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Correspondence address
Radiology and Oncology
Institute of Oncology
Vrazov trg 4
61000 Ljubljana
Slovenia

Phone: + 38 61 314 970
Fax: + 38 61 329 177

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Milica Harisch
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Radiol Oncol 1992; 26: 113-9.

Radiological aspects of hypertrophic pyloric stenosis

Marija Frković and A. Mandić

Clinical Hospital Center Rebro,
Department of Radiology, Zagreb, Croatia

The authors analyze radiologic methods and diagnostic parameters with special regard to their possibilities and diagnostic characteristics by analyzing hypertrophic pyloric stenosis (HPS) and its differentation from similar pathologic conditions of the aboral part of the stomach in newborns.

Key words: pyloric stenosis-radiography

Introduction

Hypertrophic pyloric stenosis is an acquired obstructive anomaly of the aboral part of the stomach. It is not yet known whether the etiologic factors already exist during intrauterine development. It is rarely present in the first week of life, more frequently it occurs in the period from 2nd to 8th week after birth.[1-3]

A congenital anomaly of structure or inadequate number of ganglionic cells of myenteric plexus of antropyloric part of the stomach[4-6] or the enlargement of parietal cell mass of the stomach with hypersecretion[1,7] are considered to be the etiologic cause of HPS.[8] The stress reactor theory based on the hereditary disposition to react excessively on gastrin[1] shows that the etiologic cause of HPS is hypersecretion of gastric acid.

Correspondence to: Marija Frković, M. D., Clinical Hospital Center Rebro, Department of Radiology, Kišpatićeva 12, 41000 Zagreb, Croatia.

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The clinical symptoms of hypertrophic pyloric stenosis are non-bile-stained vomiting, regurgitation, difficulties with feeding, failure to thrive or weight loss. More rare finding is an olive-like palpable "tumor" mass in the epigastric region, and sometimes peristaltic waves on the abdominal wall are seen.

Since these clinical signs are not constant nor strictly specific to differentiate hypertrophic stenosis from other pathologic conditions of this part of the stomach and to confirm the diagnosis, radiologic examination is necessary.

Radiologic methods and diagnostic parameters

The diagnosis of HPS with more or less persistent clinical symptoms can be made on the basis of the following radiological examinations: ultrasound, plain x-ray roentgenograms of the abdomen and contrast study of the upper gastrointestinal tract.

Ultrasound shows extended, liquid-content-filled stomach. If the diameter of the pyloric muscle on transversal sections is greater than 11 mm, and is more than 2.5 mm thick ("target

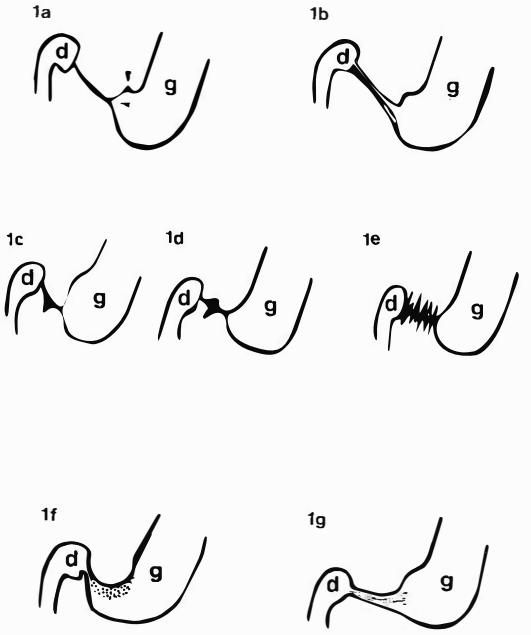

Figure 1. Radiological diagnostical signs of HPS (16). 1a – "string sign" and aditional "beak sign" and "tit sign" (◀). 1b – "double track sign". "spicula sign" and variations: 1c – "spicula sign" or "pyloric niche", 1d – "diamond sign", 1e – "spiculated antrum sign". 1f – "lasser curve identation". 1g – "funnel-shaped antrum" or "burned-out sign". (d-duodenum, g-gaster).

sign") and if on longitudinal sections the canal length is greater than 16 mm, pyloric stenosis is present.[9–11]

On plain roentgenogram, a distended stomach with unproportionally small amount of gas in the small bowel is often present.[12]

At barium examination of the upper gastrointestinal tract in about 70 % of patients, gastrointestinal reflux is found.[13] A great amount of residual content is present in the stomach and emptying of the stomach is delayed. Typical features of HPS include a narrow, band like, upward directed contrast track in the pyloric lumen ("string sign"), with a peak at the base of the pyloric canal ("beak sign") with peristaltic tension of the antral wall at the edge of hypertrophied pyloric muscle ("tit sign"). Further progression results in contraction and flattening of the entire pyloric canal, with contrast medium accumulating at one side of the flattened lumen, which gives the picture of "double track sign". If muscle hypertrophy is atypical or partial, less characteristic pyloric deformations are found: pyloric ulcus like deformations and their variations ("pyloric niche" or "spicula sign", "diamond sign", "spiculated antrum"), "lesser curve indentation" and "funnel-shaped antrum" or "burned-out pyloric stenosis",[2,14,15] schematically presented in Figure 1.

Diagnostic difficulties can occur due to the fact that in a shorter period one form can change into another, progressive or regressive. In cases of atypical or incomplete hypertrophy it is important to prove that during the passage of peristaltic wave a specific deformity of antropyloric area is constant from one roentgenogram to the other, and from one examination to the other. Atypical forms regularly develop into complete forms of hypertrophied pylorus.

In radiological finding it is important to differentiate HPS from pylorospasm, partial antral web, ulcer niche and pyloric duplication.

Pylorospasm is the narrowing and the deformation of pyloric canal, it is not fixed, and it changes during the passage of peristaltic wave. Glucagon test will eliminate possible diagnostic difficulties. Glucagon given i. v. or i. m. during examination of the upper gastrointestinal tract leads to relaxation of pyloric muscle and confirms the diagnosis of pylorospasm.[15–17]

Partial antral web is a duplication of mucosa with smaller or larger orifice which narows the antral part of the stomach so that the part of antrum aborally from the web to pylorus can be deformed similarly as in atypical form of hypertrophied pylorus type "burned out pyloric stenosis" or "funnel-shaped antrum".[17–23] Sometimes it is difficult to differentiate these cases even with directoscopic examinations.[23]

Pyloric or prepyloric ulcer accompanied by regurgitation, gastroesophageal reflux and periulcer edema, can be endoscopically confirmed. In clinical picture in a newborn this pathologic status presents with vomiting or hema-

temesis or periodical bleeding per rectum.[25–27] More constant findings at barium examination of the upper gastrointestinal tract are marked deformity, fixed spasm and edema, while ulcer crater itself sometimes may be visualized and sometimes not. Chronic fibrotic changes in newborns are not seen. The described changes in radiologic picture can be very similar to pyloric stenosis of short segment marked as "lesser curve indentation".[26] Bleeding ulcer can be confirmed endoscopically and angiographically, and possible perforation will be seen as extraluminination of contrast medium.[27, 28]

Duplication of the pylorus is a very rare congenital anomaly.[29] In radiological picture it can be similar to atypical presentation of HPS which gives picture of "double track sign".[14]

Patients and methods

Due to the pathology of gastrointestinal tract, 141 infants were hospitalized and surgically treated in the Department of Pediatrics in the period from 1987 to 1991. Sixteen of them (11.4%) in the age range of 12 days to 8 months underwent surgery due to HPS (Table 1).

In all patients the radiologic diagnosis of HPS was made on the basis of barium examination of gastrointestinal tract. Under TV control we followed perorally given barium to the distal part of the stomach and spot roentgenograms of pyloric region were done. Specific radiological signs of this pathology were then analyzed and divided into 5 groups:

Table 1. Demonstration of patients with HPS

Number	Name	Sex	Age/ days	Clinical diagnosis	Gastroesophageal reflux	RTG signs of HSP	Radiological diagnosis
1	BM	M	31	HPS	+	string sign	HPS
2	CH	M	33	HPS	+	string sign	HPS
3	RM	M	39	HPS		string sign	HPS
4	FM	M	52	HPS		string sign	HPS
5	PL	M	21	HPS	+	spicula sign	HPS Ulcus
6	PM	M	41	HPS		string sign	HPS
7	JA	M	39	HPS	+	double track sign"	Pylorospasm HPS
8	PA	M	32	HPS	+	string sign	HPS
9	RJ	F	26	HPS	+	string sign	HPS
10	TN	M	28	HPS	+	lesser curve indentation	HPS
11	DM	F	31	High ileus	+	lesser curve indentation	HPS
12	HD	M	24	HPS	+	string sign	HPS
13	KA	M	28	HPS	+	funnel shaped antrum	Antral web HPS
14	ZJ	M	236	High ileus	+	spicula sign	HPS
15	KM	M	31	HPS		funnel shaped antrum	HPS
16	SD	M	12	High ileus	+	string sign	HPS

male: female = 1 : 2 $p = 2/16 = 0.125$ $q = 14/16 \times 0.875$

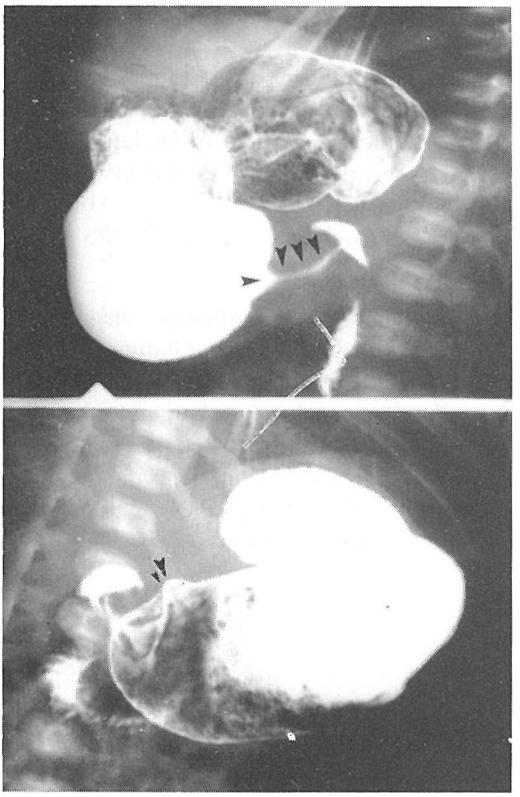

Figure 2. Specific radiological signs of HPS: "string sign" (▲▲▲), "tit sign" (▲▲) and "beak sign" (▲).

1. "string sign" and accompanied "tit" and "beak" signs, Figure 2.
2. "double track sign", Figure 3.
3. "spicula sign" – "pyloric niche", Figure 4, and etiologically identical variations of this sign "diamond sign", "spiculated antrum", Figure 5.
4. "lesser curve indentation"
5. "funnel shaped antrum" or "burned-out sign", Figure 6.

The appearance of these signs and their variations are presented in Figure 1,[16] whereas the analysis of their incidence in radiological findings is given in Table 2.

The incidence of gastroesophageal reflux as a less specific, but often present symptom was also analyzed, as well as the relation between clinical diagnosis, results obtained from radiological examinations and operative diagnosis.

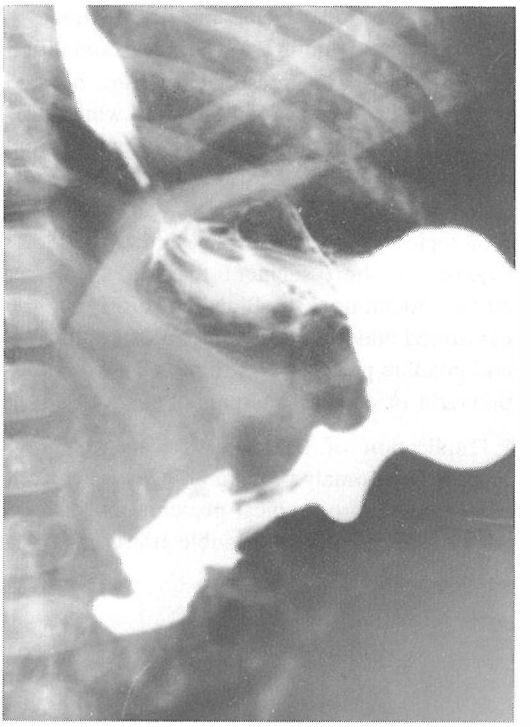

Figure 3. HPS – "double track sign".

The indication for surgery was determined on the basis of clinical picture and radiological findings.

Pyloromyotomy was performed in all patients.

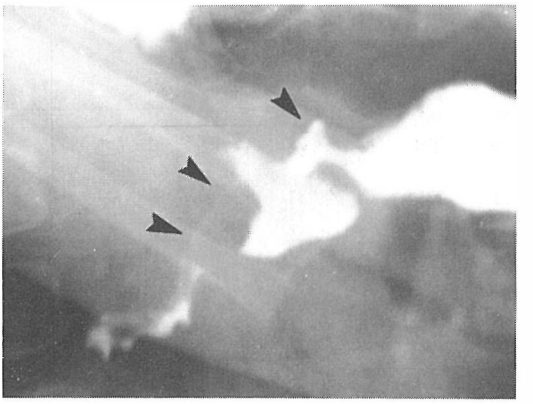

Figure 4. HPS – "pyloric niche" (▲) and additional congenital anomaly – pancreas anulare (▲▲).

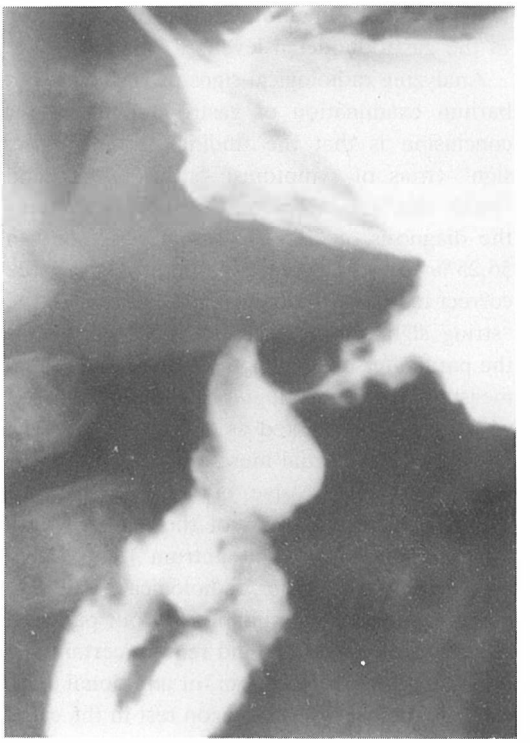

Figure 5. "Spiculated antrum" – atypical form of HPS.

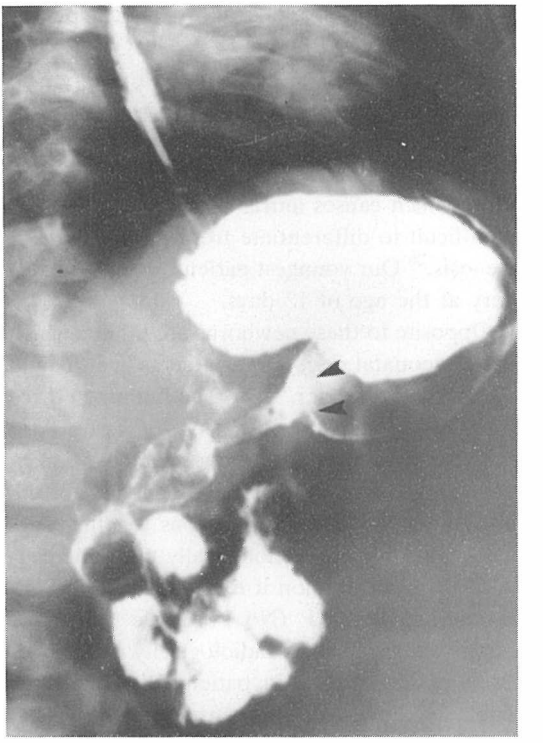

Figure 6. "Funnel shaped antrum" (▲▲) – it is necessary to differentiate it from partial antral web.

Results and discussion

HPS is one of the most common diseases in infants which requires surgical treatment.[31] Therefore, our 16 (11.4%) patients are representative sample in a group of children operated on due to gastrointestinal tract pathology.

The disease more often appears in male infants. The proportion of female diseased infants (p) is 0.125 in the total number of infants with HPS, and the proportion of male infants (q) in the total number of these patients is 0.875. This ratio of 14:2 according to the relative number of coordination shows that in the total number of 70 boys with HPS there were only 10 girls with the same pathology. Our results correlate with the results presented in literature.[3, 16]

The symptoms of HPS most frequently occur from 2nd to 8th week of life.[3,16] The average age of our patients was 44 days or 6 weeks respectively.

Very rarely this condition can present as early as the first week of life of a neonate. In such cases it is more difficult to make correct diagnosis. Such condition is characterized by less specific picture of pyloric stenosis of short segment with minimal muscle hypertrophy,

Table 2. The incidence of radiological signs of HPS

RTG finding	Number	%
gastroesophageal reflux	12	75
string sign and additional signs (tit and beak signs)	9	56.25
double track sign	1	6.25
spicula sign and variations	2	12.5
lesser curve indentation	2	12.5
funnel shaped antrum	2	12.5

which later on develops into a typical pyloric stenosis.[17]

Etiologically, these forms of HPS are connected with persistent pylorospasm which is a result of neonatal hyperacidity or it is considered to be a secondary manifestation of gastric ulcer which causes antral deformity and which is difficult to differentiate from the real pyloric stenosis.[26] Our youngest patient underwent surgery at the age of 12 days.

Opposite to these newborns are infants which in the neonatal period presented as healthy and HPS developed later.[15,25,28] The finding in these cases is very similar to other typical cases. Also in these infants HPS can be a secondary consequence of ulcer disease. The coincidence of the appearance of these 2 conditions together suggests that they have etiologically the same cause.[26-28] In our opinion it explains HPS findings in our patient Z. J. (No 14, Table 1). It also explains clinically and radiologically evident relapse of the disease in patient B. M. (No 1, Table 1) who underwent surgery at the age of 1 month and who was reoperated on when he was 10.5 months old. The relapse of HPS has not been published in literature yet, and it is difficult to explain its etiology under assumption that surgical treatment was correct. However, the recurrence of clinical and radiological finding of "double track sign" which did not respond to drug therapy indicate that if partial pyloromyotomy was done and if the circumstances which caused the first appearance of the disease persist, the recurrence of "phenotype" occurs.

The clinical picture is very specific, it develops gradually, and at the time of hospitalization it is fully developed. This is confirmed by almost exact clinical diagnosis with which the patient is referred to radiologic examination. Namely, the diagnosis of "high ileus" also includes HPS.

Gastroesophageal reflux, often present in patients with HPS, was found in 75% of our patients, which corresponds to the data known from literature.[22] However, we are not inclined to attribute significance to this symptom, because in our opinion it will also occur in identical percentage in all other cases of obstruction at the gastroduodenal level.

Analyzing radiological signs of HPS found at barium examination of gastroduodenum, our conclusion is that the finding of the "string sign" (trias of symptoms: "string", "tit" and "beak sign") is absolutely reliable in making the diagnosis of HPS. This sign was found in 56.25% of our cases. Its finding gives the correct radiological diagnosis. Analagous to the "string sign", very relable and more exact is the parameter of the length of the pyloric canal measured by ultrasonography.[9] A deformation which we have marked as "spine sign" results in the cases of partial muscle hypertrophy. For more or less progressive, etiologically identical variations, the variations of these signs ("diamond sign", "spiculated antrum") are being used. These and other radiological signs frequently found on examinations of our patients, are not pathognomonic and require certain differential diagnostic freedom, or additional diagnostic examinations – glucagon test in the cases suspective of pylorospasm, endoscopic examination in the cases suspective of antral diaphragm, ulcus and double pylorus.[14,16,23]

All of our patients underwent pyloromyotomy[31] and operative diagnosis of HPS confirmed the clinical and radiological diagnosis. Other pathologic conditions which presented additional cause of high ileus were also treated surgically, but they are not the subject of discussion in this report.

Clinically clear cases with specific symptomatology can be simply diagnosed at ultrasound.[9-11] It is not necessary to submit such patients to barium examination of gastroduodenum. However, ultrasound can not solve less specific cases of HPS, which at barium examination present with rare signs of HPS. In all unclear cases barium examination of gastroduodenum is necessary because for such rare signs of HPS there are no specific US signs. The possibility of association of another anomalies,[32] Figure 4, and preoperative differentiation of HPS from other similar conditions[19-24, 29] justify the use of barium examination in newborns in spite of irradiation risk.

References

1. Rogers IM, Macgillion F, Drainer IK. Congenital hypertrophic pyloric stenosis: a gastrin hypothesis pursued. *J Pediatr Surg* 1976; **11:** 173-6.
2. Schuman FI, Darling DB, Fisher JH. Radiographic diagnosis of congenital hypertrophic pyloric stenosis. *J Pediatr* 1967; **71:** 70-4.
3. Mardešić D, Kačić M. Prehrana i bolesti probavnih organa u pedijatriji. JUMENA Zagreb 1979; 193-200.
4. Day LR. Medical management of pyloric stenosis. *JAMA* 1969; **207:** 948-50.
5. Friesen SR, Pearse AGE. Pathogenesis of congenital pyloric stenosis; histochemical analyses of pyloric ganglion cells. *Surgery* 1963; **53:** 604-8.
6. Rintoul JR, Kirkman NF. The myenteric plexus in infantile hypertrophic pyloric stenosis. *Arch Dis Child* 1961; **36:** 474-80.
7. Spitz L, Zail SS. Serum gastrin levels in congenital hypertrophic pyloric stenosis. *J Pediatr Surg* 1976; **11:** 33-5.
8. Karim AA, Morrison JE, Parks TG. The role of pentagastrin in production of canine hypertrophic pyloric stenosis and pyloroduodenal ulceration. *Br J Surg* 1974; **61:** 327-32.
9. Stunden RJ, Le Quesne GW, Little KET. The improved ultrasound diagnosis of hypertrophic pyloric stenosis. *Pediatr Radiol* 1986; **16:** 200-5.
10. Strauss S, Itzchak Y, Manor A, Heyman Z, Graif M. Sonography of hypertrophic pyloric stenosis. *AJR* 1981; **136:** 1057-61.
11. Wilson DA, Vanhoutte JJ. The reliable sonographic diagnosis of hypertrophic pyloric stenosis. *J Clin Ultrasound* 1984; **12:** 201-7.
12. Riggs WJr, Long L. The value of the olain film roentgenogram in pyloric stenosis. *AJR* 1971; **112:** 77-82.
13. Shopfner CE, Kalmon EHJr, Coin CG. The diagnosis of hypertrophic pyloric stenosis. *AJR* 1964; **91:** 796-800.
14. Haran PJJr, Darling DB, Sciammas F. The value of the double track sign as a differentiating factor between pylorospasm and hypertrophic pyloric stenosis in infants. *Radiology* 1966; **86:** 723-5.
15. Swischunk LE, Hayden CKJr, Tyson KR. Atypical muscle hypertrophy in pyloric stenosis. *AJR* 1980; **134:** 481-4.
16. Swischuk LL. *Radiology of the Newborn and Young Infant.* IInd Ed. Williams and Wilkins, Baltimore/London 1984; 364-81.
17. Swischuk LE, Hayden CKJr, Tyson KR. Short segment pyloric narrowing. Pylorospasm or pyloric stenosis? *Pediatr Radiol* 1981; **10:** 201-5.
18. Swischuk LE, Tyson KR. "Burned-out" pyloric stenosis: an elusive gastric outlet obstruction. *Radiology* 1975; **117:** 373-79.
19. Campbell DP, Vanhoutte JJ, Smith EJ. Partially obstructing antral web – a distinct clinical entity. *J Pediatr Surg* 1973; **8:** 723-8.
20. Robinson K. Pyloric stenosis due to a mucosal diaphragm. *Br J Surg* 1967; **54:** 397-9.
21. Keramidas DC. Congenital incomplete prepyloric diaphragm in infants and children. *Surgery* 1974; **75:** 690-4.
22. Jinkins JR, Ball TI, Clements JL Jr, Elmer RA, Weens HS: Antral mucosal diaphragms in infants and children. *Pediat Radiol* 1980; **9:** 69–72.
23. Fujioka M, Fisher S, Young LW. Pseudoweb of the gastric antrum in infants. *Pediatr Radiol* 1980; **9:** 73–5.
24. Bell MJ, Ternberg JL, Keating JP, Moedjona S, McAlister W, Shackeford GD. Prepyloric gastric antral web: A puzzling epidemic. *J Pediatr Surg* 1978; **13:** 307-10.
25. Bremner CG. The lesser curve pyloric niche. *Br J Radiol* 1968; **41:** 291-5.
26. Mendl K, Jenkins RT, Penlington ER. Gastric ulcer in the newborn and its association with antral spasm resulting in hypertrophic pyloric stenosis. *Br J Radiol* 1962; **35:** 831-5.
27. Sitka U, Köstler J. Akutes Pneumoperitoneum in der Neugeborenenperiode. *Z Kinderchir* 1974; **14:** 382-90.
28. Kelsey D, Stayman JWJr, McLaughlin ED, Mebane W. Massive bleeding in a newborn infant from a gastric ulcer associated with hypertrophic pyloric stenosis. *Surgery* 1968; **64:** 979-82.
29. Grosfeld J, Boles EJr, Reiner C. Duplication of pylorus in the newborn, a rare cause of gastric outlet obstruction. *J Pediatr Surg* 1970; **5:** 365-9.
30. Gysler R, Kundert JG. Pyloric stenosis in an eightmonth-old child. *Z Kinderchir* 1973; **13:** 263-7.
31. Rickham PP. *Congenital hypertrophic pyloric stenosis.* In: Rickham PP and Johnston JH eds. Neonatal Surgery. London: Butterworths, 1970; 271-85.
32. Koch A, Rehbein F. Hypertrophische Pylorusstenose und bedeutende Fehlbildungen des Magen-Darm-Traktes. *Z Kinderchir* 1974; **15:** 163-8.

Radiol Oncol 1992; 26: 120-4.

Ultrasound guided percutaneous pancreatography (UPP)

Nikola Ivaniš, Željko Fučkar, Arsen Depolo, Relja Perić, Milivoj Rubinić, Duško Banić, Milan Prica

Clinical Medical Center Rijeka, Department of Gastroenterology, Croatia

The ultrasound percutane pancreatography (UPP) is a combination of the ultrasound and radiological methods. The use of UPP is indicated in the patients suffering from pancreatic deseases such as segmentary or completely dilated pancreatic duct, previously diagnosed by the conventional ultra sound examination. The method is also indicated in the cases where it is not possible to diagnose the pancreatic duct by endoscopic retrograde pancreatography (ERP). This method is extremely important when dealing with deseased pancreas, especially in planning the surgical drainage treatment. In the last ten months our hospital has successfully dealt with ten guided UPP procedures without any post-treatment complications or mortality.

Key words: pancreatic diseases-radiography; ultrasonography

Introduction

Visualization of the pancreatic duct is made posible by means of endoscopic retrograde pancreatography (ERP), in combination with endoscopic radiological methods, first reported by Rabinov in 1965.[1]

During the past 25 years, ERP has been introduced into clinical practice as a routine diagnostic procedure. Indications for ERP are suspected chronic pancreatitis, pancreatic carcinoma and haemorrhagic necrotic pancreatitis.[2]

For all modern diagnostic procedures it is often difficult to differentiate chronic pancreatitis from pancreatic carcinoma.

Diagnostic methods in use for this purpose are: conventional ultrasound guided biopsy, computerized tomography, endoscopic retrograde pancreatography (ERP), cytological examination of pancreatic juice, functional tests, biochemical examination of blood, determining the concentration of tumour antigens in the blood and ultrasound guided percutaneous pancreatography (UPP).

In 1977, Copeberg reported on ultrasonographically guided percutaneous pancreatography, presenting scans of pancreatic ducts of two cases obtained by this methods.[3]

Correspondence to: Dr. Nikola Ivaniš, Vladivoja i Milivoja Lenca 48, 51000 Rijeka, Croatia.

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Methods and patients

Methods

Ultrasound guided percutaneous pantography (UPP) is a combined ultrasonographic and radiological method. UPP is practicable with patients with affected pancreas. The entire pancreas is imaged by conventional ultrasound examination and the pancreatic duct dilated in its

entirety or only partly. This is done in patients in whom adequate ERP representation is not possible.[4-7] Normal diameter of the pancreatic duct is 3.5 mm in its head and up to 2.5 mm in the body and tail of the pancreas.[8, 9]

At the Gastroenterology Department of the Internal Medicine Clinical Hospital in Rijeka UPP is indicated in patients whose pancreatic duct has a diameter of 3 mm or more and in whom ERP has failed. First the patient has to be subjected to complete laboratory tests and there must be no counterindication for puncture.

When the epigastric skin gas been sterilized the pancreas and dilated pancreatic duct are exposed, the puncture point fixed on the skin, anaesthesia administered to the future puncture canal (5 ccm of lidocaine), and then a skin incision of 5 mm is made.

The needle is introduced transepigastrically under the guidance of ultrasound. While puncturing, the point of the needle is monitored on the screen of the ultrasound apparatus. When the needle has pierced the pancreatic tissue it is introduced into the pancreatic duct with a short thrust, 2 ccm of pancreatic juice are aspirated, and then 5 ccm of iodic contrast medium instilled (Omnipaq 240).

The mandren is reinserted into the needle to prevent regurgitation of the contrast medium and the image of the pancreatic duct is radiologically verified. If necessary, another 2 to 4 ccm of contrast medium are instilled, with repeated radiological scanning of the ductus pancreaticus, screening the passage of the contrast medium through the duodenum. Then the needle is deftly extracted and subsequent radiological scans of the pancreatic duct made in a number of modes.

Patients

In the period from December 1989 to September 1990 11 UPP-s had been carried out. First the patients had to undergo complete clinical examinations and laboratory tests, with no diagnoses made. A satisfactory ERP scan of ductus pancreaticus could not be obtained in these patients. By means of conventional sonography of the pancreas a scan of the duct dilatation was obtained.

Out of the 11 patients subjected to UPP, there were 8 men and 3 women. Their average age was 44.

Results

The results obtained by UPP are shown in Table 1. Out of the 11 UPP-s, 10 were successful, whereas in one patient percutaneous puncturing of the pancreatic duct had not succeeded and the duct could not be scanned. Of the successful UPP-s, in 7 patients the scan shows the pancreatic duct and in other 3 patients the scan shows a small pancreatic pseudocyst not communicating with the pancreatic duct. In a previousely taken conventional ultrasound scan the latter had been interpreted as a dilated part of the pancreatic duct.

Of the 7 patients whose pancreatic duct scans are shown, in 5 cases the obtained scan was typical of chronic steno-dilating pancreatitis, and in two cases a scan characteristic of pancreatic head carcinoma was obtained.

Including the 3 patients with scans of minor inflammatory pancreatic pseudocysts, 8 patients in the group suffered from chronic pancreatitis and 2 of them had carcinoma of the pancreatic head.

With the UPP-s performed up to now no complications have been observed.

After being subjected to UPP-s, for the first 24 hours the patients had been protected by 3×750 mg i. m. of Cefuroxim.

Table 1. Results of 11 UPP

UPP (total)	11
Successfully	10
Unsuccessfully	1
Pancreatic duct	7
Small pseudocyst	3
Chronic pancreatitis	8
Pancreatic carcinoma	2

Discussion

A detailed scan of the entire pancreatic duct is the basic requirment of modern diagnostic procedure for patients with pancreatic complaints.

The patients are subjected to the usual procedure, including the possibility of ERP use.

With some patients, however, there are contraindications for this kind of endoscopy, the impossibility of inserting cannulae into pupilae Vateri or if due to the stenosis of the pancreatic duct in the pancreatic head instillation of the contrast medium into the duct is not feasible.[2–7]

In these cases attempts have to be made to find the part of the pancreatic duct accessible to the puncture line of the ultrasound apparatus, and by means of UPP scan of the pancreatic duct, make a radiological image in different planes, and make a detailed analysis of it. Direct instillation of a contrast medium into the pancreatic duct yields very clear scans of the entire duct, its ramifications, places of stenosis and any accessory canals, at the same time providing important information on the passage of the contrast medium into the duodenum, or complete obstruction of the canal in the pancreatic head.[3–7]

Examples of these scans of the pancreatic duct are shown in Figures 4, 5, 6, 7 and 8 while

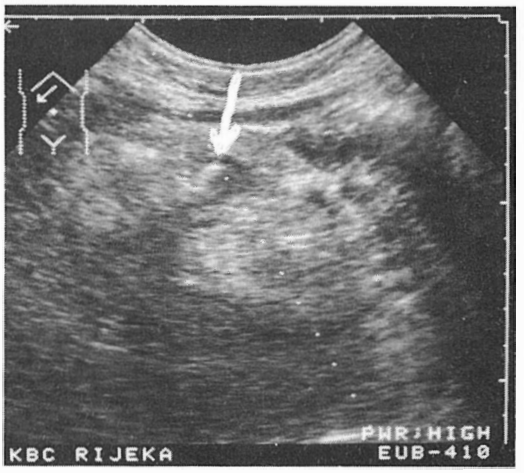

Figure 2. UPP – tip of the needle in the pancreatic duct.

Figure 1, 2 and 3 show the point of the needle in the pancreatic duct.

Scans of the ductus pancreaticus by means of ultrasound guided percutaneous pancreatography (UPP) are invaluable to patients suffering from chronic steno-dilating pancreatitis, in preoperative planning of drainage procedures (pancreaticojejunostomy).[10]

The patients are examined by two doctors and a medical technician. The doctors must

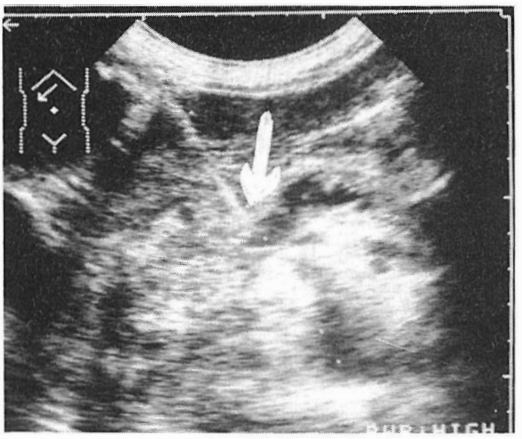

Figure 1. UPP – tip of the needle on the border of the pancreatic duct.

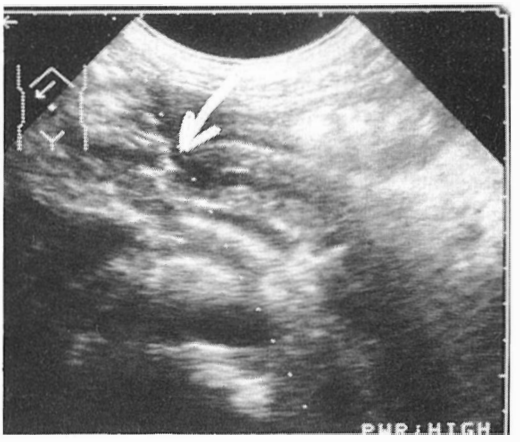

Figure 3. UPP – tip of the needle in the pancreatic duct.

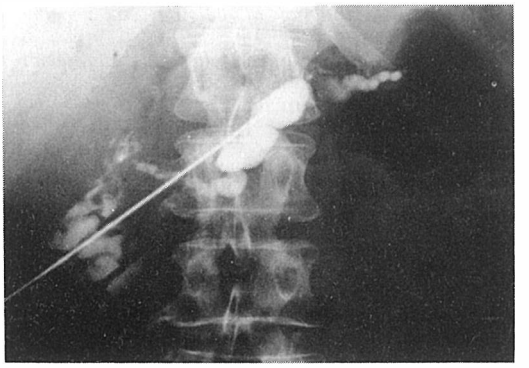

Figure 4. UPP steno-dilated pancreatitis.

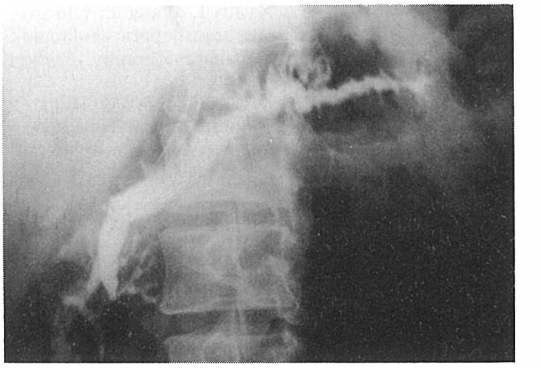

Figure 6. UPP steno-dilated pancreatitis.

have wide experience in interventional ultrasound and interventional radiology.

The 11 UPP-s described have been made under the control of ultrasound apparatus HITACHI EUB 410, with Convex probe of 3.5 MHz and lateral adapter for puncture. The needles used were Angiomed IPS *1.3* and SBK *0.95*.

By means of this method high-quality images of the pancreatic duct are obtained. Besides other findings they make possible differentiation between chronic pancreatitis and pancreatic carcinoma.

The method is indicated in strictly limited cases. With an expert and skilled team it is carried out with ease. According to our experience, so far the method has not been associated with morbidity and mortality. We believe it will find application in highly developed and adequately equipped institutions dealing with the diagnostics and treatment of pancreatic complaints.

References

1. Rabinov KR, Simon M. Peroral cannulation of ampulla of Vater for direct cholangiography. Preliminary report of a new method. *Radiology* 1965; **85:** 693–7.
2. Rubinić M, Švalba B. Endoskopska retrogradna holangiopankreatografija (ERHP). *Radiol Iugosl* 1984; **18:** 95–8.
3. Copeberg PL, Cohen MM, Grahman M. Ultrasonographically guided percutaneous pancreatography: "Report of two cases". *AJR* 1977; **132:** 622.
4. Ohto T, Saotome N, Saicho N, Tsuchiya X, Ono T, Okuda K, Karasawa E. Real-Time Sonography of the pancreatic duct. Application to percutaneus Pancreatic ductography. *AJR* 1980; **134:** 647.

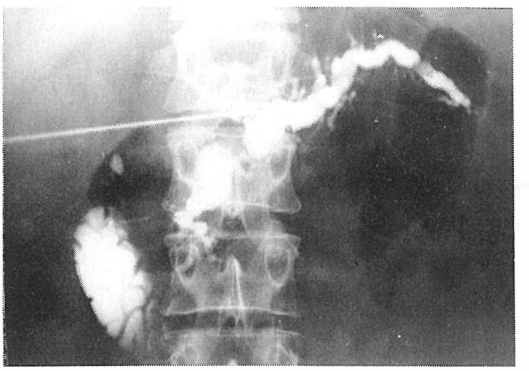

Figure 5. UPP steno-dilated pancreatitis.

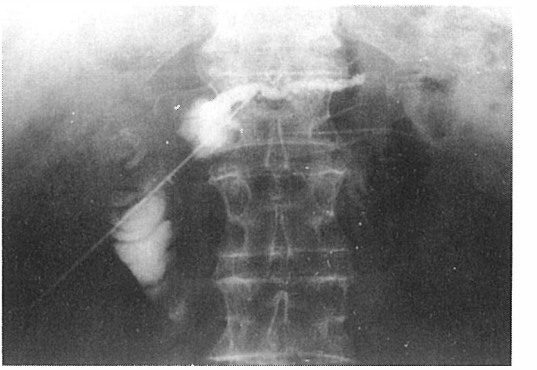

Figure 7. UPP pancreatic carcinoma.

5. Maruuchi M, Bandai X, Ito I, Wada T. Ultrasonically guided Percutaneus transhepatic cholangiography and Percutaneus Pancreatography. *Radiology* 1980; **134** (3): 767.
6. Davčev P, Serafimovski V, Neškovski M, Bidikov V. Percutaneous transabdominal Real-Time sonography of the Pancreatic duct. The third symposium of hepatology, Book of Abstracts. ●hrid, 1982.
7. Sutton D. *A textbook of radiology and imaging.* 1987: 1030.
8. Schwerk WB: *Gastroenterologische Ultraschalldiagnostik in Internist.* 1981: 23.
9. Meckler U, Hennermann KH, Caspary WF. *Ultraschal des Abdomens.* Koln: 1984.
10. Puestow Ch B, Gillesby WJ. Retrograde surgical drainage of pancreas for chronic relapsing pancreatitis. *AMA Arch Surg* 1958; **76:** 898.

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Possibilities and limitations of computed tomography in diagnosis of thoracic organs

Šerif Bešlić, F. Dalagija, A. Lovrinčević, M. Ibralić, Z. Merhemić

University Medical Center, Institute of Radiology and Oncology, Sarajevo, Bosnia and Hercegovina

During a period of 6 years and based on own material and experience with 1012 examined patients, the authors have presented the contribution of computed tomography (CT). The examinations were performed on Somatom SF "Siemens" unit. According to the coded CT diagnoses stored at computer in the Department of Informatics, CT showed the important contribution in the diagnosis of fluid, solid, cystic and fat formations in the chest. A considerable part of the findings, about 16.5 % related to the mediastinal and hilar adenopathies. The diagnostic role of CT in the analysis of vascular mediastinal structures is interesting.

Key words: thoracic radiography; tomography; x-ray computed

Introduction

CT is a new, relatively expensive diagnostic method. It changed our previous practice and algorithm of diagnostic methods and enabled improved analysis of the mediastinum, lung parenchyma, pleura and phrenico-costal sinuses. Since the end of 1978, it has been performed at our Institute. On the basis of our clinic material and data from literature, we tried to present the pathology which can be proved by this method, as well as the problems related to this diagnostics.

Correspondence to: dr. Šerif Bešlić, Institute of Radiology and Oncology, University Medical Center, Moše Pijade 25, 71000 Sarajevo, Bosnia and Hercegovina.

UDC: 616.2-073.756.8

Material and method

Clinical material

From the end of 1986 to January 1, 1992, we investigated 1012 patients. Out of this number, the clinicians requested the examination in:
686 cases – CT of lungs,
227 cases – CT of mediastinum,
78 cases – CT of thorax,
28 cases – CT of other chest organs,
12 cases – CT of the heart etc.
The analysis included patients of all ages and both sexes.

Method of work

Since 1978, we have worked on the third generation Somatom SF "Siemens" scanner with 512 detectors and 2.6 and 4.8 sec. scan time, 4 and 8 mm thick slices and immediate image reconstruction. Density level is measured

according to Hounsfield: –1024 to + 1024 HU, where water is 0. Electronic image enlargement is 2.5 times. The tube is pulsed superrotalix with graphite anode, cooled by oil. The image analysis has been performed at two levels, with the window for the analysis of mediastinum and costal pleura in one, and for the analysis of parenchyma in another. Plain images were obtained in the first series, the second after infusion of water-soluble contrast material (60 ml. i. v. in bolus and 100 ml in perfusion), for a better presentation of vascular structures.

Rarely, a reinjection of contrast material in the area of special interest was performed.

After i. v. application of contrast material fast mood scanning was performed in the following positions: decubitus, lateral decubitus and procubitus. We applied contrast material perorally (esophagus).

The thorax was investigated from the apex to the phrenicocostal sinuses (20 scans). The suspected regions required additional scans with contrast bolus.

Scanning was made after conventional radiography with possible additions.

The results were evaluated surgically, by CT-guided transthoracic biopsy, clinically and by laboratory data.

Results

Out of the total number of examined patients CT findings showed as follows:

The most of our CT diagnoses related to pleural exudations (25 %), mediastinal and hilar adenopathies (16.5 %), lung tumors (12.5 %), thymus diseases (2.47 %), esophageal neoplasms (1.97 %), solitary metastases, infiltrations and echinoccocal lung cysts (1.9 %), fat deposits in mediastinum and retrosternal struma (1.48 %) etc.

In those cases, CT made the decisive contribution. Our results are presented on Tables 1 and 2, showing that besides the mentioned pathology, CT enabled the diagnosing of cysts and pulmonary abscesses, pericardial effusions diaphragmatic hernia, pleural tumors, tracheal neoplasms, congenital vascular malformations and aortic aneurysms.

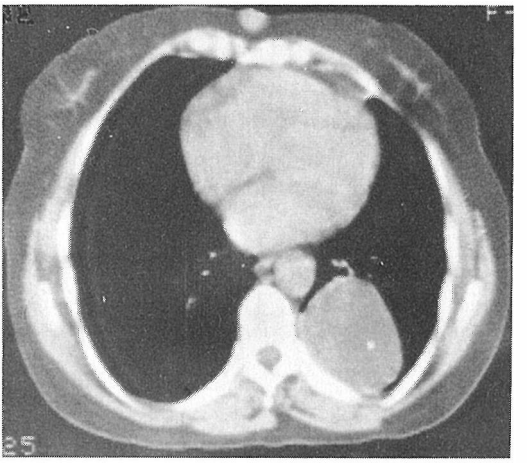

Figure 1. Echinococcus cyst left (density level + 14 HU).

Discussion

The analysed material shows that CT offers special possibilities in the analysis of all thoracic structures (ribs, spine, mediastinum, lung parenchyma etc.) in the transversal plane.

It is possible to analyse bony and muscular structures of the chest (meta changes in ribs), with the advantage in the presentation of normally radiotransparent structures, as in lesions of the chondrosternal joint (abscess).[1–4]

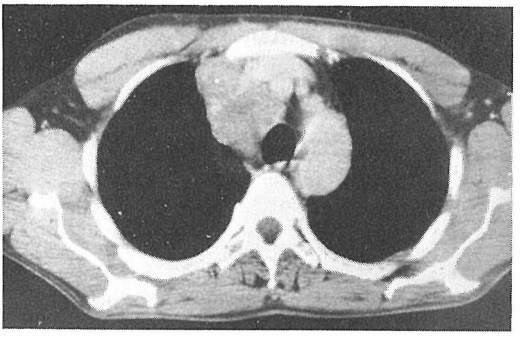

Figure 2. The solid expansive process of the superior mediastinum (density level + 53 HU).

Transversal scans enable a good analysis of lung parenchyma with confirmed solid, cystic and liquid metastatic formations.[1,2,5–10] (Figure 1,2).

Our material includes mediastinal and hilar adenopathies in 16.5 %, solitary meta of the lungs (1–2 metastases) in 1.9 %, pulmonary tumors in 12.5 %, pulmonary cysts in 3.08 % (out of that echinoccocal cysts in 1.9 %), whereas pleural effusions were diagnosed most frequently – in 25 %, in the total material. This shows the CT sensitivity which depends on the type of pathologic changes.

In the changed anatomic relations in the thorax, CT improves the explanation of the conventional radiography, eliminating the superposition.[1,2]

CT enables a precise evaluation of the expansive process border, with possible analysis of its relation with the surrounding, especially vasculary structures.[1,9,11] It enables the evaluation of locoregional (skin metastases) and metastatic expansion of the malignant process in the mediastinum, with good presentation of the retrosternal, retrocaval (Barety louge), subcarinal, back retrobronchal, posteroinferior mediastinal space (sign "ice hill" Felson), azygoesophageal recessus and phrenicocostal sinuses.[1,2,11–15]

Our material includes: thymus pathology in 2.47 % retrosternal struma 1.48 %, esophageal neoplasms 1.97 %, fat collections in mediastinum 1.48 %, diaphragmatic hernia 0.39 % (Figure 3). An adequate analysis of pleura and pleural cavity is possible.[12,16,17] Pleural effusions are found in 25 %, and pleural tumors in 0.29 % of the total material.

After intravenous application of contrast material, CT shows the vascular nature of tumorous formations in the mediastinum found by conventional radiography.[18,19]

Aortic aneurysms were found in 6 cases (0.59 %), and aberrant right subclavian artery in one case (Figure 4).

It is also possible to check the graft and endarterectomized vascular segment, and to analyse the pericard and heart, as well as to measure heart dimensions.[18,20] Pericardial exudations were presented in 0.49 % of the cases.

The scanner enables a supreme visualization of calcifications, invisible by the conventional radiography.[1,18]

In some cases CT is suggestive of the tumor type histology (fat, liquid, vascular, convolute etc.).[2,9,12–14,18] It simplifies the diagnostic procedures by making some investigations optional (angiography, tomography, endoscopy).[1,13,14,18,19]

CT helps the surgeon in the selection of surgical approach and technique, and offers additional possibility of the therapeutic follow-

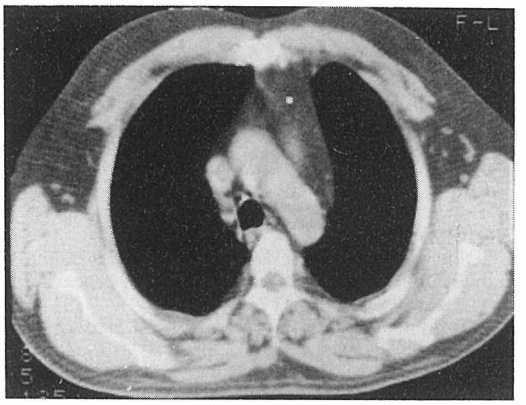

Figure 3. Fat collections of the superior mediastinum (density level – 92 HU).

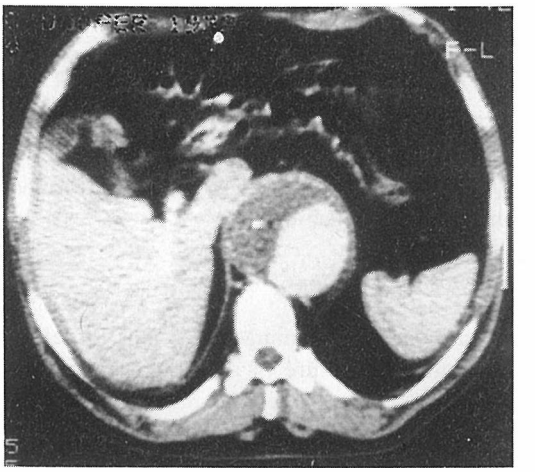

Figure 4. Thrombotic descendent aortic aneurysm (after contrast medium application).

Table 1. Distribution of positive and normal CT findings

No of positive CT findings	731	72.2 %
Normal CT findings	281	27.8 %
Total	1012	100.0 %

Table 2. Distribution of positive CT findings by diagnoses

Ordinal numeral	CT diagnosis	No. of examined patients	Percentage %
1	Pleural effusions	253	25
2	Mediastinal and hilar adenopathies	167	16.5
3	Pulmonary tumors	127	12.5
4	Thymoma and thymus hyperplasia	25	2.47
5	Esophageal neoplasms	20	1.97
6	Solitary meta of the lung (1 to 2)	19	1.9
7	Pulmonary infiltration	19	1.9
8	Pulmonary echinoccocosis	19	1.9
9	Fat deposits in mediastinum	15	1.48
10	Retrosternal struma	15	1.48
11	Pulmonary cysts	12	1.18
12	Pulmonary tuberculosis	11	1.08
13	Pulmonary abscess	7	0.69
14	Aortic aneurysm	6	0.59
15	Pericardial exudation	5	0.49
16	Diaphragmatic hernia	4	0.39
17	Pleural tumor	3	0.49
18	Tracheal neoplasms	1	0.098
19	Aortic dextroposition	1	0.098
20	Aberrant right subclavian artery	1	0.098
21	Cystic teratoma		0.098
	Total	731	72.2

up.[1,11] Transthoracic biopsy is also performed under the guidance of CT.[1,2]

Diagnostic limitations

Besides various advantages, CT fails to define the pathologic nature of the lesion (benign or malignant), but enables the prediction of this possibility (lypoma, cyst, lung sequestration)[1,6,13,14,19] CT is unable to define the structures (lymphnodes) or diffuse infiltrations of organs (liver, spleen).[1,12]

It is difficult to differentiate tumors from the near adenopathies (skin metastasis).[1,11] The evaluation of bacillosis, pneumoconiosis or pulmonary infarction is still performed by the conventional radiography, whereas analysis by CT has been discussed (the expensiveness of CT).[1]

During its first phase prehernial lypoma can be misinterpreted for intrathoracic fat collections.[14] It is impossible to differentiate between a primary and a secondary pleural tumor.[9,16,17]

There is a possibility of false positive and false negative results (cervical lymphnode considered as parathyroid adenoma; undetected tuberculoma and metastasis under 1 cm of size, due to the lack of axial cross-section.[1]

There are limitations of the technical nature (impossibility of apnea, thin patients and children, metallic protheses, partial volume effect etc.) which can change the image quality and densitometric values.[1,5,18]

Conclusion

CT is a non-invasive technique indispensable in the modern diagnostics. It is frequently the method of choice in the diagnosis of pulmonary and mediastinal diseases, especially in the regions traditionally inaccessible by the conventional radiography. It simplifies the diagnostic procedure (excluding the angiographies and tomographies). Without CT, diagnostics becomes more complex, which is the best defence for this technique.

CT does not replace conventional radiography or other techniques, but it is complementary.

References

1. Treut A, Guibert JL, Dilhuydy MH. Les bonnes indications de la tomodensitometrie en cancerologie. *Rev Prat* 1987; **37** (36): 2153.
2. Chalaoui J, Barral V, Simard P, Lefebvre R, Sylvestre J. Mesotheliome pleural: trois forms evolutives. *Ann Radiol* 1982; **25** (3): 191-4.
3. Frija J, Larde D, Katz M, Vasile N, Vadrot D, Utzmann O. Le diagnostic tomodensitometrique des anomalies des arcs chez l'adulte. *J Radiol* 1982; **63** (3): 159–65.

4. Smoger BR, Rosenberg HK, Koss J, et al. La recherche de metastases pulmonaires en pediatrie: la tomodensitometrie face aux techniques radiologiques conventionnelles. *Ann Radiol* 1982; **25 (1):** 47–53.
5. Spiro S, Edwards D, Harper PG, et. al. Computed tomography of the thorax in the diagnosis and management of malignant disease. *Br J Dis Ches* 1982; **76** (3): 209–22.
6. Belloir C, Larde D, Vasile N, Frija J, Ferrane J. Apport de la tomodensitometrie dans le diagnostic et le bilan des anevrysmes de l'aorte. *J. Radiol* 1980; **61** (8–9): 521–6.
7. Frija J, Abadie E, Fisch A, et al. Le diagnostic des hematomes de la paroi du tronc par la tomodensitometrie. *Ann Radiol* 1982; **25** (8): 528–31.
8. Kalifa G, Lalande G, Larde D, Bennet J, Kalifa C. Les fibromes desmoides chez l'enfant. *Ann Radiol* 1982; **25** (1): 25–33.
9. Collard M, Brasseur P, Sukkarieh F. Les indications et les limites de la tomodensitometrie thoracique. *Ann Radiol* 1980; **23** (8): 629–38.
10. Tschappeler H, Vock P. Computed tomography and bone tumors in children. *Ann Radiol* 1982; **25** (1): 19–24.
11. Browu RL, Muhm JR. Computed Tomography of the Thorax Current Perspectives. *Chest* 1983; **83** (5): 806–8.
12. Tschappeler H. Computed tomography (CT) and lymphoma in children. *Ann Radiol* 1980; **23** (2): 87–91.
13. Caron-Poitreau C, Mainchain HN, Rieux D, Vialle M, Caron J. Examen Tomodensitometrique des piliers du diaphragme. Apport a l'etude du mediastin postero-inferieur. *J Radiol* 1980; **61** (1): 1–11.
14. Caron-Poitreau C, Delumeau J, Dabouis G, Petitier H, Rieux D. Apport de la Tomodensitometrie a l'etude des tumeurs primitives de la plevre. *Ann Radiol* 1981; **24** (4): 247–53.
15. Frija J. Princips de la tomodensitometrie. *Rev Prat* 1987; **7:** 30.
16. Coulomb M, Terraube Ph, Vincent J, Lebas JF. Les amas graisseux du mediastin. Apropos de 21 observations, dont 16 avec tomodensitometrie. *J Radiol* 1980; **61** (1): 13–26.
17. Coulomb M, Terraube Ph, Lebas JF, Chouteau H, Geiudre M. Amas graisseux intra-thoraciques symptomatiques d'une hernie diaphragmatique chez l'adulte. A propos de 11 observations avec etude tomodensitometrique. *J Radiol* 1981; **62** (2): 85–95.
18. Coulomb M, Spinelli G, Lebas JF, Terraube Ph, Sarrazin R, Geindre M. Apport de la tomodensitometrie au diagnostic des kystes dermoides. A propos de 5 observations. *J Radiol* 1982; **63** (12): 729–37.
19. Coulomb M, Lebas JF, Sarrazin R, Geindre M. L'apport de la tomodensitometrie au bilan d'extension des cancers de l'oesophage. Incidences therapeutiques. A propos de 40 observations. *J Radiol* 1981; **62** (10): 475–87.

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Clinical advances of contrast-enhanced MR imaging A review

Vinko Kristl

Institute for Diagnostic and Interventional Radiology, University Clinical Centre, Ljubljana Slovenia

The review shows clinical use and some results obtained with contrast agent gadopentetate dimeglumine (Gd–DTPA). It may improve the diagnostic capability of MR imaging. The contrast–enhanced MR imaging is relatively new diagnostic modality and has rapidly evolved from an experimental field to a widely used clinical technique. Further studies are needed to confirm most of potential indications.

Key words: magnetic resonance imaging; gadolinium; gadolinium-DTPA, diagnostic approach.

Introduction

In a relatively short time, MR imaging became an essential diagnostic tool for the practice of medicine. Tissue relaxation times (T_1, T_2), proton density and flow are the principal intrinsic factors, that determine signal intensity on MR images. During the early development of MR imaging there was no exogenously administered contrast material. Anatomic regions that can be immobilized, such as the head, spine and extremities present few obstacles to MR imaging. Routine technique produces excellent images of these regions. MR images of the body, on the other hand, have suffered from low spatial resolution, low signal – to – noise rations and motion – related artifacts. With greater clinical use of MR imaging, however, the difficulty in differentiating lesions such as neoplasms or abscesses of the central nervous system and other organs from surrounding edema became apparent. Intensive efforts to improve the diagnostic utility of body MR imaging have resulted in a variety of specialized approaches: pharmaceutical manipulation of signal–to–noise rations, tissue contrast improved data acquisition, and image processing. Contrast agents alter the tissue signal intensity by either decreasing proton relaxation times or by altering proton density. Now it is known that MR contrast agents improve the usefulness of MR imaging which plays an increasingly important role in clinical practice. Contrast – enhanced MR imaging can simultaneously provide dynamic physiologic information (anatomic and/or biochemical) and high anatomic detail, thereby overcoming the major limitations of both nuclear scintigraphy (poor anatomic resolution) and CT (limited physiologic information).[1] Thus, in both physiologic and pathologic situations where contrast enhancement is seen with CT, a similar result should be expected with MR imaging. There

Correspondence to: Vinko Kristl, MD, IDIR, University Clinical Center, Zaloška 7, 61000 Ljubljana, Slovenia.

UDC: 539.143.43

are major differences with MR imaging depending on the pulse sequence used. T_1 dependent pulse sequences show the greatest enhancement and T_2 dependent pulse sequences show the least enhancement. Differences in CT and MR imaging are also in display of calcified tissue, flow effects.[1,2]

Gadolinium diethylene triamine pentaacetic acid in form dimeglumine salt (Gd–DTPA) is the first MR contrast agent which received Food and Drug Administration approval in June 1988, and is used in clinical practice. Gd–chelated to DTPA molecules make up a contrast agent which has no tissue specificity. Metal ion is chelated to reduce biologic toxicity, biodistribution and pharmacokinetics are ligands dependent. Toxicologically Gd–DTPA is similar to a common iodinated contrast agent.

Pharmacology of Gd–DTPA

After i.v. injection, Gd–DTPA has a plasma half–life of 90 min. This biodistribution follows a two compartment model. It is rapidly redistributed from the vascular compartment into the extracellular space and undergoes renal elimination by passives glomerular filtration.[1] The kidneys concentrate Gd–DTPA and over 90% of it is excreted unchanged with urine within 3 hours. A very small amount of it is excreted through the gastrointestinal tract. Gd–DTPA does not cross the normal blood-brain barrier. Gd–DTPA produces changes in tissue T_1 and T_2. There is no direct relationship between the concentration of Gd–DTPA and the observed signal intensity.

Toxicity of Gd–DTPA

Immediate short–time side effects have not represented a problem; for example blood pressure and pulse rate have been stable. There are some increased or decreased values in some parameters noted in hematologic testing. There is 15 – 30% incidence of transient increase in serum iron concentration. This has generally persisted for less than 24 hours and has returned to normal. A transient rise in serum bilirubin has also been observed in a few cases, although no significant clinical sequelae developed. No evidence of in vivo dissociation of the Gd–DTPA complex exists, and further trials have been planned on the assumption that these side effects are not of major clinical importance.[1,3,4]

Gd–DTPA effects on T_1 and T_2

Gd–DTPA produces a change in ralaxation rates, which are reciprocal of T_1 or T_2 relaxation time. Increasing of Gd–DTPA concentration produces a decrease in both T_1 and T_2. This reduction will be greater in absolute terms for T_1 than for T_2. Protons within fat are not as accessible to Gd–DTPA as protons in free water, thus the changes to protons in fat would be expected to be less than those for protons in water. The term "negative enhancement" is used to describe the situation where tissue signal intensity is decreased by a contrast agent. By using Gd–DTPA, a great change in signal intensity is seen in the inversion recovery sequence (IR).

The overall effect of Gd–DTPA depends on the dosage of contast agent. Dosages of 0.1 – 0.2 mmol/kg body weight are used. Delayed examinations of the brain may show a greater effect than immediate examinations because transport of Gd–DTPA across the blood-brain barrier may take time. The reverse may be true with very vascular lesions. It must also be remembered that although many pathologic processes increase T_1 and T_2, Gd–DTPA decreases T_1 and T_2. Thus considerable potential exists for "isointense" behaviour, whereby the contrast agent reduces tissue T_1 and T_2 values back to those of the adjecent normal tissue, producing a net loss of tissue conspicuity.

Clinical studies investigating the use of contrast agent in MR imaging of the body are few in comparison to studies of contrast – enhanced MR imaging of the brain and spinal canal.[1] This fact is attributable in part to the relatively greater complexity associated with contrast–enhanced MR imaging of non–neurologic disorders. For example, Gd–DTPA induced signal enhancement can result in more pronounced

motion artifacts, and the rapid diffusion of contrast into the extracellular space may neutralize soft–tissue contrast between healthy and diseased tissues. From this point of view it is sensible to presenet separately neurologic and non neurologic applications of Gd–DTPA in MR imaging.

I. Neurologic Gd–DTPA applications

Gd–DTPA does not cross the normal blood–brain barrier but is present in higher concentration in the gray matter as compared with the white matter, reflecting the different vascularity of these tissues. Owing to differences in perfusion, the gray matter will enhance more than the white matter, resulting in a loss of gray–white soft tissue contrast on postcontrast images. The pituitary stalls, pituitary gland, cavernous sinus and choroid plexus enchance also. Because of flow, vascular enhancement is more variable than it is with CT and is most obvious in the structures.

During spinal imaging the normal cord, nerve roots, and intervertebral disks do not enhance.[2]

The blood–brain barrier is generally impermeable to Gd–DTPA. In a variety of pathological conditions including tumors, infections and demyelinating diseases it becomes permeable (vascular permeability), and Gd–DTPA accumulates in an extravascular location. For screening examination of the brain highly T_2 weighted spin echo (SE) sequences (these are insensitive to contrast enhancement) and T_1 weighted sequence (either IR or SE) are used for better anatomic details. T_1 weighted sequences are sensitive to contrast enhancement.

Benign tumors

Meningioma exhibits an increase in T_1 and T_2 (Figure 1).[5] Some meningiomas display only a slight increase in T_1 as compared with the white matter, and have T_2 values within the normal range for the brain. Calcifications and bony changes are poorly shown by MR imaging. It is possible to predict meningioma (histologic

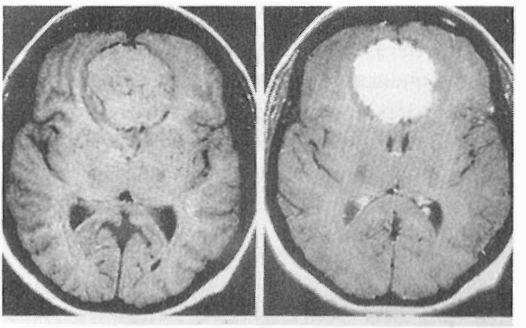


Figure 1. Meningioma without contrast agent: a – SE 2800/30, b – SE 600/20, Gd–DTPA enhanced.

subtypes) on signal intensity (SI) changes[5]. Gd–DTPA is most useful in the detection and characterization of small meningiomas.

In a case of meningioangiomatosis (rare cortical hamartomatous lesion) Gd–DTPA can show no lesion enhancement, which suggests an intact blood–brain barrier.[6]

Acoustic neuroma shows an increase in T_1 and T_2. It is located within the internal auditory canal, within the cerebellar pontine angle or within the posterior cranial fossa. With larger tumors contrast between the brain and cerebral edema is important. Sequences of T_1 and T_2 weighting are used. Contrast enhancement is of great value. Extravasation of the contrast agent molecules through the blood–brain barrier into a brain lesion results in a focal contrast enhancement. Characteristic time dependent contrast enhancement of cerebral lesions is helpful in differentiation between meningiomas and neurinomas.[7]

MR imaging with Gd–DTPA enhancement is the preferred method for depicting intracanalicular acoustic or facial neuromas, but enhancement of the nerve, even focal enhancement, is not diagnostic for the neuroma (nonneoplastic lesions, and neuritis may mimic a small acoustic neuroma on MR imaging).[8]

Other benign tumors

Enhancement has been seen with pituitary tumors, chordomas, glomus jugular tumors, and epidermoid tumors.

Malignant tumors

It is difficult to separate edema from tumor because both processes produce an increase in T_1 and T_2. Differences between them depend only on exploiting relative differences in the degree of these changes. With more imaging sequences, there is more chance to separate the tumor from edema. Highly malignant tumors show greatest enhancement with Gd–DTPA contrast. Enhancement within cystic tumors has also been seen. Sometimes enhancement of areas of apparent edema can be seen with Gd–DTPA where it probably represents tumor infiltration.[2]

Enhancement on MR imaging may be especially valuable in low grade tumors and may be an important guide to biopsy when no enhancement is seen on CT. With noncontrast imaging using a selection of T_1 and T_2 weighted pulse sequences it is not possible to obtain the same separation level of tumor from edema achieved with Gd–DTPA. So is Gd–DTPA helpful in identifying the nidus of tumor, and contrast agent clearly improves the diagnostic sensitivity of T_1 weighted pulse sequences. It is important to remember that Gd–DTPA enhancement does not delineate the borders of tumors, but rather the side of maximal blood–brain barrier breakdown. Gd–DTPA should be used for scanning tumors of the frontal, ethmoid, and sphenoid sinuses for the evaluation of intracranial spread extension of disease. Reactive edema in the inferior frontal lobes can be seen.[9] Mild focal or diffuse dural enhancement with Gd–DTPA is a normal finding on enhanced MR imaging in the pediatric patient who has undergone biopsy, craniotomy or intraventricular shunt placement for an intracranial neoplasm or associated hydrocephalus.[10]

Gd–DTPA enhanced examination is very useful in patients with metastatic disease, where it is possible to identify more lesions. After cerebral tumor resection, enhancement of residual or recurrent tumor is readily separated from postoperative changes such as encephalomalacia or gliosis. The value of Gd–DTPA in separating radiation necrosis from a residual tumor is unclear.[2]

Cerebrovascular diseases

With the use of contrast agent in MR imaging luxory perfusion is noted in the cases of cerebral infarction. Contrast agent is of diagnostic value in differentiating subacute from chronic cerebral infarctions to predict the age of the lesion. Most of the subacute lesions showed the signs of mass effect (increased blood flow represents a luxury perfusion due to collateral formation or reopening of occluded vessels) (Figure 2).[11] Furthermore, Gd–DTPA appers to be useful in the MR evaluation of early ishemia and its response to intervention.[12]

Arteriovenous malformations show a different pattern. Slowly flowing blood has great enhancement and rapidly flowing blood has no enhancement. The type of venous drainage, either superficial or deep, could be determined by contrast enhanced MR imaging. The intravenous administration of contrast adds significant information in the MR study of venous angioma.[13]

Ring enhancement in contrast MR imaging has been identified at the margin of giant aneurysms (probably reflecting proliferation of the vasa vasorum).

Enhancement of the membrane associated with subdural hematomas may be visualised.

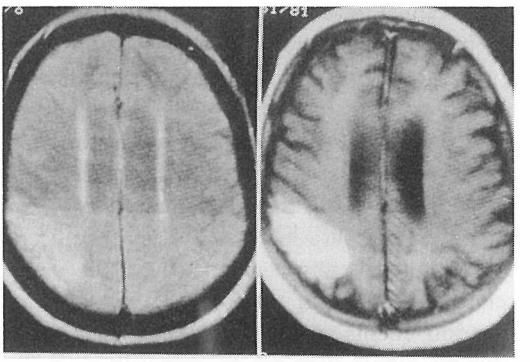


Figure 2. Subacute infarction: a – T_2–weighted image; increased signal intensity in the right parietal region. b – Postcontrast T_1–weighted image, contrast enhancement in the infarcted area.

Demyelinating diseases

Multiple sclerosis was the first disease in which MR imaging was demonstrated to have significant advantages over X–ray and CT. Multiple sclerosis is the major indication for MR imaging. Its sensitivity is increased by the use of Gd–DTPA and by delayed examination.[2] Noncontrast MR imaging is very sensitive in detecting demyelinating diseases, especially on T_2–weighted images.[14]

However, gadopentetate dimeglumine enhanced MR has been shown to be more sensitive than contrast enhanced CT for identifying regions of abnormal blood–brain barrier that may correlate with clinical activity.

In patients with chronic partial epilepsy Gd–DTPA should be used selectively to clarify or better define the nature of abnormalities encountered on unenhanced scans. The likelihood of missing an important abnormality by performing unenhanced imaging alone is small.[15]

Infections

Ring enhancement is a well known feature of cerebral abscess and other patterns of enhancement may also be seen both with abscess and other forms of CNS (central nervous system) infections. MR has been demonstrated to be sensitive for the detection of CNS involvement with viral infections. In case of acute disseminated encephalomyelitis MR typically demonstrates multiple focal areas of increased signal on T_2 weighted images within the brain stem, cerebrum and cerebellum. Predominant pathologic finding with this disorder are focal areas of demyelinization. MR abnormalities are typically located within the white matter.[16]

In a case of parasitic desease (neurocysticercosis) contrast enhancement around the cysticerci seems to occur when there are both surrounding edema and signal intensity of the cyst contents higher than cerebrospinal fluid on T_1 and proton density–weighted images. Such enhancement probably reflects degeneration of the worms and an inflammatory reaction of the adjacent brain tissue. The degree of contrast enhancement on MR imaging may indicate the degree of focal parenchymal inflammatory reaction around the cysts.[17]

Orbit

The advantages of MR imaging in this site are as follows: there radiation on the lens, high soft–tissue contrast visualizing of the optic nerve within the optic canal. The abundant orbital fat leads to chemical shift misregistration artefacts. In the cases of optic neuritis, the abnormally enhanced nerve is often masked by the surrounding high signal fat on T_1 weighted images. Post Gd–DTPA fat suppresion T_1 weighted images clearly identified the shaggy, enhanced inflammatory perioptic lesions with or without an enhanced optic nerve.[18] With this finding we can differentiate perineuritis from the smoothly outlined enhancing perioptic meningioma.

Soft tissues, nasopharynx and soft tissue of the neck

We can see differential enhancement between the lesion and normal mucosa. Mucosa has high level of vascularity and high water content so it displays a moderately high level of enhancement with Gd–DTPA. Gd–enhanced MR imaging of the cranial nerves (fifth nerve) is recommended in patients with cranial nerve sensory or motor deficit or neuralgia. Contrast enhanced MR imaging appears to be superior to noncontrast imaging, as it is possible by means of imaging characteristics, to separate benign from malignant disease.[19]

Spinal cord

With MR imaging it is possible to visualize the spinal cord directly without intrathecal contrast agents. Parenchymal changes within the cord can also be seen directly. Gd–DTPA is used for defining extramedullary lesions and for distinguishing tumor from edema, and defining the extent of metastatic spread. It is possible to differentiate scar from a recurrent disk

following surgery. Overall, the spinal cord has been one of the most promising sites for the use of Gd–DTPA. Three dimensional gradient echo steady state sequence and postprocessing gives a view of the thecal sac and the dural root sleeves.[20] It may provide enough information to eliminate the need for contrast myelography in the evaluation of extradural disease. Gd–DTPA provides conspicuity of tumors, inflammatory and infective processes. It anables differentiation of cystic tumors from syringomyelia and post–radiation cord damage, and epidural fibrosis from recurrent disc.

II. Non-neurologic applications

Thorax

Flow properties of MR imaging enable differentiation between masses and vascular structures. The indications for Gd–DTPA in MR imaging might be expected to be fewer than the indications for iodine based agents in CT. Mediastinal masses have displayed enhancement and the pattern of the proximal pulmonary vasculature can be demonstrated with them.

Contrast enhacement has been seen in the margin of areas of myocardial infarction. There are two or three zones identified in acute, subacute or chronic stages of myocardial infarction. Greater enhancement is produced in the peri–infarction zone than in the normal or infarcted myocardium.[21, 22] By diagnostic MR it is possible to determine pseudoaneurysms of the heart.[23] MR can detects intramural and intracavitary cardiac tumors which are bigger than 5 mm. MR imaging can also provide essential information on tumor extent, location, and relation to the cardiac and paracardiac structures.[24]

Gd–DTPA has proved valuable in separating neoplastic from fibrotic lesions within the breast, although difficulties in distinguishing benign and malignant tumors remain. In the case of bronchus tumor or mesothelioma the major use of MR is in the evaluation of mediastinal involvement, the relationship of the tumor to the great vessels, and the presence of chest wall involvement.[25] MR imaging is similar to CT in its ability to evaluate normal and abnormal hila and mediastina.[26] MR is superior to CT in showing enlarged hilar lymph nodes, but CT is better for demonstrating bronchial abnormalities.[27]

Because of the contrast resolution between static and flowing blood, pulmonary emboli can be demonstrated non-invasively, but the question remains whether the increased signal intensity depends only on slow flow or on the embolus itself.[28]

The central vasculature in the mediastinum can be evaluated by means of MR angiography. Two dimensional FLASH angiography (a fast low angle shot two–dimensional pulse sequence) can be postprocessed into a three–dimensional MR angiography by a maximum intensity projection algorithm.[29]

Alterations in both T_1 and T_2 reflect changes in water content of inflammatory alveolitis to fibrotic lungs.[30]

Abdomen

Liver: The normal liver parenchyma shows marked enhancement soon after an intravenous injection of Gd–DTPA but this decreases with its redistribution and excretion. The liver, pancreas, and adrenal gland enhance homogeneously, whereas the spleen, kidney and the abdominal aorta and inferior vena cava enhance heterogenously with dynamic gadolinium–enhanced MR imaging.[31]

Liver tumors show variable enhancement but may also have greater enhancement than normal liver so that they become isointense (Figure 3). Gd–DTPA enables better differentiation between necrotic and other areas of tumor, more precision in defining tumors and differentiation between portal veins and dilated bile ducts. MR correctly localized 90 % of the liver metastatic lesions. MR represents an ideal modality for lesion localization because it accuretely depicts hepatic vessels fissures that define segmental boudaris. The flow void phenomenon causes the hepatic veins to be strikingly low in

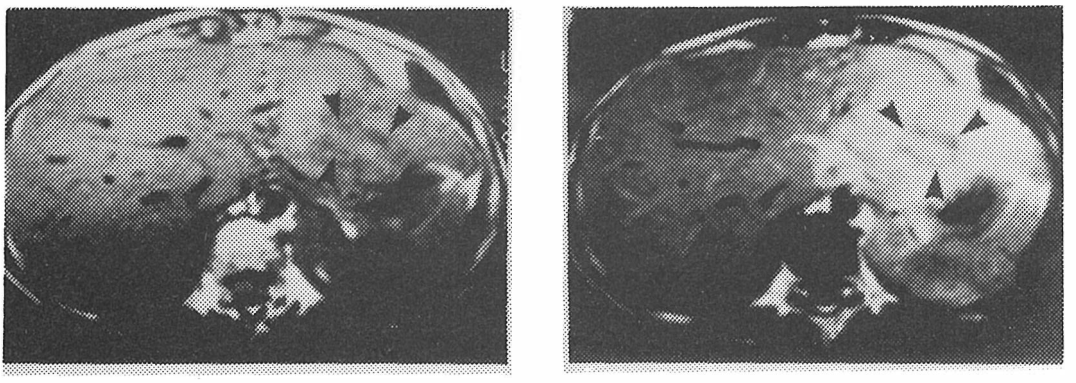
signal. Because the hepatic veins act to separate the hepatic segments, lesion site can be easily assessed.[32]

The appearance of hemangiomas in dynamic gadopentetate dimeglumine enhanced MR imaging is characterized by hyperintense peripherial enhancement followed by a fill–in phenomenon. This is quite distinct from the enhancement behaviour of liver metastases, and hepatocellular carcinomas. The difference in SI between hemangiomas and metastases is most striking on delayed images. Hypervascular metastases do not show the homogenous high SI typical of hemangiomas. Focal–nodular hyperplasia is characterized in dynamic contrast–enhanced MR imaging by a strong contrast enhancement with a peak during the first 30 seconds after contrast administration, and by a rapid decrease in SI.[1] Turbo FLASH (fast low angle shot) dynamic scanning of liver with Gd–DTPA enhancement significantly improves lesion–liver contrast particularly in the cases of focal nodular hyperplasia of the liver.[33] Improved liver–to lesion contrast is possible with intraarterial portography with Gd–DTPA.[34]

Spleen: The sensitivity of MR imaging in the detection of tumorous lesions of the spleen is low because relaxation times and SI of normal spleen and intraspleenic tumors are very similar. Contrast agents can dramatically improve tumor detection. Normal spleenic enhancement pattern during dynamic gadolinium–enhanced T_1 weighted spin–echo MR imaging is heterogeneous, with conversion to homogeneous enhancement one minute later.[35] Prolonged enhancement on postcontrast MR imaging is a useful finding in differentiation of spleenic hamartoma (rare benign lesion) from malignant lesions of the spleen (especially from nodular lesions af malignant lymphoma).[36]

Pancreas: In evaluating diseases of the pancreas, MR is still inferior to CT. Development of oral contrast agents is a first step toward improving the usefulness of MR imaging of the pancreas, because the pancreas must be first differentiated from the gastrointestinal tract. In cases of pancreatic transplant dysfunction Gd–DTPA enhanced MR imaging is a very sensitive technique.[37]

Adrenals: Malignant tumors and pheochromocytomas show a significantly greater SI than adenomas in precontrast images. After administration of Gd–DTPA only moderate enhancement and quick washout is observed in adenomas, whereas malignant tumors and pheochromocytomas show strong enhancement and slower washout.[1] With gradient echo sequences adrenocortical adenomas display a lower SI than other adrenal lesions on T_2 weighted ima-



a b

Figure 3. Hepatocelullar carcinoma a – short TR/TE (700/20) SE sequence, b – short TR/TE (700/20) SE seguence after Gd-DTPA injection.

ges. Pheochromocytomas, metastases, and carcinomas of the adrenals show a high SI. Additional dynamic contrast enhanced studies allow further classification. The physiopathologic mechanism of different enhancement patterns is based on the strong perfusion of malignant tumors. A disturbed permeability of the capillaries of malignant lesions leads to an increased diffusion of the contrast agent into the interstitial space. In the case of metastases and carcinomas, the contrast agent is retained in the extravascular space for a longer period of time.[38] Additional advantage of MR images is that multiplanar sections allow a better overview of the topographic relationships.

Kidney: In the kidney Gd–DTPA is concentrated and sharp differentiation between the cortex and medula can be produced. The concentration of Gd–DTPA in the collecting system is usually sufficient for reduction in the T_2 of urine to dominate the reduction in T_1 producing a zero signal with all sequences using the conventional doses. If a low dose is given and the patient is scanned quickly, however, an increased SI may be seen in the collecting system. Contrast-enhanced MR imaging for both tumor diagnosis and functional assessment is best achived when dynamic studies are performed in combination with a bolus injection of gadopentetate dimeglumine. Gadolinium–enhanced MR imaging is an effective method for characterizing renal lesions in patients with renal insufficiency. At the usual dosage there appears to be no nephrotoxic reaction in these patients.[39]

Retroperitoneum: A variety of retroperitoneal lesions have displayed enhancement which may produce a better deffinition of the extent of particular lesions. MR imaging has proved unreliable in the distinction of normal and neoplastic nodes by means of SI characteristics, because the relaxation times and proton densities of normal and metastatic nodes overlap.[1]

Pelvis: General considerations applicable to imaging of soft tissue outside the CNS apply to the pelvis. Pelvic tumors display enhancement and similar parallels have been seen with other pathologic processes. The bladder shows concentration phenomena, whereby a signal from the posterior bladder (concentrated Gd–DTPA) may be zero with a zone of enhancement between lower and upper zones where the concentration is optimal with essentilly normal urine above. Contrast–enhanced MR imaging appears to allow better bladder tumor staging than do precontrast T_1 and/or T_2 weighted pulse sequences. This is especially true for the distinction of superficial tumors from those infiltrating the muscle, because noninvolvement of the muscle layer is visualized as an intact hypointense line in the region underlying the tumor. The application of Gd–DTPA proved valuable in detecting small bladder tumors and in differentiating between necrotic and vital tissue within large ones. Tumors are generally characterized by a very inhomogeneous perfusion with an augmented vascularization along the edges of the tumor and a rarified capillary network within the tumor center. This probably causes an uneven distribution of contrast medium within bladder tumors. Neurofibromas show a markedly increased SI on T_2 weighted images relative to the surrounding soft tissues with marked enhancement following Gd–DTPA administration.[40,41]

Reports of MR imaging for staging of bladder neoplasms have been encouraging owing to its inherent soft tissue contrast as well as the advantage of multiplanar applicability. However, some authors suggest that the accuracy of MR imaging performed without a contrast medium in determining the depth of tumor invasion is only slightly better or even worse than that of CT.[42] However, both precontrast and postcontrast T_1 weighted images of the bladder should be obtained.

In the diagnosis of tumors of the uterus, Gd–DTPA enhanced MR imaging can yield additional information in patients with endometrical carcinoma. Viable and necrotic areas are easier to distinguish on postcontrast than on T_2 weighted precontrast images. In the evaluation of ovarian masses, Gd–DTPA improves the

visualization of the tumor structure and may allow better distinction of inflammatory adnexal processes from malignant tumors.[1]

Muscle-skeletal system

Contrast enhanced MR imaging with T_1 weighted echo pulse sequences is more variable in distinguishing different tumor components, necrosis, peritumoral edema and viable tumor tissue, than is precontrast imaging. Marked improvement occurs after contrast application compared with the T_1 weighted precontrast image, the contrast is never as strong as in T_2 weighted precontrast sequences. Application of Gd–DTPA reduces the contrast between enhancing tumor and signal-intensive fatty tissue and bone marrow. This is used for characterization and evaluation of tumors before and after treatment.[43] Gd–DTPA MR imaging is used also in the joints for delineation of cartilage and tendon tears, for differentiation between pannus and joint effusion and for the delineation of infection processes.[44]

Conclusion

Administration of Gd–DTPA has pointed out that MR imaging in no longer nonivasive in the strict sense, and the duration of the examinations may be increased. Once Gd–DTPA has been accepted, the question concerning its strict clinical indications needs to be solved. As with other aspects of MR imaging, the options are wide, and the principal agent in use at the present time, Gd–DTPA is one of the most obvious choices. Much more effort will undoubtelly be expended on developing other contrast agents, some of which will find application in clinical practice. Without a gastrointestinal contrast agent, MR imaging will be unable to provide global examination of the abdomen. With novel formulations such as the nonionic isoosmolar preparations, higher doses or prolonged infusion may further improve diagnostic information.

References

1. Saini S, Modic MT, Hamm B, Hahn PF. Advances in contrast-enhanced MR imaging. *AJR* 1991; **156:** 235–54.
2. Stark DD, Bradley WG. *Magnetic resonance imaging*. St. Louis: The C. V. Mosby Company, 1988.
3. Kristl V. Contrast agents in MR imaging. *Radiol Iugosl* 1991; **25:** 355–9.
4. Laniado M, Claussen C, Weinmann HJ, Schroeder W. Paramagnetic contrast media in magnetic resonance imaging of the brain. In: Taveras JM, Ferrucci JT. *Radiology*. Lippincott, Philadelphia. Vol. 3, part 59, 1989.
5. Kaplan RD, Coons S, Drayer BP, Roger Bird C, Johnson PC. MR characteristics of meningioma subtypes at 1.5 tesla. *J Comput Assist Tomogr* 1992; **16:** 366–71.
6. Tien RD, Osumi A, Oakes JW, Madden JF, Burger PC. Meningioangiomatosis: CT and MR findings. *J Comput Assist Tomogr* 1992; **16:** 361–5.
7. Felix R, Schoerner W, Sander B, et al. Contrast-enhanced MR brain studies: clinical experience with Gd–DTPA over four years. *Diagnostic Imaging* 1988; Supl. 13–5.
8. Han MH, Jabour BA, Andrews JC at all. Nonneoplastic enhancing lesions mimicking intracanalicular acoustic neuroma on gadolinium–enhanced MR images. *Radiology* 1991; **179:** 795–6.
9. Tassel P, Ya–Yen Lee. Gd–DTPA enhanced MR for detecting intracranial extension of sinonasal malignancies. *J Comput Assist Tomogr* 1991; **15:** 387–92.
10. Hudgins AP, Davis PC, Hoffman JC. Gadopentetate dimeglumine enhanced MR imaging in children following surgery for brain tumor: spectrum of meningeal findings. *AJR* 1991; **156:** 1237–43.
11. Cordes M, Henkes H, Roll D, Eichstaedt H, Christe W, Langer M, Felix R. Subacute and chronic cerebral infarction: SPECT and Gadolinium–DTPA enhanced MR imaging. *J Comput Assist Tomogr* 1989; **13:** 567–71.
12. Crain Mr, Yuh WTC, Greene GM, Loes DJ, Ryals TJ, Sato Y, Hart MN. Cerebral ischemia: evaluation with contrast–enhanced MR imaging. *AJR* 1991; **157:** 575–83.
13. Wilms G, Demaerel P, Marchal G, Baert AL, Plets C. Gadolinium–enhanced MR imaging of cerebral venous angiomas with emphasis on their drainage. *J Comput Assist Tomogr* 1991; **15:** 199–206.
14. Caldemeyer KS, Harris TM, Smith RR, Edwards MK, Gadolinium enhancement in acute disseminated encephalomyelitis. *J Comput Assist Tomogr* 1991; **15:** 673–75.
15. Elster AD, Mirza W. MR imaging in chronic partial epilepsy: role of contrast enhancement. *AJR* 1991; **156:** 605–10.
16. Tolly TL, Wells RG, Sty JR. MR features of fleeting CNS lesions associated with Epstein–Barr virus infection. *J Comput Assist Tomogr* 1989; **13:** 665–8.
17. Chang KH, Lee JH, Han MH, Han MC. The role of contrast–enhanced MR imaging in the diagnosis of neurocysticercosis. *AJR* 1991; **157:** 393–6.

18. Tien RD, Hesselink JR, Szumowski J. MR fat suppression combined with Gd–DTPA enhancement in optic neuritis and perineuritis. *J Comput Assist Tomogr* 1991; **15:** 223–7.
19. Sevick RJ, Dillon WP, Engstrom J, Bergman WG, Ric Harnsberg H. Trigeminal neuropathy: Gd–DTP enhanced MR imaging. *J Comput Assist Tomogr* 1991; **15:** 605–11.
20. VanDyke CW, Modic MT, Beale SM, Amartur S, Ross JS. 3D MR myelography. *J Comput Assist Tomogr* 1992; **16:** 497–500.
21. Saeed M, Wendland MF, Masui T, Connolly AJ, Derugin N, Brash RC? Higgins CB. Myocardial infarction: assessment with an intravascular MR contrast medium. *Radiology* 1991; **180:** 153–60.
22. van Dijkman PRM, van der Wall EE, de Roos A, Matheijssen NAA, van Rossum AC, Doornbos J, van der Laarse A, van Voorthuisen AE, Bruschke AVG. Acute, subacute and chronic myocardial infarction: quantitative analysis of gadolinium–enhanced MR images. *Radiology* 1991; **180:** 147–150.
23. Duvernoy O, Wikstrom G, Mannting F, Larson SG, Andren B, Dubiel T. Pre– and postoperative CT and MR in pseudoaneurysms of the heart. *J Comput Assist Tomogr* 1992; **16:** 401–9.
24. Rienmueller R, Lloret JL, Tiling R, Groh J, Manert W, Mueller DK, Seifert K. MR imaging of pediatric cardiac tumors previously diagnosed by echocardiography. *J Comput Assist Tomogr* 1989; **13:** 621–6.
25. Lorigan JG, Libshitz HI. MR imaging of malignant pleural mesothelioma. *J Comput Assist Tomogr* 1989; **13:** 617–20.
26. Heelan RT, Martini N, Westcott JW, et al. Carcinomatous involvement of the hilum and mediastinum: Computed tomographic and magnetic resonance evaluation. *Radiology* 1985; **156:** 111–5.
27. Webb WR, Jensen BG, Sollitto R, de Geer G, McCowin M, Gamsu G, Moore E. Bronchogenic carcinoma: staging with MR compared with staging with CT and surgery. *Radiology* 1985; **156:** 117–24.
28. Ovenfors CO, Batra P. Diagnosis of peripheral pulmonary emboli by MR imaging: an experimental study in dogs. *Magn Reson Imag* 1988; **6:** 487–91.
29. Kauczor HU, Layer G, Schad LR, et al. Clinical application of MR angiography in intrathoracic masses. *J Comput Assist Tomogr* 1991; **15:** 409–17.
30. Vinitski S, Pearson MG, Karlik SJ, et al. Differentiation of paarenchymal lung disorders with in vitro proton nuclear magnetic resonance. *Magn Reson Med* 1986; **3:** 120–5.
31. Mirowitz SA, Gutierrez E, Lee JKT, Brown JJ, Heiken JP. Normal abdominal enhancement patterns with dynamic gadolinium–enhanced MR imaging. *Radiology* 1991; **180:** 637–40.
32. Zeman RK, Dritschilo A, Silverman PM, et al. Dynamic CT vs 0.5T MR imaging in the detection of surgically proven hepatic metastases. *J Comput Assist Tomogr* 1989; **13:** 637–44.
33. Mathieu D, Rahmouni A, Anglade MC, et al. Focal nodular hyperplasia of the liver: assesment with contrast–enhanced Turbo FLASH MR imaging. *Radiology* 1991; **180:** 25–30.
34. Pavone P, Giuliani S, Cardone G, et al. Intraarterial portography with gadopentetate dimeglumine: improved liver–tolesion contrast in MR imaging. *Radiology* 1991; **179:** 693–7.
35. Mirowitz SA, Brown JJ, Lee JKT, Heiken JP. Dynamic gadolinium–enhanced MR imaging of the spleen: normal enhancement patterns and evaluation of splenic lesions. *Radiology* 1991; **179:** 681–6.
36. Ohtomo K, Fukuda H, Mori K, Minabi M, Itai Y, Inoue Y. CT and MR Appearances of splenic hamartoma. *J Comput Assist Tomogr* 1992; **16:** 425–8.
37. Fernandez MP, Bernardino ME, Neylan JF, Olson RA. Diagnosis of pancreatic transplant dysfunction: value of gadopentetate dimeglumine–enhanced MR imaging. *AJR* 1991; **156:** 1171–6.
38. Krestin GP, Friedmann G, Fischbach R, Neufang KFR, Allolio B. Evaluation of adrenal masses in oncologic patients: dynamic contrast–enhanced MR vs CT. *J Comput Assist Tomogr* 1991; **15:** 104–10.
39. Rofsky NM, Weinreb JC, Bosniak MA, Libes RB, Birnbaum BA. Renal lesions characterization with gadolinium–enhanced MR imaging: efficacy and safety in patients with renal insufficiency. *Radiology* 1991; **180:** 85–9.
40. Neuerburg JM, Bohndorf K, Sohn M, Teufl F, Guenther RW, Daus Hj. Urinary bladder neoplasms: evaluation with contrast-enhanced MR imaging. *Radiology* 1989; **172:** 739–43.
41. Shonnard KM, Jelinek JS, Benedikt RA, Kransdorf MJ, CT and MR of neurofibromatosis of the bladder. *J Comput Assist Tomogr* 1992, **16:** 433–8.
42. Neuerburg JM, Bohndorf K, Sohn M, et al. Staging of urinary bladder neoplasms with MR imaging: Is Gd–DTPA helpful? *J Comput Assist Tomogr* 1991; **15:** 780–6.
43. Beltran J, Chandnani V. McGhee RA? Kursunoglu–Brahme S. Gadopentetate dimegumine–enhanced MR imaging of the musculoskeletal system. *AJR* 1991; **156:** 457–66.
44. Seeger LL, Widoff BE, Bassett LW, Rosen G, Eckardt JJ. Preoperative evaluation of osteosarcoma: value of gadopentetate dimeglumine–enhanced MR imaging. *AJR* 1991; **157:** 347–51.

Radiol Oncol 1992; 26: 140-4.

The response of two vincristine resistant human larynx carcinoma cell clones to chemotherapeutic drugs

Maja Osmak[1] and Damir Eljuga[2]

[1] *Ruđer Bošković Institute, Department of Experimental Biology and Medicine, Zagreb, Republic of Croatia*

[2] *Central Institute for Tumors and Allied Diseases, Department of Gynaecology, Zagreb, Republic of Croatia*

We selected two vincristine (VCR) resistant clones: VA3 and VK2 obtained from human larynx carcinoma cells through two different resistance development shedule (acute or continuous), and determined their sensitivity to several cytostatic drugs widely used in cancer treatment. Both clones were reisistant to VCR, but VA3 was more resistant than VK2 clone. The resistance to VCR was partially reversed by addition of verapamil indicating that some additional mechanism, beside the increased activity of P-glycoprotein, has to be involved in resistance to VCR. Selected clones change their sensitivity to examined drugs. They became resistant to Adriamycin (VK2 clone), 5-fluorouracil (VK2 clone) and methotrexate (both clones). They did not change their sensitivity to vinblastine, etoposide (Et) or mitomycin C (MMC), except for low concentrations of Et (resistance of VK2 clone) and MMC (sensitivity of VA3 clone). Both clones became sensitive to cis-diamminedichloroplatinum (II), especially VK2 clone. Our results show that drug sensitivity of resistant clones depends on the VCR resistance development schedule. They empasize the complexity and difficulties of judicious choice of agents given in combined tumor therapy.

Key words: vincristine; drug resistance; cell cultures; drug therapy

Introduction

The major problem in cancer chemotherapy is the ability of tumor cells to develop resistance to chemotherapeutic drugs. While some mechanisms of resistance allow cells to survive exposure to a single agent, the phenomonom of multidrug resistance (MDR) confers upon cells the ability to withstand exposures to many structurally unrelated antineoplastic drugs. The MDR phenotype can be obtained when the cells are selected with: *Vinca* alkaloids, antibiotics and anthracyclines.[1,2] However, MDR does not result from selection with antimetabolites, most alkylating agents or bleomycin.

The MDR process has been extensively studied in animal and human cell lines.[3–9] MDR cells are characterized by reduction in intracellular drug accumulation, that correlates with overexpression of a highly conserved 170 kDa

Corespondence to: dr. Osmak M

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plasma membrane glycoprotein, termed P-glycoprotein, an energy dependent efflux pump. The *mdrl* gene coding for this glycoprotein has been isolated and sequenced. This gene is usually amplified and overexpressed in many MDR cells lines, although in some cases the overexpression of *mdr* gene with no DNA amplification was observed.

In spite of the fact that mechanims that contribute to MDR phenotype is known today, it is not possible to judge precisely and completely for the cells from each tumor, how the chemotherapy will influence the resistance development to drugs used, as well as their cross-resistance to other therapeutic agents. The drug resistant sublines of human cells developed *in vitro* may contribute to the knowledge concerning this subject.

In my previous study I reffered the resistance development of human larynx carcinoma HEp2 cells to vincritine sulfate (VCR) by two schedules: ie. by acute or chronic repeated treatments.[10] VCR resistant cells were cloned, and two clones were selected. VA3 clone was obtained from acute treated cells and VK2 from chronic treated cells. The aim of this study was to determine the sensitivity of these clones to several widely used chemotherapeutic drugs, that kill cells through different mechanisms: vincristine, vinblastine (VBL), Adriamycin (Adr), mitomycin C (MMC), etoposide (Et), 5-fluorouracil (5-FU), methotrexate (MTX), and cis – dichlorodiammineplatinum(II) (cis-DDP).

Materials and methods

Cell line

Human larynx carcinoma HEp2 cells were used in this study. They were grown as a monolayer culture in Eagle's minimum essential medium (GIBCO) supplemented with 10 % fetal bovine serum (GIBCO) and antibiotics in a humid atmosphere containing 5 % CO_2.

Drugs

Vincristine sulfate (Oncovin; Eli & Lilly, Indianapolis, USA), vinblastine (Velbe, Eli & Lilly, Indianapolis, USA), verapamil (Isoptin; Lek, Ljubljana, Slovenia), 5-fluorouracil (SBS, Bosnalijek, Sarajevo, Bosnia and Herzegovina) and etoposide (Etopol, Krka, Novo mesto, Slovenia) were dissolved in physiological saline. Cis-dichlorodiammineplatinum(II) (Johnson-Mathey Research Center, U. K.), methotrexate (Roger Belon Laboratories, France), mitomicyn C (Sigma Chemical Co., St. Louis, USA) and Adriamycin (Farmitalia Carlo Erba, Italy) were dissolved in water. Stock solutions were stored at –20° C (except 5-FU stored at room temperature and etoposide at 4° C) and kept in the dark. Drugs were diluted with medium to appropriate concentration just before use.

MTT (3-(4,5-dimenthylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) (Sigma Chemical Co.) was dissolved in phosphate buffered saline and stored at 4° C protected from light.

Resistance development

The development of resistance was described in details previously.[10] Briefly, the cells resistant to vincristine sulfate (VCR) were obtained due to two drug treatment schedule: they were treated for 1 h in serum-free medium with stepwise increased concentrations of VCR (from 1 to 8 μM) for VA15 cells, or incubated for 24 h in medium supplemented with serum with increased concentrations of VCR (from 0.05 to 0.4 μM) for VK15 cells. VCR resistant cells were cloned and two clones were selected for futher investigation: VA3 clone from VA15 cells, and VK2 clone from VK15 cells.

MTT microculture assay

Chemosensitivity of VCR resistant clones and control cells to different chemotherapeutic drugs was determined using a modified MTT dye assay.[11] This is a colorimetric assay based on the ability of viable cells to reduce a soluble yellow tetrazolium salt to purple colored formazon cristals due to mitochondrial enzyme succinate dehydrogenase. The cristals can be dissolved and quantified by measuring the absorbance of the resultant solutions indicating the number of live cells.[12]

The cells were plated into tissue culture 96-well microtiter plates at 5×10^3 cell in 0.08 ml medium/well. Next day appropriate concentrations of different drugs were added in 0.02 ml/well (each concentration was tested in quadriplicate), and were present contineously for 48 h at 37° C. After this incubation period the medium was aspirated, 20 μg of MTT dye/0.04 ml medium added to each well and incubated for 4 h. Dimethyl sulfoxid was added to each well (0.170 ml), plates were mechanically agitated for 5 min and optical density at 540 nm determined on a microculture plate reader. Each experiment was repeated at least twice.

Statistics

Significance of the differences in sensitivity between control cells and resistant clones was assessed by Student's t-test. The level of significance was set at 0.05.

Results and discussion

In the present study we examined the sensitivity of two vincristine resistant clones of human larynx carcinoma HEp 2 cells, obtained by two different resistance development procedures, to several chemotherapeutic drugs widely used in cancer patients treatment. We found that both, VA3 and VK2 clones exhibit, as expected, resistance to VCR. However, cells treated by acute schedule with VCR – VA3 clone, were more resistant to this drug than VK2 clone obtained by continuous treatment (Figure 1). Therefore, the degree of resistance to VCR was influenced by procedure of resistance development.

The mechanisms involved in resistance to VCR was explained due to addition of verapamil. Verapamil binds directly to plasma membrane P-glycoprotein.[13] Presumably by blocking cytotoxic drug binding and efflux through competitive inibition mechanism, it reverses the MDR resistance.[14] In our study addition of verapamil reversed the VCR resistance of VA3 and VK2 clones, but only partially (Figure 2). These data indicate that some additional mechanisms, beside the increased activity of P-glycoprotein, have to be involved in this phenomenom.

The cross-resistance of VA3 and VK2 clones to drugs which can induce MDR phenotype, ie. Adriamycin, vinblastine and mitomycin C, are presented in Figure 3. Both VCR resistant clones were cross-resistant to Adriamycin (with more resistant VK2 clone), as published pre-

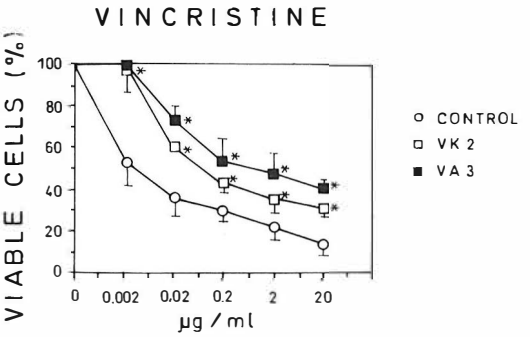

Figure 1. Dose response curves of human larynx carcinoma HEp2 control cells and vincristine resistant clones VK2 and VA3 treated with vincristine sulfate. The data are presented as the percent of corresponding control optical density. Pooled data from three experiments (mean at each point ± S D).

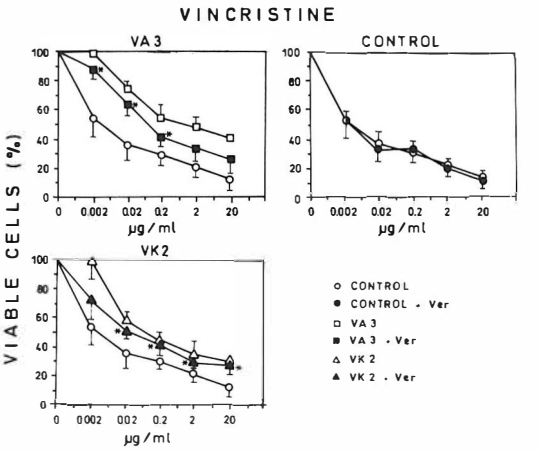

Figure 2. Dose response curves of control HEp2 cells and VCR resistant clones VK2 and VA3 following treatment with vincristine sulfate alone or in combination with verapamil. Pooled data from three experiments (mean at each point ± S D).

viously in the literature.[9, 15–18] They did not, however change their sensitivity to VBL or MMC (VA3 clone exhibits even increased sensitivity to low concentrations of this drug). It must be pointed out, that establishment of resistance and cross-resistance are distinct phenomena. In fact, in multidrug resistant cells, the resistance is almost always greatest to the drug used for initial challenge. In our study we used low concentrations of VCR for resistance development, similar to those, which are used in clinical treatment. Therefore, the resistance to challenging agent was much lower than published in the literature,[15–17] probably too low to induce cross-resistance to VBL or MMC. Similarly, the cross-resistance to etoposide was found only for low concetrations of this drug in VK2 clone. It should be mentioned, however, that MDR phenotype of etoposide resistant cells involve altered activity of DNA-topoisomerase II enzymes, not increased activity of P-glycoportein.[3,4,6]

The sensitivity of VA3 and VK2 clone to: 5-fluorouracil, methotrexate and cis-dichlorodiammineplatinum (II), which do not induce MDR phenotype, were also examined, and the

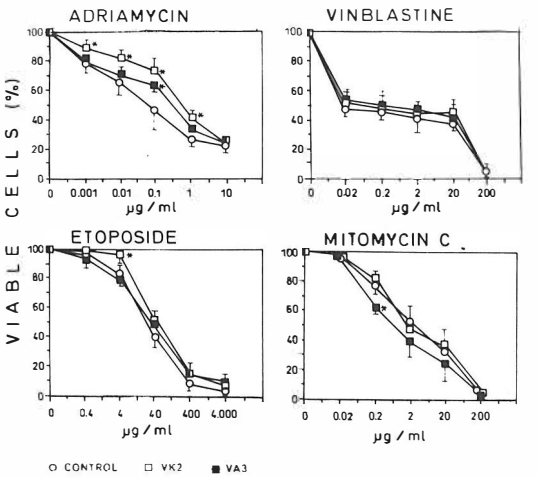

Figure 3. Dose response curves of control HEp2 cells and VCR resistant clones VK2 and VA3 following treatment with Adriamycin, vinblastin, etoposide and mitomycin C. Pooled data from at least two experiments (mean at each point ± S D).

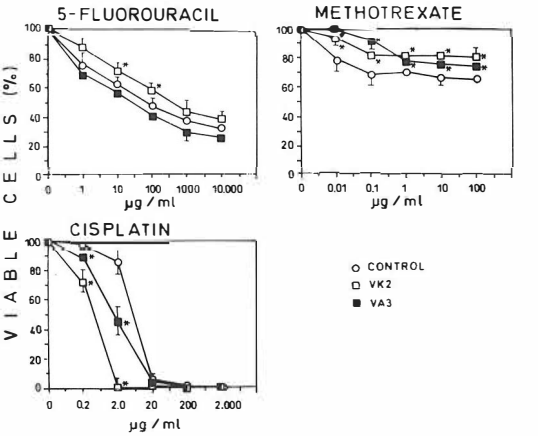

Figure 4. Dose response curves of control HEp2 cells and VCR resistant clones VK2 and VA3 following treatment with 5-fluorouracil, methotrexate, and cis-dichlorodiammineplatinum(II). Pooled data from at least two experiments (mean at each point ± S D).

results are presented in Figure 4. VK2 clone exhibited cross-resistance to 5-FU, and both clones became cross-resistant to MTX, althoug the mechanisms involved in resistance to these drugs do not involve increased activity of P-glycoprotein.[4,6,7] Both clones exhibited collateral sensitivity to cis-DDP, especially VK2 clone.

We can conclude that there is a great variety in cross-resistance pattern of human MDR lines. The basis for this diversity is not yet fully understood. It appears that factors such as tumor cell type, primary selection agent and resistance development schedule, method of assessment of cytotoxicity and variability in P-glycoprotein (in a paper published recently the diversity of cross-resistance profiles was found to depend on alternative splicing of *mdr1* gene product in different VCR resistant clones – 19) may all contribute to this subject. The finding that VCR resistant cells may (depending on resistance development schedule) exhibit cross-resistance to different anticancer drugs, which are not able to induce over-expression of P-glycoprotein, emphasize the complexity, difficulty and importance of judicious choice of agents that would be used in the combined therapy of tumors.

Acknowledgement

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References

1. Biedler JL, Chang TD, Meyers MB, Peterson RHF, Spengler BA. Drug resistance in Chinese hamster lung and mouse tumor cells. *Cancer Treat Rep* 1983; **67:** 859–67.
2. Riordan JR, Deuchars K, Kartner N, Alon N, Trent JM, Ling V. Amplification of P glycoprotein genes in multidrug-resistant mammalian cell lines. *Nature* (London) 1985; **316:** 817–9.
3. Moscow JA, Cowan KH. Review. Multidrug resistance. *J Natl Cancer Inst* 1988; **80:** 14–20.
4. Osmak M. Molecular mechanisms of chemotherapeutic drug-resistance. A review. *Radiol Iugosl* 1990; **24:** 65–70.
5. Kaye SB. Multidrug resistance. *Oncology Today* 1990; **2:** 4–7.
6. Borst B. Genetic mechanisms of drug resistance. A review. *Acta Oncol.* 1991; **30:** 87–105.
7. Dietel M. What's new in cytostatic drug resistance and pathology. *Path Res Practl* 991; **187:** 892–905.
8. Beck WT, Danks MK. Characteristics of multidrug resistance in human tumor cells. In: I. B. Roninson, ed., Molecular and Cellular Biology of Multidrug Resistance in Tumor Cells, 1991, Plenum Publishing Corporation, 3–55.
9. Melera PW, Biedler JL. Molecular and cytogenetic analysis of multidrug resistance associated gene amplification in Chinese hamster, mouse sarcoma, and human neuroblastoma cells. In: I. B. Roninson, ed., Molecular and Cellular Biology of Multidrug Resistance in Tumor Cells, 1991, Plenum Publishing Corporation, 117-45.
10. Osmak M. Collateral resistance or sensitivity of human larynx carcinoma HEp2 cells resistant to cis-dichlorodiammineplatinum(II) or vincristine sulfate. *Neoplasma* 1992; **39:** 197–202.
11. Mickisch G, Fajta S, Keilhauer G, Schlick E, Tschada R, Alken P. Chemosensitivity testing of primary human renal cell carcinoma by tetrazolium based microculture assay (MTT). *Urol Res* 1990; **18:** 131–6.
12. Mosmann T. Rapid colorimetric assay for cellural growth and survival: application to proliferation and cytotoxicity assays. *J Immunol Methods* 1983; 65: 55–65.
13. Safa AR, Glover CJ, Sewell JL, Meyers MB, Biedler JL, Felsted RL. Identification of the multidrug-resistance related membrane glycoprotein as an acceptor for calcium channel blockers. *J Biol Chem.* 1987; **262:** 2166–70.
14. Tsuruo T, Iida H, Tsukagoshi S, Sakurai Y. Overcoming vincristine resistance in P388 leukemia in vivo and in vitro through enhanced cytotoxicity of vincristine and vinblastine by verapamil. *Cancer Res* 1981; **41:** 1967–72.
15. Tsuruo T, Iida H, Ohkochi E, Tsukagoshi S, Sakurai Y. Establishment and properties of vincristine-resistant humsan myclogenous leukemia K562. *Jpn J Cancer* (Gann) 1983; **74:** 751–8.
16. Center V, Beck WT Acquisition of multiple drug resistance by CCRF-CEM cells selected for different degrees of resistance to vincristine. *Cancer Treat Rep* 1984; **68:** 831–9.
17. Lemontt JF, Azzaria M, Gros P. Increased *mdr* gene expression and dereased drug accumulation in multidrug resistant human melanoma cells. *Cancer Res* 1988; **48:** 6348–53.
18. Bradly G, Naik M, Ling V. P-glycoprotein expression in multidrug-resistant human ovarian carcinoma cell lines. *Cancer Res* 1989; **49:** 2790–6.
19. Devine SE, Hussain A, Davide JP, Melera PW. Full lenhgt and alternatively spliced pgp 1 transcript in multidrug-resistant Chinese hamster lung cells. *J Biol Chem* 1991; **266:** 4545–55.

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Stability of complex compounds distinguished by different levels in tumorous vs. identical healthy tissues

Damir Huljev,[1] M. Džajo[2], K. Košutić[2], Z. Rajković-Huljev[3]

[1] *Središnji institut za tumore i slične bolesti, Laboratorij za eksperimentalnu kancerologiju, Zagreb*
[2] *Institut »Ruđer Bošković«, Laboratorij za nuklearnu kemiju i radioekologiju, Zagreb*
[3] *Bolnica za tuberkulozu pluća, Zagreb, Croatia*

Formation constants of metals (II) complexes with several amino acids, sugars and acids have been investigated by applying Schubert's method and using ^{65}Zn, ^{57}Co, $^{89,90}Sr$ and $^{55,59}Fe$ as the radioactive tracers. Experiments were performed at pH 7.8 which was adjusted by the additio of barbital buffered solution. Experiments were carried out at constant ionic strenght ($I = 0.16$), $T = 298$ K and all systems were 0.125 M NaCl. All the complex ions formed were of the 1:1 type. Formation constants (log Kf in brackets) were determined for: Zn-glycine (3.0), Zn-serine (3.3), Zn-aspartic acid (3.4), Zn-methionine (2.2), Zn-cysteine (3.3); Co-glycine (2.5), Co-serine (2.2), Co-aspartic acid (3.6), Co-acetic acid (0.9); Sr-glutamic acid (0.7), Sr-acetic acid (0.04), Sr-ascorbic acid (0.4), Sr-diethyl barbituric acid (0.5); Fe-glycine (3.8), Fe-glucose-I-phosphate (4.0), Fe-amino glucose (3.5), Fe-ascorbic acid (2.5), and Fe-acetic acid (2.2).

Key words: organometallic compounds neoplasms-analysis; radioactive tracers

Introduction

The capacity of amino acids, sugars and organic acids to form metal complexes is of theoretical and practical significance in understanding the biological action of these metal ions. Though there is considerable information about formation constants of metal complexes of amino acids[1,2] and sugars.[3] The physical chemistry of amino acid, sugar and organic acid compounds containing zinc, cobalt, strontium and iron has not been thoroughly investigated. Therefore, data on the formation of such componds, their stability and structure are of general interest.

Previously it has been shown how ion exchange reactions, in combination with radiotracers, can be used for measuring the dissociation constants of complex ions.[4,5]

Quantitative measurements of the stability of the complex ions formed between trace metals and the compounds involved in the tricarboxylic acid cycle are of fundamental importance for the elucidation of many biochemical problems.[4] Complex organometal compounds are molecules containing an organic and an inorganic component bound to a metal as the central atom. The organic part can be an amino acid, sugar,

Correspondence to: Dr. Damir Huljev, Central Institute for Tumors and Allied Diseases, Ilica 197, 41000 Zagreb, Croatia

UDC: 616-006.6-074:547.447

methyl group etc., the inorganic component is accounted for by chlorine, bromine, iodine and other atoms or ions, whereas the usual metal atoms are Fe, Co, Zn, Cu, Mg, Se, Pt, Pd, etc. A chelate is a metal complex in which one or more ligands (attached groups) are bound to the metal atom via 2 or more donor atoms.

A carrier-free radioactive element is one which does not have weighable or visible amounts of inactive isotopes of that element associated with it.

It is believed that many complex compounds and chelates may cause a malignant process in experimental animals. These compounds can also have an antitumorigenic activity.[6]

The cytostatic activity of complex compounds depends on the type of organic and inorganic ligands bound to the central metal atom, on the metal present in the complex as well as on the type of the treated tumor.

This investigation was concerned with the determination of the chemical stability of complex compounds – organic molecules bound to essential metal – present in the human body. Their level increases or decreases as the tumor disease progresses. It is still not clear if the development of such complex compounds is due to the tumorigenic process or, conversely, if the latter is due to the development of such complex compounds in the body. Tests have shown considerable differences between stability constants of complex compounds of the same metals with different ligands, and of the same ligands with different metals, the influence of the organic ligand functional groups being nevertheless dominant.[7]

Materials and methods

The synthetic organic cation exchanger, Dowex-50, was used particularly because its capacity is independent of pH over a wide pH range. The universal veronal buffer devised by Michaelis was employed. All reagents were analytical grade. Twelve reaction flasks were prepared according to the data listed in Table 1. Flask 1 contained no ion exchanger, NaCl or ligand and was used to determine radionuclide adsorption on glass. Flask 2 contained no exchanger or ligand, and was used to determine radionuclide adsorption on glass in the presence of Na^+ ions. Flask 3 contained no Na^+ ions or ligands, and served to determine the maximum percentage of radionuclide binding to the ion exchanger without the influence of Na^+ ions and the ligand. Flask 4 was used to determine the magnitude of radionuclide adsorption on the exchanger under the influence of Na^+ ions, and it therefore contained no ligand. The remaining flasks contained all the components, the ligand concentration having been progressively higher from flask 5 through 12. The data obtained in this way can be used to calculate the percentage of radionuclide binding to the ion exchanger (Dowex 50, Na^+ form) as influenced by increasing ligand concentrations. Such data and the listed formulae can be used for calculating the stability constants of the used and obtained complex compounds. As indicated in Table 1, specific quantities of different substances were added to each of the 12 Erlenmayer flasks with ground stoppers. The flasks were sealed with paraffin coated stoppers and mixed intensely for 1 hour on an electric shaker. When equilibrium was reached, 1 ml of solution was withdrawn from each flask and the radioactivity measured on a single-channel scintillation counter. This procedure provided data on radionuclide quantity in the reaction solution. By deducing this activity from the totally added activity (flask 2), radioactivity bound to the ion exchanger was obtained. A detailed explanation with diagrams and mathematical operations has already been presented.[3,8] By introducing the value for the radioactivity of the solution and of the ion exchanger into equation (a), the constant stability of the developed complex compounds can be calculated. The results obtained are reviewed in Table 2.

Results

Formation constants (1/stability constants) K_f were calculated from the equation:

$$K_f = (Kd°/Kd) - 1/(A)^n \qquad (a)$$

where Kd° and Kd are distribution coefficients obtained in the absence and presence, respectively, of the ligand A, and n is the number of moles of A relative to the metal ion M. The distribution coefficient for the cation M is defined as:

Kd = (% M in exchanger) × (volume of solution-ml)/(% M in solution) × (mass of exchanger-mg)

the term Kd° can be obtained directly or from Kd by graphical or analytical means. It is convenient to plot 1/Kd versus $(A)^n$ and to extrapolate the straight line for proper n values to zero concentration of A, as indicated by the relation:

$$1/Kd = 1/Kd° + (A^n) \times Kf/\ Kd°$$

Equation(a) can be rewritten:

$$\log(Kd°/Kd–1) = n \log(A) + \log Kf$$

Table 1. Components of Erlenmayer flasks in the determination of stability complex compounds

Flask	Dowex-50 (Na^+-form) mg	Radionuclide (carrier-free) ml	0.125 MNaCl ml	Ligands ml	Distilled water ml
1	/	10	/	/	90
2	/	10	80	/	10
3	100	10	/	/	90
4	100	10	80	/	10
5	100	10	89	1	0
6	100	10	88	2	0
7	100	10	87	3	0
8	100	10	85	5	0
9	100	10	82	8	0
10	100	10	78	12	0
11	100	10	65	25	0
12	100	10	50	40	0

Table 2. Formation (1/stability) constants of complex Zn, Co, Sr and Fe compounds

Organic compounds (ligands), L	Metals M	Formation (1/stability) constants, Kf log Kf	Metal : ligand M : L
glycine (gly)	Zn	3.0	1 : 1
serine (ser)	Zn	3.3	1 : 1
aspartic acid (asp)	Zn	3.4	1 : 1
methionine (met)	Zn	2.2	1 : 1
cysteine (cySH)	Zn	3.3	1 : 1
acetic acid (aca)	Co	0.9	1 : 1
gly	Co	2.5	1 : 1
asp	Co	3.6	1 : 1
ser	Co	2.2	1 : 1
glutamin acid (glu)	Sr	0.7	1 : 1
aca	Sr	0.04	1 : 1
ascorbic acid (asa)	Sr	0.4	1 : 1
diethylbarbituric acid	Sr	0.5	1 : 1
gly	Fe	3.8	1 : 1
glucose-l-phosphate	Fe	4.0	1 : 1
amino glucose	Fe	3.5	1 : 1
asa	Fe	2.5	1 : 1
aca	Fe	2.2	1 : 1

A plot of log (Kd°/Kd–1) versus log (A) should be straight with slope n. The value of log Kf is the intercept of the straight line. Plots of 1/Kd vs. (A) were linear, indicating that all the complexes were of the 1:1 type, i. e. n = 1.

The results are summarized in Table 2.

Discussion

The Schubert method can also be used to determine the stability of inorganic complex compounds which also play an important role in cell and tissue composition.

All the tests are run at constant temperature, ion strength and pH values, because these factors influence the stability constants of complex ions.[5] As shown by Table 2, the Zn and Fe complexes are the most stable, followed by Co; the Sr complex is the least stable, which conforms to the data reported in the listed references.

The results of our experiments show the stability constants of the tested compounds to be fairly high, meaning that these molecules are permanent components of the cells and tissues of living beings and humans.

The determination of the stability constant of complex organic and inorganic compounds is of a manyfold importance. It is well known that compounds displaying a higher stability constant in the physiological medium are generally more stable and have a longer biological half-life. Such determinations have become even more important after the discovery that many complex compounds may cause certain disturbances, malignant processes included, in the body. Some complex compounds have also been found to possess an antitumorigenic activity.[6] All this has very much enhanced the interest in synthesis of many complex compounds and in the measurement of their stability in physiological circumstances.

Conclusions

The following conditions must be fulfilled for the method described:

a. 1. Formation of anionic or neutral complexes which do not exchange on the cation exchanger.

2. Use of a very low concentration of metal ions (Amersham) less than 10^{-8}M.

3. Use of an excess concentration of the ligands (amino acids, sugars and acids).

4. Measurements made at high and constant ion strength.

5. No significant interaction between metals (Zn, Co, Sr and Fe) and the buffer components.

6. Most of the metal ions were bound to the resin.

7. Adsorption of a complex ion on the ion exchanger was not significant.

b. Radioactivity was measured by a 3×3 inch NaI (Tl) well type crystal, scintillation counter attached to an automatic present time counter (LKB compugama, gamma-tipe no. 1282-002).

c. Due to the high and constant ionic strength, it is possible that Zn, Co, Sr and Fe have to *compete* with the excess of sodium ions in complex formation. For this reason the results for the stability constants are significantly lower than in literature.

d. Relative errors: range (2–10%).

References

1. Sillen LG, Martell AE. *Stability constants of metal ion complexes.* The Chemical Society, Special publication, No. 17, 1964.

2. Sillen LG, Martell AE. *Stability constants of metal ion complexes.* The Chemical Society, Special publication, No. 25, 1971.

3. Huljev D, Džajo M, Kristić N, Strohal P. The interaction of mercury(II) ions with sugars and amino acids. *Intern J Environ Anal Chem* 1983; **15:** 53–9.

4. Schubert J, Lindenbaum A. Complexes of calcium with citric acid and tricarballylic acids measured by ion exchange. *Nature* 1950; **166:** 913–4.

5. Schubert J. Complexes of alkaline earth cations including radium with amino acids and related compounds. *J Amer Chem Soc* 1954; **76:** 3442–4.

6. Das M, Livingstone SE. Cytotoxic action of some transition metal chelates of Schiff bases derived from s-methyl-dithiocarbazate. *Br J Cancer* 1978; **37:** 466–9.

7. Pauling L. Metal-metal bond lengths in complexes of transition metals. *Proc Nat Acad Sci USA* 1976; **73:** 4390–3.

8. Huljev D, Spaventi Š, Strohal P, Maričić Ž. Izračunavanje konstanti stabilnosti helata metodom radiotrasera. *Radiol Iugosl 1971;* **5:** 201–6.

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Personnel exposure to radiation at biliary interventional radiological procedures with an overhead tube

András Kónya and Z. Vigváry

Department of Radiology, Semmelweis University of Medicine, Budapest, Hungary

Personnel exposure to radiation was investigated during percutaneous biliary interventions (PTBD). In this study TLDs were used for each of the following sites: radiologist's eyes, thyroid, hands and assisting nurse's hand and thyroid without shielding apron, as well as radiologist's gonads under the apron. Dose during 6 PTBD sessions (68 min.) was measured by TLDs; from these data the dose/min values relevant to the given regions were calculated. In the course of 9 months during 69 interventions performed by the same staff, the fluoroscopy time necessary for the manipulation was measured, so the dose x time products relevant to the different regions could be determined. The radiologist's dose/min values were 0.17, 0.28, 0.092, 0.057 mGys/min to the right hand, left hand, thyroid and forehead, respectively, during PTBD sessions. The relative values expressing the relationship between the absorbed doses of the unprotected regions and the gonad dose measured under the shielding apron were the following: 172, 281, 91, 56 to the radiologist's right hand, left hand, thyroid and forehead, respectively. The overhead position of the X-ray tube is radiohygienically rather unfavourable and therefore it should not be used as a regular tool in interventional radiology.

Key words: biliary tract diseases, interventional radiology; radiation dosage

Introduction

At the majority of interventional radiological procedures the lengthy fluoroscopy necessary for the required manipulations exposes the personnel to considerable radiation. The more important portion of the radiation exposure is not the whole body dose measured under the protective apron but irradiation of the unprotected parts of the body (arms, hands, head and neck). During the last one and a half decade it has been a matter of debate whether the radiation dose suffered by such personnel could be adequately monitored by a single filmdosemeter, and if one employs a single dosemeter, where should it be worn, dosemeters under or above the apron are more suitable for the evaluation of the received radiation dose with respect to the differences in maximal yearly acceptable doses of different body areas.[1]

In the case of interventional radiologists the under the apron received doses are numerically reported above the value of 0.4 mGy, but in such cases in the unprotected regions very significant doses go unregistered.[1] As for the determination of the maximal yearly permissi-

Correspondence to: András Kónya, MD, PhD, Department of Radiology, Semmelweis University of Medicine, H-1082 Üllői ut 78/a, Budapest, Hungary.

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ble dose the most exposed and most sensitive parts of the body (lens, thyroid, hands) should be taken into consideration, absorbed radiation doses of the different regions of the body should be determined separately, because the radiation field is not uniform, and therefore, exposures incurred by different portions of the body cannot be even approximatively estimated from the whole body absorbed dose measurements.[2–4]

Our studies were designed to estimate the exposure incurred by certain, significantly exposed body portions of the radiologist and the assisting nurse during percutaneous biliary interventions. For dose determinations we employed thermoluminescent dosemeters (TLD). Radiation burden of the two-men team during 9 months of study period (69 interventions) was determined as the product of fluoroscopy time and doses-output, with regard to different parts of the examiners bodies.

Materials and methods

We monitored absorbed doses of the personnel (above all of the radiologist) during percutaneous biliary interventions. Detailed data are given in Table 1. The TLD dosemeters were prepared either in the form of a disc or a capsule on a ring, attached to the proximal phalanx of the third finger of the radiologist's right and left hands, his collar, outside the apron, to the centre of his forehead and at the level of gonads, under the apron. The assisting nurse was provided with only two TLDs, one on the third finger of her hand proximal to the tube, another on the collar, outside the apron.

From these data we calculated the dose/min values relevant to the given regions (Table 2).

As all the procedures were performed by the same person (A. K.), who is an interventional radiologist with 12 years' experience, the required time was not influenced by interpersonal variations of skill, experience or technique.

Interventions were performed with an overhead x-ray tube and undercouch image intensifier (Siemens Biangulix 125/12/50 tube, focus diameter 1.3. mm, with 4 mm aluminium filtration, Tridoros 5S basic equipment with dose automatics). The measured doses were solely due to fluoroscopy as manual contrast injection was never performed in the course of these interventions.

Dosimetry was realized through the thermoluminescent method (TL). The small LiF tablets could be located on different body areas of the radiologist or the technician without hindering the execution of the interventions. The received doses were determined by a comparative method. Tablets used for the interventions were compared to other ones which received known doses from a reference irradiation source (Co-60), according to the following formula:

Table 1. Percutaneous biliary interventions

Patient	Radiation field (cm)	Body diameter (cm)	kV	mA	Focus – film distance (cm)	Fluoroscopy time (min)	Intervention
1.	10 × 12.5	14	95	4	90	14	PTBD internal drainage
2.	10 × 12.5	21	110	5.5	90	17	transformation of external drainage into internal drainage
2/a.	10 × 12.5	21	110	5.5	90	10	endoprosthesis implantation
3.	10 × 12	22	110	6	90	3	control PTBD
1/a.	10 × 12.5	14	95	4	90	11	control PTBD with adjustment of drain
2/b.	10 × 12.5	21	110	5.5	90	13	control PTBD, external drain removal, its tract embolization
Total:	6 sessions/3 patients					68 minutes	

$$D_i = \frac{D_R}{T_R} T_i ,$$

where D_R: reference dose,
D_i: unknown dose,
T_R: emitted light intensity of reference tablets, and
T_i: emitted light intensity of tablets irradiated with unknown dose.

Under 200 keV the TL materials' sensitivity increases, so that at lower energy levels the same dose elicits greater signal than above 200 keV. This effect of sensitivity increased in the x-ray zone was taken into account as a 35% increase of absorbed doses.

Results

Absorbed doses in different regions of the radiologist are presented in Table 2.

For the radiologist, the registered doses were the highest on both hands (19.2 mGy and 11.8 mGy respectively). These high doses can be explained by the very unfavourable radiohygienic conditions of the percutaneous biliary interventions: the radiologist has to work in the immediate neighbourhood of the primary x-ray beam. That is why both his left hand, holding the needle, and his right hand, manipulating the catheter, are exposed to very high doses of scattered radiation. The overhead position of the x-ray tube is radiohygienically rather unfavourable which only multiplies these disadvantages.

As the assisting nurse is positioned at a certain distance (usually 1–1.5 m) from the x-ray tube, she can be regarded as being in a homogeneous radiation field. The doses measured on the hand proximal to the tube and on the jugulum were practically identical (0.028 and 0.027 mGy/min).

Since the assistant is standing further away from the x-ray tube than the radiologist, and as the dose of radiation decreases by the second power to the distance, she receives significantly lower doses.

The absorbent capacity of the protective apron, i.e. its actual radioprotective effect can be estimated from the differences in radiation

Table 2. Dose-values in different regions measured with TLDs (mGy). Percutaneous biliary interventions (fluoroscopy time: 68′)

	Radiologist		Assisting nurse	
	measured dose	dose/time	measured dose	dose/time
R. hand 3rd finger	11.8	10.4 mGy/h = 0.17 mGy/min	—	—
L. hand 3rd finger	19.2	16.9 mGy/h = 0.28 mGy/min	1.9	1.7 mGy/h = 0.028 mGy/min
Gonad (under the apron)	0.068	60.0 μGy/h = 1.0 μGy/min	—	—
Jugulum	6.2	5.5 mGy/h = 0.092 mGy/min	1.8	1.6 mGy/h = 0.027 mGy/min
Forehead	3.9	3.4 mGy/h = 0.057 mGy/min	—	—

Table 3. Radiation exposures of different body portions of the radiologist expressed in relative values compared to the corresponding gonad doses

	R. hand	L. hand	Jugulum	Forehead	Gonad (under the apron, 0.5 mm Pb equivalent)	Absolute value of the dose output
Percutaneous biliary interventions	172	281	91	56	1	1.0 μGy/min

exposure between the covered and uncovered areas; the data are detailed in Table 3. Considering these data, one has to take into account that the differences are to be ascribed not only to the apron's radioabsorption, but also to the differences in distances from the x-ray tube. Hand doses increase in proportion with gonad during the biliary interventions. If we take into account that doses registered with a film dosemeter, under the apron, at the heart level do not significantly differ from gonad doses, we can conclude that the radiologist receives unregistered irradiation in doses approximately by two orders of magnitude higher (*at least 100 times higher!*) than the values inferred from the evaluation of the dosemeter-film.

The data on radiation exposures of certain unprotected body areas of the radiologist during biliary interventions are especially important (Table 4). For the evaluation of these data it is worth mentioning that the same radiologist during the preceeding twelve years has performed several thousands of selective catheterizations and has a personal series of about two hundred percutaneous biliary interventions. This extensive experience excludes the possible counterargument that the long fluoroscopy-times could be explained by the lack of appropriate experience. It can be read from the table that one intervention consisted of four sessions on average, and a single sessions's average duration was 13.3 minutes. Fluoroscopy time in one patient ranged between 12 and 156 minutes (average 51 min). It is evident that in technically complicated obstructions and stenoses fluoroscopy took much longer than the average (e.g. multiple stenoses treated by double drainage or endoprostheses). It can be seen from these data that the radiologist exhausted more than half of his yearly dose equivalent limit of his left hand (259.16 mGy) and more than one third of the same for his lens (52.11 mGy) (500 mGy and 150 mGy, respectively).[2,3]

These great doses were received during interventions performed in only 18 patients!

Discussion

As most of the procedures of interventional radiology can be performed only under fluoroscopic guidance this results in a significant increase in radiation burden of both the patient,

Table 4. Calculated radiation exposures in percutaneous biliary drainages

Patient (n = 18)	No. of sessions	Total fluoroscopy time (min.)	Type of intervention	Exposures of the radiologist (mGy) r. hand	l. hand	jugulum	forehead
1.	2	22	internal drainage	3.74	6.16	2.02	1.25
2.	4	29	endoprosthesis	4.93	8.12	2.67	1.65
3.	3	41	internal drainage	6.97	11.48	3.77	2.34
4.	3	62	double drainage	10.54	17.36	5.70	3.53
5.	2	28	external drainage	4.76	7.84	2.58	1.59
6.	15	156	double prosthesis	26.52	43.68	14.35	7.98
7.	1	17	external drainage	2.89	4.76	1.56	0.97
8.	7	150	external drainage	25.50	42.00	13.80	7.25
9.	1	36	external drainage	6.12	10.08	3.32	1.95
10.	7	71	prosthesis + drainage	12.07	19.07	6.53	4.05
11.	3	38	internal drainage	6.46	10.64	3.50	2.07
12.	3	20	internal drainage	3.40	5.60	1.84	1.14
13.	1	12	extermal drainage	2.04	3.36	1.93	0.68
14.	4	34	double drainage	5.78	9.52	3.13	1.94
15.	5	75	endoprosthesis	12.75	21.00	6.20	4.27
16.	3	41	endoprosthesis	6.97	11.48	3.77	2.34
17.	1	22	external drainage	3.74	6.16	2.02	1.25
18.	4	59	endoprosthesis	10.03	16.52	5.43	3.36
Total 18	69	919 min.		158.99	259.16	84.27	52.11

and the personnel, with all its inherent risks. One has to take into consideration that body portions not protected by the apron, e.g. hands and arms, and the head and neck region are exposed unprotected to the scattered radiation. Thus 18% of the red marrow has no protection.[5] It is sure that as the radiation field is not humogenous, and the yearly limit of different regions' is not the same, the single film-dosemeter worn under the apron is not an adequate tool for the determination of actually received doses.[1,6]

Data in Table 5, with the exception of Cruikshank's results demonstrate radiation doses received during interventions with undercouch tubes.[7] Faulkner experimentally demonstrated, that if the radiologist is to be positioned in the close proximity of the patient, undercouch tubes are much more favourable, as the examiner's absorbed radiation dose is significantly lower than when the same interventions are performed with overhead tubes.[8]

Scattered radiation measured at the level of thorax and waist, in the immediate vicinity of the table can be reduced to at least one fourth and one sixth of the original value, respectively, simply by inverting the position of the x-ray tube and the image intensifier. In certain regions (e.g. the forehead and the lens) overhead position of the x-ray tube increases the scattered radiation level to 30 times that received with the undercouch position of the same tube.[9] These data explain why our irradiation doses so significantly exceed the similar (sometimes even with one or two orders of magnitude!) values published in the literature.

An important aggravating factor in the radiation burden is the old age of the equipment, as with our present tube adequate fluoroscopic images could be obtained only by an exceptionally high milliamperage (4–7 mA). The doseautomat prevented the manual reduction of these high values.

Drainage techniques, such as the percutaneous biliary drainage and the percutaneous nephrostomy ensuring free urine flow are especially unfavourable with regard to radiation protection, and therefore these interventions deserve special attention. During these interventions the radiologist is standing in the imme-

Table 5. Radiation doses incurred by different body portions of radiologists performing percutaneous drainages

Author	Intervention	Average fluoroscopy time (min.)	Doses (mGy) r. hand	l. hand	neck	forehead	Technical characteristics
Cruikshank 1980	PTC	1. 13.8	5.15 (0.373/min)				Overhead tube field: 100 cm^2
		2. 14.0	3.96 (0.295/min)				
Gustafsson 1981	PTC	35.0	1.5	4.0	0.11	0.12	Undercouch tube 70–90 kV, < 1.5 mA
	PTC	13.0	0.55	1.5	0.04	0.04	2.5 mm Al filtration field: 100 cm^2
LePage 1984	Endoprosthesis PTBD external/internal	35.0 11.68	25.0 8.35		1.7 0.57		No data
Geterud 1989	Nephrostomy Percutaneous stone extraction	11.6	0.34	0.63	0.13		Undercouch tube 70–90 kV, 1–3.6 mA 3.5 mm Al filtration
Kónya	PTBD (external)	36.0	6.12	10.08	3.32	1.95	Overhead tube 95–110 kV, 4–6 mA
	PTBD (external)	12.0	2.04	3.36	1.93	0.68	field: 125 cm^2 4 mm Al filtration

diate proximity of the patient, and thus also of the radiation source, while in the course of manipulation his hands are quite close to the primary beam of radiation. These interventions are rather time-consuming and require quite complicated manipulation, so the absorbed dose from fluoroscopy is considerably high.

Cruikshank reports on doses received during interventions with overhead x-ray tubes.[7] As our data were gathered under similar circumstances, our results are in accordance with the aforementioned data of Cruikshank. It is rather conspicuous that with the more optimal under-couch position of x-ray tubes the doses in the various regions significantly decreased, although the fluoroscopy times did not differ significantly.

Compared to the data of Gustafsson, our doses measured on the right and left hands were 2.5 and 4 times higher, respectively.[9] The same ratio was strikingly higher for the neck and head (forehead) region; 30–48 and 16–17, respectively. These data support Hoffman's above cited data, according to which the overhead positioning of the x-ray tube can multiply the lens-dose even by a factor of 30.[10] LePage reported exceedingly high doses for the right hand.[11] Presumably these results are to be ascribed to the fact that the radiologist had to manipulate even in the primary beam as he performed the biliary drainages from an epigastrial approach.

Based on the above published radiation doses and on the literature the following conclusions can be drawn:

1. *The problem of personal dosimetry of full-time interventional radiologists has not been solved as yet.* Film dosemeters worn under the apron do not correctly inform us about the radiologist's and the assisting nurse's real exposure, since at the same time the doses received by different regions with various radiosensitivity remain unknown. Buchen found the attenuation factor of the protective apron to be 0.04–0.005, or, in other words, areas left unprotected receive 25–200 times higher doses than the areas under the apron. These data are clearly supported by our own observations.[1]

2. *Equipment with overhead x-ray tubes is undoubtedly obsolete and from the viewpoint of radiation protection does not fulfil even the minimal requirements, so these devices should not be used as regular tool in interventional radiology.* We strongly disapprove of such practices. Especially strong is our disapproval in such cases where special techniques are employed, e.g. drainages (PTBD, percutaneous nephrostomy), as in these situations the radiologist is positioned in the close vicinity of the tube and the primary beam, and has to manipulate in this area.

Today the advantages of interventional radiology are indisputable, and one can anticipate that progress in this direction will continue. Personnel has to answer the challenges of ever-growing demands, so the health risks of the increased x-ray exposure should be minimized (using pulse generator, image manipulations, individual protective devices). An important prerequisite of this is the use of reliable local, personal dosemeters.

References

1. BIR. Recommended position for wearing of personal dosemeters. Statement of the British Institute of Radiology *Brit J Radiol* 1988; **61:** 349–50.
2. ICPR. Recommendations of the International Comission on Radiological Protection (ICPR Publication 26) Annals of the ICPR 1977; Vol. 1, No. 3.
3. ICPR. Statement and recommendations of the 1980 Brighton Meeting of the ICPR. Annals of the ICPR 1980; Vol. 4, No. 3/4.
4. NCPR. National Council on Radiation Protection and Measurements: basic radiation protection criteria. NCPR. 1971; Report No. 39, Washington.
5. Riley RC, Birks JW, Palacios E, Templeton AW. Exposure of radiologists during special procedures. *Radiology* 1972; **104:** 679–83.
6. Law J. Doses to head and arms of radiologists during fluoroscopy (Short communication) *Brit J Radiol* 1985; **58:** 187–8.
7. Cruikshank JG, Fraser GM, Law J. Finger doses received by radiologists during Chiba needle percutaneous cholangiography. *Brit J Radiol* 1980; **53:** 584–5.

8. Faulkner K, Moores BM. An assesment of the radiation dose received by staff using fluoroscopic equipment. *Brit J Radiol* 1982; **55:** 272–6.

9. Gustaffson M, Lunderquist A. Personnel exposure to radiation at some angiographic procedures. *Radiology* 1981; **140:** 807–11.

10. Hoffman JR, Staiger JW, Wollan RO et al. The Minnesota Special procedure room. *Radiology* 1971; **98:** 551–9.

11. LePage JR. Failures, complications and interventionalist radiation exposures in 108 cases of attempted biliary endoprostheses. *Ann Radiol* 1984; **27**(4): 366–70.

Radiol Oncol 1992; 26: 157-64.

Nuclear medicine in Macedonia – A continous adaptation to the challenge of medical practice

Isak Tadžer

Macedonian Academy of Science and Arts

The development of nuclear medicine (NM) in Macedonia started in 1955 after the writer of this paper as a fellow of the WHO visited Russel Fraser' Department of endocrinology at the Postgraduate medical School, Hammersmith Hospital, London. I-131 thyroid uptake was assessed there in a small closet. This gave the idea to measure uptake in goitrous patients in Macedonia particulary originating in the western parts where the endemic rate of goiter was up to 80%. Figure 1 shows the first G.M. set (Philips) in use till now.

The beginnings of NM as a convergence of many other scientific disciplines with those of medicine, as an interdependence of basic sciences, medicine and technology[8] could not be continued on an amateur basis. The Federal authority for Nuclear energy (SKNE) provided the necessary basis for professional application of NM. A special commission at this authority provided educational and financial help. After the constitution of national (republican) laboratories for NM (1959) regular work started. In the first period, problems of NM per se and safety control were a joint establishment. Very soon safety was separated as an independent entity belonging to the authority of Health and Welfare in Macedonia.

Key words: nuclear medicine-trends; Macedonia

Radiation protection

In 1966 the department of radiation protection started with regular monitoring of radioactive emitters in the environment, in atmospheric aerosols, polution of drinking water, rainfall, milk, foodstuffs, periodical measurements of water resources in rivers and lakes. In 1977 and 1986 monitoring of the ecosystem was upgraded using a 8192-channel semiconductor system (PC-AT IMB, 16-MHz-processor). The detection of H-3 and C-14, cosmogenic and from reactor (nuclear) was included. At the Veterinarian Institute where measurement facilities were installed about at the same time the research was focused on imported food and ecological problems.

Correspondence to: Prof. dr. Tadžer Isak, Macedonian Academy of Science and Arts, Bul. Krste Misirkov br. 2, pošt. fah 428, 91000 Skopje, Macedonia.

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NM in Macedonia

The Central laboratory for NM started regular thyroid uptake studies and PBI-131/D/L in 1959.

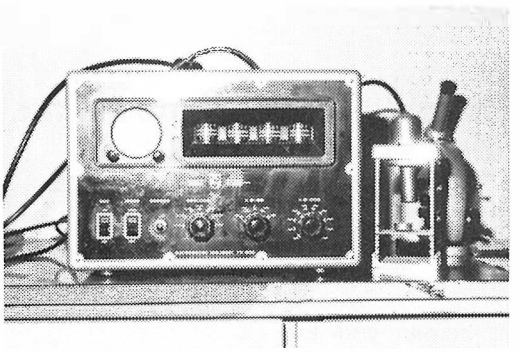

Figure 1. G.M. SET "PHILIPS" since 1956.

In 1980 a radionuclide laboratory was organized at the Military Hospital in Skopje in the new central building.

In 1983 a new laboratory was opened at the General Hospital "Dr. Trifun Panov" in the very south of Macedonia, in Bitolj.

The first nuclear medicine course (1984) in the laboratory of Skopje conveyed enthusiasm to many men and convinced them that future lies in this speciality. The principals of the laboratories in Skopje and Bitolj were among the first participants of those courses. (Figure 2).

The laboratory in Skopje was a real central laboratory providing NM diagnostics and treatment to the patients of the General Hospital in Skopje (1500 beds), in the out-patients clinics with a turnover (in some days) of 3000 patients coming from all parts of Macedonia (population about 2.2 mil.) and from the south parts of Serbia including the whole of the province Kosovo.

The use of RIA-programs and ELISA-techniques spread very fast in many clinics in independend units. The detection of hepatitis markers in vitro was transferred from our laboratory to the department of infectious diseases and to the central blood bank. Macedonia had in some years up to 6‰ of cases with A and B hepatitis and an uknown rate of non-A and non-B (HVC) and hepatitis D cases (Symposium on hepatitis, Macedonian Academy of Sciences, 1991). The search for hepatitis in the blood of donors became compulsory for the whole teritory of Macedonia employing *in vitro* RIA or ELISA tests.

Premises and equipment

In 1961 the new premises of the laboratory for NM financed by the Ministry of Health and Welfare of Macedonia and SKNE were ready. The funds for equipment (specific and general) were pending so we had to wait for investment. The earthquake in July 1963 which destroyed the city of Skopje damaged considerably the building. In 1965 the renovation was roughly completed. Most of the work was done in a hurry in unsatisfactory conditions due to extreme building difficulties experienced by the whole city (after the devastating earthquake) and other priorities in this renovation. The laboratory was transfered from the basement of the general hospital in to the nearby new laboratory (Figure 3, 4). The equippment remained incomplete, the funds were given for the purchase of a cobalt machine and accelerator for the Department of Oncology which badly needed this equipment (Figure 5).

Gradually the laboratory was equiped with cameras (a. processors). The staff is stil lobbying for advanced technology competing with our collegues who introduced CT and favoured the echotomographic explosion in allmost every department.

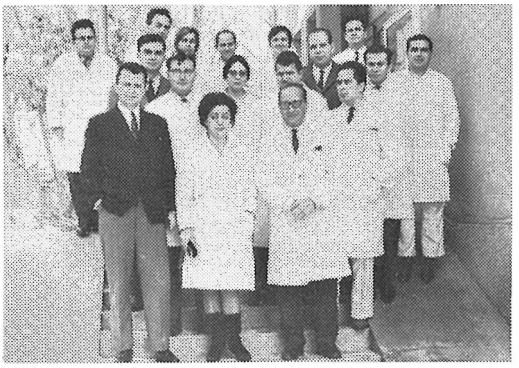

Figure 2. First course in Nuclear Medicine in Skopje 1968.

The first imaging device in late 1959 was a 4 cm G.M. lead cathode tube enclosed in a "pistole like" thick shield with a narrow cylindrical collimator (Figure 6). The instrument was produced by a commercial G.M. supplier for manual thyroid scans after a reasonable uptake of I-131 in the gland with the intent to make a plot of determined isoresponse settings of surface.

The next scanner in 1960 was designed and constructed by the Institute of Nuclear Sciences "Jožef Štefan" (Ljubljana) (Figure 7) as the first Yugoslav scanner. The NaI crystal of 1" was shielded for the use of higher photon energies (above 0.2 MeV). Thicker septa of the focussing collimator gave satisfactory I-131 thyroid scans. The first autonomic nodule was detected in Macedonia by this scanner. Autonomic thyroid nodule(s) belong to one of the typical thyroid deviations in an iodopenic environment (water supply in Macedonia has a content of 2-4 gama/L).[14] All parts of this scanner were constructed or assembled on an artisan basis. The chassis of a typewriter was employed to type analogue images. Thyroid scans were clinical useful. Adjustment for line spacing, spectrometer window setting, distance between the collimator and the patient were learned by experience.

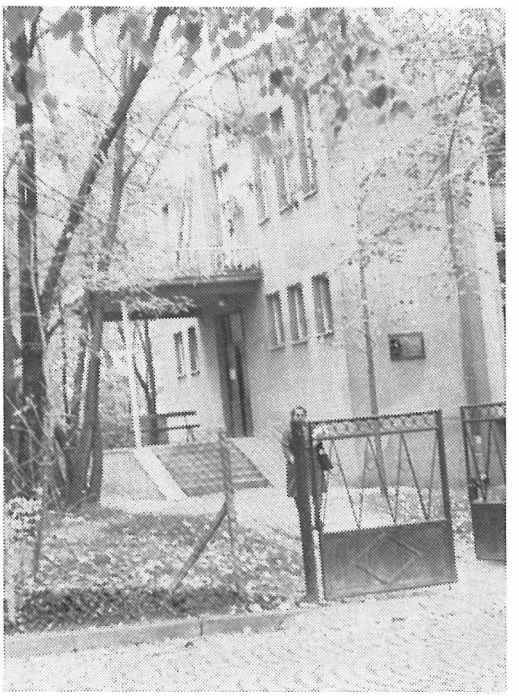

Figure 3. The new Isotope laboratory after renovation following the devastating earthquake in 1963 in Skopje.

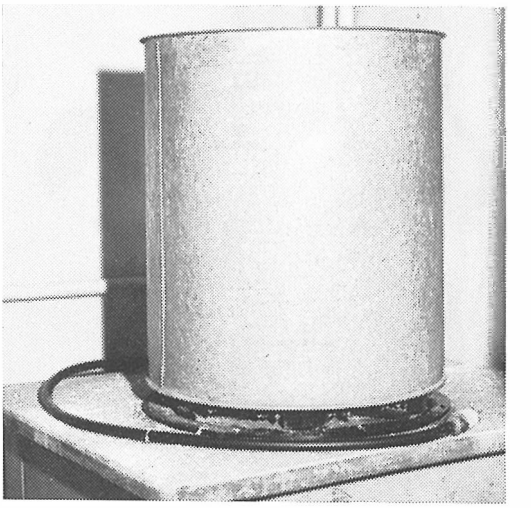

Figure 4. Specific equipment (old) in the new laboratory, RING counter: Twelve LEAD CATHODE G.M. tubes (24 cm) used for radioactivity measurements in feces and urine in 2-3 L beakers.

NM practice

The diagnostic procedures at the General Hospital during the first decades underwent an

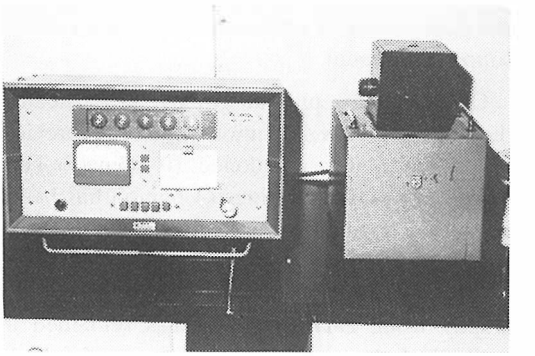

Figure 5. Gamma counter "wll type" EKCO.

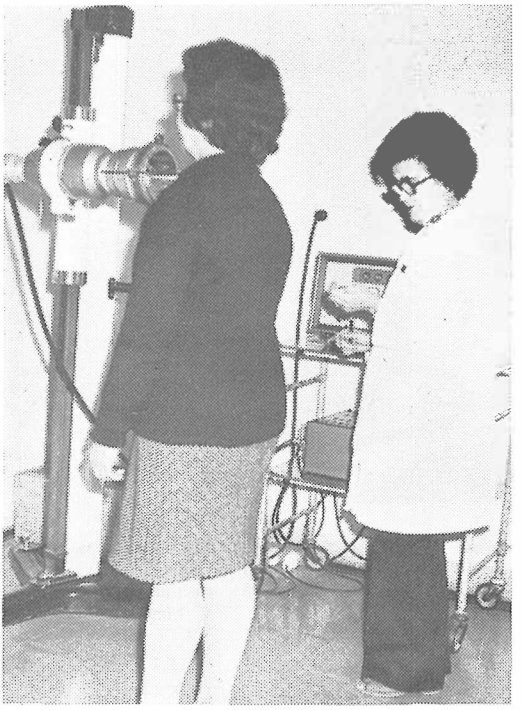

Figure 5a. Thyroid uptake set since 1962 with a home made collimator consisting of lead rings. Designed in the Institute of Nuclear sciences "Boris Kidrič" Vinča, Belgrade.

uninterrupted adaptation to the requirements of specialists and general practitioners. Table 1 shows the present state of some NM methods today. The previous importance of any particular method is arbitrarily considered as maximal (4 points). Placentography with In-113 m labeled RBC had been important (4 points) until the department of obstetrics acquired an ultrasound instrument.

Over 20 years placentography, in particular the radioisotopic exploration of placenta previa, has been totally abandoned (0 points). The number of brain scannings (4 points) has been decreased soon after the introduction of CT brain scan. Dynamic studies of the brain are done occasionally (1 point), whereas cysternography using DTPA-Tc-99 m has remained a method of choice in the evaluation and follow up of hydrocephalic children (4 points).

The application of radionuclides in hematology interested many clinical people. Ferrokinetic studies with Fe-59 were much used for the diagnosis of anemic patients. The myelopoiesis activity assessment using surface counting with one or several detectors was quietly replaced by RES skeletal Tc-99 m colloid studies; peripherisation of bone marrow activity is reserved only for myelofibrosis and patients with aplastic syndromes.

Blood volume studies with Cr-51 RBC or Tc-99 m-RBC have been done (about 10–15 yearly) exclusively for the diagnosis and follow up tests in patients suffering from polycythaemia. The interest for volume studies in surgical practice faded substantially although one of the inventors of simultaneous labeling of plasma volume and RBC volume is a member of the staff of NM.[6]

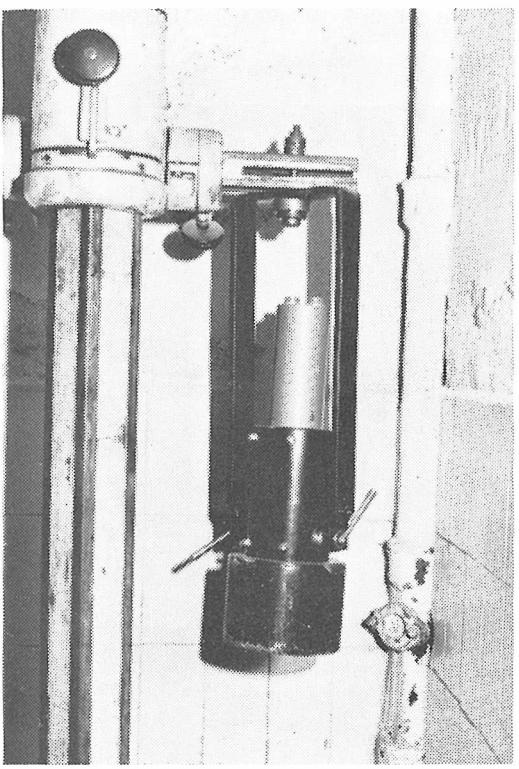

Figure 5b. Gamma probe with 2" crystal for surface counting in the extremities using Fe-59. The shielding is enforced by additional lead coating.

The determination of life span of Cr-51 RBC has been in steady demand. Macedonia is a well known endemic zone of Cooley's anemia.[3] The secondary hypersplenic destruction of RBC in homozygote cases with thalassaemia is regularly tested with Cr-51-autologous RBC; enhanced splenic activity leads to splenectomy. When splenic Cr-51 RBC trapping is enhanced in Minkovsky-Chauffard's disease, splenectomy is the method of choice.

Orthojod-hippurate-I-131 renography is still used in daily practice old gamma counter twin-set constructed in our laboratory from commercial parts examines the patients in supine position (Figure 8). OIH-I-131 is in-house prepared autoclaving radioiodine and OIH. This labeling procedure was introduced by copying the metod of Pinhas Czerniak's (Tel Hashomer Hospital, Israel, Tel-Aviv) in 1961. The rate of use is still

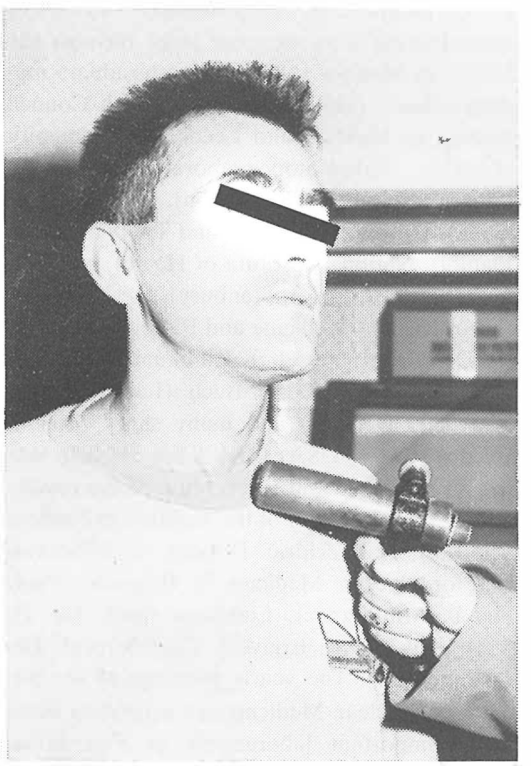

Figure 6. Manual lead cathode (4 cm) G. M. tube with lead shielding and cylindrical collimator for thyroid scanning.

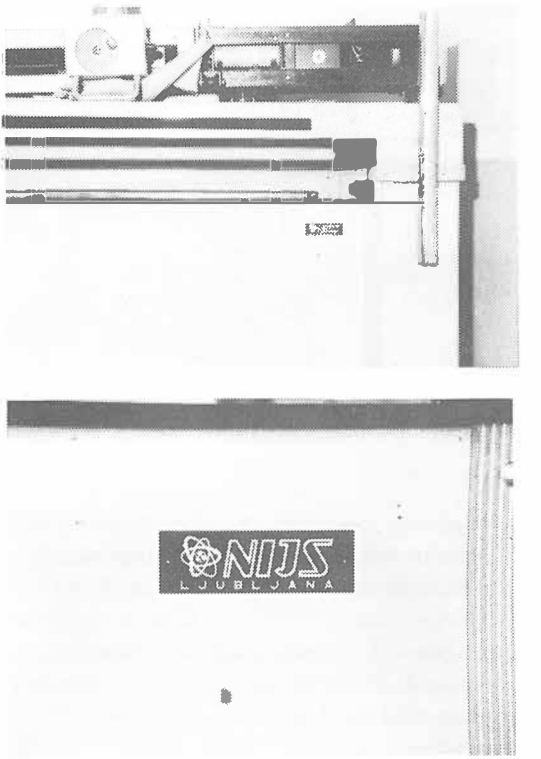

Figure 7. and 7-a: Rectilincar scanner, 1" crystal, designed and constructed in the Nuclear Institute "JOŽEF ŠTEFAN", Ljubljana.

maximal (4 points; Table 1). Probably cost/benefit is one of the important assets. The urologists prefer the screening information of separate kidney function.

Cost/benefit problems

The general economic situation of Macedonia imposed from the beginning austere introduction of NM in all phases of development. This led to "in house preparation" of many radiolabeled radiopharmaceuticals as OIH-I-131, Rose-Bengale-I-131 which was replaced also by internal preparation of Tc-99 m-sulfur colloid, Pyrrhophosphate-$SnCl_2$, DTPA-$SnCl_2$. Some N. M. labelings had an ephemeral use. The application of home-made labeled fibrinogen (I-131) for the detection of thromboses particularly in the lower extremities was introduced

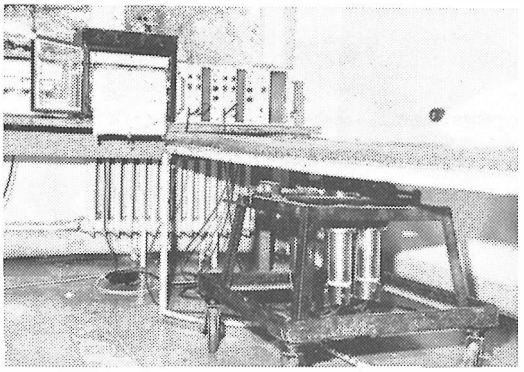

Figure 8. »Twin« gamma set for radiorenography in supine position using OIH-I-131.

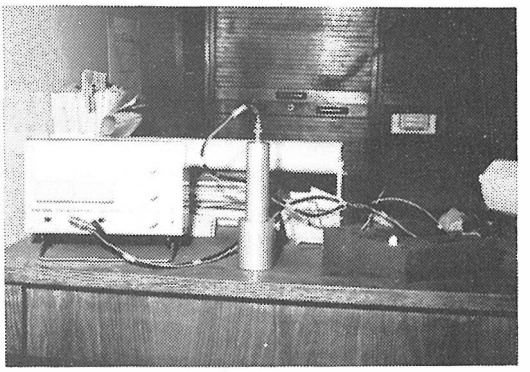

Figure 9. PITMAN (U. K.) manual battery gamma ratemeter for bedside body suface counting.

with great success,[4] but abandoned by surgeons in spite of fact that a portable gamma-detector was brought to the patient's bedside (Figure 9. PITMAN battery detector). Kladnik (Ljubljana) succeded to synthesize an iminodiacetic compound which we had used for biligraphic scaning until the Laboratory for Nuclear Pharmaceuticals, Institute "Boris Kidrič", Vinča, started commercial production. On the other hand, some elswhere obsolete and abandoned radio nuclide techniques are still in use because of the demand of the practitioners: detection of "Resturine" employing OIH-131, radiorenography even radionephrography with a fast moving rectilinear scanner.

The daily work on thyroid in vitro tests has increased to 80–100 tests. This forced the introduction of total thyroxin and trojodthyroninuptake assay in vitro by a domestic modification of Murphy's technique.[1]

Training in NM

Training of the staff was not the usual way of specialisation established by tradition and curriculum in other medical specialities. The nucleus of the assistance finished first a 4 month English course at the School for Foreign Languages, than began training at the School for application of radionuclides (Institute of Nuclear Sciences "Boris Kidrič", Vinča) where a basic course consisting of over 8 weeks of lectures and laboratory work acquainted physicians, biologists, veterinarians, physicists, chemists etc. with application of radioisotopes. For the first and following generations these courses were indispensable and very useful. At the same period parallel and complementary courses or specialisation were of great help: through the IAEA in Moscow ("Botkin" postgraduate medical school, prof. Modestov), British Council courses in Sheffeld and Leeds, Hammersmith –London, Radioisotopes laboratory at Bartholomew hospital (Dr. K. Britton), Ville-Juif (Tubiana), Hospital Pitie Paris and Tours (Therèse Planiol), National Institute of Health and Welfare (MIT, Boston, J. Stanbury), the Laboratories of Nuclear Medicine and Biology (Baltimore, Dr. H. Wagner, Jr.), Klinikum Berlin Steglitz (Dr. Oef), Berlin-Buch (Laboratory of prof. Dr. Deckart) and many short visits in Europe, SSSR, USA, CSR. Of great help was the informal and warm reception of the coworkers at the laboratory of the Institute of Nuclear Sciences, "Boris Kidrič" (Vinča), the Laboratories for Nucelar Medicine in Belgrade (Prof. Dr. P. Milutinović), Ljubljana (prof. Dr. B. Varl, prof. dr. M. Erjavec). Zagreb (prof. Dr. I. Šimunović). The yearly meetings of the Society of Nuclear Medicine on a rotating basis in all important laboratories in Yugoslavia, gave additional impetus for presentation of current results and achievements. There discussions and informal contacts at all levels provi-

Table 1. Rating of Requests for Radionuclide Procedures by Medical Practice in Macedonia (rating 0, 1, 2, 3, 4 points)

Diagnostic method and therepeutic application	Average daily work (1960–75)	Average daily work (1990/91)
II-131 thyroid uptake 24h	4	0-1
I-131 thyroid uptake 3–6h	4	0
PBI-131/DOSE/L	4	0
Tc-99 mm thyroid scanning	4	2
Thyroid echotomegraphy	0	4
Ferrokintic studies Fe-59	4	0
CR-51 RBC life span	3	2
OIH-I-131 radiorenography radiorenographic studies	0	4
DMSpTc-99 m renal scanning	0	4
Cardiac tests-Tc-99 m first pass and venticulographic studies	0	4
Tc-99 m polyphosphate bone and joint scanning	1	4
I-131 treatment of Graves' disease	4	2
I-131 treatment of toxic thyroid adenoma	3	3
Au-198-colloid treatment of pleural mesothelioma	4	1
Au-colloid treatment of peritoneal malignancies	4	0
Au-198-colloid treatment of chronic rheumatoid arthritis by synoviexeriesis	4	0
P-32 treatment of polycythemia primaria	3	4

ded the opportunity for getting acquainted with useful as well as futile methods in NM, which was essential in the view of vigurous, incessant changes of technology, electronics, radiopharmaceutics, dynamic and processing procedures and even scopes in NM.

Thus, systematic and incessant exchange of knowledge and experience was crucial at the very beginning and later on.

Expansion of NM

From its start in 1956 until nowadays the activity of the NM laboratory has been centred on the problems of NM routine considering the demands of the practice. Thyroid pathology initially representing about 90 % of the whole work, in use now involved 40–50 %, the next by the frequency of demand are bone scintigraphies and kidney studies (20–30 %) whereas the rest goes to cardiology, liver, cysternography, adrenal glands lymphography etc. (Table 1). On the other hand, part of the work could be classified as work in connection with some of the acute health problems in Macedonia: programmed thyroid studies in our typical iodopenic region: although since 1956 the federal law makes the iodination of salt compulsory (10 mgr KJ/1 kg NaCl) the water supply in all sources is under 4 gama/L. The consumption of salt decreased substantially, and some noniodinated salt is avaible in the rural regions and in the food industry. The typical expression of the thyroid pathology observed previously in iodine-deficient (former) West-Germany was confirmed in this region: autonomic toxic and nontoxis nodules, dysfunction of the thyroid after iodine contamination, familiarly iodopenic goiter in children living in isolated highland villages consuming only iodinefree salt,[9] palpable thyroid grade I in over 8 % of population.[7] The quest for scanning hydatid cysts in the liver disappeared because of the efficient erradication of the disease by the veterinary authority and, second, by the very efficient ultrasound visualisation of cysts.

Imaging of posthepatitic sequelae and non-aggressive flow studies are currently on the program imposed by the great number of patients with previous history of viral hepatitis.

NM at the University in Skopje

The staff is engaged in several curricula for undergraduate students at the School of Medicine, Dentistry and Pharmacology. Short presentations and educational courses for physicians undergoing training in different specialities are on the agenda. Education of medical technicians and biologists competing for Master's Degree are also included.

Close work with different departments of medicine and surgery brought to attention some previously unobserved phenomena which resulted in a number original papers: detection of Milroy's disease using labelled colloid,[10] iodine fractions influencing thyroid tests,[11] "hot nodule" turning cold during methimazole treatment,[12] labelling of platelets using acetyl acetone complexion of In-133 m.[13]

It is hardly possible to illustrate the merits and endeavours of all collagues who have helped, contributed and worked on the early development of NM in Macedonia.

Let me conclude by quoting G. C. Heveshy in his[5] Faraday Lecture given on March 29 1950, in Edinburgh: "The application of isotopic indicators in biology opened new lines of approach, not only to the solution of known problems, but also by directing our attention to trains of thoughts not considered previously..." perhaps this kind of thinking gave a particular stimulus for work in NM.

References

1. Aleksić Ž, Šestakov G. Kompetitivno odredivanje tiroksina RIA-metodom i kompetitivnom metodom, *Radiol Iugosl* 1978; **12**(2) 451-2.
2. Czerniak Pinhas – person. communic. (SHIBA hospital, Tel-Ashomer, Tel-Aviv, Israel/).
3. Efremov G. Huysman TA, Dimovski et al. Beta thalassaemia in Yugoslavia. *Hemoglobin* 1990; **4**(1) 15–20.
4. Georgievska B. Detekcija na dlabokite venski trombozi so radiofibrinogen. Medicinski fakultet, Univerzitet »Kiril i Metodij«, Skopje (Doktorska disertacija, 1979).
5. Heveshy GC. The Application of Radioactive Indicators in Biochemistry. *J Chemical Safety* 1951; 1918-39.
6. Korubin V, Brozović B, Lewis GM, Szur I. Simultaneous red cell and plasma volume determination by differential absorption method. *J Lab & Clin Med* 1966; **68:** 142-5.
7. Korubin-Dolgova V, Vandevska M et al. Rezidium endemske strume u Makedoniji. IV. Jugosl. Simpoz. o štitastoj žlezdi. Zlatibor, Zbornik radova 1980, 361-4.
8. Meyer W, Wagner Jr. Nuclear medicine – How it Began Hospital Practice book. Nuclear Medicine 1973: 1-14, Baltimore, John Hopkins University.
9. Simova N i sar. Pojava gušavosti kot dece usled jodnog deficita. IV. simpozium štitaste žlezde. Zbornik radova, Zlatibor 1980; 343-5.
10. Tadžer IS. A Simple Test for Milroy's Disease. Year book of Nuclear Medicine, Chicago, 1973; 159-60.
11. Tadžer IS, Šestakov G et al. Das Verhalten der Nicht als Jodid Vorliegende Radiojodfraktionen bei Isotopendiagnostik der Schilddrüse. Nuklear Medizin, verl. Schattauer, Stuttgart, 1975; **(6):** 411-6.
12. Tadžer IS, Simova N. "Hot" Nodule (autonomous nonproliferative) Turning Cold during Methimazole treatment. Proc. XIII Intern. Annual Meeting. Soc Nucl Med, Kopenhagen Proceedings ed. Fade Kopenhagen 1975; **168:** 1-4.
13. Tadžer IS. Označuvanje trombocita In-113 m i TC-99 m. *Radiol Iugosl* 1980; **14:** 240-1.
14. Tošev D i sar. Odreduvanje na sodržinata na jod vo pitkite vodi na Makedonija, trudovi 1970–1980 vo Godišen Zbornik na Prirodno-matematičkiot fakultet na Univerzitetot »Kiril in Metodij«. Skopje.

Radiol Oncol 1992; 26: 165-6.

The beginnings of radiology in Rijeka

Ivan Lovasić

Clinical Hospital Center Rijeka, Medical Faculty of Rijeka, Institute of Radiology, Croatia

The end of the 19th century represents a great progress for the city of Rijeka. The Holy Spirit Hospital achieved its autonomy and became a public health facility; sewage system, water mains and electrification were accomplished, building of schools and the theatre started, and many public libraries and various societies made their appearance during the last two decades.

The Natural Sciences Club, the members of which were physicians of Rijeka, teachers and other educated classes, as well as industrialists, wholesalers and proprietors, should be specially pointed out. Through the lectures held there, the public was informed about the most recent scientific and technical achievements in the world.

At that time, Military Naval Academy had the most selected teaching staff for the sons of archdukes, counts and ministers from Vienna and Budapest, who attended their lessons there. Among the teachers there was a man of high standing, Prof. Dr. Peter Salcher, Austrian by origin, born on August 10, 1848 in Kreuzin-Eben near Peternion, who was the president and vice-president of the Club several times.

Key words: radiology; Rijeka

Not a full month from Roentgen's lecture held at the session of Physico-Medical Society in Wuertzburg on January 23, 1896, precisely on February 20, 1896, Prof. Peter Salcher held a lecture in Rijeka on roentgen ray discovery and the first radiography was made.

On February 24, 1896, daily paper La Bilancia reported about Dr. Salcher's lecture held at the Club (nowadays Italian Secondary School in Rijeka). In the lecture the observation that the momentous significance of Roentgen's discovery was not only to make photos without light and lens, but to image body interior by means of x-rays was pointed out.

The light was replaced by electricity in this case and the word "electrography" or even better "roentgenography" should be more logically used instead of photography.

Afterwards, the lecturer carried out the following two experiments:

First, he conducted electric current from a galvanic battery via Rhumkorff's coil to Hittorf's tube, i.e. Crookes' tube. He placed a cassette with a sensitive photo plate on the table underneath, and asked one of the present ladies for her assistance in the historical "hand experiment". The greenish fluorescent light ap-

Correspondence to: prof. dr. I. Lovasić, Medical Faculty in Rijeka, Clinical Hospital Center Rijeka, Tome Strižića 3, 51000 Rijeka, Croatia.

UDC: 615.849

peared inside the tube and the "electrography" of the hand started.

In the second experiment the electric current was conducted for Crookes' tube from an influencing apparatus. Coins wrapped in paper and a cardboard box were under the tube. By the end of the lecture the photo plate had been developed. One of them revealed osseous structure of the hand skeleton with a ring shade on the finger. The coin shades and an oval plate with the inscription "Roentgen" could be seen on the other one.

Dr. Petar Salcher, the vice-president of the Club at that time, strove to establish the Committee for x-ray apparatus purchase. The elected Committee started to organize voluntary fund-raising campaign among the Club members and the apparatus was bought in Chemnitz in April 1897.

A proposal was submitted to the Municipal Council and an annual subvention in the amount of 300 florins was approved for wear and tear and maintenance expenses.

Demonstration of the apparatus, accompanied with a detailed lecture, took place on June 22, 1897. All the physicians from Rijeka, Opatija, Volosko and the Croatian coastal region were invited and 22 of them attended the presentation.

Another important date was November 17, 1899, when the roentgen apparatus was handed out by the Club and installed in the Holy Spirit Town Hospital. Namely, the Hospital suggested the Club to lend the apparatus to it against a certain fee, and the Club Committee made a hire contract for 50 florins annual compensation. Using its funds, the Committee took care of adaptations of the aparatus to electric current to avoid the use of battery-powered system. The apparatus was returned to Committee and Max Kohl was asked to perform the required modifications. Having been taken to Rijeka, it was assembled in Bacteriological laboratory of the aforementioned hospital together with manual for Dr. Izidor Garafolo.

Six years later, on November 10, 1908, the Hospital Council and the management asked the town authorities to approve a purchase of another apparatus, and the request was solved positively. Siemens-Halske firm from Budapest agreed to payment one year after delivery in the amount of 5,999.73 crowns, other expenses 1,291.52 crowns, totalling to 7,291.25 crowns.

Probably they had not been experienced in handling the machine, for the hospital management submitted the town authorities another request for the new apparatus on December 23, 1914, because the previous one was completely ruined, and by the opinion of technical experts irreparable.

According to ample documentation used by the authors of the book *"Ars aesculapii – supplements to the history of health culture in Rijeka and Croatian coast"*, my teacher and predecessor retired in 1985, longtime head of the Institute of Radiology in Rijeka and full time Professor at Medical Faculty Rijeka Dr. Marjan Matejčić and his wife Dr. Radmila Matejčić, full-time professor at Teacher-Training Faculty in Rijeka, whose work was used as the source of the presented historical review on the development of radiology in Rijeka, the following could be deduced:

Prof. Dr. Petar Salcher has been considered the first roentgenographer in Rijeka and Prof. Salvatore Bratanić and Milan Gorup the first roentgenological technicians, whereas Dr. Izidor Garafolo should be unofficially regarded as the first "radiologist" in Rijeka.

Naturally, the Committee president baron Juraj Vranyczany played very significant role in obtaining a roentgen apparatus for Rijeka among the first Central European towns already by the end of the 19th century when Wilhelm Conrad Roentgen discovered x-rays.

References

1. Matejčić M. Pokusi dra Petra Salchera s rendgenskim zrakama u Rijeci 1896. godine. *Medicina* 1974; 11–116.
2. Matejčić M. Pokusi dra Petra Salchera s rendgenskim zrakama u Rijeci 1896. godine i prvi rendgenski aparat u riječkoj bolnici »Sv. Duh«. In: Radmila i Marijan Matejčić: Ars Aesculapii – prilozi za povijest zdravstvene kulture Rijeke i Hrvatskog primorja. Rijeka, 1982; 117–33.

Radiol Oncol 1992; 26: 167-8.

The 6th postgraduate course on thoracic radiology

June 11-13, 1992, Salzburg, Austria

The course was organized by the Department of Radiology, John Hopkins University in Baltimore (Maryland, USA), and the Eberhard Karl University in Tuebingen (Germany), under the auspices of the European Society of Radiology.

Half the invited speakers were from the United States. The course took place in the Congress Centre and was attended by more than 500 participants. Thirty-minute lectures followed by a discussion were intended to present the main diagnostic methods used in the up-to-date radiology of the chest organs. The introductory lectures dealt with classical radiography in P-A and lateral projection, followed by CT, MR, radionuclide and interventional diagnostics and also by the evaluation of surgical treatment of lung and esophageal cancer.

When associated with good technique and correct interpretation, classical radiography in P-A and lateral projection is considered to be the basic examination providing a sufficiently good image of most pathology always when unnecessary exposure to X-rays should be avoided. As in children the presence of overt pathological processes in the shadow of the heart or mediastinum is less probable, lateral view imaging can be omited if the P-A radiogram is unsuspicious and there is no clinical symptoms requiring a lateral view.

As expected, most of the time and program was dedicated to CT. Technically improved HRCT (high resolution CT) enables imaging of 1-3 mm thick sections of the chest on which lesions 250-300 microns of size can be detected. Thus, pathological changes associated with diseases of the pulmonary interstice, bronchiectasies and emphysema can be detected and their clinical and laboratory properties explained even when the chest radiograms are normal. The authors claimed that, using this method, a fairly reliable differentiation between carcinomatous lymphangiosis, interstitial fibrosis and diffuse sarcoidosis is possible, which renders biopsy often unnecesary. Unfortunately, the precise CT images were mostly shown in correlation with histologic samples of the same changes, and not also with classical radiograms; being used to establishing most pathology from radiograms, we found this to be a considerable drawback. It has been easy to note the prevailing tendency to avoid biopsy and microscopic diagnosis by means of accurate CT findings, the approach which is in western countries apparently considered cheaper and simpler, whereas here it is just the opposite: with only 3 CT machines available for the whole Slovenia, it is often faster, more rational and also economical to perform a biopsy rather than waste time in waiting for CT. Perhaps, by purchase of new CT machines the situation will change also in our country.

A special lecture was dedicated to pulmonary changes in AIDS. Thus, such changes were established in as many as 60 % of AIDS patients. They appear as a result of pulmonary parenchyme infections (most frequently caused by *Pneumocystis carinii* and mycobacteria), lymph node conditions (reactive hyperplasias and lymphomas), neoplasms (Kaposi's sarcoma, metastases) as well as premature emphysema and changes associated with drug abuse. PCP *(Pneumocystis carinii pneumonia)* was found in more than 85 % of patients with AIDS, and is generally the first sign of the disease. In these cases CT is much more reliable than classical radiography which failed to evidence the disease in 5-10 %. The signs of premature aging seen in AIDS patients manifest themselves in cystic pulmonary changes which often lead to a spontaneous pneumothorax. Frequent exacerbations of tuberculosis and the consequences of pulmo-

nary embolisms result in additional pulmonary changes in patients with this disease.

As we expect to obtain magnetic resonance imaging (MR) facilities in Ljubljana next year, we found the comparison of CT and MR possibilities very interesting. Thus, in the determination of lung cancer stage, MR proved more accurate in the evaluation of soft tissue of the mediastinal organs such as large vessels, esophagus, pericardium and the external part of the tracheal bifurcation, whereas it showed no advantages over CT in the evaluation of mediastinal lymph node involvement. In the diagnosis of primary lung tumors both examinations have proved equally accurate although for the evaluation of hilar lymph nodes MR is more effective. Therefore, the latter investigation is indicated in Pancoast's tumors, suspicious hilar lymph nodes, unexplained involvement of the thoracic wall in peripheral tumors, and in the cases of enlarged suprarenal gland which are in two thirds due to benign changes. As to the evaluation of mediastinal lymph nodes, the following procedures are suggested: in nodes up to 1 cm of size – thoracotomy, and in nodes larger than 1 cm – mediastinoscopy, and provided that the site allows for it, transbronchial punction biopsy. In general, in the evaluation of mediastinal lymph nodes both CT and MR yield equal rate of sensitivity and specificity, i.e. they are successful in approximately 2/3 cases. Otherwise, 17 % of enlarged mediastinal lymph nodes are found to be free of metastases. A combination of CT and MR does not improve the diagnostic reliability in pulmonary carcinoma.

In congenital diseases of the lung, such as pulmonary sequestration, cysts, emphysema, arterio-venous malformations and scimitar syndrome, MR has some advantages over CT.

Central pulmonary carcinomas bleed more frequently from the bronchial arteries, whereas peripheral ones generally bleed from the pulmonary arteries. Hemophthysis can be stopped by the embolisation of a corresponding bronchial artery. The dilatation of collaterals from other arteries, which occurs after embolisation, generally does not lead to necrosis. Nevertheless, complications due to fistulae, as well as spinal ischemia with resulting neurological disorders and even embolisms of the aorta and lower extremities are also possible. Considering the small number of embolisations performed so far, this type of hemophthysis treatment certainly cannot be regarded as a part of routine therapy.

With the exception of perfusion and ventilation scintigraphy in the diagnosis of embolism or evaluation of pulmonary function, the presented radionuclide examinations of the lung and mediastinum, though interesting, are of no particular value for the selection of therapy. Among other things, they showed increased uptake of gallium-67 in non-small cell lung cancer – the pathophysiology of this entity has not been fully explained yet – (sensitivity 91 %), but not in small cell cancer!? In lymphomas gallium is supposed to be useful for the assessment of tumor vitality.

In the surgery for lung cancer, attention is paid to the thoracoscopic removal of smaller superficial tumors in patients with contraindications for thoracotomy.

The course proved useful so for the diagnostic radiologists as well as for clinicians. The former could follow the advances in CT and MR diagnostics, whereas the latter could find this knowledge helpful in selecting indications for individual investigations. We believe that by the access to new HRCT and MR units which will be available in the University Clinical Center in Ljubljana next year we shall get the opportunity to make use of the knowledge acquired at the course.

Prof. Miha Debevec MD, PhD.
Institute of Oncology
Ljubljana

Libri Oncologici
Croatian Journal of Oncology

It has been 20 years since Prof. Padovan and his coworkers established the journal "Libri Oncologici" in 1972 in Zagreb. The journal covered the territory of former Yugoslavia. Its publishers were the Central Institute for Tumors and Allied Diseases in Zagreb, Croatian League Against Cancer, Pharmaceutical Company "Pliva" Zagreb, and the Association of Yugoslav Cancerologists. The journal appeared quarterly and was managed by the Editorial Board and Prof. Predrag Keros, MD, as the editor-in-chief. There have been XX volumes published so far. The articles of both national and foreign authors covered all fields of experimental and clinical oncology and allied specialities.

After the Xth volume English has become the official language of the journal, so that papers could be published either in Croatian or English. By recent geopolitical changes having taken place in the territory of the former Yugoslavia, i.e. by 1992, the journal continued to appear under the same title of "Libri Oncologici", though with a new publisher: thus it has become the official journal of Croatian Oncologists (Croatian Journal of Oncology). On that occasion a new editorial board was selected and Prof. Dr. Krsto Kolarić was appointed the editor-in-chief. It has been agreed that the change calls for a new scientific scope of the journal to be defined and its graphic design changed in accordance with modern styles.

The editorial board will stick to its policy of covering the multimodal aspects of oncology, thus enabling the presence of both basic and clinical research in this field on an equal footing. Our further aim is to encompass new allied fields such as immunology, genetics, molecular biology, biochemistry and others, in order to give the most comprehensive overview of the trends in present oncological research. Another new line in the editorial policy is also to strive that a larger number of foreign authors would be attracted to collaborate in the journal, which would enable its promotion beyond the national borders in the neighbouring European countries. In order to help young perspective researchers to have their papers published without delay, the functioning of the editorial office will be organized so that the period from receipt of manuscript to its publication will not exceed 6–8 months, including the time needed for double peer review. Summarizing, the main objective of our journal is to promote a comprehensive and fruitful scientific collaboration at the international level.

The presented issue is therefore No. 1 of the XXIth volume of our journal with an up-to-dated contents and form. We leave it up to our readers to decide to what extents our new editorial policy will have been justified.

Prof. Krsto Kolarić, MD,
Editor-in-Chief of Libri Oncologici

Notices

Notices submitted for publication should contain a mailing address and phone number of a contact person or department.

Reconstruction in surgical oncology

The congress will take place in Genova, Italy, *December 3–5, 1992.*

Contact Congress Management Service, Italiana Congressi, Via Bensa, 2/6 – 16124 Genova, Italy; or call +39 10 202541 or 280924. Fax: +39 10 299382.

Breast cancer

The 15th Annual San Antonio symposium will be offered in Texas, USA, *December 9–10, 1992.*

Contact Cancer Therapy and Research Center, 4450 Medical Drive, San Antonio, TX 78229, USA.

Cell biology

The regular staff meetings at the Netherlands Cancer Institute will be offered in Amsterdam, The Netherlands, *December 14, 1992.*

Contact Ms. P. I. W. Sobels, The Netherlands Cancer Institute; or call +31 20 512 1970.

Nausea and vomiting

The seminar will be organised by European Cancer Centre and held in Amsterdam, The Netherlands, *December 15, 1992.*

Contact Robert van Bokhoven, IKA; or call +31 20 617 2903.

Immunology

The 5th annual meeting on the "Current Status and Future Directions of Immunoconjugates – Diagnostic and Therapeutic Applications in Benign and Malignant Disorders" will be offered in Key Biscayne, Florida, USA, *January 14–17, 1993.*

Contact Lidia Gutierrez, Division of Continuing Medical Education, University of Miami School of Medicine; or call +1 305 547 6716. Fax: +1 305 547 56 13.

Oncology

The 3th European winter oncology conference (E-WOC) will take place in Meribel, France, *January 23–29, 1993.*

Contact Federation of European Cancer Societies, University Hospital St. Rafael, Radiotherapy Department, Capucijnenvoer 35, 3000 Leuven, Belgium; or call +32 16 21-22-15. Fax: +32 16 21 22 41.

Anti-cancer chemotherapy

The 4th international congress will be held in Paris, France, *February 2–5, 1993.*

Contact Prof. David Khayat, 4th International Congress on Anti-cancer Chemotherapy, SOMPS-Hopital de la Pitie-Salpetriere, 47, Bd de l'Hopital, 75651 Paris Cedex 13-France.

Breast cancer

The EUSOMA consensus conference on screening methology and management of occult breast carcinomas will take place in Paris, France, *February 4–5, 1993.*

Contact EUSOMA secretariat, Piazza Tricolore 2, 20129 Milan, Italy; or call +39 2 780488. Fax: +39 2 781019.

Colorectal cancer

The conference "Towards Reducing the Incidence of Colorectal Cancer: The Role of Inheritance and Diet" will be offered in Auckland, New Zealand, *February 16–19, 1993.*

Contact Dr. L. R. Ferguson, Conference Convenor, Cancer Society, P O Box 1724, Auckland, New Zealand.

Oncology

The teaching course on "The importance of Oxygen and other Micro- environmental factors in clinical chemotherapy and radiotherapy of cancer" will be held in Los Gigantes, Tenerife, *February 22–24, 1993.*

Contact Dr. A. Villar Rodriguez, Manuel Garcia Calveras 27, 38008 Santa Cruz de Tenerife, Spain.

Supportive care in cancer

The 4th international symposium will take place in St Gallen, Switzerland, *February 24–27, 1993.*

Contact Mrs. Beatrice Nair, Conference Manager SUP-93, c/0 Prof. H. J. Senn, Dept Medicine C (Oncology), Kantonsspital, CH-9007 St Gallen, Switzerland. Fax: +41 71 256 805.

AIDS-related tumours

The ESO seminar will be held in Venice, Italy, *March 4–5, 1993.*

Contact European School of Oncology, Via Venezian, 18 20133 Milan, Italy; or call +39 2 70635923 or 2364283. Fax: +39 2 2664662.

Medical oncology

The ESO training course for the Balkans and Middle East will take place in Athens, Greece, *March 4–6, 1993.*

Contact European School of Oncology – Athens Office, 2 Adrianiu St. & Papada St., 11825 Athens, Greece; or call +30 1 6496 620. Fax: +30 1 6924 372.

Oncology

The ESO seminar "Minimal residual disease: detection and management" will take place in Venice, Italy, *March 26–27, 1993.*

Contact European School of Oncology, Via Venezian, 18 20133 Milan, Italy; or call +39 2 70635923 or 2364283. Fax: +39 2 2664662.

Brachyradiotherapy

The ESTRO teaching course will take place in Athens, Greece, *March 28 – April 1, 1993.*

Contact the ESTRO Secretariat – University Hospital St. Rafael, Radiotherapy Department, Capucijnenvoer 35, 3000 Leuven, Belgium; or call +32 16 21-22-13. Fax: +32 16 21 22 28.

Medical oncology

The postgratuate course will be organised by European Cancer Centre and held in Amsterdam, The Netherlands, *March 28 – April 3, 1993.*

Contact Robert van Bokhoven, IKA; or call +31 20 617 2903.

Melanoma

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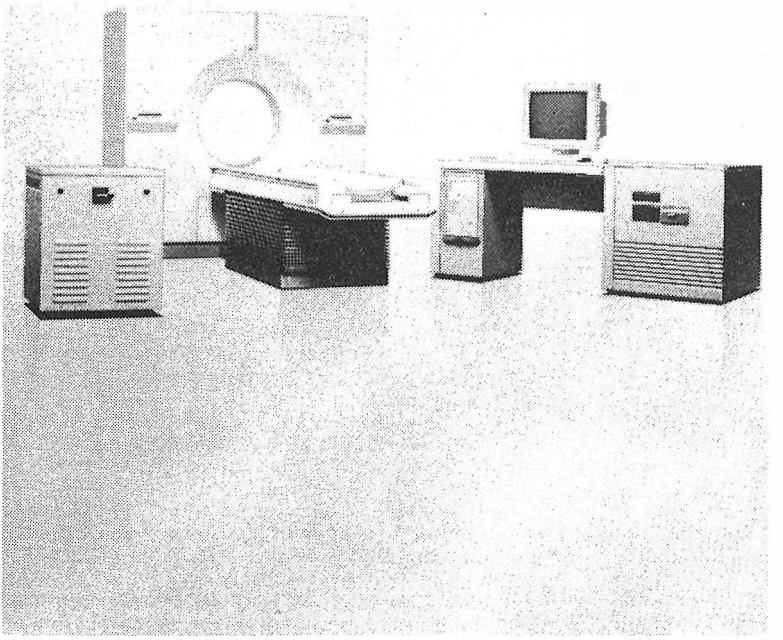

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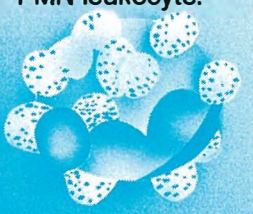

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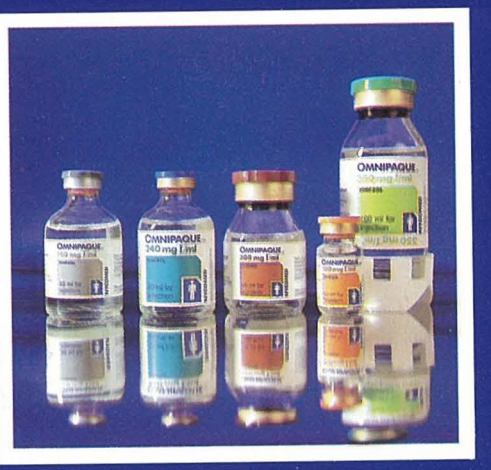

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- izuzetno rijetka pojava alergijskih reakcija
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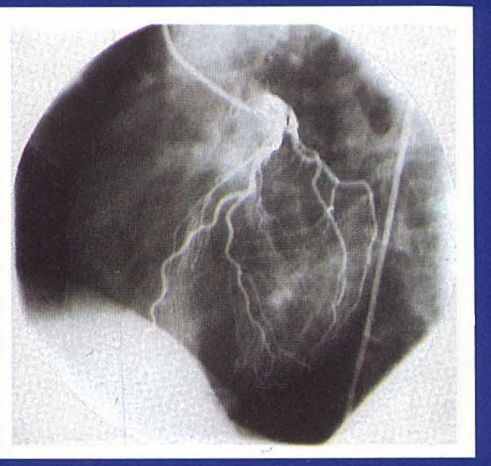

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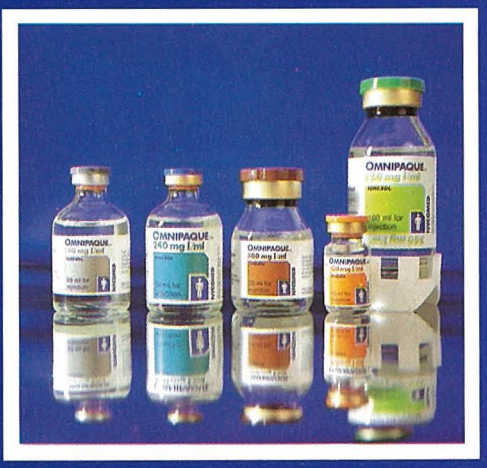

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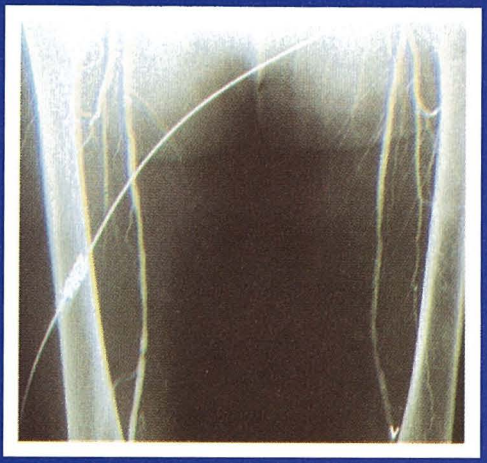

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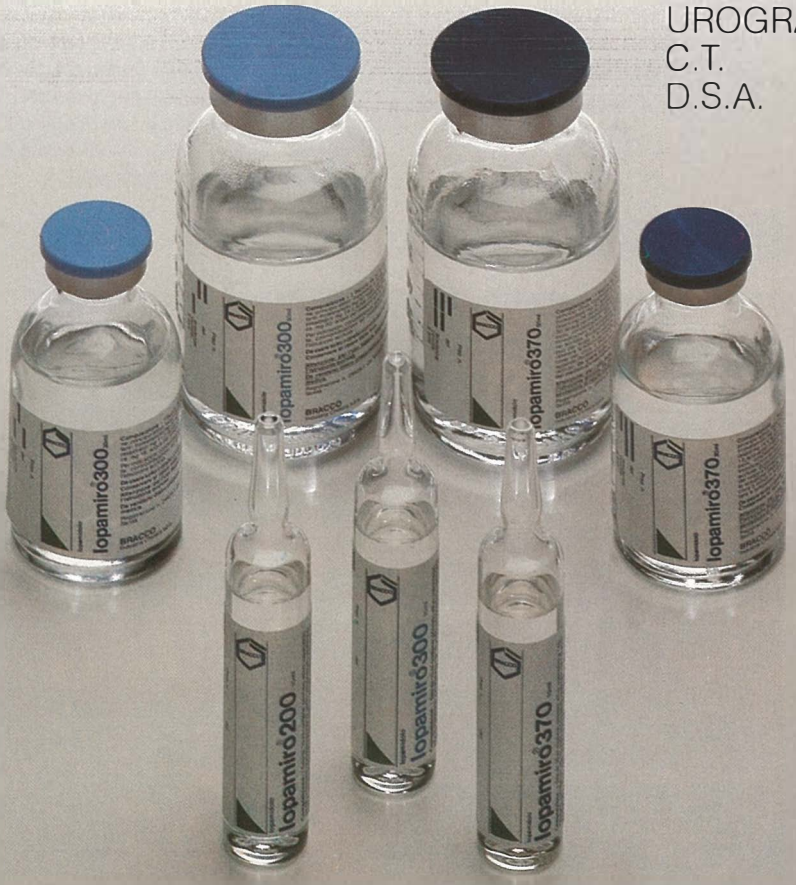

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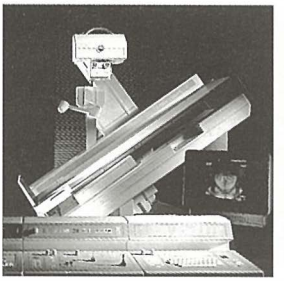

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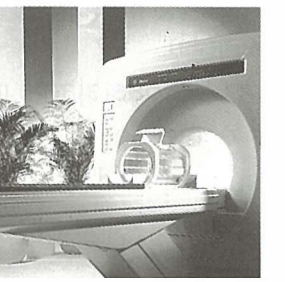

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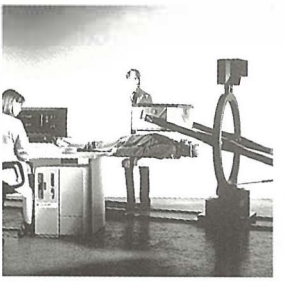

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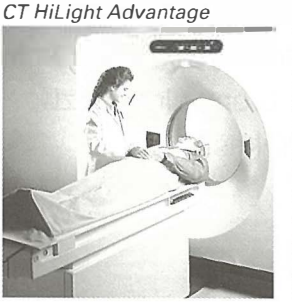

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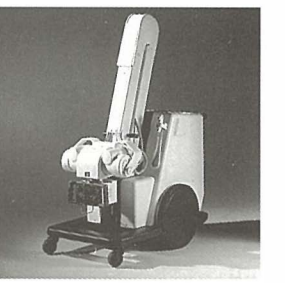

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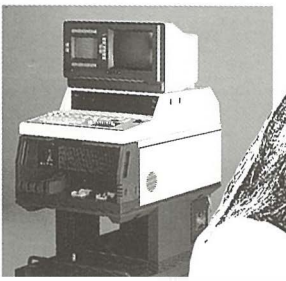

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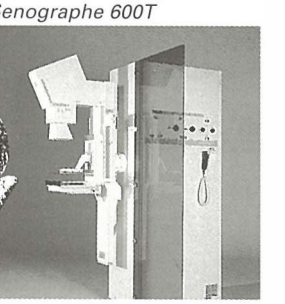

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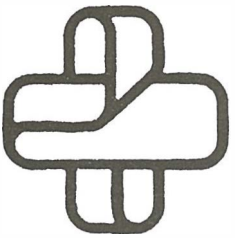

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