Partial Hepatectomy, Regeneration & Liver function

Interesting & complex relationship between partial hepatectomy, regeneration and actual liver function.

Study in rats showed that liver functions are dissociated in time following 70% hepatectomy, and that GEC is restored before regeneration can compensate for the loss in liver cell mass {Yildrim1981}.
The rapid increase in the activities of the galactose metabolizing enzymes in vitro followin 70% hepatectoy {Bauer1976} led to the hypothesis that GEC *in vivo* is restored to normal due to an increased metabolizing capacity of the surviving hepatocytes {Yildrim1981}.

In both clinical and experimental studies, a discrepancy has arisen between volumetric and functional regeneration, from which 2 contradictory theories have emerged. The first theory suggests that hepatocyte prolveration is promoted at the expense of liver function {Jochum2006}. The second theory postulates that hepatocellular function is enhanded after major PHx to compensate for reduced liver mass {Jansen1990, Yildrim1981, } {Graaf2011}.

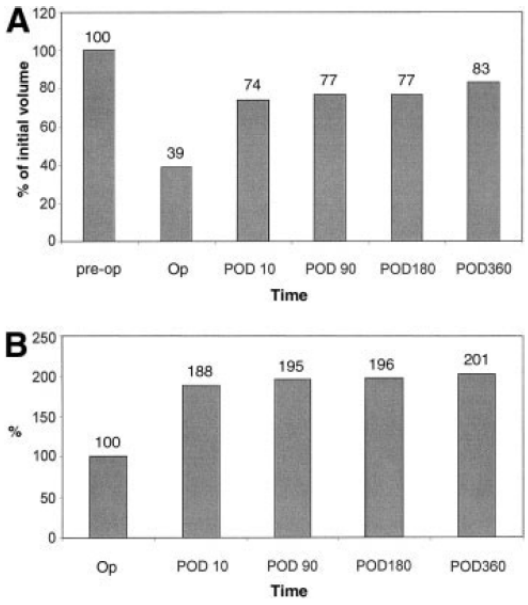

Figure 1. Kinetics of regeneration of liver volume expressed as percent of initial liver volume (A) and as percent of residual liver volume (B). POD, postoperative day.

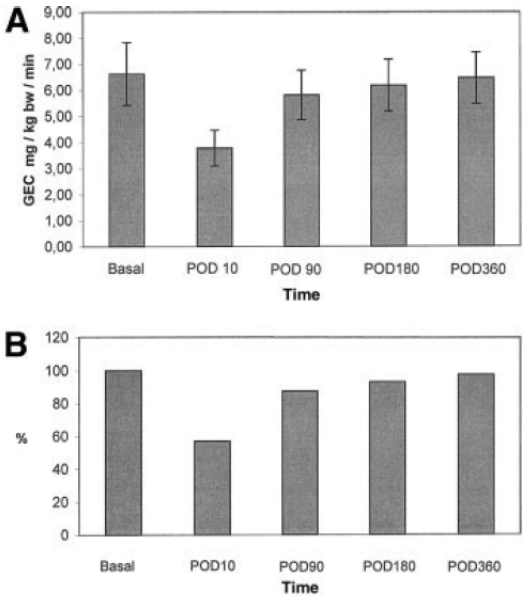

Figure 2. Kinetics of recovery galactose elimination capacity (GEC) expressed as mg/kg bw/minute (A) and as percent of initial basal value (B). POD, postoperative day.

{Nadalin2004}

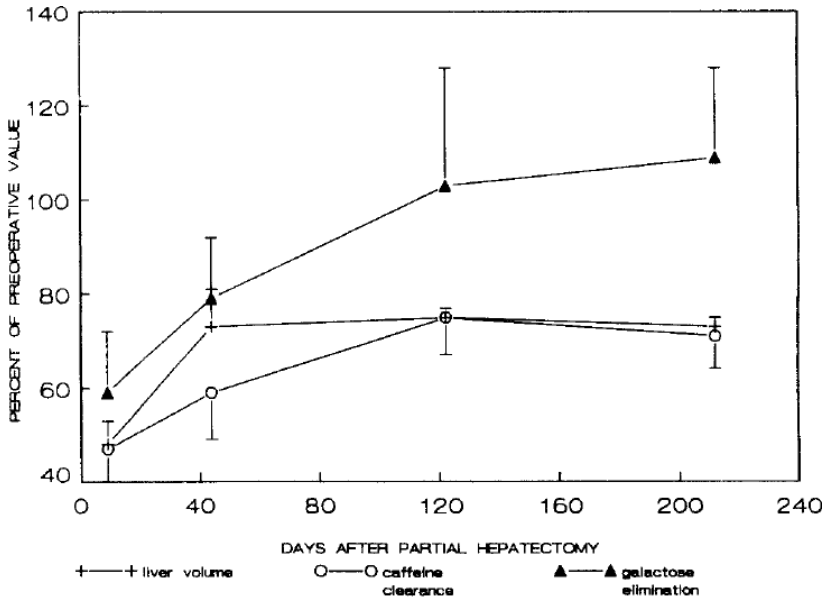

Fig. 3. Restoration of liver function and liver volume after partial hepatectomy. The liver volume, determined by SPECT scintigraphy, the caffeine clearance, and the galactose elimination capacity was measured 9, 44, 122, and 212 days after operation in six patients. The data are expressed as percentage of the preoperative value ± SEM.

{Jansen1990}

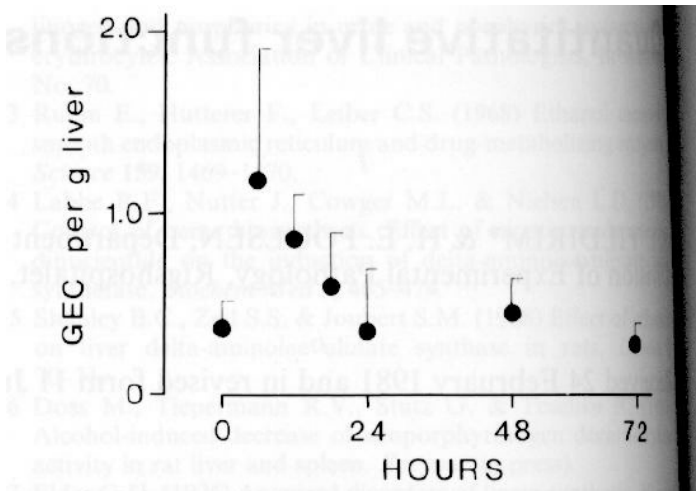

Figure 2. Galactose elimination capacity in μmol/lmin and g liver a various times after partial hepatectomy. Dots indicate mean of fou to six animals, bars indicate one SEM. Control value and zero hou value are identical (not shown).

{Yildrim1981}

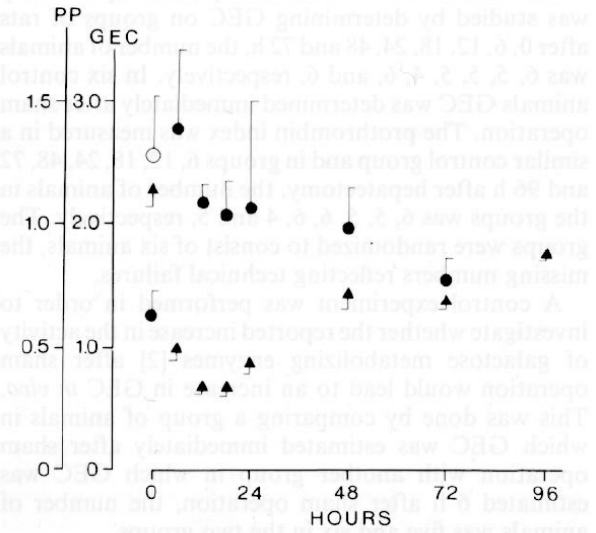

Figure 1. Galactose elimination capacity (•) in μmol/min and prothrombin index (▲) in arbitrary units at various times after partial hepatectomy. Symbols indicate mean of four to six animals, bars indicate one SEM. The open circle indicate control value of galactose elimination capacity.

{Yildrim1981}

Table 1. The values of liver weight, total hepatic DNA and total hepatic protein, mean ± SEM are indicated; the number of animals in each group is stated under Materials and Methods

	Control	6 h	12 h	18 h	24 h	48 h	72 h
Liver weight (g)	7·42 ±0·27	2·72 ±0·43	2·59 ±0·18	3·29 ±0·31	3·50 ±0·21	4·29 ±0·05	4·96 ±0·21
Total hepatic DNA (μg)	23·7 ±0·90	6·19 ±0·76	6·64 ±0·57	7·64 ±0·47	7·60 ±0·24	11·1 ±0·32	15·0 ±0·85
Total hepatic protein (mg)	1362 ±77	546 ±101	463 ±59	650 ±67	649 ±83	748 ±35	844 ±29

{Yildrim1981}

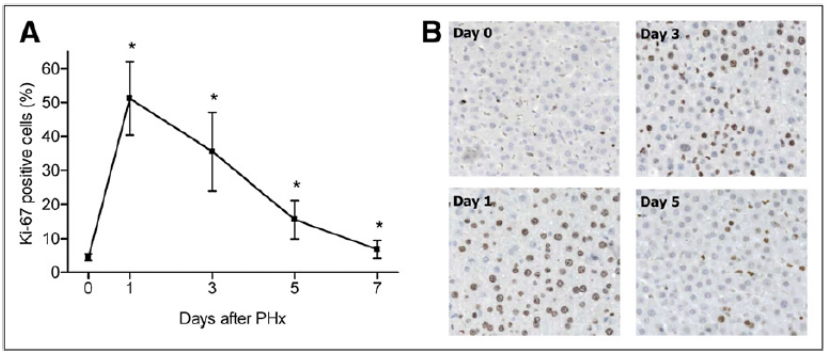

FIGURE 1. Percentage of Ki-67–positive hepatocytes (A), with representative histology (B). Percentage of proliferating hepatocytes significantly increased from 4.4% (baseline value) to 51.2% at 24 h after 70% PHx, after which it decreased on days 3 (35.6%), 5 (15.6%), and 7 (6.8%). Values are expressed as mean ± SD. * = statistically significant difference vs. baseline.

{Graaf2011}

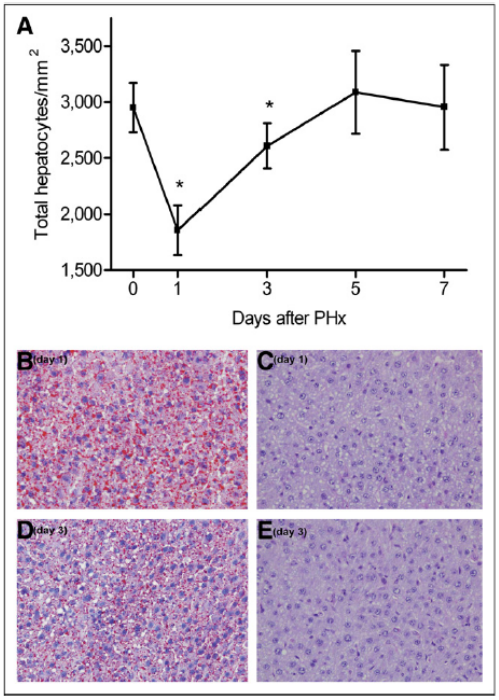

FIGURE 2. (A) Histologic evaluation revealed significantly reduced amount of hepatocytes per squared millimeter ($P < 0.0001$) at 24 h after induction of liver regeneration due to hypertrophy of hepatocytes. In addition, intracytoplasmatic vesicles were seen on day 1 and, to a lesser extent, on day 3 after PHx. (B and D) Oil red O staining confirmed presence of fat within vacuoles (stained red). (C and E) Periodic acid–Schiff staining was negative for glycogen.

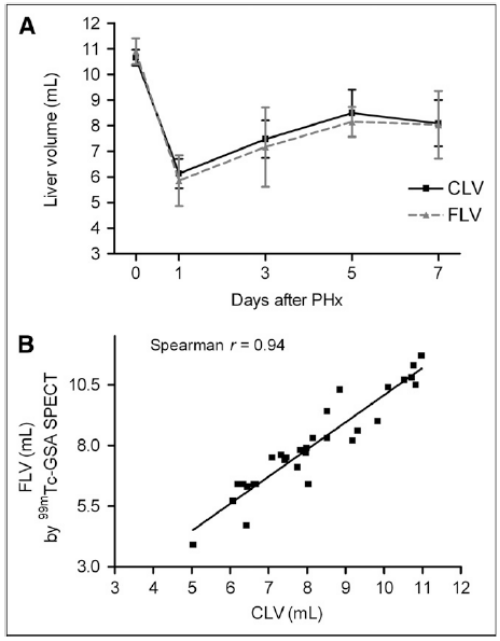

FIGURE 3. (A) No difference was found between CLV and FLV during liver regeneration. (B) CLV and FLV exhibited strong correlation (Spearman $r = 0.94$, $P < 0.0001$).

of liver regeneration (Fig. 5B). Moreover, the GEC exhibited kinetics different from those of CLV as well as different from the ^{99m}Tc-GSA and ^{99m}Tc-mebrofenin uptake rates.

{Graaf2011}

TABLE 3
Results of Liver Function Tests

Test	Day 0	Day 1	Day 3	Day 5	Day 7
GEC	100% ± 15.0%	113.9% ± 22.7%	118.9% ± 22.1%	135.0% ± 19.1%*	123.7% ± 17.2%*
ICG	100% ± 14.1%	56.5% ± 18.6%*	86.4% ± 15.0%	87.3% ± 21.1%	95.2% ± 15.4%
^{99m}Tc-mebrofenin uptake	100% ± 7.3%	68.7% ± 14.1%*	91.1% ± 13.97%	103.9% ± 15.8%	106.2% ± 16.3%
^{99m}Tc-mebrofenin excretion	100% ± 13.4%	78.8% ± 5.9%	100.2% ± 49.9%	166.6% ± 22.2%*	152.1% ± 45.1%*
^{99m}Tc-GSA uptake	100% ± 16.8%	77.0% ± 19.3%	66.9% ± 14.5%*	72.1% ± 15.8%*	83.1% ± 15.1%

*Statistically significant differences from baseline levels.
For intrinsic regulation of liver function, data derived from quantitative liver function test were divided by total liver (wet) weight and subsequently expressed as mean ± SD percentage of control.

{Graaf2011}

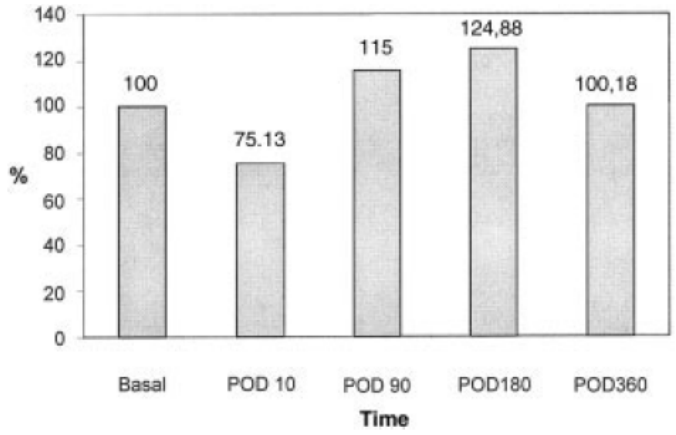

Figure 3. Kinetics of recovery of galactose elimination capacity (GEC) related to milliliter of liver volume. POD, postoperative day.

{Nadalin2004}

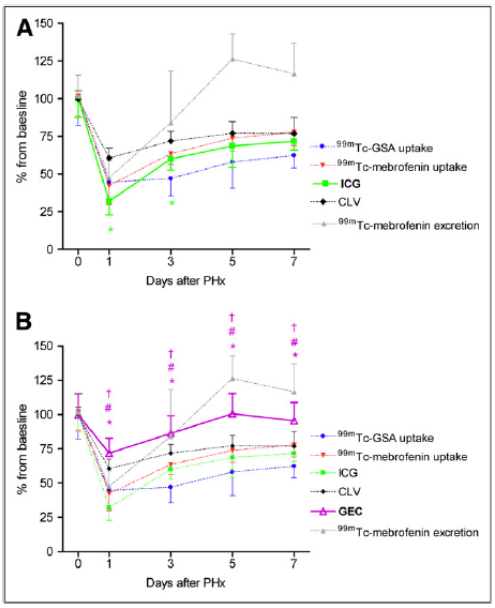

FIGURE 5. Comparative analysis between quantitative liver function tests and liver volume. (A) Liver function measured by ICG clearance test decreased to 32.1% ± 9.0% of baseline values on day 1 after 70% PHx, after which it recovered to 60% on day 3 ([*] vs. CLV). On days 5 and 7, ICG plasma disappearance rate increased to 69% ± 14% and 72% ± 6% of baseline, respectively, and exhibited no differences vs. CLV. (B) GEC was reduced on day 1 (72% ± 10.9%), after which it recovered to baseline levels. GEC was only minimally affected by 70% PHx and showed significantly different pattern, compared with liver volume (*), ^{99m}Tc-GSA uptake rate (#), and ^{99m}Tc-mebrofenin uptake rate (†).

{Graaf2011}

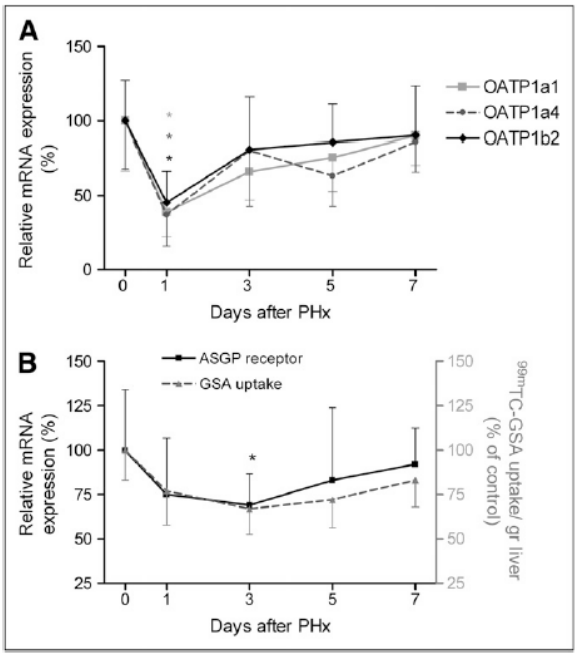

FIGURE 6. mRNA expression of 3 OATP rat isoforms and ASGPR. (A) mRNA expression of all OATP rat isoforms was significantly decreased at 24 h after 70% PHx (*). Nonparametric repeated-measurement ANOVA indicated that curve of OATP1b2 differed from OATP1a1 ($P = 0.044$) and OATP1a4 ($P = 0.028$) during liver regeneration. (B) mRNA expression of ASGPR showed a curve similar to GSA uptake rate per gram of liver, expressed as percentage of baseline. There was significant reduction in ASGPR mRNA expression on day 3 after PHx (*). mRNA levels of the experimental groups are given as percentage of control. Left *y*-axis represents ASGPR mRNA expression, and right *y*-axis represents GSA uptake per gram of liver.

{Graaf2011}

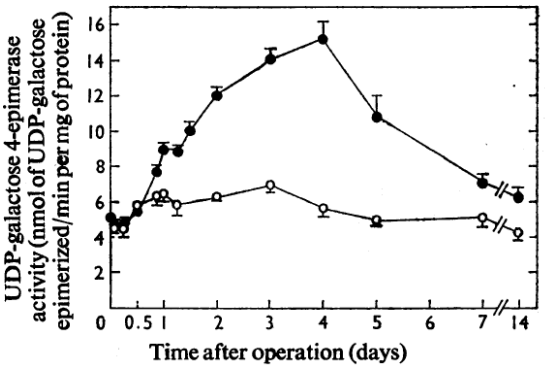

Fig. 1. *Pattern of UDP-galactose 4-epimerase activity in rat liver*

Enzyme activity was measured spectrophotometrically in a linked assay system by following the formation of UDP-glucose coupled to nicotinamide nucleotide reduction at 334 nm and 30°C. ●, Partial hepatectomy; ○, sham operation. Each point represents the mean ± S.E.M. for five rats.

{Bauer1976}

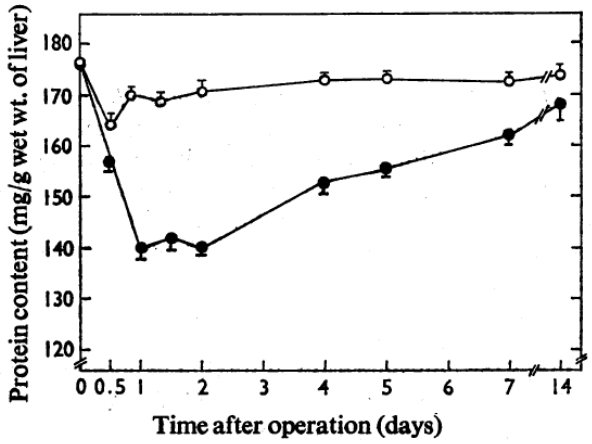

Fig. 2. *Restoration of protein content in rat liver after partial hepatectomy*

The protein content was measured by the biuret method. ●, Partial hepatectomy; ○, sham operation. Each point is the mean±S.E.M. for five animals.

{Bauer1976}

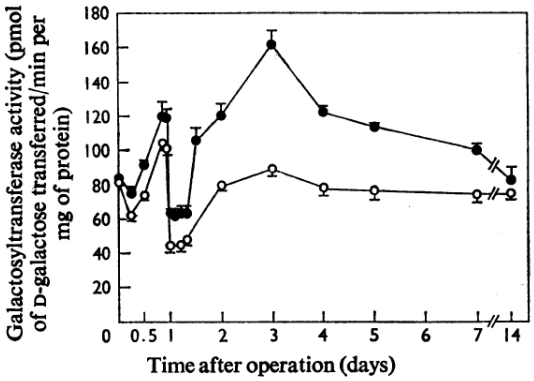

Fig. 3. *Pattern of UDP-galactose–glycoprotein galactosyltransferase*

Enzyme activity was determined in a radiochemical assay by measuring the transfer of [^{14}C]galactose to desialized and degalactosylated fetuin at 30°C. For further experimental details see the Materials and Methods section. ●, Partial hepatectomy; ○, sham operation. Each point represents the mean±S.E.M. for five rats.

{Bauer1976}

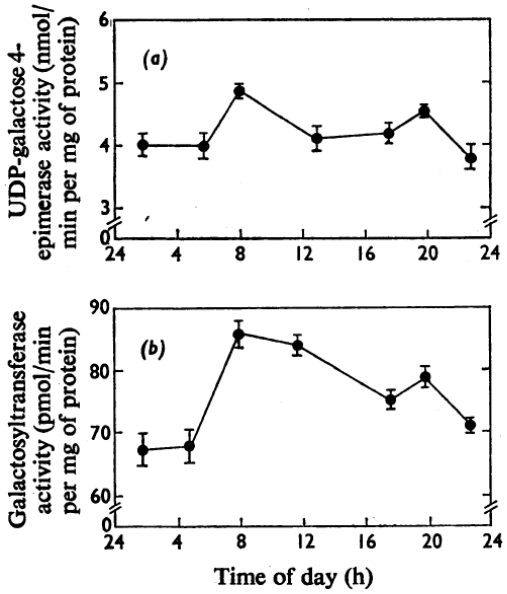

Fig. 4. *Enzyme activities at various times of the day*

(*a*) UDP-galactose 4-epimerase activity; (*b*) UDP-galactose–glycoprotein galactosyltransferase activity. Each point represents the mean±S.E.M. from five rats. $P<0.005$ for difference between minimal (02:00h) and maximal activity (08:00h) of UDP-galactose 4-epimerase and UDP-galactose–glycoprotein galactosyltransferase. {Bauer1976}

Table 1. *Time-course of sugar nucleotide concentration*

Partial hepatectomies and sham operations were performed between 08:30 and 10:00h. At the times indicated, liver lobes were instantly frozen *in situ* between metal tongs precooled in liquid N_2 (Wollenberger *et al.*, 1960). The sugar nucleotides were determined in a neutralized $HClO_4$ extract. For further experimental details see the Materials and Methods section. Values are means±S.D. from five rats. *$P<0.01$ as compared with sham-operated animals.

	Concentration of sugar nucleotides (nmol/g wet wt. of liver)			
	UDP-glucose		UDP-galactose	
Time after operation (h)	Partial hepatectomy	Sham operation	Partial hepatectomy	Sham operation
1	273±20	235±28	90± 8	84±10
3	232±32*	322±18	72±10	87± 4
6	243±35*	338±30	73±13	102±10
10	294±27*	417±40	90± 7	129±15
24	385±28	404±32	108± 9	110±12
48	378±34	357±30	105± 9	94± 9
72	376±28	320±24	107±11	95±12
96	334±41	357±51	103±12	94±13
336	332±37	336±40	89± 9	91± 5
Control (unoperated animals)	331±25		92± 7	

{Bauer1976}

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