A morphometric study of the endoplasmic reticulum in human hepatocytes

Correlation between morphological and biochemical data in subjects under treatment with certain drugs

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SUMMARY The distribution of the endoplasmic reticulum in human hepatocytes is defined in quantitative terms using the techniques of morphometry. The subjects of the study are liver biopsies from normal, untreated subjects and patients being treated with various drugs. In contrast to rat hepatocytes, the amount of smooth endoplasmic reticulum (SER) in man exceeds that of the rough endoplasmic reticulum (RER) and accounts for 76-3 % of the total endoplasmic reticulum. This is to be taken into consideration in pharmacological or toxicological studies. In addition, two components of the SER have been identified: more prominent is the type 1 or vesicular which has a regular honeycomb pattern, made up of cisternae with patent lumina and a mean width of 1500 Å; the type 2, or non-vesicular, occurs in discrete foci of densely packed smooth membranes with a spacing of about 140 Å. In subjects under short-term treatment with Benzodiazepin (diazepam) the RER remained unchanged but the SER membranes were significantly increased with a remarkable, two- to threefold increase of the SER type 2 in three out of four patients. A rise in incorporation of 14C-acetate into digitonin-precipitable sterols as measured in liver biopsy material was also noted in these three patients. The suggestion is made that the SER 2 represents the newly formed membranes whereas the SER 1 would represent 'adult' membranes. No changes were observed in two patients under short-term treatment with phenobarbital or Dilantin.

A few morphometric studies have already been conducted on animal liver in normal (Loud, 1968; Weibel, Stäubli, Gnägi, and Hess, 1969; Hess, Weibel, and Preisig, 1973) or in experimental conditions (Wiener, Loud, Kimberg, and Spirio, 1968; Stäubli, Hess, and Weibel, 1969; Hope, 1970; Riede, Seebass, and Rohr, 1971a; Riede, Strassle, Bianchi, and Rohr, 1971b; Dobbins, Rollins, Brooks, and Fallon, 1972; Bolender and Weibel, 1973) but quantitative analyses of human liver are still lacking. Ethical and practical considerations make it difficult to collect the material necessary for defining the normal base-line data necessary for comparative purposes. However, such a study appears essential, especially when dealing with toxicological or pharmacological studies. The subjectivity or the aesthetic feelings of the observer often interfere with an objective interpretation of findings and do not permit a quantitative estimation of the changes observed. In the present study, we have applied the technique of Weibel, Kistler, and Scherle (1966) and Weibel et al (1969) to the study of human liver, using the material obtained by needle biopsy in normal, untreated patients and in patients treated with various drugs. Our attention was especially concentrated on drugs metabolized by microsomal enzymes, influencing bilirubin or cholesterol metabolism. We attempted to correlate the biochemical
findings with eventual changes in the endoplasmic reticulum. The biochemical data concerning the effect of these drugs on hepatic biosynthesis of cholesterol as measured on needle biopsies have been published elsewhere (Bamonti and Dini, 1973; Orlandi, Bamonti, Dini, Koch, and Jezequel, 1974).

Material and Methods

SELECTION OF PATIENTS

Group 1: Normal untreated patients
Four biopsies of normal, untreated patients were analysed. The selection procedure considered the clinical examination, laboratory findings (BSP retention at 45 min, SGOT, SGPT, serum bilirubin, serum alkaline phosphatase). Special attention was paid to the drug-taking history and only patients ‘drug-free’ for at least three weeks were retained. The selection also took into account the light microscopy findings.

Group 2: Treated patients without liver involvement
Four patients with normal liver function tests and in need of sedative treatment were given Benzodiazepin (diazepam) according to the following scheme: Pe. M. received 20 mg per day for two days; Br. P. received 60 mg per day for three days; Ta. P. and Gi. M. received 40 mg per day for four days. The needle biopsy was taken on the morning following the cessation of therapy except in Ta. P. from whom it was taken at a four-day interval.

One patient (Ca. V.) received 50 mg per day of diphenylhydantoin (Dilantin) for seven days. A biopsy was taken at the beginning of treatment and is included in group 1. Another biopsy was taken at the end of the seven-day period.

Group 3: Treated patient with hepatic dysfunction
One patient with Gilbert’s syndrome and serum bilirubin of 2-06 mg%, received 360 mg phenobarbital per day for four days. A biopsy was taken before the beginning of treatment and another one at the end of therapy when the serum bilirubin had fallen to 0-60 mg%.

PROCESSING THE MATERIAL

The hepatic biosynthesis of cholesterol
This was estimated on biopsy material as described elsewhere (Orlandi et al., 1974).

Light microscopy
For light microscopy, a fragment of the biopsy was fixed in formaldehyde, embedded in paraffin, and stained with haematoxylin-eosin.

Electron microscopy
For electron microscopy, a small piece of tissue was cut in 1 mm³ fragments and fixed in 1% osmium tetroxide buffered with Sorensen’s phosphate buffer pH 7-4. After dehydration with alcohol and propylene oxide, the fragments were embedded in a mixture of Epon and Araldite. The blocks obtained were cut on a LKB Ultratome III. Thick (1 micron) sections were stained with Azur II-Methylene blue for examination with the light microscope. Ultrathin sections were stained with lead citrate and examined with the electron microscope Philips EM 201.

Quantitative analysis
For quantitative analysis, five blocks of each biopsy material were chosen at random and electron micrographs from each section were taken on 35 mm film, first at a magnification of 4000 on the screen, i.e., 1490 on the film due to the reduction in the microscope. The randomization of the areas to be photographed was obtained by placing the screen on the lower left corner of a mesh of the copper grid (Weibel et al., 1969). If the angle was not suitable (technical imperfections, extrahepatocyctic space, section edges) the stage was moved to another corner. Subsequently, the primary magnification was brought to 8600 on the screen (3200 on film) and 24 500 (9100) without moving the centre of the picture. Six electron micrographs were taken at each level of magnification. A total of 90 pictures was thus obtained for each biopsy. For the purpose of the present study, i.e., the analysis of the endoplasmic reticulum, measurements were made on pictures taken at a magnification of 9100. The films were examined on a projecting screen with a secondary tenfold magnification upon which was superimposed a multipurpose test screen with 84 test lines of known length (Weibel et al., 1966, 1969). The evaluation of the membrane surface density Sv of smooth and rough reticulum was performed by counting the number of intersections (I) of membrane profiles with the test lines and applying the formula Sv = 2 × I/L where L is the length of the test lines enclosed in the cytoplasm. The results are expressed in μ² per μ₃ of cytoplasm (Weibel et al., 1969). Estimation of the volumetric density (Vv) of the endoplasmic reticulum was given by the formula Vv = Pp where Pp is the fraction number of endpoints of the test lines enclosed within the profiles of the endoplasmic reticulum (Weibel et al., 1969). The mean width (d) of the cisternae was calculated from the volume to surface ratio (v/s) (Weibel et al., 1969) such as v/s = d/2 for the cisternae of the Golgi apparatus which are likened to plates and v/s = d/4 for the rough and smooth endoplasmic reticulum which are likened to cylinders.
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Fig 1. Low-power view of parenchymal cells of an untreated subject. In the cytoplasm, the SER is diffusely distributed and has a regular honeycomb pattern; only the type 1 or vesicular is present. Some RER cisternae are seen in areas free of glycogen. Numerous mitochondria (M) contain crystalline formations seen as dense inclusions at this level of magnification. The Golgi apparatus (G) is seen next to bile canaliculi (bc) \( \times 7500 \)

Results

Electron Microscopy

Group 1: normal untreated patients

Previous observations have already given a detailed account of the ultrastructural features of the normal human liver (Ma and Biempica, 1971; Jézéquel and Orlandi, 1972; Klion and Schaffner, 1968). We need only to insist on the relative paucity of the rough endoplasmic reticulum (RER), usually distributed along the nucleus, around or between mitochondria, and along the sinusoidal border of the hepatocyte.
The rest of the cytoplasm was occupied by extensive areas of smooth endoplasmic reticulum (SER) associated with numerous rosettes of glycogen (fig 1). The vesicles of the SER were usually round, small, and with a fairly regular, honeycomb appearance. This is defined as SER type 1 or ‘vesicular’. Occasionally some limited areas were occupied by densely packed, smooth membranes with a finely tubular appearance and a narrow lumen or an intricate network where cisternal lumina were not clearly recognizable. This is defined as type 2 or ‘non-vesicular’ (fig 2).
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**Fig 3** High-power view of an area of proliferated SER type 2 in a patient (Ta. P.) treated with diazepam (40 mg/day/four days); the biopsy was taken four days after the end of therapy. This picture illustrates the alternation of the areas with loosely arranged SER, and the areas fitted with densely packed smooth membranes of SER. In the latter the rosettes of glycogen are fewer than in the former. Although the biopsy was taken four days after drug withdrawal, the changes of the SER were still prominent in this patient and the incorporation of $^{14}$C-acetate showed a fivefold increase. $\times 30,000$

The surface densities of the total ER, of the RER, and the SER is shown in fig 4 which gives the mean value for the pooled data from the four subjects. In addition, we have mentioned the figures concerning the relationship of SER type 2 to the total smooth endoplasmic reticulum. For the total ER, the mean value of the surface density expressed in $\mu^2/\mu^3$ of cytoplasm was $3.80 \pm 0.52$ of which $0.89 \pm 0.22$, ie, about 23.7%, belonged to the RER, and $2.91 \pm 0.51$, about 76.3%, to the total SER (2.23 for type 1 and 0.68 for type 2). The Golgi apparatus occupied $0.23 \pm 0.17 \mu^2/\mu^3$. 
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Diazepam

Fig 4. Surface density of endoplasmic reticulum in hepatocytes of untreated patients and patients treated with Benzodiazepin (diazepam). Each bar represents the mean values of data from four subjects with the standard deviation between subjects.

The mean value for volumetric density of the total ER was 0.15. It was 0.04 for the RER, 0.092 for the SER (0.09 for type 1 and 0.002 for type 2), and 0.007 for the Golgi apparatus (see fig 5).

The evaluation of the mean width (d) of the ER cisternae gave the following figures: 1800 Å for the RER cisternae, 1600 Å for the SER type 1 whereas it came to 120 Å for the SER type 2 and 600 Å for the Golgi apparatus. This is close to the values found by direct measurement on the plates, which are 2000 Å, 1500 Å, 150 Å, and 500 Å respectively.

Group 2a: patients with normal liver treated with Benzodiazepin (diazepam)

In the four patients of this group, ultrastructural changes were observed at the level of the SER. In patient Ta. P. the SER appeared globally increased in amount with an extensive development of SER type 2 (fig 3). This sometimes gave to the hepatocyte a 'quilted' look. In Pe. M. and Br. P. the development of SER type 2 was less extensive and the hepatocytes took on a 'pepper and salt' appearance (Jézéquel, Orlandi, and Tenconi, 1971) due to the alternation

<table>
<thead>
<tr>
<th>Surface Density</th>
<th>Normal Untreated</th>
<th>Diazepam</th>
</tr>
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<tbody>
<tr>
<td>Total ER</td>
<td>3.80 ± 0.52</td>
<td>5.63</td>
</tr>
<tr>
<td>Total SER</td>
<td>2.91 ± 0.51</td>
<td>4.98</td>
</tr>
<tr>
<td>SER type 1</td>
<td>2.23 ± 0.49</td>
<td>3.29</td>
</tr>
<tr>
<td>SER type 2</td>
<td>0.68 ± 0.35</td>
<td>1.69</td>
</tr>
<tr>
<td>RER</td>
<td>0.89 ± 0.22</td>
<td>0.65</td>
</tr>
<tr>
<td>Cholesterol synthesis</td>
<td>264 ± 82.5</td>
<td>4257</td>
</tr>
</tbody>
</table>

Table I. Surface density of endoplasmic reticulum and cholesterol synthesis in untreated patients and in patients receiving diazepam

1In untreated patients, the mean values from four subjects are reported with the standard deviation for the surface density; the mean value from 12 patients is given for cholesterol synthesis (14C-acetate incorporation into DPS). Individual values are given for the four treated patients.
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of light, vesicular areas and dense, non-vesicular areas of the smooth membranes (fig 2). In patient Gi. M. the vesicles of the SER appeared densely packed but the overall architecture of the reticulum was normal.

The mean values for the pooled data for evaluation of the surface density were the following as expressed in μ²/μ² of cytoplasm: 5.75 ± 0.77 for the total ER, 0.79 ± 0.17 for the RER, and 4.96 ± 0.61 for the total SER (3.51 for SER type 1 and 1.45 for SER type 2) (fig 4). It can be seen that the total SER comes to represent 88% and the RER 12% of the total endoplasmic reticulum. Individual values are reported in table I. The application of Student's t test shows a significant difference (p < 0.01) between the surface densities of the SER as found in untreated and in treated patients.

In this group of patients the membranes of the Golgi apparatus were not identified in any of the pictures analysed.

The evaluation of volumetric density as measured on the pooled data gave the following figures: 0.17 for the total ER, 0.03 for the RER, and 0.135 for the SER (0.13 for type 1 and 0.005 for type 2) (fig 5).

The mean width of the ER cisternae was thus found to be 1600 Å for the RER, 1500 Å for SER type 1, and 140 Å for SER type 2. These values are also comparable to those obtained by direct measurements on the plates, which are 1800 Å, 1400 Å, and 150 Å respectively.

Group 2b: patient treated with Dilantin

No ultrastructural change was observed in the hepatic tissue at the end of the seven-day period of treatment. There was no significant difference between the quantitative data obtained before and at the end of treatment (table II).

Group 3

The ultrastructure of the liver in the patient with Gilbert's syndrome appeared morphologically normal before treatment. The surface density of the ER was 4.57 μ²/μ²; for the RER it was 1.12, and 3.45 for the SER (2.66 for type 1 and 0.79 for type 2) (table II). The Golgi apparatus was not identified. After four days of treatment with 360 mg per day of phenobarbital there was no change either in the ultrastructure of hepatocytes or in the surface density of the RER and SER (table II).

Cholesterol biosynthesis

The normal range of cholesterol biosynthesis in human liver biopsies has been estimated by incorporation of 14C-acetate into Digitonin-precipitable sterols (Orlandi et al, 1974). The patients studied under group 1 (normal untreated) were part of a larger series of 12 normal subjects where the mean value of incorporation was found to be 264 ± 82.5 nmoles per g of tissue in two hours of incubation. The values obtained under treatment with diazepam were greatly increased in three patients as reported...
in table I. In the patient treated with Dilantin, the values remained almost identical before and after treatment (table II). In the patient treated with phenobarbital the cholesterol biosynthesis was not measured.

Discussion

Although limited in several ways, the present study indicates that in the normal human hepatocyte, the surface density of the SER exceeds that of the RER. This was already suggested by subjective observations. However, morphometric analyses give a better term of comparison with other animal species. Weibel et al (1969) found a surface density of 8.1 μ²/μ³ of cytoplasm for the RER and 6.0 μ²/μ³ for the SER in the rat, whereas Loud (1968) found mean values of 3.32 μ²/μ³ and 2.20 μ²/μ³ respectively. In the dog, the values were 2.48 m²/cm³ and 3.73 m²/cm³ (Hess et al, 1973). The discrepancies between the two former studies have been explained by differences in counting procedures (Weibel et al, 1969). In any event, it appears that in the rat the surface of the SER is less than that of the RER whereas the contrary is true in dog as in man. The values we obtained for the total SER surface density in man are intermediary between those in rats (Loud, 1968) and in dogs (Hess et al, 1973). The RER surface density appears much less than in any of the studies previously mentioned. The volumetric density of the SER and RER is similar in rat (Weibel et al, 1969) and in man but the volume to surface ratio and consequently the mean width of the RER or SER comes to values higher than in rat as calculated by Weibel et al (1969). Moreover, instead of plates as in rat hepatocytes (Weibel et al, 1969) we considered the RER cisternae as cylinders. Evidence that this represents the true configuration of RER in needle biopsies of human liver comes from the appearance of the section of the lumen of RER cisternae—irregularly shaped but most often roughly circular or oval—and by the agreement between calculated values of the width of cisternae and values obtained by direct measurement.

The development of the SER surface in man is to be taken into consideration when dealing with pathological conditions: an increase in the SER has been described in various situations or after treatment with certain drugs, and physiopathological considerations have been made without taking into account this fundamental feature.

On the other hand, it appears that in human hepatocytes the SER does not have a uniform appearance, due to the presence of a 'non-vesicular' component. In some instances, it is difficult to draw a line between vesicular and non-vesicular components, especially in the case of small, packed vesicles. For the present study, counts were made on the pictures at a final magnification of 91 000. In these pictures we considered as non-vesicular the areas of the reticulum where the smooth membranes made an intricate network sometimes finely tubular, but where the sharp lumina of vesicles were not recognizable (ie, a distance between membranes of less than 0.02 μ). In this regard, it is important that the sections are kept at fairly uniform thickness to avoid images of superimposition. In our series, the thickness was kept around 600 A. The effect of section thickness has been previously discussed (Loud, 1968; Weibel et al, 1969). The membranous structures become difficult to identify or are 'lost' when they are tilted at an angle of more than 60° from the direction of the electron beam; this effect is least on thinnest sections but it is thought that counts of intersections should be increased by about 50% to correct for membranes present but not visible (Loud, 1968). Although such an effect should particularly interfere with the counts of SER type 2 components, no correction factor has been applied since the precise extent of error was unknown. In any case, if this might affect the absolute measurements, it should not change the terms of comparison.

The participation of a fine network (or SER type 2)
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in the composition of the SER in human liver has not been previously recognized. The variable configuration of the SER is confirmed by the evaluation of the ratio v/s and of d: this shows a difference of more than 1 to 10 between the SER type 1 and type 2, meaning that the SER type 2 is a system of extremely fine tubules.

In previous morphometric studies, the authors have counted the Golgi apparatus as part of the SER. This is amply justified since it is likely that many of the cisternae, especially when cut in a perpendicular plane, are undistinguishable from the SER. However, we preferred to count separately the Golgi elements when these were clearly recognizable as part of the system of horse-shoe-shaped bags, often with dilated ends. This distinction was motivated by the observation of various pathological conditions where the Golgi apparatus appears prominent, and the necessity of measuring this parameter. It can be seen that there are great variations around the mean value which are due to the configuration of the Golgi apparatus itself. For this reason, only when the figures are significantly higher than in untreated patients can they be taken into account in pathological situations. Low or even zero values are due either to the sampling or—when there is an intense proliferation of SER membranes—to the difficulty of identifying the elements of the Golgi apparatus.

In rat liver, some structural differences have been observed in the various lobular regions, the SER being more abundant in the cells immediately adjacent to a central vein (Loud, 1968). Others (Weibel et al, 1969; Hess et al, 1973) have made no attempt to localize the hepatocytes, and, as in the present study, the values given represent 'the averages derived from a true random sample' (Weibel et al, 1969).

In patients receiving diazepam, there was a marked increase in the total smooth endoplasmic reticulum. This increase is evident in fig 4 concerning the pooled data. However, when looking at the individual figures (table I) it appears that in one patient (Gi. M.) the increase in the SER involved the vesicular component exclusively, the values of the non-vesicular (type 2) component being in the normal range, in contrast to the other three patients.

The increase in SER membranes follows the administration of a number of substances known to induce microsomal enzymes (Remmer and Merker, 1965; Stenger, 1970), although this is not a specific feature of enzymatic induction (Stenger, 1970; Jézéquel and Orlandi, 1972; Jézéquel, 1974). Diazepam is a highly lipid-soluble drug, metabolized by microsomes (Marcucci, Fanelli, Mussini, and Garattini, 1969) with notable species differences in membranes. Further studies would be needed to metabolism (Marcucci et al, 1970). In rat, it has been claimed that diazepam reduces sleeping time and increases liver weight (Heubel, 1969) but no changes in liver weight, hepatic cholesterol synthesis, cytochrome P-450 levels, or hepatic ultrastructure have followed the administration of diazepam (10 mg/kg ip) for six days to rats or guinea-pigs (unpublished observations). In man, diazepam seems to affect the bilirubin levels in newborn and interfere with phenobarbital metabolism (Heubel, 1969; Heubel and Muhlberger, 1972). In addition, and contrary to rats or guinea-pigs, the administration of diazepam to human subjects is followed by ultrastructural changes in hepatocytes together with increased hepatic cholesterol synthesis, as shown in the present study. Then it appears likely that the parent drug or its metabolites are not handled in man as in laboratory animals.

In patients treated with diazepam, the pattern of proliferation of smooth membranes is similar to that observed after treatment with rifampicin (Jézéquel et al, 1971), a drug known as an inducer of microsomal enzymes in human liver (Schoene, Fleischmann, and Remmer, 1972a). A direct estimation of drug-metabolizing enzymes in biopsies of diazepam-treated patients would be of great interest.

A relationship between the increase in cholesterol synthesis and increase of microsomal enzymes has been demonstrated in various instances in vivo or in vitro after treatment with phenobarbital (Jones and Armstrong, 1965; Orrenius, Dass, and Gnossopielis, 1969). The unchanged lipid composition of microsomal membranes in phenobarbital-treated rats would be maintained by a decreased breakdown of phospholipids and increased rate of cholesterol synthesis (Eriksson and Dallner, 1973). The role of cytochrome P-450 in cholesterol synthesis is still a matter for discussion (Atkin, Palmer, English, Morgan, Cawthorne, and Green, 1972). Increased availability of the microsomal enzyme hydroxy-methyl-glutaryl CoA reductase—a rate-limiting step in the hepatic cholesterol synthesis (Dietschy and Wilson, 1970)—due to a non-specific enzymatic induction, might also be responsible for the increased synthesis of cholesterol. That the increase of the surface of total SER membranes is not correlated with increased cholesterol synthesis in man is shown by the patient Gi. M. (see table I). However, in the same patient the values for the SER type 2 were in the lower normal range, in contrast to the other three patients. It is then possible that the increase of the vesicular component results from a decreased catabolism of 'adult' membranes without increased synthesis, whereas the SER type 2 would be the site...
of active synthesis and represent the newly formed assess the validity of this hypothesis.

In all four patients, no correlation was found between the daily intake of diazepam or the length of treatment on the one hand and the surface increase of the SER or the changes in cholesterol synthesis on the other hand. It must be noted that four days after withdrawal of the drug, the surface of SER components and the cholesterol synthesis were still elevated in the patient Ta. P. This is in keeping with quantitative studies by Bolender and Weibel (1973) who showed that ER membranes in phenobarbital-treated rats persist at the induced level on the third day after cessation of treatment and fall to control levels on the fifth day.

It is known that both phenobarbital and phenylhydantoin provoke an increase in smooth membranes in rat hepatocytes (Herdsen, Garvin, and Jennings, 1964; Remmer and Merker, 1965) but studies conducted on animals given high doses of a drug cannot be simply extrapolated to patients given therapeutic doses. In our patient with Gilbert’s syndrome, the administration of phenobarbital was followed by a fall in serum bilirubin but no apparent change in the amount of smooth membranes. After Dilantin, there was neither an increase in cholesterol synthesis nor an increase in smooth membranes. (The apparent increase of the SER type 2 is not significant.) It may come as unexpected that no morphological change follow the administration of both phenobarbital and Dilantin, known to produce remarkable changes in SER in animals. The absence of changes in human hepatocytes after short-term administration of phenobarbital in patients with normal liver resulted from previous observations made on a non-quantitative basis (Jézéquel and Orandi, 1972; Jézéquel, 1974) and also from morphometric studies in an infant with the Crigler-Najjar syndrome (Göttze, Sidiropoulos, Hess, and Berthelot, 1972). This appears in contradiction to other reports (Whelen, Krustev, and Billing, 1968; Crigler and Gold, 1969). The fact that the normal amount and distribution of the SER before treatment have not always been taken into consideration may explain apparent discrepancies. In addition, further studies are needed to assess the effect of drug dosage, length of treatment, and individual variations in the liver response to these therapeutic agents.

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