Klin Wochenschr (1986) 64:793–799

Klinische Wochenschrift

Influence of a Cod Liver Oil Diet in Healthy and Insulin-Dependent Diabetic Volunteers on Fatty Acid Pattern, Inhibition of Prostacyclin Formation by Low Density Lipoprotein (LDL) and Platelet Thromboxane

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Summary. Ten healthy and twenty diabetic volunteers (type 1) received 15 capsules (à 450 mg) cod liver oil for 2 weeks daily in addition to a "normal" diet. The levels of eicosapentaenoic acid in the plasma phospholipids of both groups were increased after the treatment. The inhibition of the prostacyclin formation by LDL was diminished when the LDL was isolated after the treatment in comparison to LDL taken in the same concentration and from the same donors before it. The thromboxane B_2 (TXB_2) synthesis capacity of clotting whole blood, thrombin-induced TXB_2 formation by platelets as well as the 15(S)-hydroxy-11α,9α-epoxymethano-5Z, 13E-prostadienoic acid-induced platelet aggregation were not altered by the treatment in healthy volunteers, whereas in diabetics the TXB_2 formation capacity of clotting whole blood was decreased after the treatment in comparison with before it.

Key words: Cod liver oil – Prostanoids – Fatty acid pattern – Low density lipoprotein – Diabetes

In recent years, studies have focused attention on whether and by which mechanisms a high dietary intake of n-3 polyunsaturated fatty acids (PUFA), especially of all-cis 5, 8, 11, 14, 17 eicosapentaenoic acid (EPA), may explain a low incidence of cardiovascular disorders [6]. Recently we have demonstrated that a linseed oil diet (Table 1) in healthy humans diminished the inhibition of the PGI_2 formation by high LDL concentrations [19], whereas the same diet did not alter the action of lipoproteins (LP) taken from patients with type 1 diabetes mellitus [11]. The difference in the action of linseed oil in diabetic vs healthy humans was associated with a different fate of dietary linolenic acid (18:3, n-3). The linolenic acid was partly transformed to EPA in healthy humans [19], whereas in diabetics the level of EPA remained unchanged after the diet in comparison with before it [15]. The purpose of our study was to investigate the influence of LDL taken from healthy or diabetic humans after an EPA-rich treatment on the prostacyclin (PGI_2) formation. The diet was adjusted to induce approximately the same changes in the EPA level in plasma phospholipids, as were caused by linseed oil diet in healthy humans. Additionally the influence of this treatment on the level and the fatty acid pattern of plasma phospholipids, TXB_2 synthesis capacity of clotting whole blood, platelet aggregation, and bleeding time were investigated.

Abbreviations: EPA = eicosapentaenoic acid; HDL = high density lipoprotein; LDL = low density lipoprotein; MDA = malon dialdehyde; PGI_2 = prostaglandin I_2; PUFA = polyunsaturated fatty acids; TXB_2 = thromboxane B_2

Subjects, Material and Methods

Subjects

Without Treatment. Serum was prepared from venous blood of 24 healthy men (23–50 years of age; median, 36 years), 22 healthy women (19–40 years of age; median, 32.5 years), 27 diabetic men (19–30 years; median, 24 years), and 31 diabetic women (19–30 years; median, 23 years).

Table 1. Fatty acid composition of cod liver oil

Fatty acid	14:0	16:0	16:1	18:0	18:1	18:2	20:4	20:5	22:6	Rest
%	10.0	14.0	18.0	2.5	19.0	1.0	3.0	12.5	11.2	9.9

Treatment with Cod Liver Oil. Group 1: Nine healthy students (four females and five males) ranging in age from 22 to 26 years (median, 23.5 years) received 6.75 g (15 capsules) of cod liver oil for 14 days daily in the course of a "normal" diet. The capsules of cod liver oil were prepared by VEB Jenapharm (Department for Galenic Research) and contained 450 mg cod liver oil, 1.0 mg α-tocopherol acetate, 99 mg gelatine, 33 mg glycerine, 0.6 mg pigment yellow for foodstuffs (No. 75) and 1.2 methylhydroxybenzoate (quality according to 2.AB-DDR for all substances) per capsule. Blood samples were taken 7 days before and immediately before the treatment commenced, after 7 and after 14 days of treatment and again 4 weeks after cessation of treatment. The consumption of the capsules was carried out under control.

Group 2: Twenty diabetic patients with type 1 diabetes mellitus (average duration of disease, 8 years; 10 women and 10 men) ranging in age from 20 to 32 years (median, 24 years) received cod liver oil capsules in the same regimen. Blood samples were taken before and after 2 weeks of treatment. All diabetics had a significantly reduced C-peptide secretion (0.047 ± 0.007 nmol/l), normal lipid values, and a satisfactory balanced metabolism (HbA_1-C: $10.0\% \pm 1.3\%$ of total hemoglobin); 40% of the diabetics had a diabetic retinopathy state I.

Clinical Assays

Blood pressure and ECG were simultaneously registered on a multichannel recorder, and the heart rate was determined from the RR intervals. Lipid status was determined using standard methods. Additionally the HDL_2-cholesterol was determined according to Khan et al. [19]. Drugs influencing the platelet aggregation were not taken by the volunteers throughout the study as well as in the 2 weeks beforehand.

The bleeding time was estimated according to Schulz [24] in a modified way. An ear lobe was punctured 4 mm deep at its lower part with a standard lancet and then immediately dipped into a sterile isotonic saline solution at 22° C being in a 25-ml measuring glass. The time between appearance and disappearance of the blood stream observed in the fluid held to the light was determined with a stopwatch. All measurements were made by the same investigator.

Biochemical Assays

LDL were isolated from serum by ultracentrifugation and ultrafiltration and quantified by estimating the cholesterol part of the LDL [1]. The LDL were incubated with the microsomal fraction of pig aorta (contains the PGI_2 synthase) and prostaglandin H_2 (substrate) according to the method described earlier in detail [1, 2]. Briefly, 5 mg of the microsomal fraction of pig aorta were resuspended in 0.5 ml 0.05 mol/l phosphate buffer pH 7.5. The LDL were added in 0.5 ml 0.05 mol/l phosphate buffer. LDL taken from the volunteers without treatment was adjusted to a concentration between 0.5 and 2.0 mg LDL cholesterol per ml incubation fluid. LDL taken before the treatment and LDL collected after the treatment period was added in the same concentration to the incubation fluid. This concentration represented the highest common concentration for every volunteer isolated before and after the treatment and may be different for the individual volunteers. This influence of LDL was compared with a control, containing buffer instead of LDL. The mixture was kept at 0° C for 10 min, then at 37° C for 5 min and subsequently 10 µg PGH_2 in acetone (20 µl) was added. After an incubation time of 20 min the mixture was acidified with 1 mol/l HCl and extracted with ethyl acetate. The isolation and determination of 6-keto-$PGF_{1\alpha}$ by gas liquid chromatography (GLC) using $PGF_{1\alpha}$ as internal standard was carried out according to [2].

The fatty acid pattern of serum phospholipids under the influence of cod liver oil was analyzed by GLC using a flame ionization detector according to the standard method [2].

U-46619-Induced Platelet Aggregation [3]. This was determined as the initial rate of increase in light transmission in citrated platelet rich plasma (PRP). The cuvette contained a final volume of 0.4 ml: 0.3 ml PRP and 0.1 ml of 0.9% NaCl solution in which the aggregation inducer was dissolved giving a final concentration of 0.1, 0.2,

0.4, 0.8 or 2.0 µmol/l. The PRP was preincubated for 2 min at 37° C and after addition of the U-46619 [15(S)-hydroxy-11α, 9α-epoxymethano-5Z, 13E-prostadienoic acid] solution the progress of aggregation was recorded for 90 s. The rate of increase in light transmission obtained in the sample using 2 µmol/l U-46619 was taken as representing 100% and the EC_{50} was evaluated graphically on the basis of the other aggregation tracing with the lower inducer concentrations.

Thrombin-Induced Formation of Malondialdehyde (MDA). Citrated PRP (330 µl) was incubated with 300 µl 0.9% NaCl solution and 330 µl 0.15 mol/l Tris-HCl buffer pH 7.4 for 5 min at 37° C. The reaction was started by addition of 5 U thrombin (in 40 µl 0.9% NaCl solution) and terminated after 3 min by adding 0.8 ml of 20% trichloroacetic acid, containing 0.5% $SnCl_2$. The formed amount of MDA was estimated spectrometrically as thiobarbituric acid reactive substance [22].

TXB_2 Synthesis Capacity of Clotted Whole Blood. Peripheral venous blood samples (5 ml) were collected in glass tubes without any anticoagulant and immediately allowed to clot for 60 min at 37° C [21]. Serum was removed from clotted blood following centrifugation and the formed amount of TXB_2 was estimated by GLC [4].

Statistics. Data were statistically analyzed using Student's *t*-test for paired (influence of LDL on the PGI_2 formation in clotted whole blood) and unpaired (fatty acid pattern) samples. A P value <0.05 was considered to be significant.

Table 2. Influence of a cod liver oil treatment (15 capsules daily for 14 days; 450 mg cod liver oil per capsule) on clinical parameters (A); on the fatty acid pattern of serum total phospholipids (B) (in weight% of the whole fatty acids); and on platelet parameters (C) of healthy volunteers ($n=9$)

	7 days before treatment was commenced	Immediately before treatment was commenced	After commencement of the treatment		4 weeks after cessation of treatment
			1 week	2 weeks	
A. Clinical parameters					
Heart rate (beats/min)	73±3	70±3	71±4	70±3	71±3
Systolic blood pressure (mm/Hg)	127±4	124±4	123±5	123±5	119±6
Diastolic blood pressure (mm/Hg)	85±2	82±2	81±3	79±3	78±3
Bleeding time (s)	305±30	277±22	338±69	401±63	251±20
Platelet count ($\times 10^3$/µl blood)	133±11	134±8	123±9	155±12	121±5
B. Fatty acid pattern					
Fatty acid					
16:0	25.5±2.0	26.8±1.8	27.4±1.8	25.0±1.3	24.2±2.0
18:0	11.3±0.6	13.1±1.4	14.5±1.5	13.3±1.2	14.0±1.2
18:1 (n-9)	17.0±2.0	15.0±1.6	11.8±0.8*	17.8±1.0	13.9±1.2
18:2 (n-6)	12.6±1.3	12.3±1.2	13.1±1.0	13.1±1.2	13.3±0.9
18:3 (n-3)	1.0±0.3	1.6±0.5	0.6±0.3	0.7±0.3	1.4±0.2
20:3 (n-6)	1.9±0.3	1.7±0.4	2.4±0.3	1.7±0.3	2.7±0.5
20:4 (n-6)	10.3±0.9	8.5±0.8	8.1±1.0	9.8±0.4	10.3±0.9
20:5 (n-3)	0.8±0.2	0.6±0.3	2.4±0.3*	3.6±0.6*	2.1±0.5*
22:6 (n-3)	10.4±2.0	11.8±0.6	11.8±0.9	9.9±0.9	10.7±1.2
C. Platelet parameters					
U46619-induced platelet aggregation (in µmol/l)	0.63±0.08	0.67±0.13	0.54±0.07	0.57±0.09	
Thrombin-induced production of TXB_2 (nmol MDA formed by 2×10^8 platelets)	0.16±0.02	0.18±0.02	0.21±0.04	0.18±0.03	
TXB_2 formation by clotting whole blood (ng TXB_2/ml serum)	522.8±81.1	475.0±57.7	531.6±71.9	488.9±89.0	506.2±72.9

* Significantly different in comparison with the level immediately before the treatment was commenced ($P<0.05$)

Table 3. Influence of a cod liver oil treatment (15 capsules daily for 14 days, 450 mg cod liver oil per capsule) on the fatty acid pattern of serum total phospholipids (A) and on platelet parameters (B) of diabetic volunteers

Fatty acid	Immediately before treatment was commenced	After 14 days of treatment
A. Fatty acid pattern ($n=20$)		
16:0	25.6±0.7	27.9±0.7
18:0	13.2±0.4	13.0±0.5
18:1 (n-9)	14.1±0.4	13.6±0.3
18:2 (n-6)	24.7±0.6	23.7±0.5
18:3 (n-3)	1.1±0.1	0.9±0.1
20:3 (n-6)	3.0±0.2	2.8±0.3
20:4 (n-6)	12.1±0.4	11.0±0.4
20:5 (n-3)	1.7±0.1	2.8±0.3*
22:6 (n-3)	5.1±0.4	5.3±0.4
B. Platelet parameters ($n=10$)		
TXB_2 formation by clotted whole blood (ng TXB_2/ml serum)	377.7±93.8	138.5±25.8*

* Significantly different in comparison with the level immediately before the treatment was commenced ($P<0.05$)

Results

All values for heart rate, systolic and diastolic blood pressure, as well as bleeding time are not statistically changed by the treatment in healthy humans (Table 2, part A). The modifications in the fatty acid pattern of serum phospholipids from healthy volunteers are demonstrated in Table 2, part B. On the one hand the percentages of saturated fatty acids, oleic acid, (n-6)PUFA, linolenic acid, and docosahexaenoic acids, were either unchanged or slightly changed only. These changes are not correlated with the dietary regimen. On the other hand EPA is increased after 1 or 2 weeks of cod liver oil treatment, and decreased after cessation of the treatment ($P<0.05$). But after 4 weeks, the level of EPA remained increased compared with the starting value. Similar changes in the level of EPA as in the phospholipids of healthy volunteers were observed in the fatty acid pattern of serum phospholipids from diabetic humans after the EPA-rich treatment (Table 3, part A).

The TXB_2 formation capacity by whole blood, the thrombin-induced production of MDA as well as the U-46619-induced platelet aggregation were not influenced by the low-dose cod liver oil diet in healthy humans (Table 2, part C), whereas under the same dietary conditions of cod liver oil in diabetics the TXB_2 synthesis capacity was significantly decreased (Table 3, part B).

In a prestudy the influence of LDL taken from healthy and diabetic humans on the PGI_2 formation by the microsomal fraction of pig aorta was investigated without treatment (Fig. 1). The slopes as well as the position of the lines are not significantly different between LDL, sampled from healthy volunteers, and the LDL taken from diabetics. LDL obtained from males and LDL from females influenced the PGI_2 formation in a different way. This influence of LDL from healthy or diabetic humans is modified by the cod liver oil diet, independently whether the LDL was obtained from males or females. LDL (1.71±0.14 mg LDL cholesterol/ml) taken from the serum of healthy volunteers, inhibited the PGI_2 formation by 46.4%±8.2% in comparison with controls when it was sampled before the diet, and inhibited it by 12.8%±20.8% in comparison with controls

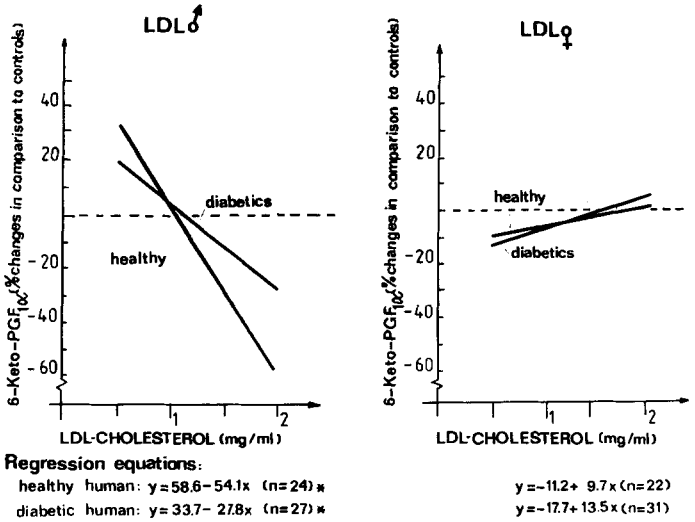

Fig. 1. Influence of LDL on the PGI_2 formation by the microsomal fraction of pig aorta. *Lines* represent regressions for the influence of LDL obtained from healthy volunteers (*healthy*) or diabetic (type 1) humans (*diabetics*). Below the diagrams the equations for the regression lines with significance level are demonstrated. * The slope of the regression line is significantly different from zero ($P<0.05$; t-test). The differences between the slopes of the regression lines for LDL from healthy and diabetic humans are statistically not significant

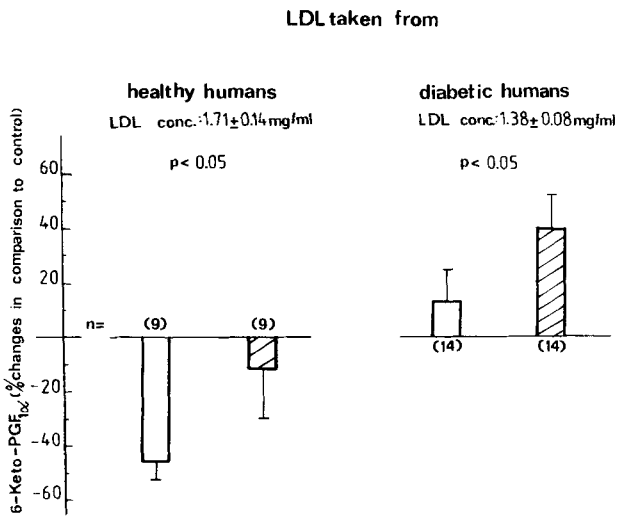

Fig. 2. Effect of cod liver oil diet (15 capsules à 450 mg daily for 2 weeks) on the influence of LDL on the PGI_2 biosynthesis. LDL was isolated from the venous blood of healthy and diabetic humans (type 1) before and after the diet. The LDL from each volunteer was adjusted to the same LDL-cholesterol level in the incubation fluid (for details see Methods). □, before diet; ▨, after diet

when the LDL was taken at the end of treatment. The difference in the influence on the PGI_2 formation is significant ($P<0.05$, t-test for paired samples). LDL (1.38 ± 0.08 mg LDL cholesterol/ml) obtained from diabetics stimulated the PGI_2 formation by $12.4\%\pm12.1\%$ before the diet and by $40.5\%\pm13.1\%$ after the diet ($P<0.05$). The difference in the action of LDL before and after the diet is significant, too ($P<0.05$, t-test for paired samples).

Discussion

A cod liver oil treatment diet raised the content of EPA of plasma total phospholipids in diabetic as well as healthy humans, whereas the levels of (n-6)PUFA, linolenic, docosahexaenoic, oleic, and saturated fatty acids remained unchanged. This treatment with low-dose cod liver oil did not influence the amount of plasma triglycerides, total cholesterol, HDL cholesterol, HDL_2 cholesterol, and LDL cholesterol either in diabetic or in healthy humans (not demonstrated). In healthy humans the U-46619-induced platelet aggregation and the TXB_2 synthesis capacity of clotting whole blood also remained unchanged. The same diet in diabetics caused an inhibition of the ADP-induced platelet aggregation [23] and a decrease in the TXB_2 synthesis capacity in clotting whole blood. At present we do not have an explanation for this difference in the response of the TX system on the cod liver oil treatment in healthy and diabetic humans.

It was demonstrated that diets enriched in EPA induced an incorporation of (n-3)PUFA in membranes of platelets and vascular walls at the expense of (n-6)PUFA [7, 23], that it increased the bleeding time [7], decreased the platelet counts [13], diminished platelet aggregation upon ADP or collagen [8, 13], decreased the platelet survival time [13], and induced a fall in the concentration of plasma triglycerides, total cholesterol as well as the level of LDL cholesterol, whereas the level of HDL cholesterol was increased after a diet rich in EPA [13, 25]. The statistically unchanged level of plasma lipids and the unchanged bleeding time which only tended to increase during the diet may be a result of the small amount of EPA in the diet, because most of these effects were observed when the amount of EPA in the diet was higher than 2 g EPA daily for 6 weeks or 7–11 g EPA daily for 9 days [14].

Recently we found that a linseed oil diet induced a small rise in the level of EPA, which could induce a shift in the inhibitory action of LDL on the PGI_2 formation. The rise in the level of EPA in the plasma phospholipids was only observed after the administration of 30 ml linseed oil daily for 4 weeks in healthy volunteers, but not after the same diet in diabetics [15]. As a result of the diet, the inhibitory potency of LDL sampled from healthy volunteers on the PGI_2 formation was diminished to a statistically significant extent after linseed oil diet [19], whereas the inhibitory potency of LDL obtained from diabetics was not influenced by the diet [11]. An increase in the content of EPA in the plasma phospholipids approximately similar to that after linseed oil diet can be induced by our low dosing of the cod liver oil in the lipids in healthy as well as diabetic humans. The inhibitory potency of LDL obtained from venous blood of diabetic or healthy volunteers was significantly diminished after the cod liver oil diet. From these results we concluded that the same diet in healthy or diabetic humans induced different effects when the transformation of the dietary fatty acid into EPA was blocked. In the case of diabetics, a metabolic abnormality in the elongation and desaturation system for fatty acids [5] may be responsible for the unchanged level of EPA after the linseed oil diet [15].

If the changed influence of LDL on the PGI_2 formation is important for the antithrombotic action of the (n-3)PUFA-rich diet, it may be more effective to use cod liver oil in diabetic patients

rather than linseed oil, whereas in healthy humans both diets could be effective. The increase in the level of EPA resulted not only in a changed influence of LDL on the PGI_2 formation. Further possible mechanisms for the antithrombotic action of EPA-rich diets are described in the literature. Hornstra et al. [16] suggested that the low thrombogenicity of (n-3)PUFA-rich diets is primarily due to the fact that platelets cannot produce sufficient amounts of TXA_2 to maintain the platelet aggregation reaction, caused by an inhibition of the cyclooxygenase by EPA [18]. As a result of this small thrombogenic tendency of platelets, a diminished production of PGI_2 is without consequences. Secondly, EPA inhibits platelet aggregation by mechanisms independent of those of prostanoid synthesis. This hypothesis is supported by results of Thorngren et al. [26] demonstrating that the mechanism by which a fish diet delays primary hemostasis is different from the apparently similar effect of acetylsalicylic acid. Thirdly, if any conversion of EPA into prostanoid-like substances takes place, as it was postulated by Dyerberg [9], TXA_3 is a very weak proaggregator, whereas PGD_3, nonenzymatically formed from PGH_3, and PGI_3 have strong antiaggregatory properties [12]. But the conversion rate into prostanoids of the 3-family is rather low [10] and may be dependent on the presence of a lipoxygenase product of the arachidonic acid metabolism, the 12-hydroperoxyeicosa-5,8,10,14-tetraenoic acid [20]. Further possible mechanisms of action of an EPA-rich diet on platelet-vessel wall interactions are an inhibition of arachidonic acid release from membranes [20], a very effective block of TXA_2 receptors in the platelet membranes [12], or a block of the prostanoid-independent thrombin receptor [12].

In conclusion, the present paper demonstrates that the findings from investigations on a diet rich in (n-3)PUFA were markedly different in healthy humans in comparison with diabetics.

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Received October 29, 1985
Returned for revision January 1, 1986
Accepted April 14, 1986

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Buchbesprechungen

Brunner KW, Nagel GA (Hrsg) Internistische Krebstherapie. Mit Beiträgen zahlreicher Fachwissenschaftler. 3., völlig überarb. Aufl., Springer, Berlin Heidelberg New York Tokyo 1985. XVI, 664 S., 48 Abb., 189 Tab., geb. DM 148,–.

Die erste Auflage der „Internistischen Krebstherapie", herausgegeben von Brunner und Nagel, erschien 1976 als Gemeinschaftswerk der Schweizerischen Arbeitsgruppe für Klinische Krebsforschung mit der Zielsetzung, internistischen Onkologen in Klinik und Praxis den aktuellen Stand der medikamentösen Behandlung maligner Erkrankungen darzulegen. Der Praxisbezug und die auf großer persönlicher Erfahrung der Autoren beruhende Kompetenz bewirkte eine weite Verbreitung des Werkes, so daß 1979 eine zweite Auflage erforderlich wurde. Jetzt liegt die dritte, völlig überarbeitete Auflage vor.

In der dritten Auflage ist die Zahl der beteiligten Autoren von 21 auf 31 angestiegen. Dies ist dadurch bedingt, daß – dem interdisziplinären Charakter der Onkologie entsprechend – angesehene Fachvertreter benachbarter Disziplinen als Mitautoren gewonnen werden konnten. Der Umfang des Buches ist von 513 auf 664 Seiten angestiegen. Wichtige neue Kapitel beschäftigen sich z.B. mit den Spätfolgen der Chemotherapie; Urogenitaltumoren, malignen Tumoren der Knochen und Weichteile, HNO-Tumoren, Malignome der Haut, die in der ersten Auflage mehr kursorisch behandelt wurden. Unverändert lesenswert im allgemeinen Teil sind z.B. die Kapitel „Medikamente und Methoden ohne nachgewiesene therapeutische Wirkung" (G. Martz und S.B. Hauser) und „Organisatorische Probleme von Diagnose, Theapie und Forschung bei Krebskranken" (KW. Brunner und K. Batz). Im speziellen Teil ist die internistische Therapie der einzelnen Neoplasien auf modernem Stand unter Berücksichtigung internationaler Erfahrungen übersichtlich und praxisnah dargestellt. Ergebnisse der Grundlagenforschung und hypothetische Konzepte werden nur insoweit dargestellt, als sie zum Verständnis erforderlich sind.

Zusammenfassend kann festgestellt werden, daß den Herausgebern und Autoren der dritten Auflage der „Internistischen Krebstherapie" eine praxisbezogene Darstellung der Möglichkeiten der Chemotherapie maligner Tumoren im Gesamtkonzept der interdisziplinären Tumortherapie, dem modernen Stand der Forschung und klinischen Empirie entsprechend, gelungen ist. Dabei wurden die Zielsetzungen der ersten Auflage beibehalten. K. Wilms (Würzburg)

Tang Z-Y (ed) Subclinical Hepatocellular Carcinoma. China Academic Publishers, Beijing/Springer, Berlin Heidelberg New York Tokyo 1985. 366 pages, 136 figs, 144 tabs, hard cover DM 236,–.

Das hepatocelluläre Carcinom ist weltweit einer der häufigsten malignen Tumoren mit einer besonders hohen Inzidenz in Südostasien und Subsahara-Afrika. Während das hepatocelluläre Carcinom früher erst in klinisch weit fortgeschrittenen Stadien mit schlechter Prognose oder bei der Autopsie diagnostiziert werden konnte, ermöglichen heute insbesondere der Nachweis erhöhter Alphafetoprotein-Konzentrationen im Serum sowie verschiedene bildgebende Verfahren (Sonographie, Szintigraphie, Angiographie, Computertomographie etc.) die Erkennung klinisch nicht apparenter Formen des hepatocellulären Carcinoms (‚subclinical hepatocellular carcinoma') und häufig dessen kurative Behandlung. Durch Untersuchung von ca. 2 Millionen Chinesen in der Region von Shanghai auf Alphafetoprotein-Erhöhung im Serum konnten 300 Patienten mit hepatocellulären Carcinomen identifiziert werden, von denen 45% in einem subklinischen Stadium (subclinical hepatocellular carcinoma) und resezierbar waren. Das aus diesen Studien resultierende Konzept des subclinical hepatocellular carcinoma, charakterisiert durch ausgezeichnete Überlebenschancen bzw. Heilung, hat die klinischen Perspektiven des hepatocellulären Carcinoms wesentlich verbessert (‚secondary prevention') zu einem Zeitpunkt, zu dem die ‚primary prevention' durch Hepatitis B Virus-Impfung noch nicht weltweit praktikabel ist. Der vorliegende Band ist eine umfassende Darstellung der epidemiologischen, pathogenetisch-molekularbiologischen, diagnostischen und therapeutischen Aspekte des subclinical hepatocellular carcinoma durch Dr. Tang und 23 weitere Wissenschaftler am First College of Medicine, Institute of Biochemistry und Institute of Cell Biology in Shanghai/China in insgesamt 29 Einzelkapiteln. Trotz einiger Überschneidungen und stilistischen/inhaltlichen Inhomogenitäten zwischen einzelnen Kapiteln bietet das außerordentlich breite Spektrum der in dem Band angesprochenen Aspekte des hepatocellulären Carcinoms/subclinical hepatocellular carcinoma Neues und Wissenswertes insbesondere für Epidemiologen, Kliniker und Wissenschaftler, die sich für Entstehung, Erkennung, Behandlung und Prävention von hepatocellulären Carcinomen und anderen malignen Tumoren interessieren. H.E. Blum (Freiburg)