitors [85]. However, the IAP family members are emerging as new targets of cancer therapy [72].

N-3 PUFAs and cell growth inhibition/arrest

The mechanisms mediating the inhibitory effect of n-3 PUFAs on cancer are a matter of debate. Alterations of several different cell processes have been reported, but complete knowledge of the functional mechanisms is missing.

Studies have indicated that DHA lowers Ras activation by reducing Ras localization to the plasma membrane and by suppressing levels of activated Ras in the plasma membrane [86]. This may in part explain the antiproliferative effect of DHA.

Other studies suggest that n-3 PUFAs affect proliferation by modulating the production of eicosanoids, which are signaling molecules important for cell growth and apoptosis. This occurs by inhibition of the cyclooxygenase-2 (COX-2) enzyme [21,87].

A third type of mechanism through which n-3 PUFAs may alter cell proliferation is by acting directly as ligands for nuclear transcription factors, like peroxisome proliferators-activated receptors (PPARs) [88] or retinoid X receptor alpha [89]. These transcription factors regulate extensive gene expression, thereby mediating biological functions like cell death and intracellular homeostasis. However, PPARs have been shown to bind both n-3 and n-6 PUFAs, and appear to lack FA class specificity [90-92]. Therefore, the unique protective effects of n-3 PUFAs are not necessarily only mediated through activation of PPARs.

A fourth mechanism of inducing apoptosis/growth arrest has been linked to the ability of n-3 PUFAs to increase the levels of secondary products of lipid peroxidation [93]. The apoptotic effect of n-3 PUFAs in some cancer cell lines have been shown to be blocked in the presence of antioxidants [23,94]. However, other studies find equal effect with or without antioxidants [56,95]. Some of the most recent studies suggest that activation of

the unfolded protein response (UPR) may be involved in the cytotoxic effect of n-3 PUFAs [96].

ER Stress and the unfolded protein response

The endoplasmic reticulum (ER) is a central organelle of eukaryotic cells as the place of lipid synthesis [97] and protein maturation. It provides an optimal and unique environment for folding, assembly and disulfide bond formation of proteins of the plasma membrane, secreted proteins as well as proteins of the Golgi apparatus and lysosomes [98]. Homeostasis within the ER lumen is meticulously monitored and maintained. Conditions interfering with the function of ER are collectively called ER stress. The stress is induced by changes in Ca^{2+} concentration, nutrient deprivation, alterations in the oxidation-reduction balance, failure of post-translational modifications, or excessive protein synthesis, and can lead to the activation of a coordinated adaptive program called the UPR [99].

UPR is an evolutionary conserved signaling pathway that is induced in response to the accumulation of unfolded proteins in the ER. The rate of general translation initiation is attenuated, the expression of ER resident protein chaperones and protein foldases is induced, the ER compartment proliferates, and ER-associated degradation (ERAD) is activated to eliminate the irreparably misfolded proteins.
This co-ordinated response halts the build up of proteins, allows time for the elimination of unfolded proteins, and re-establishes cellular homeostasis [100].
Figure 4 gives an overview of the UPR transducers and the response initiation following ER stress.

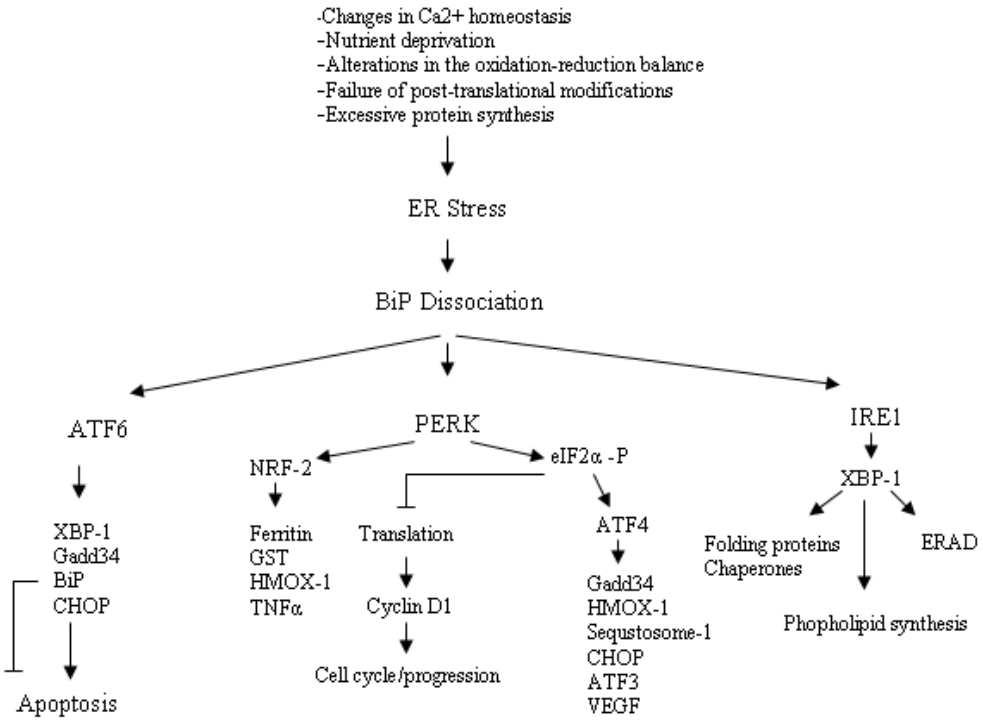

Figure 4. Overview of the unfolded protein response.

There are three identified proximal sensors of the UPR. These are the PKR-like ER protein kinase/pancreatic eIF2α (eukaryotic translation initiation factor 2, α subunit) kinase (PERK/PEK), the activating transcription factor 6 (ATF6) and the inositol-requiring enzyme 1 (IRE1). All of the transducers are associated with the chaperone BiP/GRP78 (immunoglobulin heavy chain-binding protein/glucose-regulated protein of 78 kDa) in their inactive state. It is proposed that BiP preferentially binds to and is sequestered by unfolded/misfolded proteins that accumulate in the ER lumen in the presence of ER stress. As a consequence, BiP dissociates from the UPR transducers and permits their signaling [101-104].

PERK

PERK inhibits protein biosynthesis through phosphorylation of eIF2α. This leads to prevention of formation of the ternary translation initiation complex eIF2α/GTP/Met-

$tRNA_i$. As a consequence, mRNA translation is attenuated, and the workload on the ER is reduced. However, selective mRNAs important in the UPR are translated in the presence of phosphorylated eIF2α [105]. Among these is the activation transcription factor 4 (ATF4), which induces growth arrest- and DNA damage-inducible gene 153/C/EBP-homologous protein (GADD153/CHOP). CHOP suppresses activation of B-cell CLL/lymphoma 2 (Bcl-2) [106] and nuclear factor-kappaB (NF-κB) [107].
ATF4 also initiates production of growth arrest and DNA damage gene 34 (GADD34), which is part of a protein complex which dephosphorylates eIF2α, thus mediating recovery of translation [108,109]. Recent studies have suggested that PERK also increases degradation of certain proteins, like cyclin D1 [110].

ATF6 and IRE1

ATF6 and IRE1 both induce transcription of x-box binding protein 1 (XBP1). XBP1 in addition to ATF6 itself induces transcription of BiP. BiP then binds to unfolded protein to prevent further accumulation. Both ATF6 and IRE1/XBP1 also induce ER degradation-enhancing α-mannosidase-like protein (EDEM). EDEM is an ERAD-related protein which eliminates misfolded proteins in response to ER-stress [107].

Apoptosis meditated through the PERK/CHOP-singaling pathway

If the stress cannot be resolved, the cell dies by apoptosis. The interplay between cell death and survival revolves around the balance of proapoptotic and antiapoptotic signals, which appears to be the ratio of CHOP to BiP in ER stress induced cell death. The suppression of Bcl-2 by CHOP is suggested to play a particularly important role in inducing ER stress mediated apoptosis [107]. Studies suggest that Bcl-2 regulates ER as well as mitochondria Ca^{2+} homeostasis and inhibits apoptosis [111]. The mechanisms are not completely understood, but studies suggest a connection to the proapoptotic BEK and BAX, and inositol 1, 4, 5-triphosphate receptor (IP3R)/ ryanodine receptor (RyR), which are involved in the release of Ca^{2+} during ER stress induced apoptosis [107,112,113].

Suppression of Bcl-2 will lead to further alterations in the Ca^{2+} homeostasis, which activates the calcium-dependent protease m-Calpain, which subsequently activates a cascade of caspases leading to apoptosis [114,115].

Intracellular Ca^{2+} homeostasis

The ER serves as an important intracellular Ca^{2+}-buffer. The concentration of Ca^{2+} inside the ER is several times higher than in the cytosol and is tightly regulated. ER Ca^{2+} controls ER homeostasis by modulating numerous enzymatic cascades, the endomembrane Ca^{2+}-uptake and activation of ER-located Ca^{2+} release channels [116]. Eukaryotic cells can increase their cytosolic Ca^{2+}-levels via two mechanisms: release of Ca^{2+} from intracellular stores or influx via plasma membrane channels.

Sarco/Endoplasmic-Reticulum- Ca^{2+}-ATPases (SERCA) pump Ca^{2+} against the Ca^{2+}-gradient into the ER, whereas the IP3R and RyR release ER Ca^{2+} [117]. The Bcl-2 protein family members play an important role in regulating ER Ca^{2+}-release [118]. Channels in the plasma membrane, like the store-operated Ca^{2+} channels (SOC), regulate the influx of Ca^{2+} into the cell [119].

Intracellular Ca^{2+} is important for a wide range of cellular functions like protein processing, secretion, membrane transport and permeability, ATP production, the activity of several enzymes, as well as apoptosis and cell proliferation [120-122]. Growing evidence suggests that altered Ca^{2+}-signaling may contribute to carcinogenesis [117]. Several studies have found altered expression of Ca^{2+}-channels and pumps in cancer cells, which again may stimulate Ca^{2+}-regulated cell proliferative signaling pathways, or contribute to resistance to apoptosis. Hence, the role of Ca^{2+} signaling as target in cancer therapy is being increasingly acknowledged [123].

PUFAs and Ca^{2+} release

Studies on different cancer cells have shown that the growth inhibitory effect of EPA and DHA may be mediated through the depletion of Ca^{2+} from intracellular stores [124,125]. Alterations in Ca^{2+} concentration causes ER-stress, which activates the PERK/ eIF2α pathway in the UPR [126].

PUFAs like EPA induce Ca^{2+} release from intracellular Ca^{2+} stores and inhibit Ca^{2+} influx through SOC in the plasma membrane [124,125,127]. Over time this leads to depletion of intracellular Ca^{2+} due to leakage through the plasma membrane, and causes ER stress and activation of the UPR through the PERK/ eIF2α pathway that may lead to apoptosis as described [120,124].

Studies indicate that PUFAs may mobilize Ca^{2+} from the same intracellular pool as that mobilized by econazole (Ec) in leukaemia cells [128]. Ec is an antifungal imidazole that depletes Ca^{2+} from the ER and blocks Ca^{2+} influx in mammalian cells [129,130]. This results in sustained depletion of Ca^{2+} from ER stores, activation of the UPR and eventually cell death [131]. However, Ec resistant cell lines have been isolated, like the E2R2 cell line, which is a clone of the human promyelocytic cell line HL60 [132]. E2R2 cells display increased SOC influx and resistance to depletion of Ca^{2+} stores in the ER by Ec. E2R2 cells also maintain protein synthesis after treatment with Ec as well as thapsigargin, most likely due to overexpression of ribosomal proteins. The increased SOC activity is likely to be responsible for the continuous replenishment of Ca^{2+} into the ER store, compensating for the ER Ca^{2+} store depletion caused by Ec. The HL60 cells on the other hand, do not display any of these properties and Ec treatment of these cells results in ER stress related cell death [132].

PUFAs and cancer therapy

Colon cancer is one of the most common types of cancer as well as a major cause of cancer death in Europe [133]. For treatment of advanced colorectal cancer, 5-fluorouracil (5-FU) remains one of the most effective chemotherapeutic options available [134]. However, colon cancer tumors are in many patients either inherently resistant or develop resistance to chemotherapy and the prognosis is poor [135]. As previously mentioned, epidemiological studies indicate a protective effect of n-3 PUFAs against different types of cancer, including colon cancer [17-21]. Furthermore, substantial experimental work from *in vitro* and animal models has shown that n-3 PUFAs inhibit cancer cell proliferation, promote cell differentiation, induce apoptosis and limit angiogenesis [22-24,68]. In addition, n-3 PUFAs have been shown to suppress cancer-associated cachexia [136]. Together these findings indicate that n-3 PUFAs may have a

role in cancer therapy. However, the extent of this role is unclear, as studies on the topic are scarce.

There is currently a growing interest for n-3 PUFAs as an adjuvant in cancer treatment. This has been supported by reports on various human cancer cell lines both in cell culture and animal-bearing models, showing increased sensitization to the effect of chemotherapy following DHA treatment [25,137-139]. In addition, studies suggest enhanced efficacy of cancer radiotherapy following n-3 PUFA treatment [140,141]. However, the molecular mechanisms involved are unclear.

Summary of papers

Paper I: "Regulation of desaturase expression in HL60 cells."

Expression of D5D, D6D and D9D was upregulated with time in HL60 cells. The addition of FAs to the culture medium suppressed upregulation of all desaturases. N-3 and n-6 PUFAs appeared to be more effective than n-9 or saturated FAs. When FAs were added after 72 h, further upregulation during the next 24 h was generally suppressed, except for D5D when OA or SA was added. In cells cultured with restricted amounts of fetal bovine serum (FBS), desaturase expression increased with decreasing concentrations of FBS. Cellular FA content decreased, being most prominent in the sum of n-3 and n-6 PUFAs of the neutral lipid fraction. The results indicate that when the supply of FA to HL60 cells is limited, the intracellular content of n-3 and n-6 PUFAs decreases, leading to upregulation of the desaturases, particularly D5D and D6D. Since HL60 cells resemble human leukocytes, the results suggest that desaturase expression in leukocytes may be exploited as a biomarker for FA status.

Paper II: "Fatty acid desaturase expression in human leukocytes correlates with plasma phospholipid fatty acid status."

Associations between and changes in composition of plasma PL FAs and expression of D5D, D6D and D9D in leukocytes were investigated both before and during n-3 PUFA supplementation for two weeks in 20 healthy individuals. Before starting supplementation (t=0), concentrations of n-3 PUFAs in plasma PL were significantly lower in the Lowfish group compared to the Highfish group. During supplementation, n-3 PUFAs increased whereas n-6 PUFAs decreased in both groups. D5D expression was significantly higher in the Lowfish group compared to the Highfish group at t=0. No difference in D6D or D9D expression was observed. D5D expression was inversely correlated with EPA, DPA, DHA and total n-3 PUFAs, and positively correlated with the ratio total n-6 PUFAs/total n-3 PUFAs at t=0. Expression of D5D in Lowfish as well as D6D in both groups significantly decreased relative to the expression at t=0 during the first day of supplement. PUFA concentration was generally predicted by its precursor FA and D5D or D6D expression. The correlations mentioned disappeared

after two weeks supplementation. The results indicate that steady state FA desaturase expression is associated with plasma PL FA composition. Whether leukocyte desaturase expression may have potential as marker of PUFA status, merits further investigation.

Paper III: "The antiproliferative effect of EPA in HL60 cells is mediated by alterations in calcium homeostasis."

EPA inhibited growth of HL60 cells strongly, while E2R2 cells were much less affected. Gene expression analysis of HL60 cells revealed extensive changes in transcripts related to the ER homeostasis, Ca^{2+}-homeostasis and cell cycle/apoptosis. Protein levels of important UPR hallmarks like phosphorylated eIF2α, ATF4 and SQSTM1 increased, whereas levels of the cell cycle progression protein cyclin D1 decreased in HL60. In contrast, EPA concentrations that strongly inhibited and caused activation of the UPR in HL60 cells had no effect on the expression level of these UPR markers in E2R2 cells. Given that the only known difference between these cells is Ec-resistance, our results strongly suggest that the inhibitory effect of EPA on HL60 cells is initially meditated through alterations of the Ca^{2+} homeostasis followed by activation of the UPR.

Paper IV: "DHA alters expression of target proteins of cancer therapy in malignant colon cancer cell line."

Cell cycle check point proteins such as p21 and stratifin were increased at mRNA and protein level, whereas cell cycle progression proteins like Cdc25c and CDK1 were reduced after DHA treatment of the SW620 cells. This indicates that DHA treatment causes simultaneous cell cycle arrest in both the G1 and G2 phase. Protein levels of IAP family members associated with chemotherapy resistance and cancer malignancy, survivin and livin, decreased after the same treatment, likewise expression of NF-κB. Levels of the pro-apoptotic proteins phosphorylated p38 MAPK, as well CHOP, increased. In conclusion, DHA affects several target proteins of chemotherapy in a favorable way. This may explain the observed enhanced chemosensitivity in cancer cells supplemented with n-3 PUFAs, and encourage further studies investigating the role of n-3 PUFAs as an adjuvant to chemo- and radiotherapy *in vivo*.

Discussion

The present studies have focused on some of the different effects of n-3 PUFAs on gene expression and cell signaling, with special attention to regulation of FA desaturases and the growth inhibitory effect of n-3 PUFAs on cancer cells.

Desaturase expression in HL60 cells

We demonstrated that expression of desaturase mRNA was regulated in response to FAs in cultured human leukocytes. Our data suggest that upregulation of the desaturases is caused by a cellular deficiency of essential n-3 and n-6 PUFAs. This is in accordance with similar findings in HepG2 cells [142] and in animals fed a fat-free high-carbohydrate diet [143,144].

We also examined how various FAs affected desaturase expression. The addition of FAs from the start of incubation suppressed upregulation of all desaturases. In contrast to previous reports in animal models [145,146], we found that OA prevented the upregulation of all desaturases. This result is also in contrast to one report on HepG2 cells [147], but is supported by a later study on D6D [148]. The observed difference in the latter two reports may be due to the inclusion of insulin and dexamethasone by Nara *et al.* [147], because these two hormones influence desaturase expression [149].

However, in line with the same reports [145-148], we found that n-3 and n-6 PUFAs appeared to be more effective in suppressing upregulation than the n-9 or the saturated FAs, although the difference was statistically significant for D5D only. The n-3 PUFAs were apparently more effective than the n-6 PUFAs, since they achieved the same degree of effect at 10 μM as the n-6 PUFAs achieved at 25 μM.

When FA addition was delayed to 72 h after the start of incubation, the effect was generally to prevent further upregulation of the desaturases. Together with the presented results when FA was added from the start, these findings indicate that the effect on desaturase expression is due to FA depletion and not to depletion of other substances in the medium. It also indicates that the effect is not caused by peroxidation processes in the medium. However, the addition of FA was not sufficient to return desaturase expression to the levels seen at the start of incubation. Furthermore, in this situation, OA and SA had no significant effect on D5D expression, underlining the findings that n-9 and saturated FAs appear to be less effective than n-3 and n-6 PUFAs in suppressing desaturase upregulation.

The results from **Paper I** suggest that desaturase expression may be exploited as a sensitive biomarker reflecting FA status.

Desaturase expression in leukocytes from blood samples

Having established that 1) FA desaturases were upregulated concomitantly with depletion of cellular FAs, and 2) that this upregulation could be suppressed by addition of FAs to the cell culture in HL60 cells, we examined whether similar changes occurred *in vivo* depending on FA status. As expected from their low intake of marine n-3 PUFAs, the Lowfish group had lower levels of n-3 PUFAs than the Highfish group. The opposite was the case for the n-6 PUFAs DHGL and adrenic acid, as well as OA and mead acid. Total n-3 PUFA concentration increased in both groups during the two weeks of n-3 PUFA supplement, but the relative increase was largest in the Lowfish group. The total n-6 PUFA concentration decreased in both groups. This could indicate that n-3 PUFAs, if

abundant, may substitute n-6 PUFAs in the plasma PL. Similar findings have been reported after dietary interventions [150,151].

The FA levels seen at t=0 are likely to reflect the habitual, long-term dietary intake of PUFAs of the participating individuals. Apparently, the expression of at least D5D at t=0 also reflects long term FA intake, since its expression was significantly higher in the Lowfish group compared to the Highfish group. This is in line with our findings from cell culture, that low levels of n-3 PUFAs increase expression of D5D. In a study of PBMC desaturase expression in relation to FA intake in Chinese and European subjects, Xiang *et al.* reported that both D5D and D6D expression were significantly lower in the Chinese compared to the Europeans [52]. The latter group consumed significantly more SFA and MUFA and less PUFA than the Chinese. Xiang's study was based on 3-day dietary records, and we can only assume that the differences in reported FA intake were reflected in differences in plasma PL FA concentrations. The higher PUFA intake in the Chinese was largely due to a 50% increase in n-6 PUFAs (mainly LA), so our study is not directly comparable with Xiang's. However, both studies show that desaturase expression may reflect the amount of FAs consumed over some period of time.

By the use of a multiple regression model we tested the hypothesis that the concentration of individual PUFAs was determined by the concentration of precursor FA and the expression of the intermediate FA desaturase or desaturases. At t=0 this was confirmed for many but not all FAs. After two weeks of n-3 PUFA supplementation desaturase expression did no longer make a significant positive contribution to the regression model. This suggests that the associations are seen during, but not outside steady state conditions, and that other factors play a larger role than the desaturase

expression in determining individual PUFA concentrations outside steady state conditions.

There was a significant correlation between D5D expression and the plasma PL concentrations of EPA, DPA, DHA, total n-3 and the ratio n-6/n-3 at t=0. We did not observe this correlation for any other FAs, nor D6D or D9D. This is in contrast to Xiang *et al.* who found a positive correlation between desaturase expression and SFA or MUFA intake, as well as a negative correlation between LA or LNA intake and the expression of the D5D and D6D desaturases [52]. The observed lack of correlation in our study following two weeks of supplementation indicates that it takes longer time to re-establish the correlations after modifying the dietary intake of FAs.

Following one day of n-3 PUFA supplementation the expression of D5D and D6D significantly decreased relative to the starting levels. This rapid effect on mRNA expression was also seen after supplementing cultured HL60 cells with FAs, and suggests that the individual day-to-day variation of desaturase expression might be rapid and significant. The high D5D expression seen at day 3 in the Highfish (Figure 3a, Paper II) group might partly reflect significant day-to-day variations. However, this high value was due to three individuals with an extreme and rapid response to n-3 PUFA supplementation (10.3, 12.7 and 18.5 respectively), while the mean for the remaining eight individuals was 3.0. Several clinical studies on the effect of supplementing patients with n-3 PUFAs have suggested that there is heterogeneity in the individual response to n-3 PUFA supplementation [152]. The three extreme responders in regard to D5D expression seen after 3 days in the Highfish group suggest that regulation of desaturase mRNA could be the biochemical reflection of the observed clinical heterogeneity in n-3

PUFA response. However, it also may also raise questions regarding reproducibility of the metods used.

The return of desaturase expression towards starting level after supplementation is not in line with our cell culture study, and may be ascribed the existence of various compensatory mechanisms acting *in vivo*. It may also be explained by the time frame of the study as stated above, hence giving the impression of an apparent lack of correlation between FAs and desaturase expression compared to t=0.

The antiproliferative effect of EPA on HL60 cells

We showed that HL60 cells were strongly growth inhibited by EPA, while the Ec-resistant HL60 clone E2R2 was much less affected by the same treatment. The observed differences in EPA-sensitivity between the two cell lines were most likely mediated through alterations of Ca^{2+}- homeostasis and activation of ER stress and UPR.
This is agreement with other studies showing that PUFAs like EPA may affect Ca^{2+}-homeostasis in different cancer cell lines [96,124,125,127]. Alterations in ER Ca^{2+}-homeostasis cause ER stress and activation of the UPR [99]. The effect of saturated and monounsaturated FAs on ER-stress and ER-stress induced apoptosis has previously been investigated [153-155]. However, the effect of n-3 PUFAs and other PUFAs on these processes is quite unexplored. We recently demonstrated that DHA, but not OA, causes activation of the UPR in a colon cancer cell line [96]. This suggest a possible unique effect of n-3 PUFAs in causing this activation in cancer cells. Here, we show that EPA also causes activation of the UPR in a leukemia cell line.

PUFAs inhibit proliferation and induce apoptosis in a dose and time dependent manner in HL60 cells [56], and other leukemia cell lines [23]. As mentioned in the introduction, a number of ways of how n-3 PUFAs may inhibit cancer cell growth have been described. Activation of the UPR by n-3 PUFAs has not been considered earlier to explain the beneficial effect of these FAs on cancer cells. However, additional studies are needed in order to clarify the effects of these FAs on the UPR in both normal as well as cancer cells, both *in vivo* and *in vitro*.

Several genes involved in the UPR response were affected at mRNA as well as protein level in the HL60 cells (Table 2; Figure 3a, **Paper III**). In particular, we found elevated levels of the selective translation inhibitor and UPR hallmark phosphorylated eIF2α [156]. Altered mRNA expression of UPR transcripts as well as increased level of phosphorylated eIF2α following n-3 PUFA treatment are in line with previous reports on other cancer cell lines [96,124]. Furthermore, upregulated mRNA levels of chaperones, foldases and transcripts involved in the ubiquitin/proteasome system indicate that EPA alters ER homeostasis. Altogether, these data indicate that EPA treatment of HL60 cells causes ER stress. In contrast to the HL60 cells, EPA treatment of the E2R2 did not increase protein levels of key mediators of the UPR like phosphorylated eIF2α, ATF4 and sequestosome-1 (SQSTM1) compared to control cells. This confirms that EPA treatment of the E2R2 cells does not result in activation of the UPR.

The UPR is an evolutionary conserved defence signaling pathway in response to the accumulation of unfolded proteins in the ER. Loss of cyclin D1 caused by phosphorylated eIF2α during ER stress leads to G1-arrest and provides the cell with an opportunity to restore cell homeostasis [157]. This is in agreement with the finding that cyclin D1 was downregulated at mRNA as well as protein level in HL60 (Table 2; Figure

3b, **Paper III**), and in line with previous reports [96,124]. Furthermore, this may explain why previous studies have shown that n-3 PUFA treatment of HL60 and other cancer cells increase the portion of cells in the G1 phase of the cell cycle [56,158]. In line with the same reports stating that EPA treatment inhibits cell cycle and causes apoptosis, we found several genes involved in cell cycle/progression to be downregulated, and genes involved in apoptosis to be upregulated.

Cyclin D1 has been shown to be important for the development and progression of several cancers including lymphoma, parathyroid adenoma and cancer of the breast, oesophagus, lung and bladder [159-164]. Cyclin D1 is therefore used as a key marker of cell viability and established as an important prognostic marker in different types of cancer [165,166]. In contrast to HL60 cells, protein level of cyclin D1 was not downregulated in response to EPA in the E2R2 cells, but equally expressed in control and EPA treated cells , indicating that cell cycle is not affected. This also confirms the differences found in cell proliferation after EPA treatment (Figure 2, **Paper III**).

The only known difference between HL60 and E2R2 cells is that E2R2 is resistant to the imidazole Ec, which depletes Ca^{2+} from the ER and blocks Ca^{2+} influx in mammalian cells [129,130]. Ec treatment of E2R2 cells does not cause ER stress by phosphorylation of eIF2α or cell death [132]. The different response to EPA in these two cell lines, strongly suggests that the inhibitory effect of EPA on HL60 cells is meditated through alterations of the Ca^{2+} homeostasis, leading to activation of the ER stress response. This is to be expected, as studies have shown that PUFAs mobilizes Ca^{2+} from the same intracellular pool as that mobilized by Ec [128]. E2R2 cells have been shown to display increased SOC influx compared to HL60 [132]. We therefore speculate that this

is one of the main mechanisms that maintain cell viability in E2R2 cells compared to HL60 cells when exposed to EPA.

The effect of DHA on expression of target proteins of chemotherapy

The SW620 cell line was originally isolated from a lymph node metastasis from a Duke's stage B colon adenocarcinoma from a 50 year old Caucasian male [167]. The SW620 cells have been shown to be more resistant to apoptosis induced by chemoradiotherapy than the cell line isolated from the primary tumor, the SW480 cells. This includes resistance to apoptosis induced by the anti-Fas antibody CH-11, TNFα, cisplatin as well as ionizing radiation [168-170]. This feature makes these cells particularly interesting to investigate. Our research group have previously shown that DHA has a strong growth-inhibitory effect on SW620 cells [95]. However, normal colon cells are not affected [171]. We chose to add DHA because it has been shown to be one of the primary tumor suppressive n-3 PUFAs in colon cancer cells [95,172]. The DHA concentration used was assumed to be within the physiological range which can be reached in plasma with fish oil supplementation [173].

We have shown that DHA treatment of SW620 cells causes downregulation of cyclin D1 at both mRNA and protein level, and that this is likely to be caused by phosphorylated eIF2α [96]. Phosphorylation of this protein has been shown to attenuate cyclin D1 translation and cause cell cycle arrest (G1 phase) in response to prolonged stress in the ER [174]. However, cell cycle analysis of these cells after DHA treatment showed a 2.5-fold increase of cells in the G2/M phase compared to control cells [95]. A

strong inhibitory effect on growth indicated, however, that other phases were affected as well.

Several studies on different types of cancer cells have reported a G1/S cell cycle arrest after treatment with n-3 PUFAs [24,56,175]. The observed G1/S phase arrest has generally been attributed to increased levels of p21 and p53, and decreased levels of cyclin D1. However, arrest in the G2/M phase has been reported as well [172,176]. Here, we present evidence that DHA treatment affected key cell cycle regulatory proteins involved in both the G1 as well as the G2 phase in SW620 cells.

The CDK inhibitor p21 inhibits both the cyclin D/ CDK4/ 6 and cyclin E/ CDK2 complexes important for G1/S phase progression, as well as the cyclin B/ CDK1 complex important for G2/M progression [74,79,84]. P21 has also been shown to inhibit proliferating cell nuclear antigen (PCNA), also causing G1 and G2 cell cycle arrest [177]. PCNA was downregulated at mRNA level in the SW620 cells following DHA treatment (Table 1, **Paper IV**). Expression of p21 can be induced by the tumor suppressor p53 in response to DNA damage or independently of p53 [80]. Both mRNA as well as protein level of p21 were increased in SW620 after DHA treatment (Figure 2A, **Paper IV**). This is in line with previous reports on other cell lines [24,178]. It is likely that p21 inhibits both cell cycle phases in the SW620 cells after DHA treatment, and that cell cycle is arrested in either G1 or G2 phase depending on the current cell cycle stage of each cell.

Stratifin plays a key role in regulating the G2/M checkpoint by anchoring CDK1 in the cytoplasm where it cannot induce mitosis [84]. Stratifin has been directly implicated in the etiology of human cancer, as stratifin inactivation or low expression has been detected in a number of cancer types, including prostate cancer [179], breast cancer [180] as well as colonic polyps [181]. These data suggest that stratifin acts as a tumor

suppressor and that its inactivation contributes to tumor progression. In line with the inhibitory effect of DHA on colon cancer cells, stratifin was upregulated at both mRNA and protein level in the SW620 cells following DHA treatment (Table 1; Figure 2A, **Paper IV**). However, it should also be noted that increased levels of stratifin have been detected during carcinoma progression in a subset of colorectal carcinomas [182]. Therefore, upregulation of stratifin alone is not sufficient to explain the growth inhibitory effect of DHA on colon cancer cells.

The Cyclin B/CDK1 complex plays the key role in the G2/M checkpoint and induces mitosis [84]. CDK1 was downregulated at both mRNA and protein level (Table 1, Figure 2A, **Paper IV**). Cyclin B was downregulated at mRNA level (Table 1). The mitotic inducer Cdc25c phosphatase, which activates Cyclin B/CDK1 complex [183], was also found to be downregulated at both mRNA and protein level (Table 1, Figure 2A, **Paper IV**). The described changes in stratifin, Cdc25c and CDK1 confirm that the G2 cell cycle phase is affected. Studies have reported simultaneous arrest of colonic carcinoma cells in the G0/G1 and G2/M phase following different treatments, like chemotherapeutic agents and short chain FAs [184,185]. Our studies on SW620 cells indicate a similar effect caused by DHA treatment.

It has been suggested that survivin, a member of the IAP family, may in part mediate the resistance to chemoradiotherapy observed in the SW620 cells [170]. Studies have shown that SW620 cells display increased protein levels of survivin compared to the more benign SW480 cells [170]. DHA treatment has been shown to cause a dose- and time-dependent decrease of survivin levels in SW480 cells [186]. In contrast, normal colon epithelium does not express survivin [187]. Overexpression of survivin is associated with increased clinical resistance to taxol-based regimen for ovarian

carcinomas [188]. Esophageal cancer patients with lower levels of survivin expression were more responsive to preoperative chemotherapy with 5-FU and cisplatin [189]. In addition, knockdown of survivin mRNA by small interfering RNA studies sensitized colorectal cancer cells to radiation-induced apoptosis [190]. Survivin is over expressed in several malignancies [191]. High levels of survivin is correlated with poor outcome, and may be used to predict survival rate in colon carcinomas [187,192]. It is therefore particularly interesting that survivin was downregulated at both mRNA and protein level after DHA treatment of the malign SW620 cells (Table 1, Figure 2B, **Paper IV**).

Livin is another member of the IAP family and has been suggested as a potential therapeutic target for the treatment of cancer malignancy [193]. Livin is not detectable in most normal tissues, but is highly expressed in several types of malignant cancers, including colon cancer [194]. Livin has been suggested to play an important role in resistance to chemotherapy, as knockdown of livin has been shown to enhance chemosensitivity in cancer cells [195-197]. Both the α and β isoform of livin were downregulated at protein level following DHA treatment of the SW620 cells. Furhtermore, we detected an increase in the apoptotic cleaved livin, tLivin, stressing the inhibitory effect of DHA on these cells.

CHOP is a pro-apoptotic transcription factor which mediates ER stress induced apoptosis. CHOP is induced by the ATF6 and PERK pathways [157,198], leading to reduced expression of Bcl-2 and increased expression of a number of pro-apoptotic genes [106,199]. Induction of CHOP has been shown to increase sensitivity to various chemotherapeutic agents in gastric cancer cells, including 5-FU [200]. In addition, increased level of CHOP mRNA has been associated with increased response to treatment with chemotherapeutic agents in cancer patients [201,202]. CHOP was

increased at protein level following DHA treatment of the SW620 cells (Figure 2B, **Paper IV**). This is in agreement with our recent studies where we showed that DHA causes ER stress in these cells [96].

P38 MAPK is activated by different types of cellular stress and associated with apoptosis and cell differentiation [203]. Studies have shown that p38 MAPK function as a tumor suppressor, and that it augments CHOP induced apoptosis [204-206]. Many chemotherapeutic agents require p38 MAPK to induce apoptosis [207,208]. DHA treatment of the SW620 cells resulted in increased protein levels of activated p38. Similar findings have been reported in other cancer cell lines [209].

NF-κB is a well studied transcription factor controlling genes involved in the immune and inflammatory cell response [210,211]. NF-κB induces expression of cell regulatory proteins which stimulate cell proliferation, such as cyclin D1 [212], and several anti-apoptotic proteins, including survivin [213-215]. Activation of NF-κB has been shown to stimulate cell growth and inhibit apoptosis in several cancer cell lines [216]. Studies suggest that NF-κB may play an important role in carcinogenesis, and therefore is a potential target of cancer therapy [217,218]. Many chemotherapeutic agents have been shown to induce NF-κB activation [219]. Activated NF-κB has been shown to play an important role in cancer resistance to ionizing radiation [220], as well as chemotherapy resistance, as inhibition of NF-κB enhances the cytotoxic effect of anticancer agents. The latter has been shown with several different cytostatics in several different types of cancer, including 5-FU treatment of colon cancer cells [221,222] and gastric cancer cells [223]. Inhibition and/or reduced levels of NF-κB, may therefore be a useful strategy for improving cancer treatment. We found that DHA treatment of SW620 cells reduced levels of NF-κB (Figure 2B, **Paper IV**). This is also in line with similar

reports showing that n-3 FA treatment inhibits mRNA expression of NF-κB [224] and transcripts downstream in the NF-κB pathway [138], as well as reduces activation of NF-κB in cancer cells [225]. To our knowledge, we are the first to show that DHA reduces total NF-κB protein level in a malignant colon cancer cell line.

Several of the cell cycle proteins and transcripts discussed in **Paper IV** are targets of conventional chemoradiotherapy aiming at inhibiting cancer cell growth. Our results indicate that DHA affects these proteins in a favorable way with respect to cancer treatment. Together with other anticancer agents, DHA supplementation may therefore synergistically enhance the cytotoxic effect of the cancer treatment. This is supported by previous reports on various human cancer cell lines both in cell culture and animal-bearing models, showing increased sensitization to the effect of chemotherapy following DHA treatment [25,138,139]. In addition, studies suggest enhanced efficacy of cancer radiotherapy following n-3 PUFA treatment [140,141]. Our results may offer an explanation to these effects. It is possible that by combining safe, readily available dietary PUFAs with standard cancer treatment, the dose of chemotherapeutic agents as well as radiation may be reduced, thereby also reducing the deleterious side effects of these treatments. However, knowledge of the molecular mechanisms involved is essential to initialize such treatment.

Resistance to N-3 PUFAs in relation to Ca^{2+}-homeostasis

An obvious question from our studies is: why do not n-3 PUFAs kill normal cells? A possible explanation may be that cancer cells display increased sensitivity to alterations in Ca^{2+}-homeostasis compared to normal cells. Several reports have shown altered Ca^{2+}-homeostasis in cancer cells [117]. Cancer cells survive and proliferate because of

disruption of the balance between cell death and cell survival signals [226]. They may become reliant on one or a few survival pathways, a phenomenon termed oncogene addiction [227]. This is opposed to normal cells, which have a complex signaling network that can respond to diverse stimuli. Hence, if cancer cells are reliant on certain Ca^{2+}-levels, the presence of n-3 PUFAs may disrupt these survival signals, and cause cell death in these cells, but not in normal cells. Furthermore, several cancer cells display altered expression of different Ca^{2+}-channels as compared to normal cells [123]. Hence, it is also likely that n-3 PUFAs affect Ca^{2+}-levels in these cells differently than normal cells. This may be important to investigate further.

Another question is why some cancer cells are sensitive to n-3 PUFAs and others not. Again we can only speculate, but one explanation may be that these cancer cells are unequally sensitive to altered Ca^{2+}-levels. They may have the ability to display altered Ca^{2+}-channel activity, like for example the E2R2 cells, so that they can oppose the effect of n-3 PUFAs on the Ca^{2+}-homeostasis. Studies suggest that changes in expression of proteins that reduce the Ca^{2+}-content of the ER Ca^{2+}-store might increase resistance to apoptosis [228]. This could arise from increased expression of proteins that cause increased Ca^{2+}-leakage from the ER, like the IP3R or RyR Ca^{2+}-channels, or decreased expression of the SERCA Ca^{2+}-pump, which increases ER Ca^{2+}-levels. This again, may prevent the rice in cytoplasmic Ca^{2+} needed to induce apoptosis.

Conclusion

N-3 PUFAs have a wide range of beneficial effects in both health and disease. It is therefore important to have sensitive diagnostic methods to detect both overt deficiency

as well as a suboptimal dietary supply of these essential FAs. We investigated whether desaturase expression may serve as a potential biomarker of FA status. We showed that expression of desaturase mRNA was regulated in response to FAs in cultured human leukocytes. This indicates that mRNA expression of the desaturases reflect FA status. Furhtermore, we presented a pilot study correlating desaturase expression to the concentration of essential PUFAs in plasma total PL. The results suggested that desaturase expression is partly regulated in response to both long-term and short-term dietary n-3 PUFA intake. Further clinical studies on patient populations at risk of having or at risk of developing essential FA deficiency are required to establish whether mRNA desaturase expression may serve as a clinically useful biomarker for essential FA status.

The mechanisms mediating the inhibitory effect of n-3 PUFAs on cancer are a matter of considerable debate. Most likely there are several mechanisms involved. Defining these mechanisms is important for PUFAs potential impact on cancer therapy as well as cancer prevention. We showed that EPA treatment induced activation of the UPR in HL60 cells, but not in the Ec resistant HL60 clone E2R2. This indicates that the antiproliferative effect of n-3 PUFAs is mediated through alterations in the Ca^{2+}-homeostasis in these cells, leading to activation of the UPR and thereby growth arrest/apoptosis.

An increasing number of reports suggest a role of n-3 PUFAs in combination with established chemoradiotherapy in cancer treatment [25,138,140]. We investigated the effect of DHA on several key targets of conventional cancer therapy aiming to inhibit cancer cell growth. Our results showed that DHA affected these proteins in a favorable way. This may explain the observed enhanced chemosensitivity in cancer cells

supplemented with n-3 PUFAs, and encourage further studies investigating the role of n-3 PUFA as adjuvant to chemoradiotherapy *in vivo*.

Future aspects

Our results indicate that desaturase expression may be exploited as a biomarker for FA status. This finding calls for more studies on the relationship between desaturase expression and FA status. Any new clinical biomarker needs to be evaluated in the clinical setting it is intended to be used in, not only in healthy volunteers. Such target groups may for example include premature infants and geriatric patients with a diet insufficient in n-3 PUFAs. In such studies, it would be useful to expand the study population and follow them for longer time periods. If clinical patient studies should support the hypothesis that desaturase expression might be a biomarker of PUFA status, more information on possible confounders, like for example the effect of a recent fish meal must also be gained. Furthermore, careful assessment of analyzing reproducibility must also be performed.

Our studies also suggest a role of n-3 PUFAs in cancer therapy. It would be useful to investigate whether n-3 PUFA treatment of other types of cancer both *in vitro* and *in vivo* induces the same response. Furthermore, it would be useful to investigate why n-3 PUFAs do not affect normal cells, but only certain cancer cells. This may give clues to why some types of cancers are n-3 PUFA sensitive and others not, which again can be exploited in individual cancer therapy. Further studies investigating the role of n-3 PUFAs as adjuvant to chemoradiotherapy may have important clinical implications in future cancer therapy.

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38. Eirik Helseth: GROWTH AND PLASMINOGEN ACTIVATOR ACTIVITY OF HUMAN GLIOMAS AND BRAIN METASTASES - WITH SPECIAL REFERENCE TO TRANSFORMING GROWTH FACTOR BETA AND THE EPIDERMAL GROWTH FACTOR RECEPTOR.
39. Petter C. Borchgrevink: MAGNESIUM AND THE ISCHEMIC HEART.
40. Kjell-Arne Rein: THE EFFECT OF EXTRACORPOREAL CIRCULATION ON SUBCUTANEOUS TRANSCAPILLARY FLUID BALANCE.
41. Arne Kristian Sandvik: RAT GASTRIC HISTAMINE.
42. Carl Bredo Dahl: ANIMAL MODELS IN PSYCHIATRY.

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43. Torbjørn A. Fredriksen: CERVICOGENIC HEADACHE.
44. Rolf A. Walstad: CEFTAZIDIME.
45. Rolf Salvesen: THE PUPIL IN CLUSTER HEADACHE.
46. Nils Petter Jørgensen: DRUG EXPOSURE IN EARLY PREGNANCY.
47. Johan C. Ræder: PREMEDICATION AND GENERAL ANAESTHESIA IN OUTPATIENT GYNECOLOGICAL SURGERY.
48. M. R. Shalaby: IMMUNOREGULATORY PROPERTIES OF TNF-α AND THE RELATED CYTOKINES.
49. Anders Waage: THE COMPLEX PATTERN OF CYTOKINES IN SEPTIC SHOCK.
50. Bjarne Christian Eriksen: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.
51. Tore B. Halvorsen: PROGNOSTIC FACTORS IN COLORECTAL CANCER.

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52. Asbjørn Nordby: CELLULAR TOXICITY OF ROENTGEN CONTRAST MEDIA.
53. Kåre E. Tvedt: X-RAY MICROANALYSIS OF BIOLOGICAL MATERIAL.
54. Tore C. Stiles: COGNITIVE VULNERABILITY FACTORS IN THE DEVELOPMENT AND MAINTENANCE OF DEPRESSION.
55. Eva Hofsli: TUMOR NECROSIS FACTOR AND MULTIDRUG RESISTANCE.
56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
59. Arne Z. Henriksen: STUDIES ON CONSERVED ANTIGENIC DOMAINS ON MAJOR OUTER MEMBRANE PROTEINS FROM ENTEROBACTERIA.
60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.

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65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.
66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.
68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

1992

74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

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82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

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92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

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104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

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110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANCER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.

134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.

163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS

193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN

218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
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