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Treatment of congenital pulmonary artery stenosis with transluminal balloon dilatation in childhood

Vladimir Ahel, Goran Palčevski, Anton Šepić and Vojko Rožmanić

Klinika za dječje bolesti KBC Rijeka, Kirurška klinika KBC Rijeka

Percutaneous transluminal balloon dilatation is a new therapeutic method in the correction of cardiac and valvular stenoses. In our work we presented the application of the method on isolated pulmonary artery stenosis in a 10 year old girl. The results of the performed dilatation treatment have proved its value as a satisfactory alternative therapy of congenital and acquired cardiac defects.

Key words: pulmonary valve stenosis--congenital; balloon dilatation; child

Introduction

For many years an open heart surgery has been the only way of correcting the cardiac and valvular stenosis.

The first ideas about the transluminal treatment of artery stenosis were recorded in 1964,[1] but their feasibility was limited owing to inadequate catheters which dimensions represented an obstacle to satisfactory treatment. Due to the technical improvement of catheters, the transluminal balloon angioplasty was performed first in adults and latter on, in 1962 in children.[2]

The application of balloon angioplasty in childhood was performed for the first time in an isolated pulmonary artery stenosis.[3, 4, 5] In the meanwhile the indications included the dilatation of mitral and aortal valvular stenosis, coarctation of the aorta (primary and postoperative) the dilatation of the pulmonary artery valve stenosis[6, 7, 8, 9] and palliative therapy in the tetralogy of fallot in case of asphyctic crisis.

All these catheters had one lumen which resulted in the interruption of blood flow after the inflation, with consequential bradycardia and CNS symptoms. Meanwhile, the development of biluminal and triluminal catheters eliminated such possibilities.[10, 11]

In this paper we described a succesful balloon valvuloplastic application in a 10-year old girl with isolated pulmonary artery valve stenosis, under haemodynamic value monitoring during and after the dilatation procedure.

Case report

A 10-year old girl was repeatedley treated in our clinic. At the age of three months the heart murmur was registered for the first time. The development was normal.

Physical examination revealed a systolic murmur, grade 4/6 on the left parasternal border

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with maximal intensity in the 2nd intercostal space.

An x-ray examination of the heart showed prominent pulmonary arch. An ultrasound examination showed a pulmonary artery valve atenosis (10 mm) with poststenotic dilatation. ECG recording showed a distinct rught ventricle hypertrophy.

On catheterisation and haemodynamic examination the pressure in the right ventricle was found to be 120 mmHg (transvalvular gradient 90 mmHg). The right ventriculography showed a valvular stenosis of the pulmonary artery with poststenotic dilatation (Figure 1).

An usual catheter was placed in the right femoral vein and the right ventricle. Pressures and oxygen saturation were measured and then a balloon dilatation catheter (Schneider, trefoil F 7) was placed in the optimal position in pulmonary artery truncus. Repeated inflation (in duration of 10 seconds) and deflation were performed (Figure 2). After the treatment the pressures were measured again.

Results

After the performed treatment the murmur intensity decreased. Before the balloon dilatation right ventricular pressure was 120 mmHg whereas after treatment it was 70 mmHg. This treatment reduced the previous gradient from 90 mmHg to 40 mmHg which is considered satisfactory (Figure 3).

No complications were observed during and after the procedure. The girl was discharged after two days with rutine follow-up examination in the clinic for 4 months, and reevaluation after one year (ECHO and invasive diagnostics).

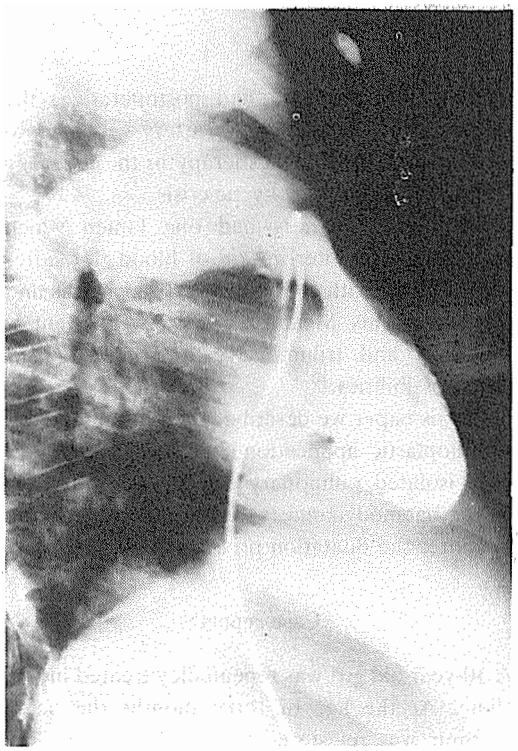

Figure 1. Angiographic presentation of pulmonary valve stenosis with poststenotic dilatation (L–L projection).

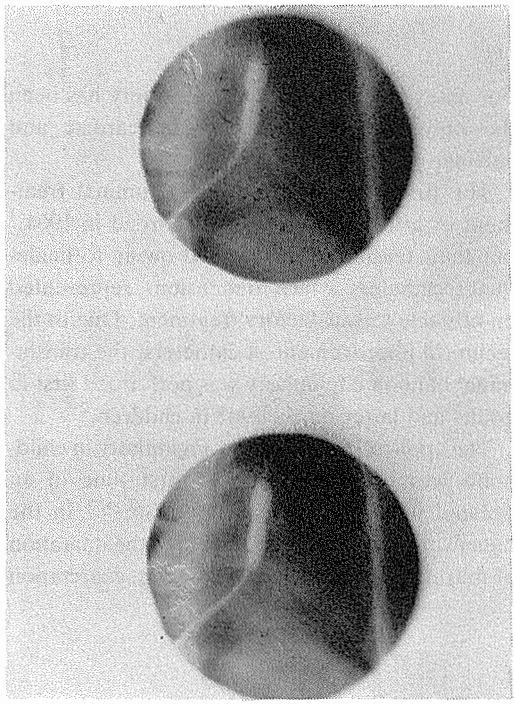

Figure 2. Balloon catheter presentation in the moment of stenosis dilatation.

Discussion

For a long time surgical treatment was for definitive correction of valvular and vessel stenosis. A risk of open heart surgery, cosmetic defects a long-term hospitalisation and expenses, led to the invention of new ways of treating the stenoses. In the meanwhile percutaneous balloon valvuloplasty became as acceptable as surgical treatment in the case of moderate stenosis. Better materials enabled the reduction of catheters dimensions. This is very important since the catheter diameter must be 2 mm smaller than the valve diameter.

In order to avoid bradycardic episodes caused by complete occlusion of the blood vessel during application, uniluminal catheters have been reaplaced by catheters with two or three separat lumens which enable unobstructed blood flow during the whole treatment. Besides the mentioned bradycardy, other possible complications may occur during the procedure: cardiac arrest, rupture of the blood vessel due to balloon overinflation a reversible fall of blood pressure, and balloon rupture.[12, 13, 14]

The application of the mentioned method in children in our country has been reported in verbal communications (Marinović, Simeunović).

The application of this technique in a large nubmer of patients enables definitive correction in 2/3 of the cases, whereas the remaining 1/3 require surgical treatment. The described method represents a satisfactory alternative therapy of congenital and acquired heart defects. Open heart surgery is applied in the cases in which the previously described method has failed to produce satisfactory results.

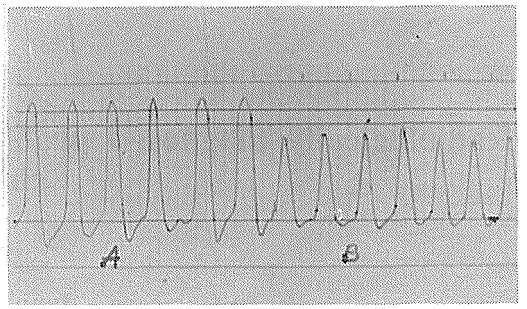

Figure 3. Pressure curve in the right ventricle before, (a) and after (b) balloon valvuloplasty (RANGE 100 mmHg).

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Radiologically diagnosed problems of the pulmonary tumors in children

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A review of relatively rare group of pulmonary tumors, different in shape and in evolution is presented. Conventional diagnosis was common whereas CT has been introduced later. A stress has been laid on the hydatid cysts which are relatively frequent. The primary problems of malignant tumors are presented with own clinical, radiological and autopsy findings. General prognosis is unfavourable.

Key words: lungs neoplasms-radiograpy; child

Introduction

The rapid progress of radiological diagnosis (CT, MR) has improved the possibility of early diagnosis of different primary and secondary tumors of the lungs. It has become clear that children are not protected from tumors in the lungs. The characteristics of benign and malignant tumors, as well as the presence of secondary involvement are sure indicators of the disease.

Early radiological diagnostics is associated with the leading symptomatology. The scarce literary references on this group of diseases motivated us to present a group of children suffering from these conditions.[1]

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Material and methods

In the period between 1978 – 1988, about 20 children of different age and sex with tumor pathology had been diagnosed in the Department of pediatric radiology of the Institute of Radiology. Here the male sex was prevailing in the rate 11 : 9, whereas the age ranged between infant and nursing age.[2] This group of tumors consisted mainly of heterogeneic tumors subdivided into benign and malignant tumors. The other group dealt with secondarry tumors, with or without decay of the deposits.[3, 4, 5,6]

The diagnosis was based on conventional methods, mainly radiography and tomography. Bronchography was used as a necessary diagnostic help. CT was not used in the group since it was established in the institute later. All children had been operated on, with the exception of two children who died soon after they were hospitalised, so that there was no time to make CT nor

US–tomography. This was obtained solely with a snapshot of the lungs. According to the pathology, the patients were distributed into three groups.

Results and discussion

First group: tumors of benign nature that represented the majority – 15 children altogether – their age varying from 2 to 10 years, mainly females. The common symptomatology was poor and problematic; sometimes cough, sometimes a loss of weight and inappentence. The cough was unproductive.

An exception to this symptomatology were only the following two children: a 10-year old female child admitted as an urgent case, with dyspnea, weak breathing on the left, and the admission diagnosis of pneumonia. Radiological findings: two well demarcated tumors, situated closely along the heart silhouette, in profile localised in the middle and lower mediastinum (Figure 1).

During the first night of hospitalisation, the child fell into e deep dyspnea and the cough gave signs of aspiration; the child died despite the emergency therapy given. The planned CT could not be done. Autopsically as well as radiologically, two cystic tumors were identified, with starting drainage of the perforated hydatid cyst through the bronchi.[1, 5, 7, 8, 9] There were three more children with persistent receding attacks included into this group. Their radiological findings were suspicious for mediastinal tumors. The surgical intervention proved some bizarre form of echinococcosis. One of them, A. M., 4-year old male (pat. rec. no. 2831/82) was admitted as an acute long sufferer, without convincing auscultatory findings. The radiogram showed a tumor with smooth contours along the mediastinum. Bronchography: dislocation of the bronchi branches in the upper and lower part. Bronchial cyst was confirmed on surgery (Figure 2).

In the second group of primary malignant tumors we present three children: a rare malignant tumor was evidence in our youngest patient, a 10-month old infant A. M. (pat. rec. no 2369/79). History was atypical: discrete inappetence, subfebrility and occasional coughing. The radiogram showed a big soft–tissue formation along the mediastinum on the left, of identical homogeneity, which disappeared toward the thoracal wall. Solomon et al.[3, 10] have presented an identical casual situation as ours, with identical localisation and appearance; it was a case of pulmonary blastoma (Figure 3).

The case of L.A., approx. 10-year old male child, is not exceptional: symptoms comprised a considerable weight loss, pallor and dry cough mostly at night. Radiological findings: a paratracheal tumor on the right, which was lined dosally

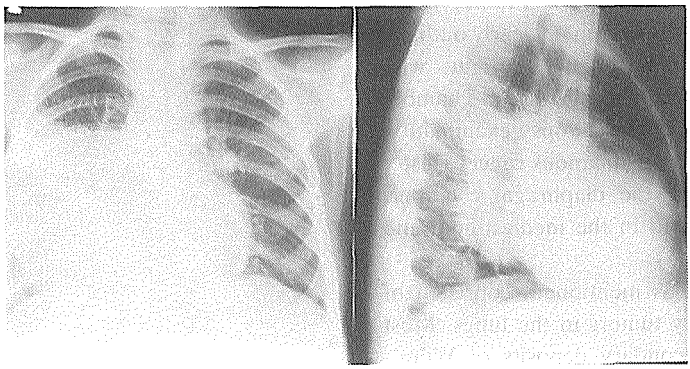

Figure 1. Cystic hygroma on the left – a 10-year old female child. Radiological findings: two well demarcated tumors lying well in the heart silhouette.

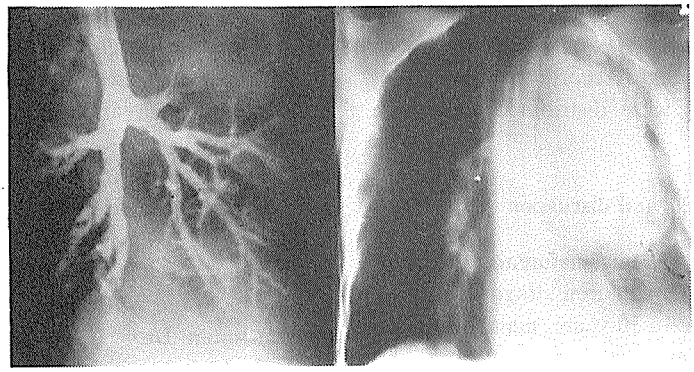

Figure 2. Bronchogenic cyst. The radiography shows a tumor with smooth contours along the mediastinum; bronchographically evident dislocation of the bronchi.

in profile and exerted pressure on the trachea.[11] Damgaard – Petersen in his work on the value of diagnosis in malignant tumors with reference to the diagnosis of malignant tumors in children included hepatoblastoma in the group of miscellaneous types.[11] The tumor was found to be neuroblastoma (Figure 4.)

Among the rare tumors are Ewing sarcoma, osteogenic sarcoma and neuroblastoma. In our child the diagnosis was proved radiologically.

Another male child, 12-year old M. S. (pat. rec. no. 1924/79), malnutritioned, had dyspnea and was dehydrated. Snapshoted a few times, with a fast progression of the pathological process evident on the radiograms. His general condition was rapidly worsening all until death after few days of hospitalisation. A radiogram as well as a tomogram showed an unclearly outlined homogeneic mass mainly on the right, with accompanying ascites. The diaphragm chamber was almost indistinct. The autopsy examination showed the presence of squamous cancer (histologically) destructing the diaphragm chamber, with metastatic spread in the mediastinum and peritoneum (Figure 5).

The third group, as mentioned, consisted of metastatic secondary tumors in the lungs. Most often, these are secondary deposits of Wilm's tumor, embryonic, with specific changes. In most cases these deposits are smooth, well outlined, numerous formations in the lungs, which were described in detail by Magilli,[1, 4, 5] with changes that are mostly seen in the mediastinum.

Another group includes deposits of Wilm's tumor in most bizarre forms, with unilateral or

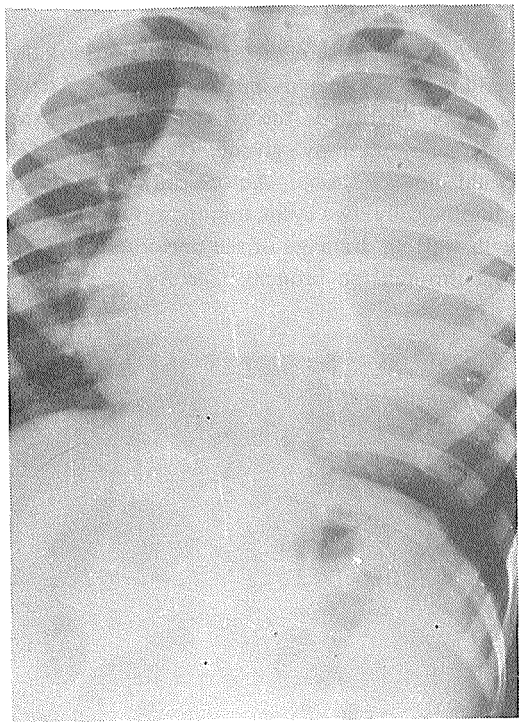

Figure 3. Pulmonary blastoma – a 10-month old infant; the radiogram shows a large soft-tissue formation along the mediastinum on the left.

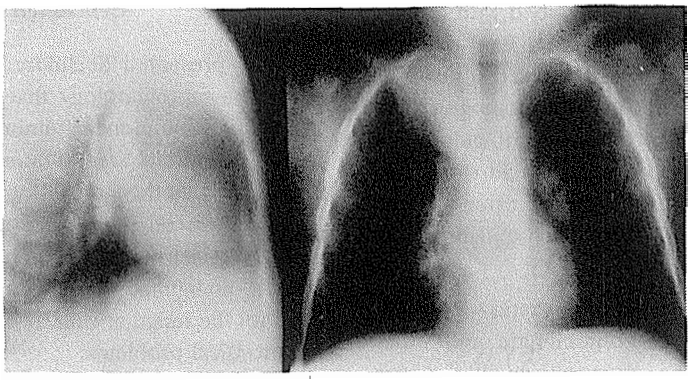

Figure 4. Neuroblastoma – a 10-year old boy, paratracheally on the right discrete mass projecting over the right upper lung, displacing the trachea.

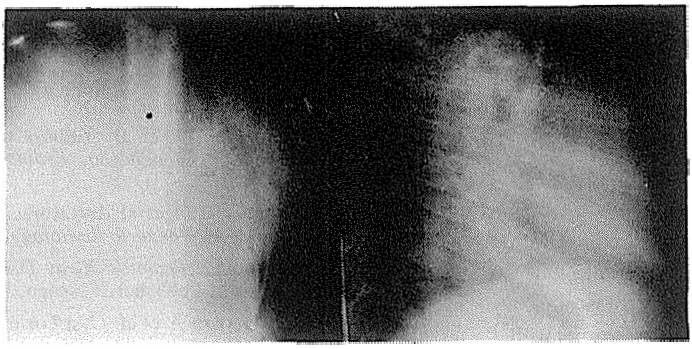

Figure 5. Primary squamous cell carcinoma – The radiogram as well as the tomogram shows a vaguely outlined homogeneic mass mainly on the right, with accompanying ascites. The diaphragm chamber is not distinct. Cancer was histologically confirmed on autopsy.

bilateral cavities in the lung with regular cystic formations, as described by Daneman.[4]

Fortunately, this kind of metastatic spread is relatively rare. In our group of examined children, two presented with necrotic formations in the tissue, which corresponded to the type of changes described by Daneman.[4]

According to the recent concepts, childhood tumors represent rare pathology. Wasch[3] believes that bronchial cancers are unknown in children, but he shows a rare case of an 11-year old boy with bronchial cancer; Cardelle of Havana[3] also described a child with malignancy, but this was a boy of the same age and with the same pathology.

In later years the pediatric radiology still gives mainly casual descriptions of malignancy.[1, 7, 9, 10] Metastatic tumors with cavities are also reported.[3, 4, 7, 11]

Pulmonary blastoma is specially rare in infant pathology, with a remark that all until 1982 there had been only a few cases of this kind of pathology described. It is considered exceptionally rare in the infant population.[10]

Shelly and Lorenzo[12] in 1983 described a progressively fatal primary tumor in a child. They pointed out that all until 1974, 29 casualities had been noted in children under 16 years of age. Then in 1977. one more case of bronchoge-

nic squamous cancer was described with remark that a new case was described in 1983 by these authors. Our patient was diagnosed in 1979 or perhaps even earlier. Computer tomography is by all means a superior method of pulmonary tumor diagnosis, so for primary and secondary as well as for benign and malignant tumors. The reports by Damggard[11] with their statistical data clearly support this statement.

Which is our most frequent cystic tumor. By all means, considering our climate and widespread stockbreeding, zoonosa – hydatid cyst is most characteristic, with most bizarre forms and course described in 14 children.[1, 2, 7, 8, 9] Dedić gives a reference in his monograph, just as well as Grivčeva et al., that these are more frequent in children. Whereas the complicated forms of bigger cysts are found in central position, the smaller ones appear sporadically. The central ones tend to cause complications, ruptures, as well as disseminations, like in our case no. 1. Advanced diagnostics by all means leads to an exact diagnosis. Thus the initial diagnosis in our infant patient was thymoma, but on surgery it proved to be primary blastoma. An identical description was by Solomon as well.[10]

Sometimes the diagnosis is neither typically radiological nor clinical, and in that situation, team work is needed in the diagnosing of the disease. That was the case with an older patient who had a long–lasting unexplained process associated with advanced malnutrition and equivocal radiological findings, which was proved to be primary squamous cell carcinoma on autopsy.[12] Unfortunately, the diagnosis was not proved by CT.

Finally, a few words about other round shades such as bronchial cysts (easily identifiable on CT, we recognised it on bronchography). Is the diagnosis of secondary deposits or decay of Wilm's tumor always radiologically clear? Are mistakes not possible?[3, 9] Caffey[3] reports on a casualty abscess pneumonia, understood as multiple deposits of decay.

Conclusion

We have presented 20 children, of different age, sex and symptomatology that have one feature in common: pulmonary tumors. The conventional investigations are common, but the leading radiological method today by all means CT and NMR. A special emphasis is laid on the benign hydatid cysts which are most frequent. The primary malignant pathology is presented together with the range of clinical–radiological as well as autopsical problems.

In the conclusion, it should be pointed out that long–lasting pulmonary symptoms raise suspicion of a persistent process in the lungs, which demands team approach in the diagnosis.

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Radiological appearance of the gastroduodenum following modern surgical treatment of duodenal ulcer

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The paper presents the radiological appearance of the gastroduodenum following surgical treatment of duodenal ulcer. These surgeries are mostly proxymal or supraselective vagotomy with drainage operations, without gastric resection.
Supraselective vagotomy leaves the antral ramification of the vagus nerve intact, and orderly gastralevacuation. In patients with of benign stenosis of duodenal bulb, together with selective proxymal vagotomy, drainage operations (gastro-duodenal anastomosis Jabouley's, and gastro-jejunal anastomosis), can be done. Patients were examined by standard and by biphasic techniques which have brought improvement into radiological diagnostics.

Key words: duodenal ulcer-surgery; stomach-radiography; duodenum-radiography

Introduction

The number of surgical methods used in gastroduodenal surgery has increased to such an extent, because of the various modifications of the standard surgical interventions, that folowing gastroduodenal surgery a good radiological examination can be performed only when the operation protocol is known, i.e. when the surgical interventions carried out are precisely known.

From the radiological aspect, surgical interventions on the gastroduodenum can be divided into three groups:

A. Total gastrectomy with esophago-entero anastomosis
B. Gastric resection with gastro-entero anastomosis
C. Gastric surgery without resection

This study deals with the radiological appearance of the gastro-duodenum following gastric surgery without resection, comprising:

1. Selective proximal vagotomy
2. Suture of perforated or bleeding ulcers
3. Gastric drainage surgery, including:
   - gastroduodeno anastomosis according to Jabouley, and
   - gastrojejuno anastomosis

Vagotomy is a surgical method used in the treatment of duodenal ulcer. It denotes division of the branches of the vagus nerve with the aim of exluding the cephalic secretory activity of parietal cells in order to reduce their responsive-

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ness to humoral stimuli, especially to stimulation by gastrin.[1,2,3] As a surgical method, vagotomy was introduced by Exner in 1912, and later improved by Laterjet, Mayo and others. In selective proxymal vagotomy, the antral ramification of the vagus remains intact, which ensures normal innervation of the antral, pyloric and duodenal areas and normal emptying of the stomach. Thus, a drainage operation is unnecessary if the pylorus and bulbus are patent.[1,3]

Suture closure of a perforated or bleeding ulcer is a palliative intervention, allowing sanation of bleeding or perforation while the ulcer remains.

This surgical intervention can be combined with selective proximal vagotomy. Hemostatis by suture closure combined with vagotomy and a drainage operation gives better results.[1,2]

Gastroduodeno anastomosis according to Jabouley consists of incision of the anterior wall of the descending part of the duodenum and of the gastric antrum paralelly with a greater curve for the formation of the gastroduodenal anastomosis.[1,2]

A gastrojejunal anastomosis can be obtained also by the antecolic method consisting of attaching an isolated jejunal loop to the stomach by antecolic approach. The attached jejunal loop has an isoperistaltic course. The efferent part of the anastomosis should be, if possible, at the lowest part of the greater curve of the stomach to ensure safe passage of food through the anastomosis. The afferent loop of the anastomosis should be placed more proximally. The anastomosis is 6 cm wide and its position is oblique. To prevent backflow of food from the afferent loop into the stomach, an entero–entero anastomosis according to Braun is formed and, thereby, food is channelled into the efferent loop.

The retrocolic gastrojejunal anastomosis is a retrocolic attachment of the stomach to the jejunum. The mobilized jejunal loop is drawn through the hole in the mesocolon and anastomized to the stomach. The jejunal loop is placed transversally to the longitudinal axis of the stomach, so that the afferent jejunal loop comes upon the lesser curve and the efferent loop upon the greater curve of the stomach.[1,2]

Materials and methods

In view of the fact that gastroentero anastomosis without resection of the stomach combined with selective proxymal vagotomy is a fairly recent surgical method, we studied a small group of 30 patients, 29 men and 1 woman, aged between 30 to 60 years. In 25 of these patients gastrojejunal anastomosis was performed and in the remaining 5 patients gastroduodenal anastomosis according to Jabouley. Both operations were carried out without gastric resectio and combined with selective proxymal vagotomy. The patients had been referred to us by the outpatient Unit of Surgical Gastroenterology which was also in charge of their follow–up.

The motility and tonus of the stomach during the early postoperative phase were evaluated using routine radiological techniques. Thanks to the advancement of radiology, these techniques are highly satisfactory.

For the diagnosis of late postoperative organic changes the biphasic examination technique was used. This method includes pharmacoradiography (Buscopan, Reglan, Glucagon), enchanced double–contrast visualization, dosed compression and x–ray imaging in various projections. This method is well tolerated by patients. It is carried out during the late postoperative period, two months after surgery, because of the potential risk of dechiscence and bleeding due to distension of the stomach wall.

The contrast media used were homogeneous suspensions of micropulverized barium, perfectly adhering to the mucosa, as well as the above listed pharmacological preparations affecting the tone and peristalitics of the gastroduodenum.[2,4]

Radiological apperance and discussion

Following selective proxymal vagotomy, the radiological picture shows intact tonus and peristaltics of the antral part of the stomach, while the fundus and corpus of the stomach are markedly distended and hypotonic (Figure 1). Gastric

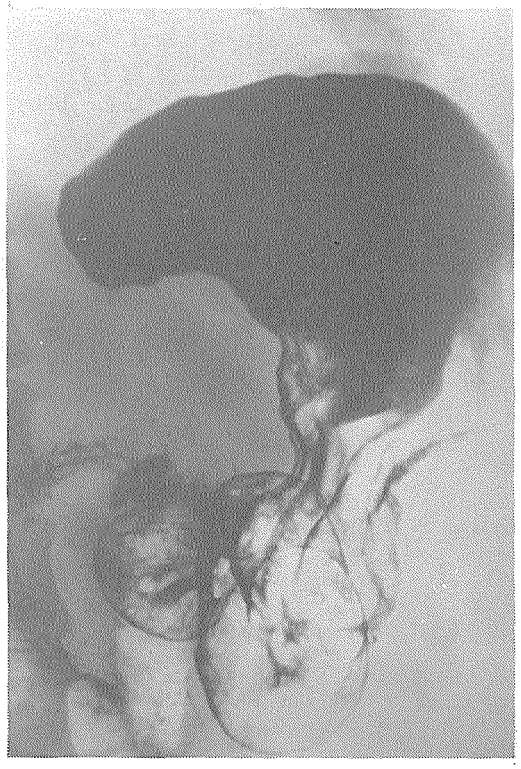

Figure 1. Condition after selective proximal vagotomy. Moderate dilatation of the fundus and initial part of stomach corpus. Regular tonus and peristaltics of the antral part of the stomach can be seen.

Figure 2. Sutures after perforation of duodenal ulcer. Deformation of the duodenal bulb.

evacuation and propulsion of the contrast through the duodenum and the other part of the small intestine are normal.

The sutures, after bleeding or perforation of the ulcer, do not present a pathognomic radiological picture. The scarring deformities of the bulbus due to sutures are of widely different shapes and can hardly be differentiated from the scarring after healing of the ulcer (Figure 2).

Following gastroduodeno anastomosis according to Jabouley, the X–ray picture shows about 3 to 4 cm wide stoma (Figure 3). In some cases, one can see a small band of contrast close to the proxymal part of the anastomosis which corresponds to the remainder of the narrowed part of the bulbus of the duodenum, i.e. to the natural passage. Dynamic X–ray examination (diascopy) is performed to evaluate the functional capacity of the anastomosis. This evaluation is based on the width of the jet of the contrast medium and the amount passing through the anastomosis.

Gastrojejuno anastomosis is easy to identify. The contrast medium passes directly from the stomach into the efferent jujunal loop, so that the antral part of the stomach and of the duodenum – the natural route – is poorly visualized (Figure 4). The functional effect can be considered satisfactory when most of the contrast medium passes on the route stomach–efferent loop of the jejunum, i.e. when this route is dominant, rather than the natural one.

The radiological appearance of the stomach is normal and peristaltics slightly sluggish and shallow. The appearance of gastric mucosa shows changes, the mucosal folds converge towards the

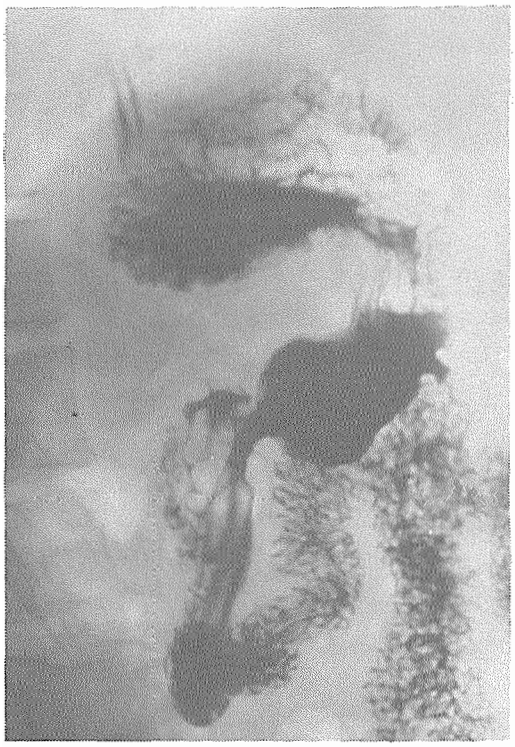

Figure 3. Gastro–duodenal anastomosis according to Jabouley. Aboral part of the duodenal bulb is stenosed and hardly passable. Anastomosis about 1 cm wide without dificulties in passage can be seen.

Figure 4. Gastro–jejunal anastomosis. Common appearance of anastomosis with narrow communication.

stoma. The stoma is oblique in relation to the position of the lesser curvature, and lies along the very margin of the greater curvature on the posterior stomach wall. Reflux of the contrast medium into the afferent loop is not considered pathological if it does not show signs of stasis. Differentiation between the efferent and afferent loop present no problem, though it is often difficult to ascertain whether the anastomosis is positioned into the iso – or aniso peristaltics, because the loops spontaneously change their position after surgery. The mucosal folds of the afferent loop look tender, yet instead of the »fern pattern« which is normal, they often exhibit the pattern of stasis with dilation of the afferent loop.

Routine examination techniques allow good analysis of functional changes during the early postoperative phase – up to two months following surgery. During this phase, we did not find complications in our patients. The biphasic technique is more suitable for follow–up examinations during the late postoperative phase, i.e. more than two monts after surgery. This technique enables better analysis of the antral part of the stomach, of the anastomosis and of the afferent loop to the small intestine and also makes it possible to diagnose very small pathomorphological lesions.

Postoperative peptic ulcer is the most common complication following gastroentero anastomosis. Its most common site is the initial portion of the efferent loop, at a distance of 1-2 cm from the anastomosis, and on the anastomis itself (Figure 5).

Figure 5. Gastro–duodenal anastomosis according to Jabouley. A recurrent peptic ulcer on anastomosis.

According to old statistical data, following gastric resection with gastroentero anastomosis and without vagotomy, this complication developed in a very high percentage of cases (according to Starliner in 89% and according to Alessandri in 84%).

After the introduction of selective proxymal vagotomy, the incidence of postoperative peptic ulcer following this operation decreased to about 30 to 40%.[1,5]

In 25 out of the 30 patients included in our control group, gastrojejuno anastomosis without gastric resection, accompanied by selective proxymal vagotomy was performed. Among these 25, there was also a female patient. In this group we found seven complications of postoperative ulcer. All of these were detected in the late postoperative phase.

Among the 5 patients with gastroduodeno anastomosis without resetion of the stomach, combined with selective proxymal vagotomy, there was only one patient who developed a postoperative peptic ulcer during the late postoperative phase.

The results show that we have found a total of 8 postoperative ulcers among our 30 patients, which accounts for an incidence of 27%.

Conclusion

Gastroentero anastomosis without gastric resection, combined with selective proxymal vagotomy in the treatment of chronic duodenal ulcer and its complications represents by far smaller surgical trauma for the patient, and it also significantly decreases the incidence of postoperative ulcers as complication following surgery.

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Radiol Oncol 1992; 26: 14-5.

From practice for practice: case presentation

Jurij Us

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A 46-year old man, locksmith by profession. He is referred to X-ray of the lumbar vertebra because of lumbago; referral diagnosis: lumboischialgia, lymphadenopathia colli.

History

For a number of years he has been treated for gout. During sporadic attacks he takes Indocid.

In 1989 he was treated at the University Department for Infectious Diseases because of trichinosis. The source of infection was pork meat (from a home-bred pig).

The present difficulties, i.e. pain in the lumbar region and legs and paresthesias of the lower limbs have been ascribed to the trichinosis, their form and intensity being the same as before treatment. During the past six months the patient has been observing enlarged lymph nodes on his neck and complained of unbearable itching of the skin – the symptom, which becomes particularly bad at night, has been persisting throughout the past four months. The patient has also noted that he can hardly manage to perform more straining tasks. He does not have any respiratory disorders, his excretory functions are within normal limits.

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Status

Eupnoic, unaffected. Head and neck NED. A 5x7 cm mass of enlarged lymph nodes is found on the left side of the neck. The lymph nodes appear soft on palpation. No other enlarged nodes can be found elsewhere in the body. Lung: respiration is vesicular, resonant on auscultatory percussion, lung bases are mobile. Heart: rhythmical cardiac action, the sounds are clear, without noises. Abdomen: NED on palpation. No evidence of peripheral edemas.

Findings

Bloodd count and chemistry: SR 34/87 mm, L 9.6, E 4.21, Hb 132 g/L, HT 0.362, MCV 82.3 fl, MCH 31.3 mg, MCHC 364 g/L, Thrombo. 274, Differential Blood Count: band forms 0.02, Segm. 0.83, Lympho. 0.14, Mono. 0.01, Proteinogram: normal.

Urate 499 umol/L, Alk. phos. 1.57 nkat/L, gamma GT-GOT 0.26 Uat/L, Total bilirub. 10 μkat/L, ALT (GPT) 0.19 ukat/L, LDH 3.81 μkat/L, Total protein 76 g/L, Prothrombine time 0.75, INR 1.21

X-ray: see Figure 1., Figure 2. and Figure 3.

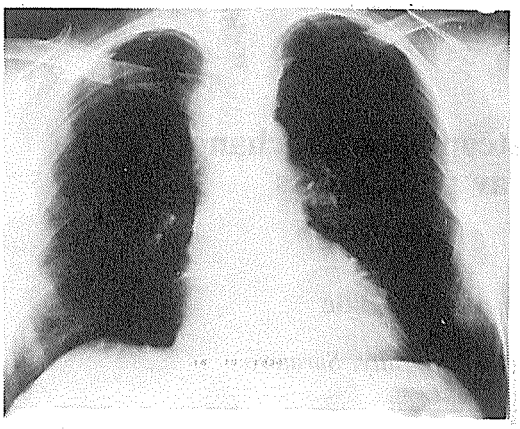

Figure 1.

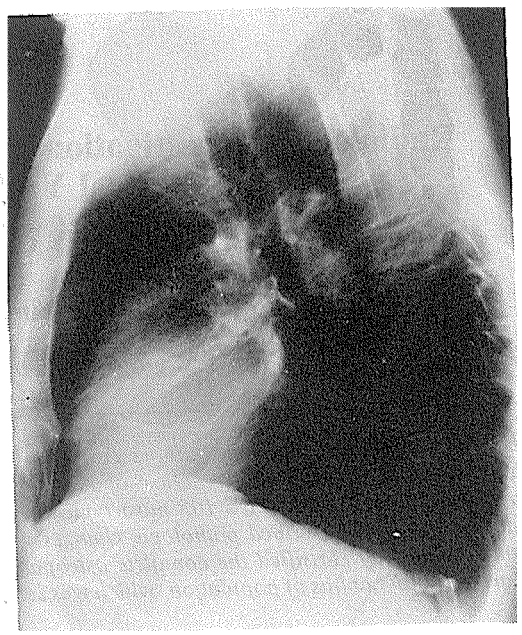

Figure 2.

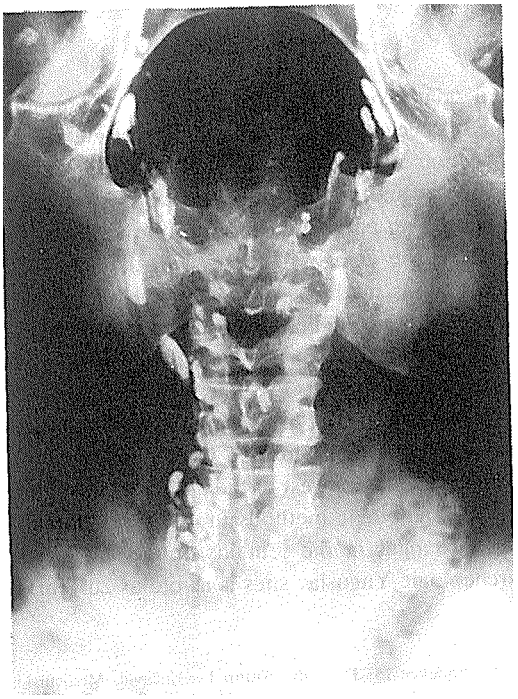

Figure 3.

Task:

1. Explain the radiograms
2. Differential diagnosis
3. Diagnosis
4. Confirmation of diagnosis (methods) (classification of disease)
5. Further diagnostic procedures (classification of disease)
6. What i needed for treatment selection?
7. Suggested treatment.
8. Prognosis

(see page 44)

Radiol Oncol 1992; 26: 16-24.

Radiological investigation of osteopathologic changes of the hystorical Yugoslav populations

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During several year work the authors examined almost 10 thousand of skeletons from different sites in Yugoslavia, belonging to the period of the last two milleniums – historical period. Out of the total material the authors selected 105 most typical specimens and investigated the characteristic pathologic changes. All the described pathologic changes were classified in chapters according to the distribution and in that way classified the complete osteopathologic material. Therefore, they got an insight into a part of health habitus of population, which was settled in the particular regions in the hystorical period.

Key words: bone and bones–radiology; bone diseases–classification

Introduction

Paleopathologic investigations and diagnosing are of special importance for the complete reconstruction and interpretation of our older and younger ancestors. All diseases, which were lasting long enough to destruct the osseous tissue, can be diangosed today with the safety by the various methods of modern medicine. The use of X-rays enables the visualization of anatomic and pathoanatomic skeletal changes in vivo and post mortem. Only three years after the discovery of X-rays, in 1898, the first rentgenologic imaging was performed in the analysis of a mummy.[1] The interest of the author of this work to use radiologic methods in diagnosing pathologic changes in the remains of the man from archeologic Yugoslav sites is as old as 20 years.

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UDC 616./1-073.75

The osteologic findings from the grave chapel of the kings of the Middle Bosnia in Bobovac[2] were used and the method of xeroradiography in the anthropologic series from the necropolic tombstones Raška Gora near Mostar.[3] This was followed by the idea to collect the most characteristic findings from different sites. Those findings were anthropologically elaborated, preserved and described in details in the publication »Atlas of Osteopathologic Changes of the Hystorical Yugoslav Populations«.[4]

The aim of the previous long-range work of the authors, as well as of this work was to improve the knowledge of the health habitus through the several last milleniums (hystorical period) of the populations from our teritory.

Material and method

During several years work the authors examined almost 10 thousand of bones from Antic Viminacium – about 7 thousand – Middle Aged Vinča –

about 1 thousand, Raška Gora near Mostar, Puhovac near Zenica, Pavlovac near Sarajevo and Cipuljić near Bugojno – about 2 thousand of skeletons. Of the total material, the authors selected 105 osteologic remains and investigated and described all characteristic pathologic changes. The selected specimens, considered as the most typical by authors, were preserved enough to enable a most detailed paleopathologic analysis. The site, number of the skeleton, as well as sex and age of the skeleton with pathologically changed bone are quoted below the corresponding images for every specimen. Relating to the fact that the bones belong to poorly preserved skeletons, there was no possibility to define accurate age. The age was estimated approximatelly, defining the age group at the same time. There were no difficulties in sex definition. The authors have regularly found a sufficient number of preserved primary morphologic elements, defining the sex of the skeleton. In both cases, the authors used the suggestions of the European anthropologists in the Hungarian city Scarospatak in 1978.[5] Radiologic methods of investigation were directed to the parts of osteologic skeletal remains with pathologic supstrate. Every bone or a group of bones was photographed and radiographed in the identical size and projection.

The imaging was performed by the optimal projections with identical bone positions during photograph and radiograph taking. Pathologic changes were analysed after obtaining radiographs, and the text of the analysis was placed below the images. Since the osteologic remains presented only the osteoid substance without soft tissue, which would fill and surround the pure osseous stroma, the authors used a liquid of the defined chemical content into which every bone was submerged during imaging, providing a better imaging quality.

We used the following radiologic examination methods:

1. conventional radiography,
2. combination of conventional radiography and panoramic technique of mandible imaging,
3. for special cases – computed tomography.

The selected material has been clasified according to the following regions of the human skeleton:

1. bones of the head,
2. bones of the spine,
3. bones of the shoulder joint and upper extremities,
4. bones fo the pelvis and lower extremities.

According to the material the authors made the following distribution of pathologic changes in the investigated osteological remains:

I Variations and distortions of the bones and joints
1. congenital variations and distortions
2. acquired variations and distortions

II Traumatic changes of the bones and joints
1. fracture
2. luxations
3. amputations
4. cuts

III Inflammations of bones and joints
1. non-specific inflammations
2. specific inflammations

IV Degenerative diseases of the bones and joints

V Tumours of the bones and joints
1. cysts
2. other tumours.

Such a distribution was not aimed to include all pathologic changes of the skeletal bones, but only those observed in the available material.

Results

Our results are presented in Figures by the analyses descriptions of pathologic changes in 105 characteristic osteologic specimens. The obtained results – described types of pathologic changes were classified according to the distribution presented in Material and methods for every skeletal part separately.

Pathologic changes of the osteologic remains of the skull

The pathologic changes of skull bones found in 14 skeletal parts of different individuals from Viminacium and Vinča. The arrangement of the elaborated material has been classified according to the described distribution into the following arrangement:

I. Anatomic variations and distortions of skull bones:
1. Congenital variations and distortions:/
2. Acquired variations and distortions:
   Skeleton No. 501. Preserved sutura metopica (or frontalis), premature pneumatisation of the frontal sinus and protuberance of maxillary sinus fundus on the side of canine root.
   Skeleton No. 533. Cribra orbitalia.
   Skeleton No. 1507. Last molar placed horizontally
   Skeleton No. 105. Atrophia of the alveolar part of the mandible.
   Skeleton No. 2.847. Epactal bone – epipteric or pterion bone.

II. Traumatic changes of skull bones:
1. Fractures:
   Skeleton no. 382. Exostosis of the occipital bone.
   Skeleton No. 683. Fractura mandibulae.
   Skeleton no. 1501. Fractura mandibulae.
2. Luxations:/
3. Amputations:/
4. Cuts:
   Skeleton No. 1163. Frontal bone cut.
   Skeleton No. 1772. Frontal bone cut associated with a fracture.
   Skeleton No. 1987. Cut of the lower border of the left side of the mandible.

III. Inflammations of skull bones:
1. Non-specific:
   Skeleton No. 335. Chronic granuloma and ossifying periodontitis.
2. Specific: /

IV. Degenerative diseases of skull bones:/

V. Tumours of skull bones:/
1. Cysts:/
   Skeleton No. 630. Cysts localized on the right side of the maxilla.
2. Other tumours of skull bonse:
   Skeleton No. 661. Frontal bone thickened according to the osteogenous type of the tumour – osteosarcoma?!, the left maxillary sinus shadowed osteoidely.
   Skeleton No. 661. Computed tomography slice shows the homogenous shadow in the left maxillary sinus of the osteoid structure.

The presented results show that there were no congenital variations and distortions, luxations and amputation or specific inflammations and degenerative skull diseases.

However, we found the acquired variations and distortions in 6 examples: fractures in 2, cuts in 3, non-specific inflammations in one and cysts and other tumours in one example.

Pathologic changes of the osteologic remains of the spine

The pathologic changes of the bones of the spine, found in 8 skeletal parts of different individuals from Vinča, Viminacium, Raška Gora and Puhovac (Zenica).

The elaborated material has been classified according to the described distribution into the following arrangement types:

I. Variations and distortions of the bones and joints of the spine:

1. Congenital variations and distortions:
   Skeleton No. 229. The rest of the fissure (intervertebral space) between the second and third sacral segment.
   Sceleton No. 9. Sacralization of L_5 vertebra.
   Skeleton No. 503 Sacralization of L_5 vertebra.
   Skeleton No. 3155. Lumbarisation of S_1 segment.
   Skeleton No. 458. Sacralization of L_5 vertebra.

2. Acquired variations and distortions:/

II. Traumatic changes of the bones of the spine

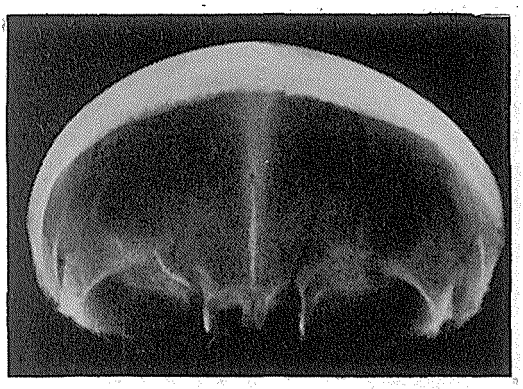

Figure 1. Skeleton No. 533, child 8 – 10 years old. Site: Vinča.
Photography and radiography of forehead: Radiograph shows unpneumatised frontal sinus, corresponding to the child's age. (The frontal sinus begins to pneumatise in the ages of 10–12). There is a stranier – like bone change – type »cribra orbitalia« – placed at the roofs of both orbits.

III. Inflammations of bones and joints:

1. Non–specific inflammations:
   Skeleton No. 1. Spondylarthritis ankylopoetica – M. Bechterew.
   Skeleton No. 1. Ankylosing spondylarthritis, Two lumbar vertebrae associated with spondylarthritis ankylopoetica – M. Bechterew.

2. Specific inflammations of the bones of the spine:/

IV. Degenerative diseases of the bones of the spine:
Skeleton No. 3052. Ankylosing spondylarthrosis of the atlas and axis.

V. Tumours of the bones of the spine: /

The pathologic changes of the osteologic remains of the spine are presented in the form of congenital variations and distortions in 4 osteologic remains, non–specific inflammations in 2, and degenerative disease in one case.

There were no acquired variations and distortions, traumatic changes, specific inflammations or bone tumour.

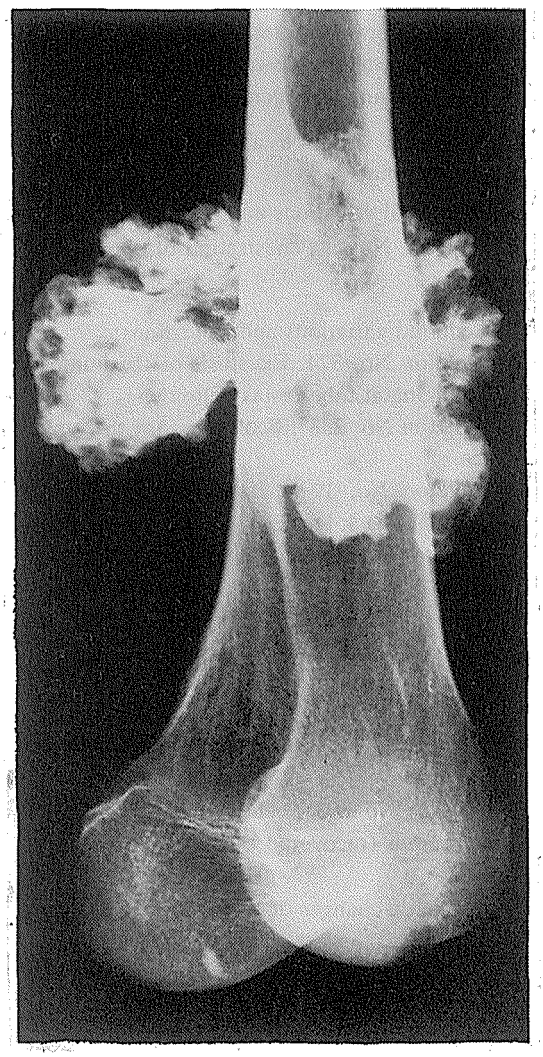

Figure 2. a) Skeleton No. 3317, male up to 45 years. Site: Viminacium.
Photography and radiography of the distal third of the same femur: Radiographs of femur shows a coralliform lacelike small fist sized formation along with the lateral end of distal third of femoral diaphysis. With quite a broad base, the formation is fixed to the bone base. The shadow intensity is strong, because of the marked ossification of the described formation. »A rare form« of exostosis.

Pathologic changes in the osteologic remains of the shoulder joint and upper extremities.

The pathologic changes of the shoulder joint and upper extremities, found in 36 skeletal parts of different individuals from Vinča, Viminacium and Pavlovac, Sarajevo).

The elaborated material has been classified according to the described distribution into the following arrangement:

I. Anatomic variation and distortions of the bones and joints:

1. Congenital variations and distortions:
   Skeleton No. 5. Fenestration of corpus sternum.

2. Acquired variations and distortions:
   Skeleton No. 374. Exostosis of the humerus beginning at tuberositas deltoidea.
   Skeleton No. 2387. Scoliostosis of the humerus.
   Skeleton No. 1934. Exostosis of the ulnar diaphysis back border.
   Skeleton No. 2056. Marked endostosis of the ulnar diaphysis.
   Skeleton No. 2704. Bending of both humeral diaphyses (deformity of growth and development).
   Skeleton No. 1677. Hyperostatic protuberance of the humerus (posttraumatic? muscle extension?).
   Skeleton No. 503. Scoliostosis of the humerus and radius (recovered rickets?!).

II. Traumatic changes of bones and joints:

1. Fracture:
   Skeleton No. 2698. The state after clavicle fracture.
   Skeleton No. 593. The state after pseudoarthrosis claviculae.
   Skeleton No. 2361. The state after fracture of the anatomic humeral neck.
   Skeleton N. 1381. The state after fracture of the anatomic humeral neck.
   Skeleton No. 1560. The state after fracture of surgical humeral neck.
   Skeleton No. 3686. The state after fracture of humeral diaphysis.
   Skeleton No. 3044. The state after fracture of humeral diaphysis.
   Skeleton No. 3044. The state after cured fracture of the diaphysis of the radius.
   Skeleton No. 2005. The state after cured fracture of the radial diaphysis.

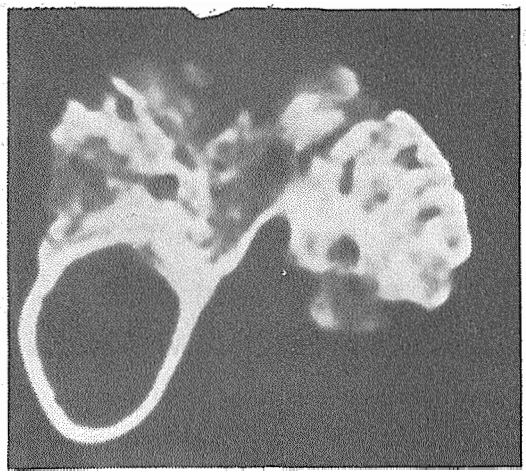

Figure 2. b) Skeleton No. 3317.
The transversal CT – computed tomography 8 mm thick scan shows the relation of a lacelike – coralliform exostosis and diaphysis of the femur, in the form of a elliptical ring–like shadow of a thin osseous wall. (enhanced scan).

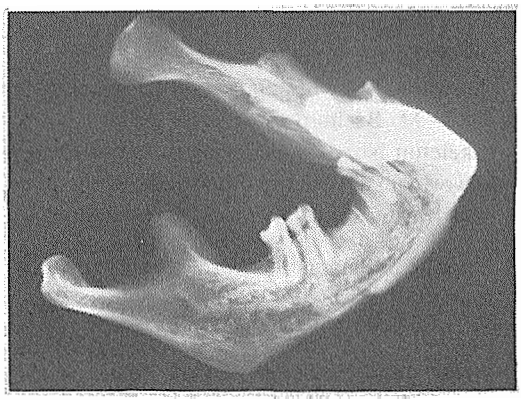

Figure 3. Skeleton No. 1987. male up to 45 years old.
Site: Viminacium.
Photography and radiography of the mandibula; the back half of the lower left mandibular leg missed, without reactive changes at the surrounding bone. The finding suggests the recent trauma (bone cut), after which this individua died.

Skeleton No. 308. The state after cured fracture of the distal end of the radius.
Skeleton No. 1593. The state after cured fracture of the ulna.
Skeleton No. 1471. The state after cured fracture of the ulnar diaphysis.

Skeleton No. 1390. The state after cured fracture of the distal third of the ulnar diaphysis.
Skeleton No. 164. The state after the oblique fracture of the distal third of the diaphysis.
Skeleton No. 756. The state after double fracture of the ulnar diaphysis.
Skeleton No. 1689. The state after cured fracture of the diaphysis of the radius and ulna.

2. Luxations:/
3. Amputations:
Skeleton No. 2295. The state after traumatic amputation of the distal humeral end.
Skeleton No. 2759. The amputation of the lateral epicondyle and capitulum of the humerus.
Skeleton No. 131. The state after traumatic amputation of a part of the distal end of the radius.
Skeleton No. 622. The state after traumatic amputation at the level of distal third of the ulnar diaphysis.
4. Cuts:/

III. Inflammations of bones and joints:
1. Non-specific:
Skeleton No. 113. Sclerozation of the humeral diaphysis, medullary duct invisible.
2. Specific:
Skeleton No. 308. Tuberculosis of the hand.
Skeleton No. 308. Enhanced computed tomography - CT scan through the osseous conglomerate of the carpal bones.
Skeleton No. 308. Enhanced computed tomography – CT scan through metacarpal bones.

IV. Degenerative joints disease of the shoulder bones and upper extremities:
Skeleton No. 2941. Arthrotic changes of clavicular ends.
Skeleton No. 114. Arthrosis of the distal end of the humerus.
Skeleton No. 1994. Arthrotic changes on cover planes of all bones in the elbow joint.
Skeleton No. 394. Arthrotic (postraumatic) changes of the elbow joint and distal end of the radius.
Skeleton No. 1380. Arthrosis of the distal joint plane of the radius and proximal ulna.

V. Tumours of the elbow joint and upper extremities:
1. Cysts:
Skeleton No. 2412. Cystic changes of the lateral epicondyle of the humerus.
2. Other tumours: /

Out of total 36 skeletal parts of shoulder joint and upper extremities, there was 1 congenital variation and distortion, 7 acquired variations and distortions. In the group of trauma, 16 fractures in different stages and 4 amputations were presented. In the group of inflammations there was 1 non-specific and one specific case of inflammation. In 5 cases, pathologic finding was characterized as a degenerative change, in the group of tumours – one case of cyst. However, there were no cases of luxations, cuts or other types of tumour.

Pathologic changes of the osteologic remains of the pelvis and lower extremities.

The pathologic changes of the bones of the pelvis and lower extremities, were found in 47 skeletal parts of different individuals from Vinča, Viminacium and Cipuljić (Bugojno).

The elaborated material has been classified according to the described distribution into the following arrangement:

I. Anatomic variations and distortions of bones and joints of the pelvis and lower extremities:
1. Congenital variations and distortions:/
2. Acquired variations and distortions:
Skeleton No. 352. Exostosis of supra-acetabular segment.
Skeleton No. 3317 A »rare« type exostosis of the distal third of the femur.
Skeleton No. 3317 A »rare« type exostosis of the distal third of the femur (enhanced).
Skeleton No. 3317. Computed tomography of »rare« type exostosis.
Skeleton No. 327. Exostosis of the femur.
Skeleton No. 2807. Exostosis of the fibula.
Skeleton No. 285. Exostotic tips of the fibula below the head.

Skeleton No. 2105. Endostosis of the fibula.
Skeleton No. 1869. Bone bridge connecting borders of the upper thirds of the tibia and fibula.
Skeleton No. 405. Thickening of the compacta and periostosis of the tibia.
Skeleton No. 393. Subperiosteal reactions – sclerosation of the tibial diaphysis.
Skeleton No. 2507. Thickening of the compacta of tibial fragments.
Skeleton No. 1625. Hyperostosis of the tibia.
Skeleton No. 1621. Scoliostosis and hyperostosis of the tibia.
Skeleton No. 1380. Thickening and sclerosation of the diaphyses of the compacta and periost of the both fibulae.
Skeleton No. 432. Scalloped bone border of the lineae asperae of the femur.
Skeleton No. 424. Periostosis of the fibula.
Skeleton No. 2354. The osseous hyperplasia of the muscle holder of the great femoral trochanter.
Skeleton No. 503. Scoliostosis of both femurs – genu valgum.
Skeleton No. 591. Coxa vara.
Skeleton No. 3347. Calve–Leeg–Perthes (aseptic osteonecrosis of the hip).
Skeleton No. 2096. A deep malleolar fissure (Sulcus malleoli tibiae).
Skeleton No. 421. Marked ventral convexity of the diaphysis of the tibia.
Skeleton No. 438. More marked ventral convexity of the diaphysis of the tibia.

II. Traumatic changes of bones and joints of the pelvis and lower extremities:

1. Fracture:
Skeleton No. 133. The state after fracture of the femur. Skeleton No. 1710. The state after irregulary cured fracture of the diaphysis of the femur.
Skeleton No. 5. The state after irregularly accreted fracture of the distal third of the diaphysis of the femur.
Skeleton No. 651. The state after transversal fracture of the right femur with marked dislocation and latus cum diaslocationem.
Skeleton No. 651. Transversal CT scan through callus.
Skeleton No. 486. The state after cured fracture of the diaphysis of the femur with scoliostosis.
Skeleton No. 1473. The state after cured fracture of the tibia with consecutive changes (fragments angulations, scoliostosis, compacta thickening, waved bone contour).
Skeleton No. 1525. The state after fracture of the left tibia.
Skeleton No. 370. The state after cured fracture of the tibia.
Skeleton No. 513. The state after consolidation of the fracture of the diaphysis of both shranks.
Skeleton No. 105. The state after cured fracture of the diaphysis of the tibia and sinostosis of the distal ends of the tibia and fibula.

2. Luxations:
Skeleton No. 3518. The state after traumatic luxation of the hip.
Skeleton No. 3754. The shallow acetabulum (luxation).
Skeleton No. 229. Hypoplasia of the elements of the hip skeleton (luxation).
Skeleton No. 141. Chronic hip luxation with consecutive changes.

II. Inflammations of bones and joints of the pelvis and lower extremities:
1. Non–specific:
Skeleton No. 3155. The state after inflammatory process of the pelvis (posttraumatic).
Skeleton No. 1339. Ostitis deformans of the femur (Paget).
Skeleton No. 1525. Ostitis deformans fo the tibia (Paget) (the late stage).
Skeleton No. 436. Chronic inflammatory process of the tibia with consecutive osseous pseudocyst.

2. Specific:
Skeleton No. 412. Postinflammatory changes – bones between the proximal ends of the tibia and fibula; suspected tuberculosis osteoarthritis).

IV. Degenerative joint diseases of the pelvis and lower extremities:
Skeleton No. 463. Deforming gonarthrosis.
Skeleton No. 407. Gonarthrosis.
Skeleton No. 2537. Deforming arthrosis of the distal end of the tibia.

V. Tumours of the pelvis and lower extremities:
1. Cysts: /
2. Other tumours:
Skeleton No. 467. Osteolytic process of the upper third of the diaphysis of the femur.
Skeleton No. 1995. Osteoma of the tibia – exostotic type.

In the osteologic remains of the pelvis and lower extremities the authors found 22 cases of acqui red variations and distortions of the bone, 10 cases of fractures of different forms and stages, 4 signs of luxations, 5 cases with signs of non–specific and one case of specific inflammatory changes. Besides, 3 cases of degenerative changes and two cases with the signs of other tumours were detected. There were no cases of congenital variations and distortions, traumatic changes such as amputations and cuts, as well as bone cyst.

Discussion

This study was performed using the methods of radiologic examination, to show the details of pathologic changes in the osteologic remains better than when they are covered by the soft tissue.

Besides, the authors tried to show the diseases, which left the trace on the bones of populations living in the last two milleniums on this territory. It is shown in our cases that is historical period is characterized by the diseases, rare or completely absent in the contemporary population. The example is Cribra orbitalia (Fig. 1), as a result of the disorder in the hemoglobine distribution, caused by Malaria falciparum or inadequate nutrition. The extreme exostoses (Fig. 2 a, b) which would be surgically cured today have been presented.

There are also characteristic injuries – especially cuts, which reflect an example of the utilization of the weapons from that time (Fig. 3)

The sacralization of lumbar and lumbarization of sacral vertebras appeared frequently as variations in growth. M. Bechterew has also been presented as a disease noted in the series of the investigat osteologic remains. The bones of upper and lower extremities show evidence of fracture related conditions cured with more or less success. Besides the specific inflammations, frequent non–specific inflammations such as ostitis deformans – Paget and various arthrotic changes were found. The amputations, with the cause very difficult to discuss, are also presented.

We also found cases of the acquired variations and distortions, preceded by various exostoses, hyperostosis, periostosis, scoliostosis. Calve – Leeg – Perthes – aseptic osteonecrosis and another distortions Coxa vara and luxations are found in the zone of hips. Cyst and tumours were also found.

Conclusion

Information on the health habitus of population, which were settled in an area in the hystoric time can be found in the written material or based on the findings of human skeleton remains.

In the study, the authors investigated and presented a selected material of the most typical cases of pathologic skeletal changes of that population. The complete statistic analysis can not be made, but it is possible to provide an insight into the character of pathologic changes of the bones, which was the aim of this study.

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Detection of changes in the area of sella turcica and the algorithm of neuroradiologic investigations

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The paper describes clinical symptomatology and radiodiagnostic imaging of different intrasellar tumours and pseudotumors with special emphasis on the normal and pathological changes of the sella turcica. A radiodiagnostic examination algorithm has been proposed.

Key words: sella turcica–radiography; pituitary neoplasms–radiology

Introduction

Sella turcica (sella) and the parasellar region have very prominent clinical and neuroradiological importance. Sella is a millimetre thin wall of the sphenoid bone body, positioned in the central part of the skull base and thus connected with all three skull cavities. Of the whole skull base the sella wall is the least resistant. Therefore the changes within it as well as in the remaining cranium can reflect on its size and bone structure.

In this region there are many structures of vital importance: the pituitary gland as the central regulator of all somatotropic endocrine functions and the hypothalamus which builds the floor and a part of the lateral wall of the third ventricle being the basic source of instinctive, vegetative and emotional life. Here are the neuroophthalmologic structures of the optic chiasm and the optic nerves as well. The pathological changes in the hypophyseal fossa or in its neighbourhood will first reflect on the pituitary gland's function as the stimulation or suppression of somatotropic action on other endocrine glands and on neuro-ophthalmologic structures also. This explains why the patients is referred to different specialists, such as endocrinoligist, ophthalmologists, neurologists and then to the radiologist. His arbitrage is very important in the evaluation of changes in the sella area.

Normal sella and radiological pathological changes

From the rich retrospective material we analysed the radiologic changes on standard radiograms of the sella region affected by different intrasellar and suprasellar expansive process of tumorous and pseudotumorous character. It is necessary firstly to describe the shape and size of the normal sella, and then its pathological changes in size and bone structure.

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Standard sella radiogram

1) Sella shape: The greatest diagnostic ramblings are associated with the sella shape and size. The sella shape is an individual characteristic and can be of use for personal identification in the same way as the fingerprints. Regardless the different individual variations, there are three general shapes with regard to the constitutional skull shape. In the brachycephalic skull the sella is round, in mesocephalic oval, and in dolichocephalic it is flat (Figure 1). In children, the round sella dominates, but in adults other two forms prevail. The sella shape is influenced also by the angulation of the skull base. The angulation occurs on the border between the presphenoid and basisphenoid; the sella is in the centre of that occurrence as well as in the centre of the neurocranium and splanchnocranium. The pneumatisation of sphenoid sinus influences its shape, since the sinus hyperpneumatisation causes its greater growth in length than in depth.

2) Sella size: The evaluation of sella size usually causes problems. We can freely say that the size is subject to free estimate by every radiologist, either »by eye« or using different measurements. Earlier, the length and width as well as the surface and volume in sagittal and frontal planes were usually determined. Different authors obtained different values. So, e.g. a small sella in sagittal plane does not indicate that the whole sella is small, since its width in the frontal plane can be same as in a normal sella. By measuring the pituitary gland and sella volume, no concordance has been established between the anatomic specimen and radiologic measurement. When all these parameters disagree for the normal sella, how will the sella size be determined in the borderline cases and in small enlargement. Constant relation between the sagittal skull diameter and the sella length has been known since earlier; in 1964 Martinez–Farinas[1] has proposed an index of the sella size based upon the greatest sagittal diameter of the sella (from its tuberculum to dorsum), measured in continuation of the skull base (the greatest sagittal skull diameter from the tabula interna of the frontal bone to the same of the occipital bone). So the craniosellar index can be determined by the following formula:

$$CSI = \frac{s\,(cm)}{c\,(cm)} \cdot 100$$

According to Martinez-Farinas,[1] the normal CSI averaged to 5,7, but by Avdonin[2] this index amounted to 6.8 until 18 years of age, and from 19 years to 7.3. Our investigation of the domestic population was in agreement with the latter finding that the highest limit of a normal sella amounted to 7.3.[3] Consequently, the sella size

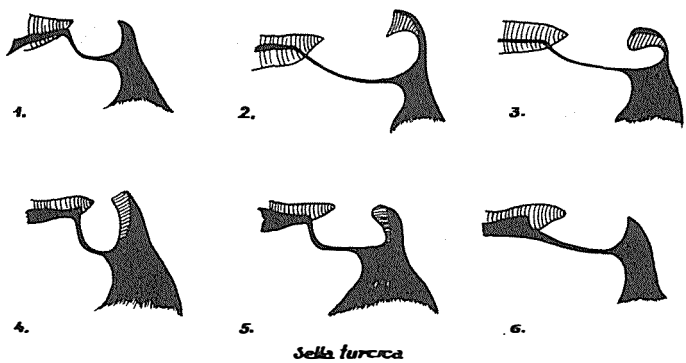


Figure 1. Three basic shapes of the sella turcica with their variations by Martin. 1 – round, 2 – oval, 3– flat, 4 – cavernous, 5 – quadrangular, 6 – shallow.

will be determined on the standard latero-lateral craniogram, not on the target radiogram. FF distance must be at least 1 m, since a lesser distance influences the mentioned relationship. A distance greater than 1 m does not have effectual influence. The target sella radiogram, possibly with tomography, can be performed later with the aim to better explain changes in the bone structure.

3) Small sella: It has been mentioned that a small sella on the lateral craniogram does not signify that the sella as a whole is small. Some authors have presented on the cadaver measurement by means of plastelin that there was no direct relation between the volume of the pituitary gland and the sella; namely, the volume of the pituitary gland was less than 19% that of the sella. This signified that a normal pituitary gland can lie in a small sella. We have found such small sella in completely normal individuals, but it can be as well found in the familial obesity and emaciation. If the sella is small in both planes, then there indeed exists the congenital pituitary gland hypoplasia within it. Panhypopituitarism and pituitary nanism have been found in such sellas in our three patients (Figure 3a). We have investigated how much a small and bridged sella or only bridged sella can influence the somatic state of the patient. Different diencephalic lesions have been found such as diabetes insipidus, diabetes mellitus, hypogonadism, adiposis, emotional immaturity and insomnia. The bridged sella over a single or between all clinoid processes is more frequent in adult persons, and twice as frequent in males than in females. It is considered as anatomical variation being a consequence of partially ossified cartilaginous interclinoid tenias normally present in human embryos and anthropoids. The bridge between the sella tubercle and the anterior clinoid process forms foramen clineoideocaroticum through which the internal carotid artery enters the cavernous sinus. This can cause spastic reaction of the artery and its later narrowing. In some patients the change results in a headache – hemicrania and epileptic convulsions (Figure 2a).

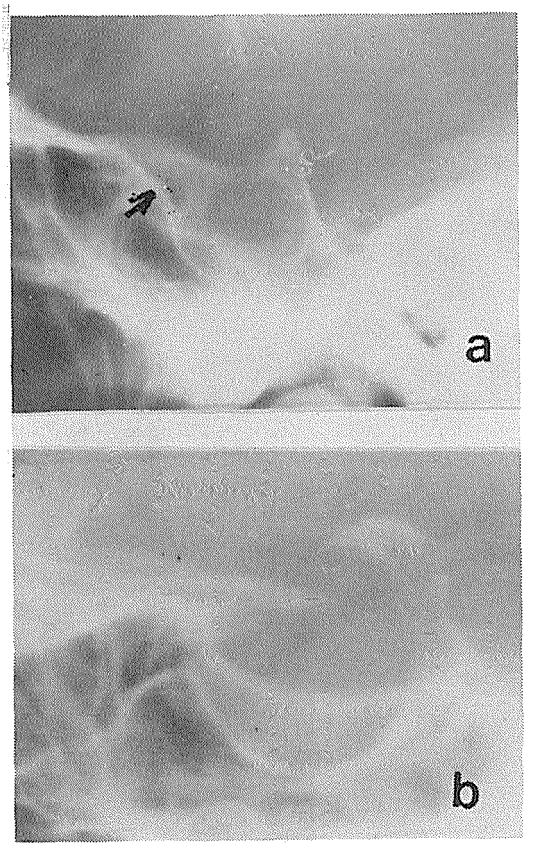


Figure 2 (a) bridged sella over the anterior to posterior clinoid processes and over the sella tuberculum to the anterior and posterior clinoid processes with the formation of foramen clinoideocaroticum (arrow) for the passage of the internal carotid artery into the cavernous sinus (spasm of the carotid artery and headache hemicrania): **(b)** duplication of the enlarged sellar floor by asymmetrically growing intrasellar adenoma (acromegaly).

4) Enlarged sella: The sella can be enlarged uniformly or asymmetrically, and its single parts decalcinated or destructed. The diagnostic question is, however, whether this is a result of primary intrasellar tumor and pseudotumor, or of a remote intracranial process. Decalcination with sellar enlargement starts on the anterior wall in intrasellar tumors since a majority of these tumors are located in the anterior part of the pituitary gland. The process progresses toward the other part of the sella which adapts to the tumor growth by enlargement. The sella

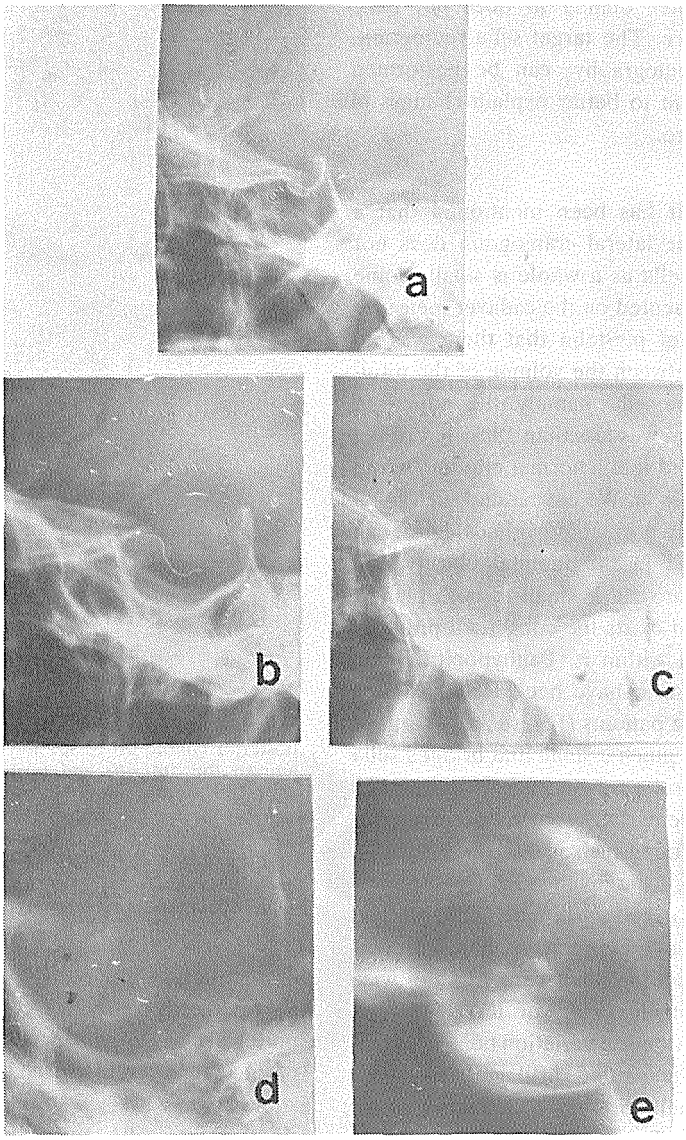


Figure 3 (a) small sella (pituitary nanism); **(b)** – enlarged sella (primary sella) in acidophilie adenoma with preserved contours; CSI–9 (acromegaly); **(c)** – totally destroyed sella in adenocarcinoma of the pituitary gland; **(d)** enlarged sella with thinned wall and widened entry in chromophage pituitary adenoma. CSI–11 (headache, amenorrhea and papillary atrophy); **(e)** – enlarged sella and its entry with decalcinated dorsum, nodular intrasellar and spheric suprasellar calcifications in partially cystic craniopharingioma (hypopituitarism, diabetes insipidus and papillary atrophy). Note: all craniograms have been shortened for space saving reasons.

dorsum offers less resistance if its structure is spongy and more when it is pneumatised. The position of sella dorsum becomes more upright, and the entry into the hypophyseal fossa widens if the tumor propagates suprasellary. The normal width of hypophyseal fossa entry is up to 7 mm, and the values over 10 mm can be regarded as a sign of its enlargement. All greater intrasellar tumors cause equal sella enlargement, i.e. primary sella. Its characteristic is that the top of the sella dorsum always lies over the line which makes the sella length. With the exception of hypophyseal adenocarcinomas, intrasellar tumors as a rule do not cause sellar destruction (Figure 3c). Of our three patients with adenocarcinomas, one presented with sellar destruction which cleary indicated the presence of malignant hypophyseal adenoma. Asymmetric sellar enlargement is characteristic of those tumors which lie in the lateral part of the pituitary gland, respectively, the sella with double contour of the sellar floor (Figure 2b). That may not be misinterpreted for an incorrect skull position on the radiogram.

Different parasellar expansive processes in the skull base such as chiasma and hypothalamus gliomas, meningiomas, chondromas, chordomas, trigeminus neurinomas, epipharynx and skull base invasive carcinomas can destruct individual parts or whole sella.

Remote expansive intracranial processes influence the sella, particularly after the closing of the cranial sutures. The intracranial pressure is transmitted on the sella by volumen auctum or directly by an obstructive internal hydrocephalus with enlarged influndibular recess of the third ventricle. The least resistance is offered by the sella dorsum, especially when its structure is spongy. This leads to the destruction of the dorsal processes and a part of the dorsum, i.e. secondary sella. Its characteristic is that the dorsum top always lies under the line of the sella length. Consequently, it is very important to evaluate carefully the sellar size and view on a standard radiogram during initial diagnosis.

Intrasellar tumors

By Lanksch' statistics[4] the pituitary adenomas and craniopharyngiomas represented 12% of 3750 intracranial tumors diagnosed by CT, thus taking the 3rd place. Therefore, neurodiagnostic investigations of the sellar region are of great importance. Adenomas and craniopharyngiomas are the most frequent intrasellar tumors, whereas the intermedial cysts and epithelial cysts (Rathke) are rare. Adenomas can be acidophile, chromophobe, mixed, basophile and prolactinomas. Craniopharyngiomas amount to a quarter of all intrasellar tumors. Of adenomas the prolactinomas are the most frequent. There is a group of pituitary adenomas which appear as a result of the lost recurrent activity after a long lasting medication, misinterpreted for primary hypothyreosis (TSH adenomas), as well as for Nelson's syndrome due to inadequate substitutional therapy after total bilateral suprarenalectomy. After adequate therapy these adenomas show regression.

1) Acidophilic adenomas: These adenomas are located in the anterior lateral part of the pituitary gland. They cause hyperproduction of the growth hormone with clinical characteristics of acromegaly and splanchnomegaly, respectively gigantism. They have slow evolution and can be stationary for a long time with periodical remissions. This can explain why the sella retains its mineralisation, and even can be hypermineralised during remission (osteoplasia overpowers osteoclasia) (Figure 3b). The location of these adenomas is most frequently intrasellar, whereas suprasellar propagation is less common. The suprasellar growth is greater if they are mixed with chromophobe cells. We analysed the sellar changes in 80 operated patients.[5] Asymmetric sellar enlargement was found in 30%, round shape in 41%, oval in 59% and enlarged entry into the hypophyseal fossa in 39% of patients. Craniosellar index ranged between 7.8 – 12 in relation in the disease evolution (the lowest 7.8 in three cases). In addition we registered the internal cranial hyperostosis in 42.5% of pa-

tients. Intrasellar location of these adenomas was found in 37.5%, whereas intrasellar and suprasellar in 62.5% of patients. The concordance between the aymmetric adenoma growth and the enlarged lateral ventricle ipsilaterally was registered in 76% of patients.

2) Chromophobe adenomas: These adenomas are most often found in females. They are characterised by a great suprasellar growth. The sella can be more calcinated, its wall thinned with the enlarged entry and upright dorsum (Figure 3d). Headache is present in all adenomas as they exert pressure on the sellar diaphragm, but it stops after their suprasellar propagation. Clinically, the patients suffer of hypopituitarism with hypogonadism and amenorrhea. Changes in the sight field are present as well in all adenomas with the suprasellar growth. Bellini et al.[6] described three cases of hypophyseal nanism in children with the chromophobe adenoma.

3) Basophile adenomas: They cause hypophyseal dependent Cushing's syndrome with hypercorticism due to increased ACTH secretion. These adenomas are most often microadenomas without repercussion on the sellar wall or with discrete changes. Their location is in the central dorsal part of the pituitary gland. When other possible causes of Cushing's syndrome such as some cortisol productive adenomas or lung tumors are excluded, then it is necessary to search for adenoma within the pituitary gland. It is believed that hypophyseal-dependent Cushing's syndrome is partly associated with the corticotropic cells, and partly with pars intermedia substance.[7]

4) Prolactinomas: Prolactinomas are the most frequent pituitary gland adenomas, and are more common in females than in males. These prolactin–secreting adenomas are located in the dorsolateral part of the pituitary gland. It is believed that 10-40% of females with menstrual disorders have these microadenomas.[7] Their hormonal characteristics are hypogonadism with amenorrhea and galactorrhea. In the case of microadenomas, the stationary stage can continue for a longtime without changes in the sella. Macroadenomas tend to grow faster, the symptoms progress and the sella changes. Therefore, they can be discovered early.

5) Craniopharyngiomas: These tumors appear in younger population, and a half of them are found in the second decade. They are characterised by asymmetric intrasellar and extensive suprasellar growth. Their suprasellar part is several times greater than intrasellar, whereas the sellar changes are similar to those seen in chromophobe adenomas. They can be differentiated from chromophobe adenomas since they are mostly calcified (55-60%) which is rarely the case with chromophobe adenomas (3-6%). Therefore, an uncalcified craniopharingioma can be difficult to differentiate from a chromophobe adenoma. The calcifications lie intrasellary, but more often suprasellary, their appearance is nodular or spheric. The spheric calcifications are characteristic for partially cystic craniopharyngioma (Figure 3e). Their hormonal characteristic is hypopituitarism with hypogonadism and diabetes insipidus. In relation to hypophyseal adenomas, they can cause hydrocephaly with an increased intracranial pressure due to great suprasellar growth.

6) Diagnostic algorithm: Previously employed classical methods were completely abandoned after the start of computed tomography (CT). CT is the method of choice since it can discover microadenomas even in the cases of normal sella. (Table 1).

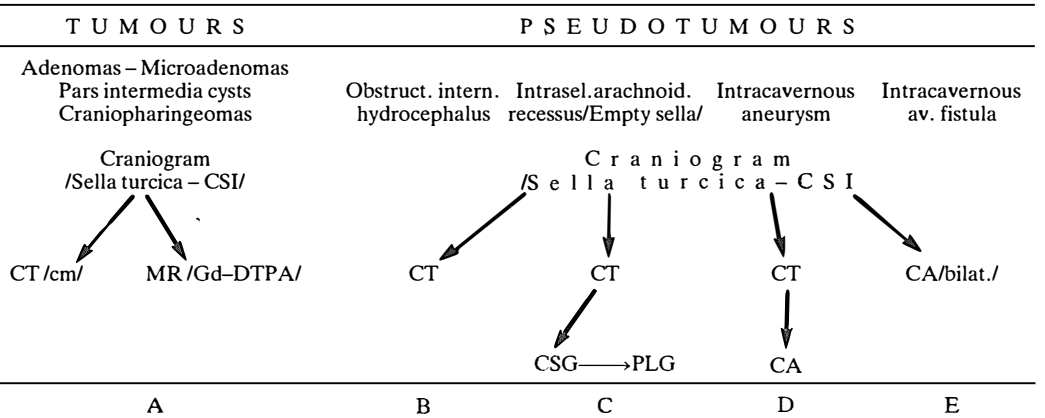
A normal pituitary gland has the attenuation values between 14-25 HU on the precontrast scan, and 43 ± 15 HU on the post contrast scan, somewhat less in the anterior part than in the posterior.[8] Turaki and Watanabe[8] report that an average height of the normal pituitary gland ranges between 5.3 ± 1.7 mm, regardless sex (Figure 4a). The upper contour of the pituitary gland is flat or slightly concave in downward direction. According to Syvertsen and Haugh-

ton,[9] its greatest height is 7 mm in females and 5 mm in males. Height values exceeding the mentioned limit and a convex upper contour are reliable signs of tumor. Pituitary gland adenoma has the attenuation of 25-38 HU on the precontrast scan and its appearance is non-homogenenous. The pituitary gland requires multiplanar scanning in axial and coronal planes, which enables imaging of asymmetric and suprasellar growth.

Microadenomas are very frequent tumors. Robertson and Newton[10] have found 73 (50%) microadenomas among 146 pituitary gland adenomas, of which prolactinomas were the most frequent. A majority of authors failed to find skeletal changes in the sella. The mentioned authors[10] found on conventional tomograms in all cases discrete changes in form of slight enlargements, most often on the anterior wall, and in prolactinomas on the whole sellar wall. Syvertsen and Haughton[9] consider that microadenomas less than 10 mm of size cause no skeletal changes of the sella. It is possible to discover microadenomas only on the postcontrast scan by applying 100-150 ml of contrast medium in 2-3 min and by the reconstruction in sagittal and coronal planes. Prolactinomas have a low density, but chromophobe and basophile adenomas are mostly hyperdense (Figure 4b). The pars intermedia cysts, which are located dorsally near the neurohypophysis, are very interesting (Figure 4c). Turski and Watanabe[8] reported these cysts in 13-20% of autopsy materials and asserted that they presented normal variations without clinical significance. Parent and Bebin[11] found post-mortem 8-9% occult and non-secreting adenomas, whereas Robertson and Newton[10] have registered 25% of non-secreting adenomas. Turski and Watanabe[8] described hypodense changes in the pituitary gland, which represented breast carcinoma metastases in 25% of hypophysectomised females.

Most authors consider that the magnetic resonance imaging (MRI) is more sensitive method for discovering the pituitary gland microadenomas than CT.[12,13] The diagnosis of microadenomas has been improved by means of paramagnetic contrast medium Gd-DTPA. Even if the contrast medium can sometimes mask microadenomas, the above mentioned authors[12,13] have discovered 30% of them in the cases of negative CT examinations. Even though MR yields very favourable results, many findings show that diagnosis by high-resolution CT in microadenoma is very successful.[14,15,16]

Table 1. Examination algorithm of intrasellar tumors and pseudotumors. MR – magnetic resonance, CT – computed tomography, CA – carotid arteriography, CSG – cisternography, PLG – planography, CSI – craniosellar index, CM – contrast medium.



Intrasellar pseudotumors

1) Obstructive internal hydrocephalus: Liquor flow obstruction behind the third ventricle, due to some slow developing processes such as aqueductus Sylvii stenosis or basal arachnoiditis, gives rise to hydrocephalus with the infandibular recess enlargement. It exerts an indirect pressure on the sellar diaphragm, or directly enters into the hypophyseal fossa in the case of hypoplastic or agenetic diaphragm. Its pressure and pulsations cause enlargement of the sella and its entrance as well as hypopituitarism (Figure 5a). As far as it occurs in the early childhood, the condition results in a pituitary nanism as it has been the case in our six infantile patients.[17]

2) Intrasellar arachnoid recess (empty sella): We have denoted this entity with the expression »recessus intrasellaris arachnoideae«. The old name »empty sella« was not suitable since it designated the consequence but not the etiology of this entity. So far it is believed that this is a congenital anomaly with parallel anomalous development of the subarachnoid space and agenesis of the sellar diaphragm. This leads to the herniation of the suprasellar cistern into the

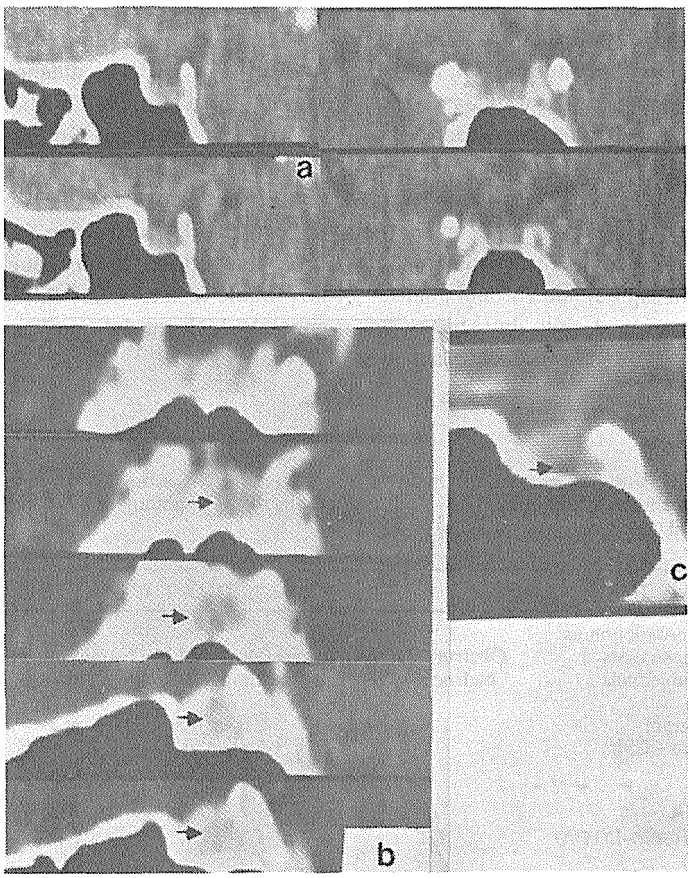


Figure 4. (a) – normal sella on the postcontrast CT scans in sagittal and coronal planes: **(b)** – a low–density lesion < 10 mm in the anterior and lateral part of the pituitary gland in both planes (prolactinoma – arrow); **(c)** – pars intermedia cyst (arrow).

hypophyseal fossa with its partial or complete filling. This entity is twice more frequent in females. So far, we have reported on 12 patients plus four included later on; of these 10 were females and 6 males.[17,18] General radiologic characteristic of this entity is the enlarged sella

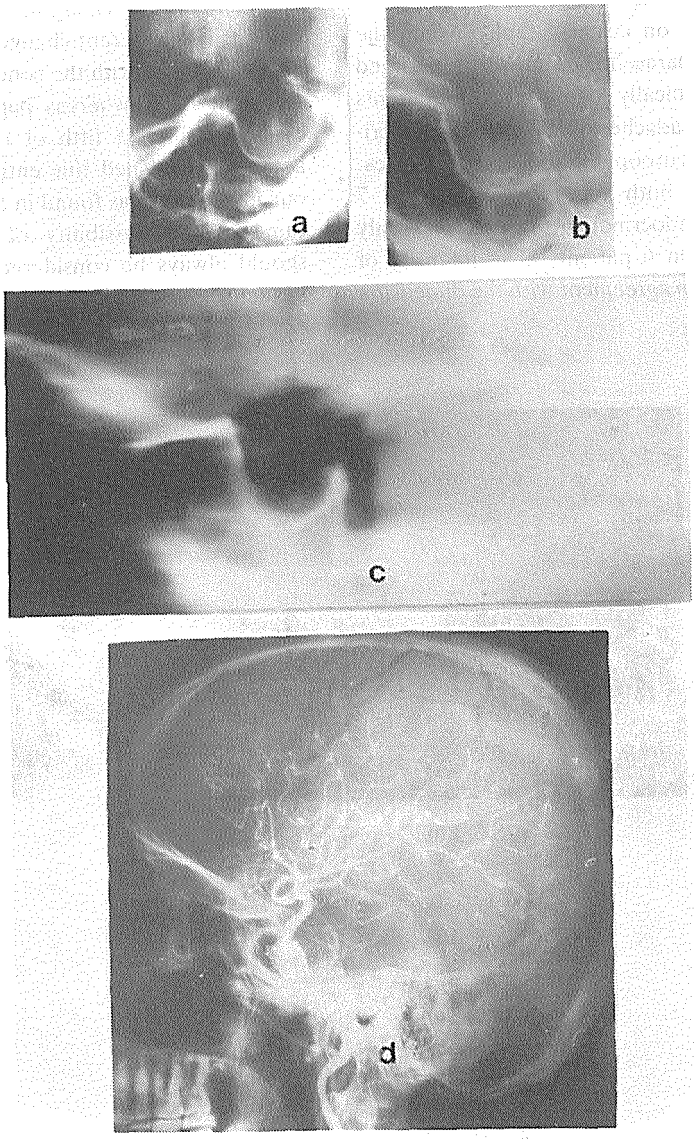


Figure 5. (a) – enlarged sella and its entry in the case of obstructive internal hydrocephalus due to the stenosis of aqueductus Sylvii with herniated enlarged intrasellar infandibular recess of the third ventricle. CSI–8,2. The sella simulates primary sella as well as the real intrasellar tumor (nanosomia pituitaria); **(b)** – enlarged sella due to the intrasellar arachnoid recess (empty sella). CSI–9.1; **(c)** – intrasellar arachnoid recess filled with air on cisternography, totally occupying the hypophyseal fossa. Enlarged sella and its entry as well as the parasellar cisterns (hypopituitarism and concentrically narrowed sight field; **(d)** – intracavernous carotid aneurysm causing asymmetrical changes of the sellar wall and its size.

which simulates the primary sella seen in the intrasellar tumor (Figure 5b). The hypophyseal fossa is filled partially or totally with arachnoid pseudocyst. It is always filled with air or positive contrast medium on cisternography, when the suprasellar and parasellar cisterns are enlarged (Figure 5c). Clinically two thirds of patients present with a headache as well as with endocrinological and neuroophthalmological changes. Thus we found both types of changes in 7 patients, only endocrinological in 3, and only opthalmological in 6 patients. The intensity of these changes is in agreement with the dimension of the intrasellar recess. One half of patients presented with diencephaloses and one quarter with mild or stronger hypopituitarism. Of the ophthalmological changes, more than a half of patients had different changes in the sight field / almost one half with the concentric narrowing of the sight field, whereas papillary atrophy was evidenced in one fifth of the patients. Soviet authors established this entity in 2.5%, but in our material it was found in 5% of all intrasellar tumors. The possibility of this pseudotumor should always be considered owing to its high incidence.

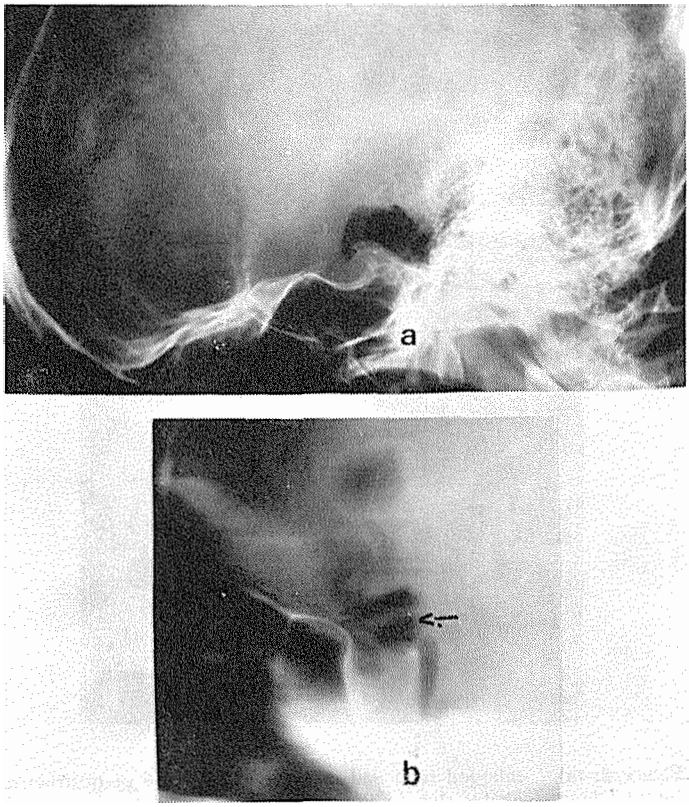


Figure 6. (a) – typical appearance of opticochiasmal arachnoiditis on cisternography, with stretched interpeduncular cistern and without air penetration toward the opticochiasmal cistern (posttraumatic basal arachnoiditis with concentrically narrowed sight field); **(b)** – cystic opticochiasmal arachnoiditis on cisternography with the supradiaphragmal airfilled pseudocyst – arrow (postirradiational cystic arachnoiditis with strong concentrally narrowed sight field).

3) Intracavernous aneurysm of the internal carotid artery: This location of the internal carotid artery is very rare. It can be calcified and thrombosed. The location and permanent pulsation of the aneurysm influences the sellar wall and can generate its enlargement (Figure 5d).

4) Intracavernous a-v fistula: The enhanced blood-flow fast change of the pressure in the fistula can produce changes in the sella.

5) Diagnostic algorithm: The intrasellar pseudotumors are very rare, with the exception of the intrasellar arachnoid recess. According to our findings, the sellar changes caused by them are almost the same as by the real primary sella. The initial examination CT in almost all pseudotumors as well as in intrasellar tumors (Table 1 – B,C,D).

In the obstructive internal hydrocephalus we can visualize the intrasellar hypodensity of enlarged infundibular recess of the third ventricle and establish the cause of obstruction by CT, which is enough to explain the intrasellar changes (Table 6,B).

In the intrasellar arachnoid recess the suprasellar and intrasellar hypodensity as well as usually narrower ventricle system accentuates the doubt on this entity, but a definitive diagnosis requires cisternography on which the intrasellar recess is always filled with air or positive contrast medium (Table 6,C).

A round or oval hyperdensity in the cavernous sinus evidenced by CT is enough to suspect the presence of intracavernous aneurysm of the carotid artery which can be confirmed by carotid arteriography (Table 6,D).

The diagnosis of intracavernous a-v fistula with clinical symptoms such as noise and pulsating exophthalmus represents no problem. Ipsilateral and contralateral carotid arteriography is the method of choice (Table 6,E). As far as there is a suspicion of an orbital tumor in nonpulsating exophthalmus, fistula can be discovered by enhanced CT or CT angiography.

From the point of differential diagnosis, it is necessary to mention cystic opticochiasmal arachnoiditis. Most frequently this disease is of posttraumatic and postirradiational etiology. It can cause a diagnostic problem in relation to the intrasellar arachnoid recess. These pseudocysts are rarely filled with air on cisternography, and lie, as a rule, over the sellar diaphragm causing no sellar changes (Figure 6a,b). Its intrasellar location can be present only when there exists the agenesis of the sella diaphragm. Some authors refer to the intrasellar arachnoid recess as to the cystic arachnoiditis. The cystic opticochiasmal arachnoiditis has characteristic ophthalmologic symptoms such as concentric narrowing of the sight field, with preserved sight and ophthalmologically normal arterial caliber. With added planography, cisternography represents the method of choice.

Conclusion

The diagnostic consideration of the sellar region is complex and based upon clinical and radiological findings.[19] Since the patient is referred to different specialists because of a headache, endocrinological and ophthalmological symptoms, and finally also to the radiologist, he must dispose of the clinical information. Therefore, a close cooperation with the corresponding clinicians is of essential importance. Initial examination and conclusion about the sellar changes may not be based upon an individual subjective estimation »by eye«. In limited cases, craniosellar index is the only reliable parameter to establish the sellar size. Every small sella in the sagittal plane may not be invariably interpreted as a pathologic sella. Also, the possibility of microadenoma existence in the cases of normal sellar size and appearance should not be excluded, which justifies the need of further investigations. The greatest difficulties are caused by pseudotumors, particularly the intrasellar arachnoid recess, since the sellar changes cannot be differentiate from those seen in intrasellar adenomas. In that case, the endocrinologic changes can be very helpful. Namely in a great majority of pituitary gland adenomas (except chromophobe

adenomas) hyperpituitarism is prevailing whereas hypopituitarism is dominant in pseudotumors because of the compression exerted on the pituitary gland. The neuroophthalmologic changes are not specifically characteristic for any entity; they can be similar for all processes associated with the suprasellar growth. Therefore, the radiologist has a great responsibility for further correct diagnostic algorithm.

The sellar region represents a complex neuroradiological problem. Because of the variety of clinical symptoms, the patients are referred to different specialists, but the radiologic examinations, including the initial standard sella examination, are very important for correct final diagnosis. Therefore, it is essential for the radiologist to be familiar with the clinical symptoms and radiologic images of different intrasellar tumors and pseudotumors.

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Simultaneous measurement of faecal alpha – 1 – antitrypsin, In – 111 – oxin–granulocyte and Cr – 51 – albumin excretion in assessment of disease activity in chronic inflammatory bowel disease

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In 16 patients with chronic inflammatory bowel disease (CIBD) (active, n=10; inactive n=6) the inflammatory activity was assessed by faecal In-111 excretion using In-111-oxin labelled 'pure' granulocytes. The enteral protein loss was simultaneously determined by faecal Cr-51 albumin excretion and compared with alpha-1-antitrypsin (AT) stool concentration and clearance in identical native and lyophilised stool specimens.

Faecal In-111(%)- and Cr-51(%) excretion correlated highly significantly ($r = 0.42$, $p = 0.001$), whereas alpha -1- AT clearance (ml/d) in lyophilised stool showed only a weak correlation ($r = 0.1$, $p = 0.049$) with In-111-excretion. Cr-51 albumin excretion correlated with alpha-1-AT stool concentration(mg/g) in the native stool ($r = 0.17$, $p = 0.04$) and alpha-1-AT-clearance (ml/d) in lyophilised stool ($r = 0.12$, $p = 0.05$). In spite of the correlation between In-111- and Cr-51-excretion, both values were different in the individuals. This was due to the different time course of the decrease of inflammatory activity and protein loss, especially under drug treatment. But always both the Cr-51 and alpha-1-AT excretion run parallel.

In conclusion, inflammatory activity and intestinal protein loss run parallel in CIBD. Alpha -1 AT stool concentration and alpha -1- AT clearance can be used as a marker of intestinal protein loss. Under steroid of 5-ASA the inflammatory activity decreases more rapidly, than the intestinal protein loss does.

Key words: inflammatory bowel disease; feces–analysis; alpha 1–antitrypsin; indium radioisotopes; chromium radioisotopes

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Introduction

In a previously published study[1] we compared alpha 1 antitrypsin (AT) faecal excretion and clearance with faecal excretion of In-111-labelled granulocytes in patients with chronic inflamma-

tory bowel disease (CIBD). No correlation could be found between this highly specific marker of intestinal inflammation and the intestinal protein loss measured by alpha-1-AT. We have concluded that the enteric protein loss does not only depend on mucosal inflammation, but may be influenced by prior resections, complications like stenosis, extent and localisation of disease of other factors such as bacterial overgrowth, secondary intestinal lymphangiectasia and other unknown parameters, too. *Karbach, Florent and Hill*[2, 3, 4, 5] found an accurate correlation of faecal excretion and clearance of alpha-1-AT, and the intestinal protein loss as diagnosed by Cr-51-albumin, whereas *Haeney et al*[6] failed to confirm such a correlation between these parameters. On the other hand, *Saverymuttu et al*[7] found in a small number of patients a correlation between faecal In-111 lekocyte excretion and faecal Cr-51-excretion.

For elucidation of these discrepancies we designed a prospective study in patients with CIBD, to compare simultaneously the faecal alpha -1-AT, In-111-oxin granulocyte and Cr-51 albumin excretion for the assessment of disease activity.

Methods

Patients

Thirteen patients with Crohn's disease (30.7 +/- 9-4 years; range: 20 - 48 years, 5 women, 8 men) and 3 patients with ulcerative colitis (31.6 years +/- 12.5years; range 23-47 years, 1 woman, 2 men) were prospectively investigated. Seven patients with Crohn's disease had ileocolitis while 2 respectively 4 patients suffered from ileitis and colitis solely. Two patients with ulcerative colitis had a manifestation of rectum and sigma, another patient suffered from pancolitis.

The diagnosis of Crohn's disease was based on the criteria published by the European Cooperative Crohn's disease Study Group (ECCDS).[8] Ulcerative colitis was characterised by typical endoscopical and histological features and the characteristic localisation pattern. Infectious causes have been excluded. Alpha -1- AT stool concentration could be determined in 15 patients. The percentage of faecal excretion of In-111-labelled autologous granulocytes and Cr-51 albumin was studied simultaneously in identical stool samples. Small bowel radiographic examination and coloileoscopy as well as routine laboratory parameters, orosomucoid, serum alpha-1-AT and clinical indices (SDAI, AI, TRUELOVE INDEX)[9, 10, 11] were evaluated in all patients. These investigations were all carried out within eight days.

Patients with CIBD were classified as 'active' if the following criteria were fulfilled: for all cases of CIBD histologically diagnosed acute bowel inflammation; additionally for Crohn's disease CDAI>150 and/or A I van HEES>100; for ulcerative colitis 'severe' or 'moderately severe' according to the TRUELOVE index.[10] Eighteen healthy volunteers (24.8+/- 3.3 years, range 19-34 years, 13 women, 5 men) served as controls for the determination of alpha-1-AT parameters. All of them completed a reliable stool collection. In-111-faecal and Cr-51 faecal excretion was non available in patients in this control group because of the radiation exposure.

Determination of Alpha-1-Antitrypsin (AT)

Serum alpha-1-AT concentration was measured by laser nephelometry with a monospecific antiserum against alpha-1-AT (Behring AG, FRG) and expressed in mg/dl.

Faecal alpha-1-AT was determined by radial immunodiffusion using commercially available partigen plates (LC-partigen, Behring AG, FRG). According to the method of *Crossley and Elliott*[12] an aliquot of lyophilised stool (250mg) was extracted with 5 ml 0.9% saline by mixing over 30 minutes at 22°C. Using native stool specimens an aliquot of stool (1g/ wet weight) was extracted with 5ml 0.9% saline. After centrifugation (12000 g for 15 minutes at 4°C) 20ul of the supernatant were placed into the wells of partigen plates. The diameters of the precipitating rings were measured after 72 hours. A reference curve established by serum of known alpha-1-AT concentration served as control. Faecal alpha-1-AT was expressed in mg alpha-1-AT/

g dry respectively wet stool weight.

Median daily stool weight was determined from four-day stool collection and alpha-1-AT clearance was calculated by the formula: C = F x W/P (C = clearance, F = faecal alpha -1-AT (mg/g stool), W = daily stool weight (g) and P = serum alpha -1-AT (mg/dl).

Using lyophilised stool, faecal alpha-1-AT concentrations > 0.6 mg/g and alpha-1-AT clearance > 81 ml/d were diagnosed as pathological[1]. In case of native stool specimens, faecal alpha-1-AT concentrations > 0.2 mg/g were considered to be pathologic.

In-111-oxin granulocyte labelling and determination of faecal In-111-excretion

Isolation of white blood cells and labelling of granulocyte preparations with In-111-oxin were carried out as described[13]. In-111-activity of stool samples was measured in a gamma counter and expressed as per cent of the reinjected dose (4.2 MBq = 250 μCi) after decay correction. A faecal excretion < 2% was judged to be normal, > 2% to be pathologic.

Per Cent excretion of Cr-51-Albumin

Human albumin labelled with Cr-51 in physiologic saline for human use (specific activity 15-50 μCi/mg albumin; concentration 150-500 μCi Cr-51/ml; < 3% free Cr-51) was commercially obtained from BEHRING AG, FRG. Cr-51 labelled human serum albumin and autologous IN-111-oxin labelled granulocytes were simultaneously injected intravenously. Radioactivity was measured in the collected faeces.

Normally less than 1% of the radioactivity of intravenously injected Cr-51 labelled albumin is excreted in the faeces over a four day period[12]. Protein loss was diagnosed if the faecal excretion of Cr-51 increased over 1.5% of the injected dose.

Simultaneuous measurement of the faecal In-111 and Cr-51 excretion

After 4-day faecal collection in daily aliquots the total In-111- (γ: 90%:173 keV : 84%:247 keV) and Cr-51 (γ: 10%:323 keV) in the faeces or lyophilised stool correlated significantly with window between 110 and 300 keV and measurement of activity in the different windows was performed by the formula: In-corr = (In) - 0.48 (Cr) and Cr-corr = (Cr) - 0.01 (Cr). After the calculation of the measured activity as a percentage of the injected dose a decay correction was performed.

Statistical analysis

Statistical analysis was undertaken using the arithmetic mean and its standard error of the mean ($\bar{x}$+/- SEM) and the SPEARMAN's rank correlation coefficients. All correlation coefficients with p>0.05 were considered not significant.

Results

The faecal In-111 and the faecal Cr-51 excretion correlated significantly ($r = 0.42$; $p < 0.001$) in 17 patients with CIBD (Table 1). In comparison with these two radioactive parameters only the alpha-1-AT clearance in lyophilised stool showed a slightly significant correlation with the faecal In-111-excretion ($r = 0.01$, $p < 0.049$, $n = 15$). Neither the clearance measured in native stool nor the alpha-1 AT stool concentrations in native or lyophilised stool correlated significantly with the faecal In-111-excretion (Table 1).

There was a slightly significant correlation between the alpha-1 AT clearance in lyophilised and native stool and the faecal Cr-51-albumin excretion ($r = 0.12$; $p < 0.05$, $n = 14$; $r = 0.17$, $p < 0.04$, $n = 16$), while the alpha-1-AT stool concentration did not correlate with this radioactive stool parameter (Table 1).

All patients classified as suffering from inactive CIBD ($n = 6$), excreted less than 2% of the intravenously injected In-111-activity (treatment : 0.64 +/- 0.2; no treatment: 0.12%) (Figure 1,2). Patients classified as having active CIBD ($n = 10$) excreted more than 2% regardless the current treatment (Figure 3,4) (treatment: 14.6 +/- 7.4%; no treatment : 8.2 +/- 1.5%).

The Cr-51 albumin excretion was slightly elevated (1.8%) in an untreated patient who was clinically inactive (Figure 2), whereas 5 patients with inactive disease under steroid and 5 – ASA treatment (steroids and 5-ASA: n = 2; 5-ASA n = 3) excreted pathologically high amounts of Cr-51 (7.8 +/- 2.1%) (Figure 1). All patients with active CIBD (n = 10) showed elevated levels of Cr-51 labelled albumin (Figure 3,4) (treatment: 16.4 +/- 1.9%; no treatment : 25.1 +/- 2.7%).

The alpha-1-AT clearance (lyoph) in all the patients with inactive disease was elevated (treatment: 250+/– 65 ml; no treatment: 320 +/- 100 ml) (Figure 3,4). Patients with inactive disease, however, showed a slightly elevated clearance as well (no treatment: 153 ml, treatment: 110 +/- 43

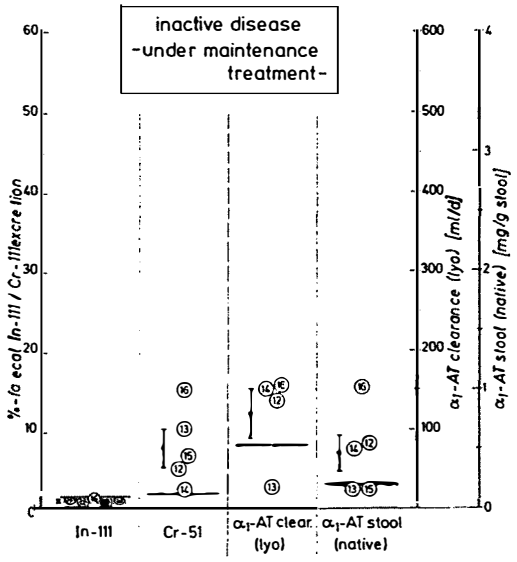

Figure 1. Results of faecal In-111 and Cr-51 albumin activity and alpha - 1 - antitrypsin clearance in lyophilized stool and alpha - 1 - antitrypsin concentration in native stool in patients with inactive disease under maintenance treatment.

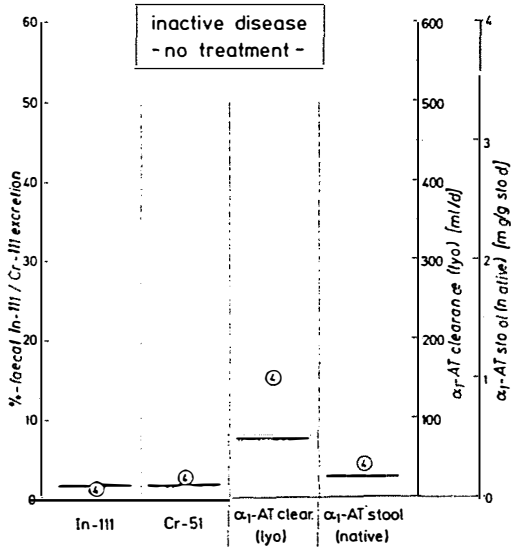

Figure 2. Results of faecal In-111 and Cr-51 albumin activity and alpha - 1 - antitrypsin clearance in lyophilized stool and alpha - 1 - antitrypsin concentration in native stool in one patient with inactive disease without any treatment.

Table 1. Spearman's rank correlation coefficient and significance between faecal In-111 oxin and Cr-51-albumin excretion, and alpha - 1 - antitrypsin stool concentration and clearance in native and lyophilized stool.

Correlated Parameters	Correlation Coefficient (r)	Significance Level (p)	Significance	Patient Number (n)
In-111 – Cr-51	0.42	0.001	s	16
In-111 – stool nat	0.06	0.1	n.s.	16
In-111 – stool lyo	0.14	0.09	n.s.	16
In-111 – clear nat	0.02	0.14	n.s.	15
In-111 – clear lyo	0.01	0.049	s	15
Cr-51 – stool nat	0.17	0.04	s	16
Cr-51 – stool lyo	0.2	0.19	n.s.	16
Cr-51 – clear nat	0.11	0.16	n.s.	14
Cr-51 – clear lyo	0.12	0.05	s	14

nat = native; lyo = lyophilised; s =significant, n.s. not significant

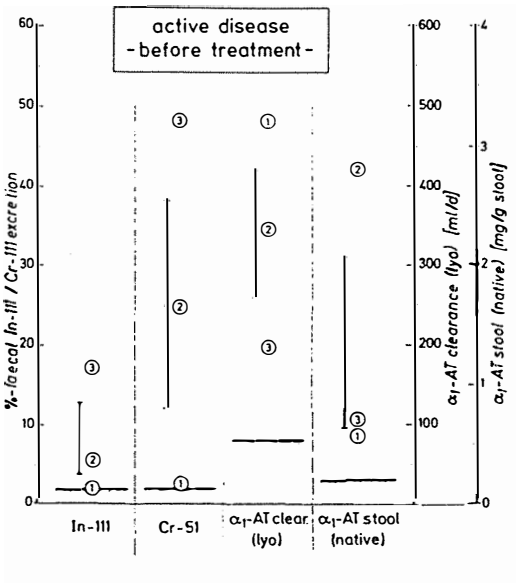

Figure 3. Results of faecal In-111 and Cr-51 albumin activity and alpha - 1 - antitrypsin clearance in lyophilized stool and alpha - 1 - antitrypsin concentration in native stool in patients with active disease before treatment

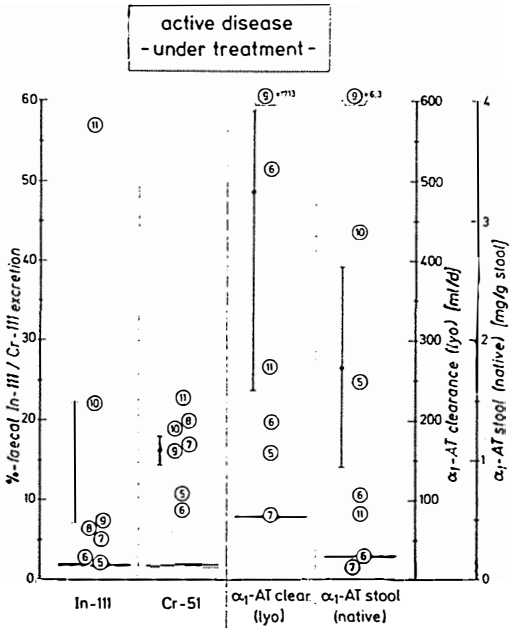

Figure 4. Results of faecal In-111 and Cr-51 albumin activity and alpha - 1 - antitrypsin clearance in lyophilized stool and alpha - 1 - antitrypsin concentration in patients with active disease under treatment.

ml) (Figure 1,2).

Comparable results could be established for the native faecal alpha-1-AT concentration. All the patients with active (treatment: 0.6+/- 0.24 mg/g ; no treatment: 0.64 +/- 0.07 mg/g) and inactive disease (treatment: 0.55 +/- 0.17 mg/d; no treatment: 0.28 mg/g) showed pathologically elevated levels (Figure 1–4).

Considering the small number of patients examined, no correlations between the single parameters were calculated.

The faecal In-111 excretion in 14 patients was lower than the actual Cr-51 excretion. Only in 2 (Figure 4: pat. 10,11) patients with Crohn's disease (1 male, 1 female) the In-111 excretion (22%, 57%) widely exceeded that of Cr-51 (19%; 23%). The male patient underwent ileocaecal resection 10 years before. The female patient showed an apparently low serumalbumin in comparison with all the other patients.

Discussion

In accordance with previously published data,[14] faecal In-111 excretion in all patients with inactive CIBD was normal (< 2 %/ 96 h). Patients with active inflammatory bowel disease, however, excreted more than 2 %/ 96 h of the injected In-111 activity. By this way active and inactive diseases were clearly separated (Figure 1, 2, 3, 4). Comparable findings were reported by other groups dealing with the determination of quantitative feacal In-111 labelled leukocyte excretion in the assessment of inflammatory bowel disease.[7] This method, which has been made still more specific for acute inflammation by labelling pure granulocyte fractions rather than conventional mixed leukocyte preparations,[15] can be used as the golden standard of intestinal inflammatory activity. To our opinion this is justified because of the excellent correlation of the faecal In-111 excretion with endoscopy and histology as well.[16]

The gastrointestinal loss of protein is a major factor in the hypoproteinemia of CIBD.[17] In comparison with other methods using radionuclides for determination of intestinal protein loss, the use of Cr-51 albumin is simple and reliable.[18] The sensitivity of this test is very high. No false negatives have previously been found in more than 200 studies.[19,20] According to these data, all our patients with active CIBD before and under treatment excreted more than 2% of the injected Cr-51 (Figure 3,4). Patients under maintenance treatment showing no signs of disease activity still excreted pathologically high amounts of albumin whereas the faecal In-111-excretion was already within the normal range. Corticosteroids and sulfasalazine (5-ASA) both block the synthesis of lipoxygenase products in vitro. Corticosteroids additionally affect lymphocyte proliferation, and sulfasalazine blocks lymphocyte cytotoxicity.[21,22] Either of these effects can contribute to their therapeutic efficiency in CIBD. In-111-excretion correlated significantly with Cr-51 albumin excretion (Table 1).[7] This can be well explained. In-111-excretion is in correlation with the number of diseased segments.[7,14] On the other hand, therapy with corticosteroids and sulfasalazine primarily normalises In-111 excretion, which correlates with the leukocyte infiltration of the diseased bowel mucosa[7] and clinical activity. The remaining high Cr-51 albumin excretion at that time seems to reflect the diseased mucosa with a still increased capacity of albumin permeability. By this way the normalisation of the inflammatory mucosal infiltration preceeds the enteral protein loss. Furthermore, the protein loss from the gut measured with Cr-51-albumin excretion, does not always reflect the actual individual degree of intestinal inflammation.[1] Our own histomorphological studies seem to confirm this. We found a significant increase of the granulocyte infiltrate in biopsy specimens with increasing amounts of faecal In-111-oxin excretion, whereas the intestinal protein loss run parallel to the lymphoplasmacellular infiltration.[23] We previously summarized that the enteric protein loss does not only depend on the mucosal inflammation but may also be influenced by prior resections, complications like stenosis, extent and localisation of disease, bacterial overgrowth and lymphangiectasia.[1] Obviously it may be influenced by the current medical treatment, too.

There was no correlation between the faecal In-111 excretion and alpha-1-AT stool concentration in native or lyophilised stool (Table 1). These findings are in accordance with previously published data.[1] A correlation between faecal Cr-51 excretion and lyophilised alpha-1-AT stool concentration failed as well, whereas a slight correlation could be calculated between the faecal Cr-51 loss and the native alpha-1-AT stool concentration. According to this faint correlation in all the patients with increased faecal Cr-51 loss, however, the alpha-1-AT stool concentration (native) was increased as well (Figure 1.) These results run parallel with the reports of other authors[2,3,5] and confirm faecal alpha-1-AT as a parameter of intestinal protein loss.

The protein loss determined by alpha-1-AT clearance in lyophilised stool correlates with In-111 faecal excretion. No clear distinction between active or inactive disease, however, is possible in an individual case. Perhaps these results and discrepancies can be explained to some extent by biochemical changes of alpha-1-AT in the intestine resulting in two main alpha-1-AT biochemical forms of respectively 38 000 51 000 molecular weight which has recently been reported.[24]

The reported data do not provide statistically relevant information, because of the small number of patients examined and the lack of controls in the radionuclide study due to ethical aspects of radiation exposure to volunteers, but the results are confirmed by non-radioactive permeability measurements.[25] Nevertheless, the data clearly demonstrate a correlation between intestinal inflammatory activity and intestinal protein loss. Both parameters, however, show a normalisation at different times, especially under drug therapy.

Obvious differences between the determination of alpha-1-AT in native or lyophilised stool are not discussed in this paper, because studies

in a greater number of patients will be more informative (in preparation).

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From practice for practice

(Solution of the problem on p. 15)

1. Chest radiogram: Upper front mediastinum extended to the right. Mediastin. diameter on the level of the 6th rib is 70 mm, thorac. diameter on the same level is 270 mm; rate 0.26.
2. Suspicion of malignant lymphoma. In differential diagnosis the possibility of thymoma, carcinoma of the central bronchus or any other disease should be considered.
3. Suspicion of Hodgkin's disease is based on the evidence of skin itch and mass of enlarged neck lymph nodes, specially when these symptoms are associated with enlarged mediastinum. Lumbago, pains in the legs and paresthesia can be due to the enlarged retroperitoneal lymph nodes. The possibility of paraneoplastic syndrome should also be considered.
4. Diagnosis of Hodgkin's disease is confirmed by fine–needle aspiration biopsy of the enlarged lymph nodes on the left side of the neck.
5. Confirmed diagnosis of Hodgkin's disease requirs staging of the disease in order ot determine its extent. As histologic type should be established as well, the following procedures are suggested:
   a) *Abdominal US:* no evidence of enlarged lymph nodes in the abdomen.
   b) *Thoracal and abdominal CT:* tumorous formations are seen in the right front part of the mediastinum and on the left side of the neck. There is no evidence of malignant lymphoma in the liver, spleen and retroperitoneum.
   c) *Pedal lymphography:* Evidence of displaced and structurally altered retroperitoneal lymph nodes on the level of L2–L3 paraaortally to the left, i.e. the initial site of malignant lymphoma. In Hodgkin's disease, pedal lymphography is indicated in the case of negative US and CT findings. This procedure enables us to assess non only the size of lymph nodes, but also their structure.
6. Ga–scintiscan images the sites in the mediastinum and left supraclavicular region, whereas there is no evidence of Ga–67 uptake under the diaphragm.
   Lymph nodes on the left side of the neck are surgically removed for histologic examination and determination of the type of malignant lymphoma. Histologic diagnosis: Hodgkin's disease, mixed–cell type. Thus the diagnostic and staging procedures are completed and the type of disease determined as Hodgkin's disease, Type IIIA.
7. *Therapy:* chemotherapy according to MOPP/ABV schedule

M– Mustagen (Antimit)	A– Adriablastin
O– Oncovin	B– Bleomycin
P– Procarbasine	V– Vinblastine (Velbe)
P– Pronison	

   After completed chemotherapy, irradiation of the affected sites with the dosis of 30 cGy
8. *Prognosis:* relatively favourable

Radiol Oncol 1992; 26: 45-55.

Survival and disease–free interval of malignant melanoma patients in relation to the prognostic factors

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In the present study 236 patients with malignant melanoma of the skin treated at the Institute of Oncology in Ljubljana during the years 1970–1983 were included, 100 males and 136 females, with mean (and median) age of 54 years, ranging from 16 to 92 years. Overall 5-year survival for the whole group was 57.5%, and median survival 108 months; 5-year survival by sex was 66.4% for females and 38.5% for males, thus being markedly better in the former group of patients. Therefore, female sex can be regarded as a favourable prognostic factor. Mean disease–free interval (DFI) for all patients was 56 months, whereas 5-year DFI was 48.6%. For the female patients 5-year DFI was 52.6%, and for males 26.3%; their median DFI was 81 and 20 months respectively. Obviously better DFI observed in female patients indicate that female sex represents a favourable prognostic factor for DFI. Using univariate analysis of the influence of sex and investigated clinical and pathohistological variables on the survival in our group of patients, a statistical significant difference was established so for sex as well as for the extent of invasion by Clark levels. In order of relevance, these parameters were followed by the stage of the disease at diagnosis, the type of the primary tumor excision and patients age at diagnosis. Survival was better in the group of patients with lower grade of invasion, localized disease, as well as with radical excision off the primary tumor and younger age at diagnosis. Irrespective of sex, a statistically significant better survival was found in the group of patients with thinner melanoma. Data on preexisting nevus or other skin alterations, localization of the primary tumor and pathogenetic type of melanoma were not found to be statistically important prognostic factors for the survival and DFI.

Key words: melanoma; skin neoplasms; prognosis

Introduction

In the world, patients with malignant melanoma (MM) represent aproximately 1% of all cancer patients. The incidence of MM has been rapidly increasing, reaching its double value every 6-10 years, and likewise, also MM-related mortality has been exhibiting a trend of constant increase. Also in Slovenia, the yearly incidence of cutaneous MM by sex shows tendency of slow in-

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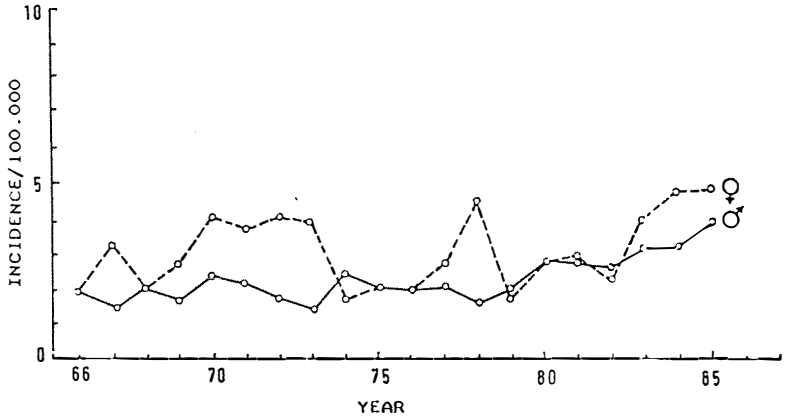

Figure 1. Annual incidence of malignant melanoma of the skin in Slovenia from 1966 to 1985 (Cancer Registry of Slovenia 1985)

crease (Figure 1) which is slightly more evident in women. In 1986, the respective rate for men was 4.7 and for women 6.1 new cases per 100.000 inhabitants, with the highest frequency of appearance evident in the middle age group[1] whereas the disease is less frequent during childhood and adolescence. Basically, MM is a rare tumor and its course is frequently unpredictable, ranging from spontaneous regressions to rapid disseminations ending in the fatal outcome, which can be partially explained by the numerous biological properties of the tumor.[2]

Considering the high mortality rates observed in patients with metastatic MM as well as ineffective treatment of the advanced disease, several authors worldwide have been investigating the natural course of MM, trying to explain the role of clinical and pathohistological characteristics as prognostic factors in evaluating the survival and disease-free interval (DFI) in order to predict the course of disease and enable sensible treatment planning. Factors influencing the survival of MM patients are associated with the stage of disease[3,4] according to TNM classification, depth of invasion and tumor volume, which are considered to be the most relevant prognostic factors. However, clinical practice and numerous publications show that the old system[5] classifying the disease into Stage I (localized disease), Stage II (regional progression) and Stage III (distant – systemic dissemination) is used more frequently.

The greatest influence of prognostic factors has been noted in Stage I MM, i.e. in the phase when the disease is still curable by surgery. These factors are as follows:

A) *Pathohistologic properties of the primary tumor:*

– tumor thickness according to Breslow,[6] classified by Balch et al.[7] into four classes with regard to their influence on prognosis and survival; greater tumor thickness is associated with worse survival[8-16]

– depth of invasion according to Clark,[17,18] which highly correlates with the survival[10-13, 19-20] and represents an additional information to »tumor thickness«;[21, 22]

– intensive growth period (radial, vertical);

– histogenetic type: superficially spread (SSM), lentiginous (LM), nodular (NM), and acral lentiginous (ALM); there SSM, LMM and ALM are associated with a better prognosis owing to their long radial phase of growth and late metastasizing, for the difference from NM which has got only the vertical phase of growth and shows tendency of early metastasizing;[10,11,19,23] generally, the subclassification of MM exhibits minor correlation with the survival, except perhaps in the cases of LMM;[2,24]

– mitotic activity, where a lower speed of cell division is associated with better survival;[11,15,25]

– ulceration: its presence in the primary tumor represents an unfavourable prognostic sign;[8,10,11,15,24,25]

– immune response;[2,11,15]

– tumor cell type (epitheloid-, spindle-cell, mixed);[2,15]

– vascular invasion;[2,11]

– microscopic satellites;[2]

– histologic signs of MM regression: a majority of authors failed to establish any correlation between the latter factor and survival.[8,10-12,15,26]

At this time, investigations such as the determination of DNA aneuploidy,[27] estrogene receptors[28] and MM cell phenotype changes[29,30] are being used only for research purposes, and therefore their prognostic relevance for predicting the course of disease has not been confirmed by clinical practice yet.

B) *Clinical factors:*

– age: younger age at diagnosis is associated with a better survival prognosis;[9-11,24, 31-33]

– sex: in a majority of studies, female sex has been considered a favourable prognostic factor;[9,10,31-33] Shaw et al.[34] have reported more MM sites on the extremities, a higher proportion of tumors of lesser thickness, and a higher proportion of patients under the age of 50 years among women, all of which is believed to be associated with a more favourable prognosis and may explain better survival rates in women.

– site: in comparison with the extremities, primary tumor sites on the trunk are considered prognostically less favourable in both sexes; the most frequent MM site in women is the lower extremities, which can partially explain their better survival;[9,10,24,25,31,33-36] lesions in the scalp have worse prognosis than those situated on the face and neck.[12,14]

The more advanced the stage of malignant disease (St. II, St. III), the lesser is the prognostic value of pathohistologic characteristics of MM (ulcerations, tumor thickness[7] for patients survival, and the higher the value of the number of metastatically involved lymph nodes,[8,14,23,37] distant metastatic sites,[23,24] tumor volume and cell kinetics[38]).

As to the numerous previously mentioned prognostic factors by different stages of malignant disease, which were reported to be of varying prognostic value for survival and DFI of MM patients, practical clinical value was confirmed for some of them only, i.e. pathohistologic characteristics of MM in the stage of localised disease (tumor thickness, depth of invasion, intensive growth period, histogenetic type), whereas of clinical variables, relevance was established with age at diagnosis, sex and MM site.

Considering better survival results in patients with localised MM, i.e. in the stages when the disease is still curable by surgery, and taking into account ineffective treatment of metastatic disease with consequentially high mortality rates, our study was aimed at following the survival and DFI of MM patients diagnosed and treated in the period 1970-1983 at the Institute of Oncology in Ljubljana, and the prognostic factors which to the largest extent influence them. We also tried to establish possible correlation between individual factor and compare our results with those reported in literature.

Patients and methods

The study represents a retrospective analysis of data on 258 MM patients diagnosed in the period from January 1, 1970 to December 31, 1983 at the Institute of Oncology in Ljubljana. The duration of follow up was till the patient's death or at least five years after the inclusion of the last patient. The last follow up examinations and the patient condition data collected at that time dated back to the first months of 1990.

Of the total 258 patients, 22 were excluded from further analysis owing to unreliable MM histology, insufficient data, or because they were lost to follow up or had »in situ« MM (Clark I), so that the number of included patients totalled to 236 (100 males and 136 females; median and mean age 54 years, range 16-92 years). Their survival and disease-free intervals were assessed in correlation with different prognostic factors

such as age, sex, stage, depth of invasion, tumor thickness, histogenetic type, cell type, extent of surgery (radicality), MM site and anamnestic data on previous nevus.

The data were processed using univariate analysis and stratified by means of BMDP 1 L statistic program[39] for survival curve calculation and difference testing. Survival curves and DFI for individual groups of patients were calculated by the method of limit product,[40] whereas the comparison and evaluation of possible statistically significant differences between the groups was done by means of log-rank test[41] or Mantel-Cox statistic test with statistical significance at $p < 0.05$.

Results

Five-year survival for all patients was 57.5%, and median survival 108 months. Following surgical removal of MM, in 129 patients dissemination or recurrence appeared within a certain period of time, i.e. they presented with DFI, whereas 84 patients were without evidence of the disease on the last follow up examination. Five year DFI was 48.6%, median 56 months.

Tables 1 and 2 present the distribution of patients according to the observed clinical and pathohistological variables and the calculated values of 5-year survival, median survival and p-values by comparing the survival curves in different subgroups of patients.

Distribution by sex shows for one third higher rate of female patients which is associated with an almost 5-times longer median survival and statistically significantly better survival than in males (5-year survival 66.4% vs. 38.5%) (Figure 2).

Five-year DFI for females was 52.6% and for males 26.3%, i.e. statistically significantly better for the former. The surviving male patients are considered free from the risk of death due to MM when they have managed to survive over 10 years, whereas the same can be said of female patients only after 16 years when they are regarded as practically cured.

Table 1. Analysis of 5-year and median survival in patients with malignant melanoma according to the sex and age distribution

	No of pat.	Survival 5-year (%)	median (months)	
SEX				
males	100	38.5	38	
females	136	66.4	175	p=0.001
AGE				
< 39	46	66.0	193	
40 – 49	50	63.6	125	
50 – 59	49	52.0	78	
60 – 69	41	33.0	39	
> 70	50	50.0	82	
< 54	120	61.4	125	
> 55	116	46.3	58	p=0.01
males				
< 54	52	48.5	49	
> 55	48	26.6	33	p=0.006
ALL	236	57.5	108	

Table 2. Analysis of 5-year and median survival in patients with malignant melanoma according to the level of invasion (Clark), tumor thickness and stage of the disease.

	No of pat.	Survival 5-year (%)	median (months)	
Clark level				
males II	5	40.0	38	
III	18	50.9	–	
IV	37	47.0	60	
V	20	27.5	17	p < 0.0001
females II	6	83.3	–	
III	43	94.7	–	
IV	26	83.4	175	
V	21	32.5	21	p < 0.0001
Thickness (mm)				
< 0.75	6	100.0	–	
0.76 – 1.50	15	85.0	–	
1.51 – 4.00	28	88.7	–	
< 4.00	22	57.3	175	p=0.003
Stage				
localized	180	63.5	141	
regional	45	22.7	11	p < 0.0001
disseminated	11	30.3	12	
ALL	236	57.5	108	

By distributing the patient into two larger age groups according to the median age (54 years) in order to assess their survival in relation to age at diagnosis, a significantly longer median survival 125 vs. 58 months) and a longer DFI, as well as

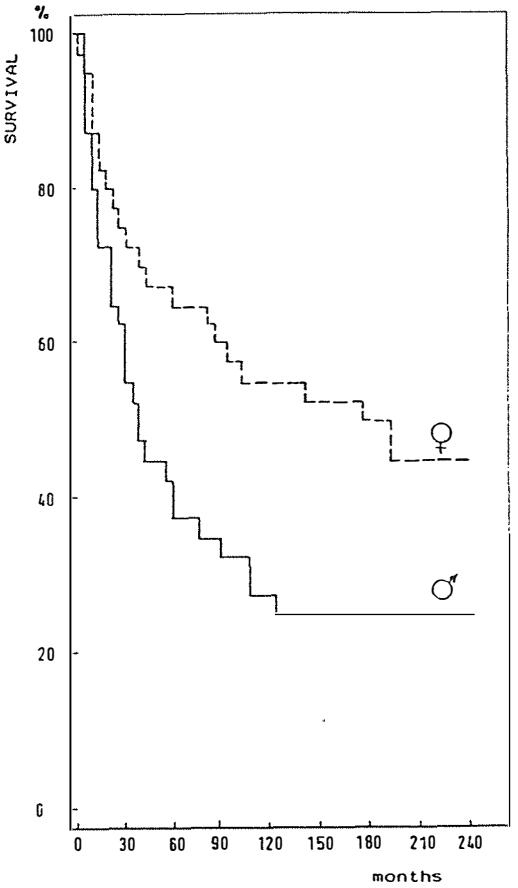

Figure 2. Survival of malignant melanoma patients treated at the Institute of Oncology in Ljubljana from 1970-1983 according to sex distribution.

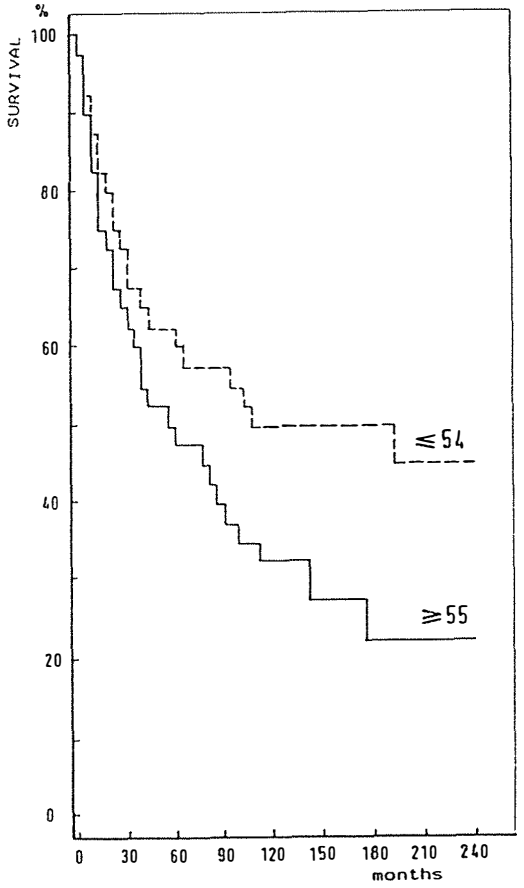

Figure 3. Survival of malignant melanoma patients treated at the Institute of Oncology in Ljubljana from 1970-1983 according to the median age.

statistically better survival and DFI were established in the younger age group (Figure 3).

Also,stratification by sex and age showed a better 5-year survival (71.6% and 48.5% for the younger, and 61.0% and 26.6% for the older age group) as well as DFI in the younger group of patients of both sexes, whereas in the same age group a better DFI was observed in female patients in comparison with males; the differences were statistically significant.

In 73% of patients with history of previous pigmented nevus a better survival and DFI were registered, though they were not statistically significant.

In 107 patients MM was situated on the extremities, in 93 on the trunk in 36 on the head and neck, whereas after stratification by sex, in males 66% of MM were found on the trunk and only 25% on the extremities, in opposition to females who had 60% of MM on the extremities and 23% on the trunk, which can partly explain the worse survival of male patients.

In males the best 5-year survival was found with MM situate on the extremities; this site was followed by the head and neck where survival results were somewhat worse, and the trunk with 29.5% survival rate; in females the 5-year survival for all three localizations ranged between

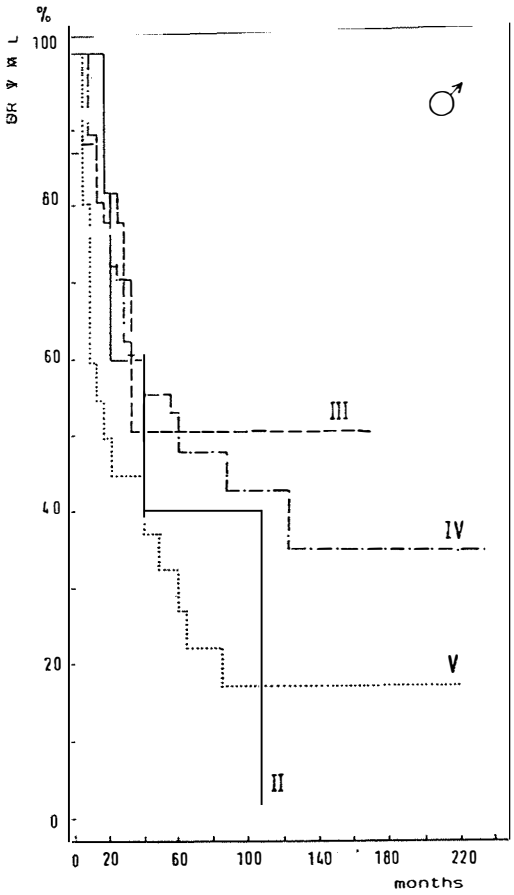

Figure 4. Survival of malignant melanoma patients treated at the Institute of Oncology in Ljubljana from 1970-1983 according to the level of invasion (Clark), group of female patients.

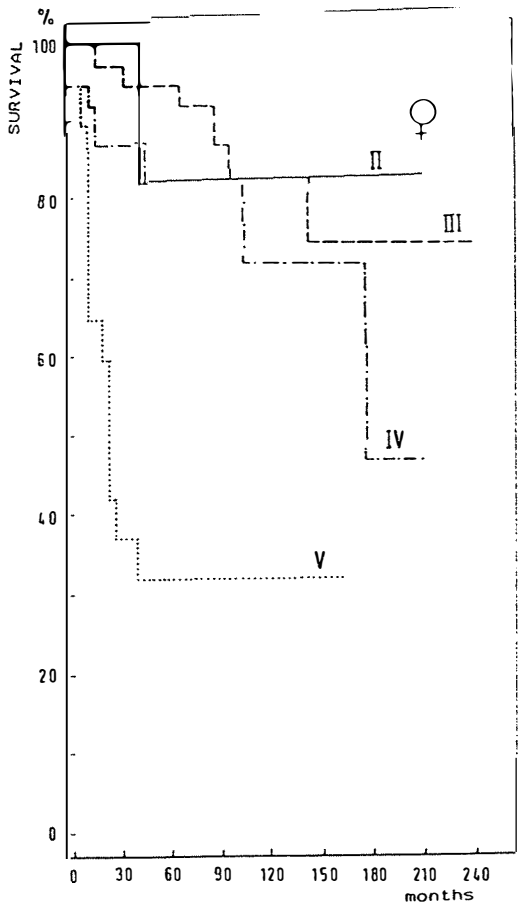

Figure 5. Survival of malignant melanoma patients treated at the Institute of Oncology in Ljubljana from 1970-1983 according to the level of invasion (Clark), group of male patients.

58-69%, without statistically significant differences in the survival curves for both sexes; the same findings applied to DFI as well.

The depth of invasion according to Clark gradation was determined in 176 of 236 patients. After data stratification by sex, a significantly better survival was established in lower grades and female patients. Thus, marked differences were seen in Clark IV and V, with respective survival rates of 47.0% and 27.5% in males, and 83.4% and 32.5% in females. The latter also presented with a higher rate of MM with lower grade of invasion (Clark III) which can be regarded as a favourable prognostic factor believed to be responsible for better survival of female patients (Figures 4 and 5). When disregarding the factor of sex owing to the insufficient number of cases, increasing Clark grade was directly associated with a decrease in 5-year DFI; the differences were statistically significant (Figure 6).

Tumor thickness according to Breslow was determined in 71 of 236 patients only, which rendered the analysis of stratification by sex meaningless. The survival (Figure 7) and DFI (Figure 8) of patients with lesser MM thickness

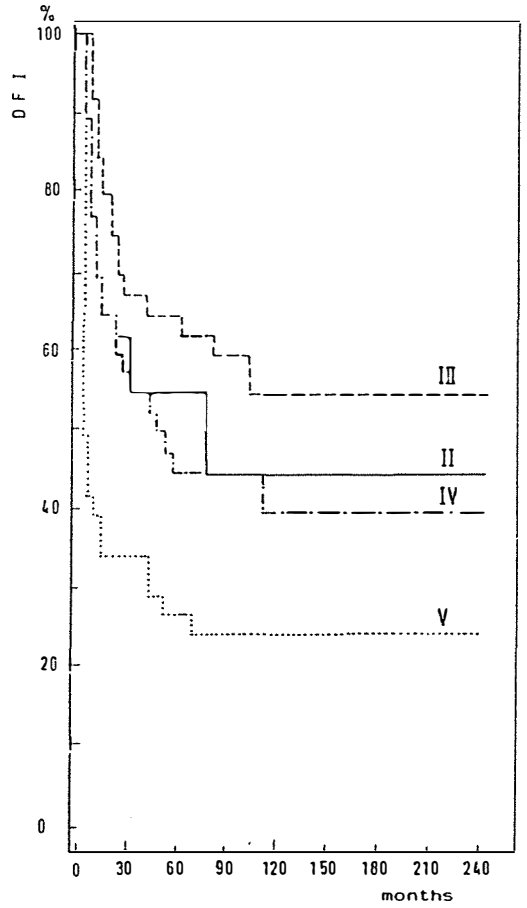

Figure 6. Disease-free interval (DFI) in malignant melanoma patients according to the level of invasion.

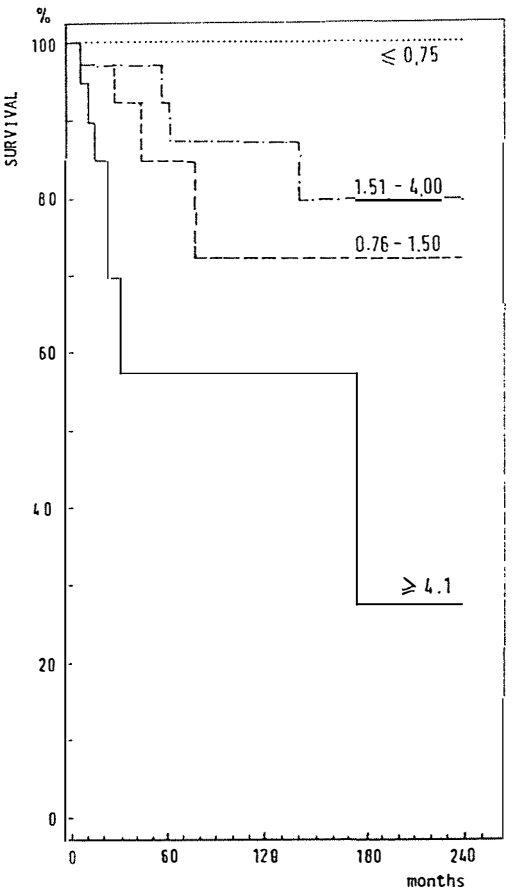

Figure 7. Survival of malignant melanoma patients according to the tumor thickness.

was significantly better; the difference is particularly evident with thickness exceeding 4.1 mm.

The stratification of patients by sex and stage of disease pointed out a statistically significant better survival in the stages of localized disease where 5-year survival for females was 76.6% and for males 45.5%. The rate of female patients with St. I MM was 80%, and of male 71%, which could partly explain generally better survival observed in all women. Males are considered to be cured after 10 years, whereas women are regarded as such only after 16 years.

Cell type of MM was determined in 19 patients only, and therefore our results pointing out a better survival of patients with epitheloid cell type vs. spindle cell type are not statistically significant.

Discussion

Univariate and stratified analysis of possible clinical and pathohistological prognostic factors enabled us to identify those which to the largest extent influenced the survival and DFI. The factors were as follows: sex, age at diagnosis, type of surgery, depth of invasion (Clark), tumor thickness (Breslow), and stage of disease at

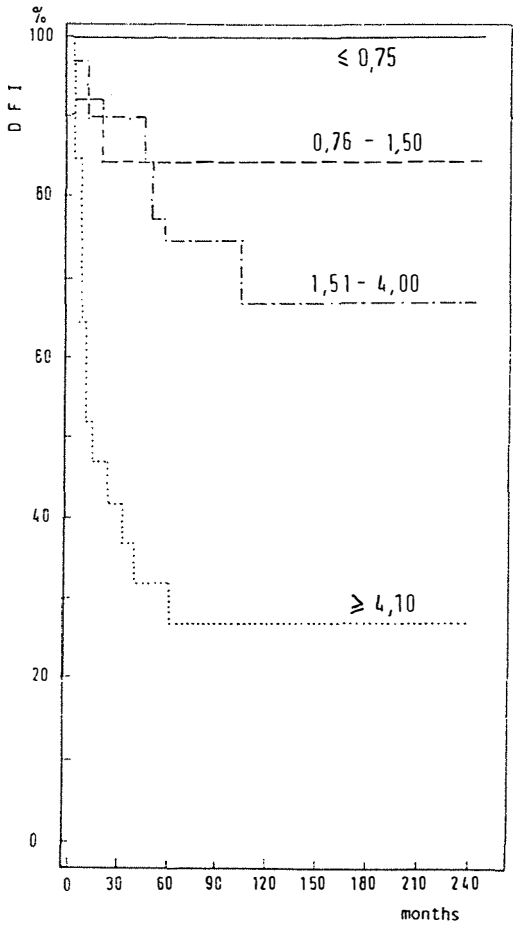

Figure 8. Disease-free interval (DFI) in malignant melanoma patients according to the tumor thickness.

diagnosis. Anamnestic data on previous pigmented nevus, site of primary tumor, pathogenetic and cell type of MM were not found to be statistically relevant prognostic factors.

The comparison of our results with the findings of other national studies and clinical trials carried out by foreign authors showed no controversion of the results; thus, female sex, younger age, lesser thickness of MM, lower depth of invasion, primary tumor site on the extremities, pathogenetic type of SSM and lower stage at diagnosis are associated with better survival and DFI.

The findings of earlier studies on the influence of sex and age on patients' survival were controversial[7,9,35] because the investigated groups of selected patients were small and non-homogeneous by age, the follow up was too short or incomplete, and the registration of the cause of death other than MM was inaccurate.

Some later large-scale national studies such as e.g. an American study covering 10% of American population,[32] as well as a Swedish national study[33] and a Finish national study,[31] which were based on population registry data, have confirmed a better survival in younger patients, and a more favourable course of disease in females. These findings are in accordance with the results of our study.

The advantage of large-scale national studies over hospital ones is in the large number of randomized patients, long follow-up period, and 100% following of the patients till the end of study.

Similar conclusions on statistically significantly better survival in females and patients younger then 50 or 60 years were obtained also in a study carried out at the Cancer Center in Arizona,[10] and in the West Canadian Study,[11] apart from some other prognostically relevant factors (MM thickness, ulcerations and selected regional lymph node removals).

There is no definitive explanation for better survival of female patients. It is well known, however, that in females MM is more frequently situated on the extremities and face, which is associated with a better prognosis, whereas MM site on the trunk more frequently seen in males prognosticates a worse survival,[7,24,34,35] which has been confirmed also by our analysis. Also, MM in females are to a lesser extent exulcerated[24] and have lesser thickness at diagnosis;[11,36] this finding applies to our female patients as well.

Better survival of women in different age groups, which has been established by our analysis, points out that there is no direct correlation between sex hormones and survival. A higher prevalance of estrogene receptors found in women is associated with a less malignant course of MM and accordingly also a better prognosis for survival.[28]

The established better survival in younger patients[24,31,33] could be attributed either to the fact that older patients search surgical help in more advanced stages of disease, or to a decreased immune response in advanced age,[42] though all these explanations are just hypothetical as none of them is based on any substantial biological facts.

Female sex and younger age are associated with a better prognosis for survival of MM patients, which points out the existence of age – and sex-specific factors influencing the course of growth and dissemination of MM.[33]

The distribution of MM sites by sex is in agreement with the findings of other authors;[33,35] the prevalence of lesions on the trunk in males, and on the extremities in females could be associated with different exposure to UV rays.[43]

An increased number of head and neck lesions, particularly in women, associated with a relatively high proportion of LMM type situated on the face[44] was established in a number of studies.

Site on the extremities usually represents a more favourable prognosis than trunk or head & neck sites;[9,25,31,34-36] this finding has been confirmed also in our male patients though the differences were not statistically significant, which is in agreement with the results obtained by Worth et al.[11]

In our study, NM type associated with worse survival and DFI – in men more obvious than in women – prevails, however, without statistically significant differences. In a majority of other studies, the prevailing type is SSM which is associated with more favourable prognosis for survival[10-12] sometimes even significantly better.[19]

In our study, the increasing depth of invasion was found to correlate with worse survival and DFI in both sexes; particularly unfavourable prognosis was associated with Clark grade V. There were more lesions with lesser depth of invasion found in women, which can partially explain better survival of female patients. Better survival with lower Clark grades was established also by other authors.[9-16,19]

The increasing thickness of MM statistically significantly correlates with worse prognosis, particularly the thickness exceeding 4mm, which is in agreement with the results of a study performed in Arizona;[10] in the latter study, some other critical points for survival were associated with tumor thickness.

Many authors in their analyses found a highly significant influence of MM thickness on survival; the significance was even more evident than that established for the depth of invasion.[8,12-15]

At the time of diagnosis, a majority of our patients of both sexes presented with localised stage of the disease – women more frequently than men. Their survival was statistically significantly better in comparison with the stages of regional or systemic dissemination. Similar results were obtained also by Wanebo et al.[12] and by the authors of Finish National Study.[31]

A better survival, though insignificant, established in patients with epitheloid-cell MM type, is of no statitical value in our analysis owing to insufficient data. In the West Canadian Study,[11] the prevailing cell type failed to correlate with survival.

The extent of surgery for MM, which was in our study found to have favourable influence on the prognosis, was not considered in a majority of other studies. Most other authors also have not studied DFI in correlation with prognostic factors.

Conclusion

The prognosis in patients with MM of the skin, and related to it survival and disease-free interval, depends on a number of clinical, pathohistologic and immunohistochemical factors, the so-called prognostic factors. Only some of which, however, proved to be of practical clinical value. It has not been explained yet why findings of different authors on the relevance of individual prognostic factors are sometimes controversial. Using univariate and stratified analysis of possible prognostic factors, we have identified those believed to be of statistically significant prognostic value for the survival and DFI; thus, better

prognosis was associated with female sex, younger age at diagnosis, radical surgical removal of primary tumor, lower grade of invasion depth, leser tumor thickness, and stages of localized disease vs. regional and systemic dissemination (the latter applies to survival only).

Though tumor site on the extremities, history of previous pigmented nevus and SSM subtype were found to correlate with a more favourable course of the disease, the finding lacked statistic significance. Nevertheless, the results are in agreement with those reported by other authors.

Unfavourable prognostic factors were used to identify the gropus of patients at risk requiring a special follow-up regimen and additional treatment.

It has been found that the proportion of patients with localized disease at the time of diagnosis is approximately 75%, and is higher in women than in men. The distribution of MM sites by sex is in agreement with the findings of other authors, the prevailing site in men being the trunk, and in women the extremities. According to our data, the proportion of NM subtype is twice as high as that of SSM type, though in some other studies the SSM type is reported to be prevailing. A history of previous pigmented nevus has been registered in 73% of patients, whereas a higher number of lesions with lesser depth of invasion has been found in women than in men; tumors exceeding 1.50 mm of thickness were prevailing.

With respect to the findings on better survival and DFI in patients with a lesser tumor thickness and a lower grade of invasion depth, more efforts should be directed into the organization of general and professional education in order to increase the level of primary and secondary prevention.

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Management of a patient with solitary brain metastasis of unknown origin

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A case of a patient with solitary brain metastasis is presented. The primary tumor was found only after radiography of the lung in lateral projection. The change evident on CT scan was difficult to evaluate because of a thrombosis in the internal cervical artery and related to it infarction in the region of the median cerebral artery, which, however, was discovered only on autopsy.

Key words: brain metastases, brain neoplasms-secondary; primary tumor detection, lung neoplasms-radiography, brain CT;

Introduction

Presently, in our conditions CT is of decisive importance for the diagnosis of brain invasive processes. As evident from CT scans, corticosteroids effectively eliminate brain edema surrounding the tumor. In search of the origin of a suspected solitary brain metastasis, apart from directed oncological anamnesis and clinical examination, X-ray of the lung is considered by far the most important diagnostic procedure. In the presented case of a patient with solitary brain metastasis, the origin was later on found in the lung, whereas the changes evident on brain CT were obscured by the affected cerebral vascular system.

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Case report

A 71-year old female patient, smoker of many years, was admitted to the Medical Department because of a few-days lasting dysphasia and paresis of the right facial nerve, and a few month history of rheumatoid pains in the hand joints. X-ray of the lung was unsuspicious (Figure 1). The findings of Doppler US examination of the neck arteries were within normal limits. The eyeground showed evidence of grade II hypertension. During the investigation period the patients deteriorating neurologic condition manifested itself with paresis of the right hand, pronounced disorders of speech and writing, and right-side positive Babinski test. Brain CT (Figure 2) showed a 2 cm large tumor formation in the left temporal region with circular uptake of the contrast medium, and edema of the left cerebral hemisphere. The finding indicated a strong probability of metastatic spread.

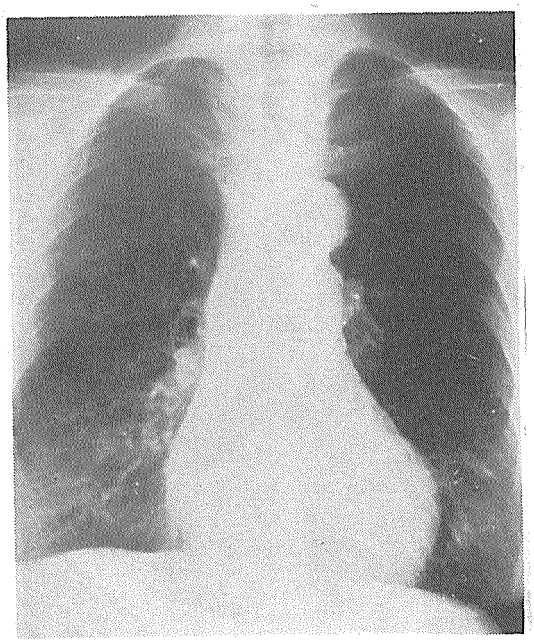

Figure 1. Lung X-ray in January 1991.

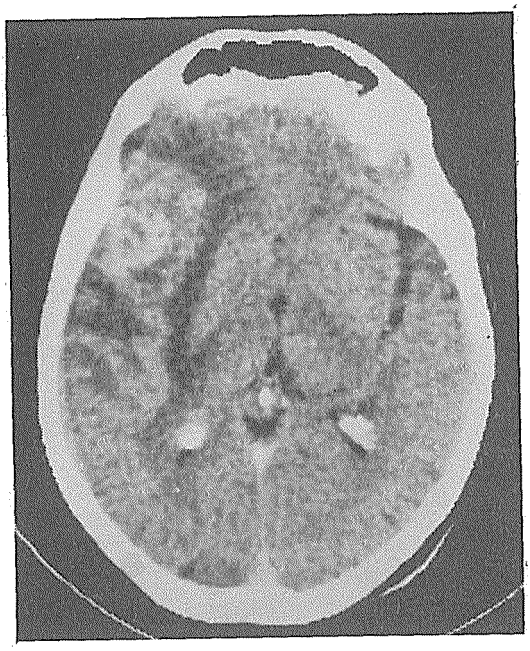

Figure 2. Brain CT in January 1991.

Based on the results of diagnostic procedures, the patient received Dexamethason treatment and had X-ray of the lung taken in the lateral view. The radiogram (Figure 3) imaged an infiltrate in the right lower lobe. On bronchoscopy, there was no direct evidence of tumor, whereas transbronchial biopsy proved the presence of poorly differentiated adenocarcinoma.

The patient's brain was irradiated on telecobalt with TD 3.000 cGy with two opposite fields, in daily fractions of 300 cGy delivered to the whole brain. Dexamethason treatment given in 4 mg injections was maintained throughout the duration of radiotherapy and was ceased on its completion. The treatment resulted in a complete regression of brain symptoms, which lasted 11 months. During that time the lung findings remained unchanged: there was no clinical evidence of pulmonary tumor, and radiograms did not differ from the previously taken images.

After 11 months, the patient's condition suddenly worsened: again dysphasia, right-sided hemiparesis, sphincteral disorders and psychoorganic alterations were noted. Dexamethason treatment was ineffective. X-ray of the lung remained unchanged. Follow-up CT of the brain (Figure 4) showed practically identical tumor lesion in the left temporal region, more distinct changes of the white matter accompanied by enlarged ventricles. The patient died a few days later with the signs of pulmonary edema.

Autopsy revealed a primary pulmonary adenocarcinoma, and its metastasis in the brain, and thrombosis of the left internal carotid artery associated with the signs of acute infarction in the region of the middle cerebral artery.

Discussion

The presented case is interesting so from the point of primary tumor detection as well as with reference to the evaluation of changes evidenced on brain CT.

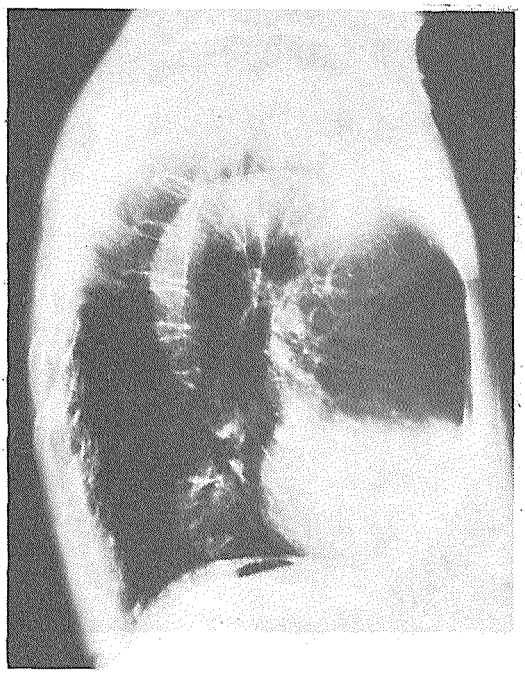

Figure 3. Lateral lung X-ray in January 1991.

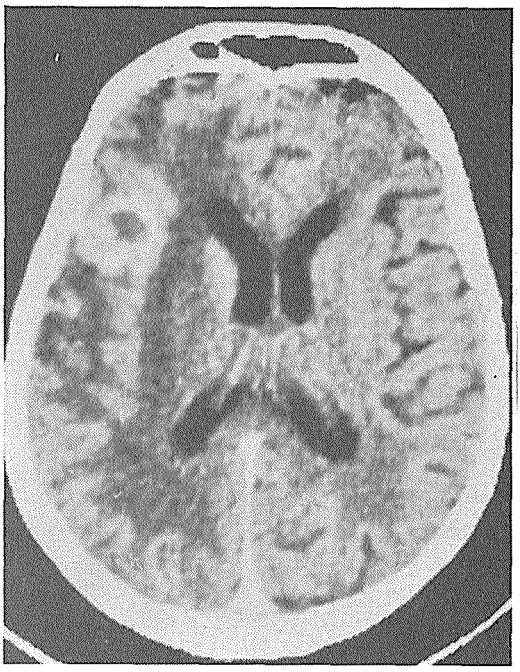

Figure 4. Brain CT in February 1992.

According to foreign[1,2,3,4,5] and our own experience[6], brain metastases of unknown origin are most frequently associated with primary tumors of the lung. This turned out to be the case in 40 of 78 such patients in our series. Search for possible primary tumor in the lung requires X-ray imaging in P-A and lateral view, considering that smaller tumors may be hidden behind the heart, mediastinum or hilus and can thus be clearly differentiated in the lateral view only – the case of our patient. This is particularly important in bedridden patients who undergo radiography in lying position using A-P view; in such cases the mediastinum is flattened and the diaphragm lifted as a result of lying, which renders the assessment of possible tumorous changes even less reliable.

The most frequently seen CT changes associated with brain metastases are as follows: relatively small lesions, well stained with contrast medium, and surrounded by considerable edema. A marked regression or complete disappearance of the edema after corticosteroid treatment is noted. Therapy with sufficiently high doses or radiation may in due time result in atrophy of the brain and cerebral ventricle enlargement, whereas further high doses of irradiation cause demyelinization. Infarction is associated with similar changes of the white matter as seen in edema, however, these should correspond to the orifice of the affected artery. In our case, the changes of the white matter of the brain appeared as a consequence of tumor, irradiation and infarction of the left middle cerebral artery. Doppler US examination, which could reliably detect thrombosis of the internal carotid artery, was not repeated. It is quite evident, however, that repeated irradiation of the brain would not improve the patient's condition.

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Fundamentals in incorporation dosimetry and patient risk from nuclear medicine procedures

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This work is a review of the fundamentals of internal dosimetry based on the MIRD-Conception. First, the simple relation between activity and dose / dose rate serves as starting point for the transformation of these parameters to the field of incorporation dosimetry. The parameters absorbed fraction and dose constant are discussed. The equation for the average dose of a specific radionuclide in an organ is the result of work carried out by the members of Medical Internal Dose Committee (MIRD).

In the second part, practical problems of radiation dose assesment are discussed, such as the estimation of age-dependent internal dose, whole-body retention studies, and doses related to X-ray examinations. Finaly the problems of radiation dose and risk to patients undergoing nuclear medical procedures are explained with own results.

Key words: radiography; radiotherapy; radiation dosage

Fundamentals

The growing application of radioisotopes in diagnosis and therapy results in increasing radiation doses for the individual examined as well as for whole population.

Generally, the internal radiation absorbed dose depends on biological parameters, the distribution and kinetics of a radiopharmaceutical as well as on the physical properties data of the corresponding radioisotopes.

Physicists working in X-ray departments or in radiation therapy use measuring instruments to solve dosimetric problems. Up to now there have been no dosimeters to measure the internal radiation dose in the field of incorporation dosimetry. Therefore, the radiation dose has to be calculated for different organs after application of radiopharmaceuticals. The most recent concept for calculating the internal radiation dose results from work carried out by the members of the Medical Internal Radiation Dose Committee (called MIRD).

The development of a relation between activity and dose or dose rate must be the first task. We choose an experiment for this purpose (Figure 1). A great river without a bridge in the environment separates two high mountains. A radioactive source is located on the right side of the river. A dosemeter is positioned on the other side. We read the measuring instrument and learn: The greater the activity the greater the dose rate, which means that dose rate is strictly proportional to activity. The distance d between

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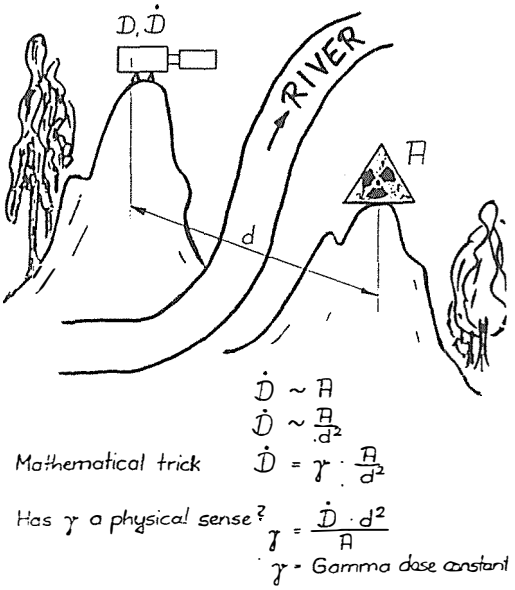

Figure 1. An example of the derivation of the activity–time relation.

Table 1. Parameter of MIRD – Conception

Remarks to the single parameters
$\dot{D} \rightarrow \mathbf{D}$ organ dose
$\bar{\dot{D}} \rightarrow$ mean value
$A \rightarrow A(t) = \tilde{A}$
$m \rightarrow$ organ mass
$\frac{A}{m} \rightarrow \frac{A(t)}{m} = C(t)$
$d \rightarrow$ only for point sources
$\downarrow$ volume sources
$\varnothing_i$ = absorbed fraction
source $\tau \leftrightarrows$ **target** σ
$\gamma \rightarrow \Delta_i$ = sum of all the components of decay scheme
$T_p \rightarrow$ physical half-life
Metabolism $\rightarrow T_b \rightarrow$ biological half-life

the mountains is the next parameter for our study.

Knowing that the quadratic-distance relation is valid for gamma radiation, we can formulate:

The dose rate is proportional to activity and inversely proportional to the distance d. A mathematical trick is necessary to formulate an equation. Now, a question: Has the new parameter γ a physical sense?

We convert the equation to γ and ask: What is the meaning of this new equation with γ as a function of dose rate, activity and distance?

The answer is: a dose rate related to the unit of activity and to a constant distance. This parameter must be a constant value for each radionuclide, i.e. the so-called gamma-dose constant. There are tables for all radionuclides with gamma radiation.

So far we have discussed the basic parameters of external dosimetry, but our theme is the internal dosimetry. We have to transform these parameters in the field of incorporation dosimetry (Table 1).

In the internal dosimetry the basic parameter is the dose in an organ or in the whole body, strictly speaking, the mean value of radiation dose.

The activity in an organ is more or less uniformly distributed and, because of metabolism, always a function of time. We need an integral over the time from zero to infinite over the variation of activity. A tilde over the symbol for activity denotes this time integral. This quality can be measured with a clinical whole-body counter.

We take into account the organ mass. The cumulated activity $\tilde{A}$ with a tilde divided by the organ mass is the time integral of radioactivity concentration in an organ, which is called retention function.

The distance d between a radioactive source and the dosemeter will be now the distance between the source and the target organ. That is the »organ of interest« for dose calculation. Only this part of gamma radiation absorbed in target volume is important; it is called absorbed

fraction ϕ_i. That is the first new parameter of the MIRD–Conception.[1]

$$\sum_i$$

Absorbed fraction defined as energy from the i^{th} radiation component in source absorbed in target volume divided by energy of i^{th} radiation component emitted by the source region. It is assumed that both the source and the target are regions in a homogeneously absorbing material, and the activity is uniformly distributed in the source region. In practice one finds a uniform distribution of activity only in rare cases. This is a source of errors. If the energy is largely absorbed in a single target and only a small fraction of the energy is absorbed, the absorbed fraction is relatively insensitive to alterations in both the size and the shape of source and target. The absorbed fraction will approach the unity at low energies.

Generally, the absorbed fractions can be found in the tables of MIRD for photon sources which are uniformly distributed in various organs of a heterogeneous human phantom. The total-body phantom consists of three main sections (reference man):

a) An elliptical cylinder representing the arms, torso and hip;

b) an elliptical cone representing both the legs and the feet;

c) an elliptical cylinder representing both the head and neck.

This adult human phantom (Figure 2) is valid for a standard man (m = 70 kg). Furthermore, there are mathematical descriptions for single organs. These »mathematical« organs approximate the major features of size, shape, mass and location of the real organs.

For these different phantom organs there are tables indluding the quantity ϕ as a function of the photon energy.

The second and also the last parameter of the MIRD concept is the replacement of the gamma dose constant, because all radiation components

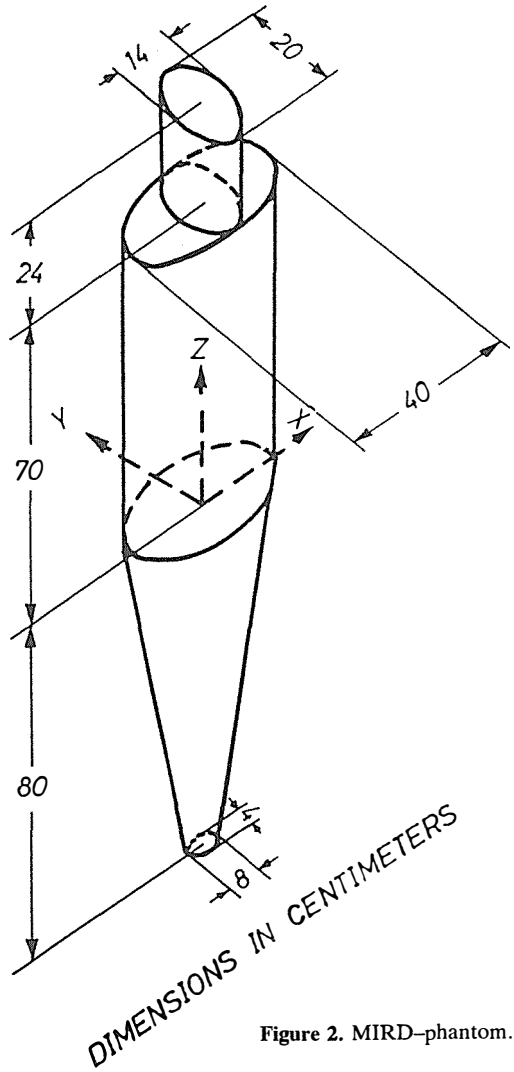

Figure 2. MIRD–phantom.

of radionuclide must be taken into account, that is Δ_i

$$\left(\frac{\text{Gy} \cdot \text{kg}}{\text{Bq} \cdot \text{s}}\right).$$

Δ_i = Mean energy emitted per unit cumulated activity for i^{th} radiation component of the decay scheme with high – and low-energy photons, beta particles, conversion electrons and Auger electrons. It is necessary to know the actual decay scheme of the radioisotopes.

Now we have developed the complete MIRD formula. According to the new formula, the absorbed dose from radiopharmaceuticals can

be calculated with the following general equation (Table 2).

Table 2. Mathematical formalism of MIRD–Conception.

$$\bar{D}(\tau \longleftarrow \delta) = \frac{\tilde{A}}{m_\tau} \cdot \Sigma_i \, \Delta_i \, \varnothing_i$$

$$\frac{\tilde{A}}{m_t} = \int_0^\infty C(t)\, dt$$

$$C(t) = \int_0^\infty C_i(0)\, e^{-(\lambda_r + \lambda_b)(t/T_{eff})}$$

$$T_{eff} = \frac{T_p \cdot T_b}{T_p + T_b}$$

$$\bar{D}(\tau \leftarrow \sigma) = \tilde{A} \cdot S(\tau \leftarrow \sigma)$$

Δ_i = equibrilium dose constant
$\varnothing_i$ = absorbed fraction
$\tilde{A}$ = cumulated activity
T_{eff} = effective half–life

As to the time factor, both the radioactive decay and the metabolism are strictly parallel. Therefore, an effective half-life must be defined.

By means of graphic evaluation it is possible to determine the biokinetic data which are necessary for radiation dose calculation, namely:

– the biological half-life of intake and excretion;

– the percentage of single components of the retention function;

– the proportion of the totally administered radioactivity deposited in an organ extrapolated to the time of administration of the radionuclide.

It is very important that the fundamental equation for radiation dose is quite general and not restricted to any particular kind of radiation. This formula is independent of the specific gamma-dose constant and of the average geometrical factor for the absorber in an earlier mathematical formula.

In MIRD-concept, the mean energy per unit cumulated activity (equilibrium dose constant), the mass m of the target organ and the absorbed fraction ϕ are summarized. This is convenient to introduce the quantity

$$S(\tau \leftarrow \sigma) = \frac{1}{m_\tau} \cdot \frac{\Sigma}{i} \Delta_i \cdot \phi_i$$

Most of the biological data needed for dose estimation are embodied in the cumulated activity $\tilde{A}$, while the remaining parameters in the equation involve physical and anatomic data. Therefore, S can be tabulated as defined for radionuclides and source target configurations commonly used in nuclear medicine. The average dose from a specified radionuclide can be calculated now by the simple formula:

$$\bar{D}(\tau \leftarrow \sigma) = \tilde{A} \cdot S(\tau \leftarrow \sigma)$$

As the MIRD scheme refers only to absorbed dose calculations for specified pairs of source and target organs, including the total body, the concept was extended to the estimation of the additional target dose resulting from radioactivity distributed within the remaining parts of the body.

Generally, the totally absorbed dose $\bar{D}_\tau$ in any target organs consists of three parts (Figure 3), where

$\bar{D}\ \tau \leftrightarrow \tau$ = dose due to self-irradiation of the target organ
$\bar{D}\ \tau \leftarrow \sigma$ = dose due to irradiation from other source organ
$\bar{D}\ \tau \leftarrow RB$ = dose due to irradiation from radioactivity in the remaining body

Practical problems for radiation dose calculation

a) Estimation of the age-dependent internal dose from radiopharmaceuticals

The age–dependence of the radiation dose absorbed in a target organ or in the total body is determined by the mass, the size, the shape of the organs and the distance to the other organs.

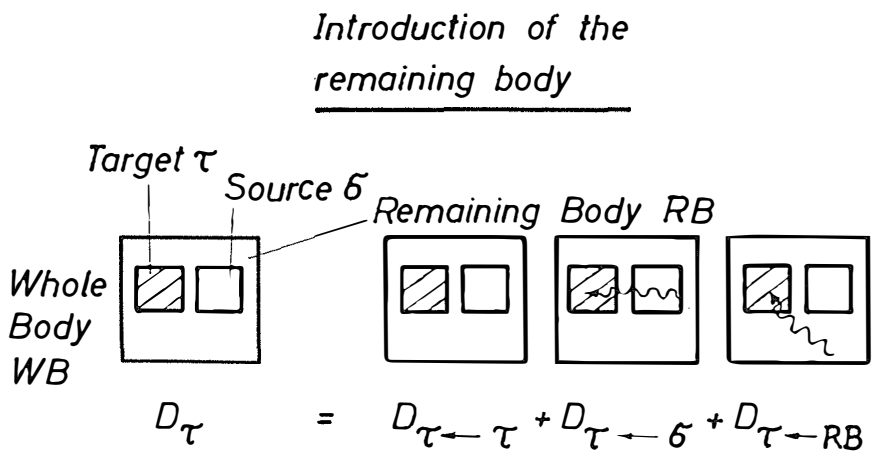

Figure 3. The relation of target, source an remaining body.

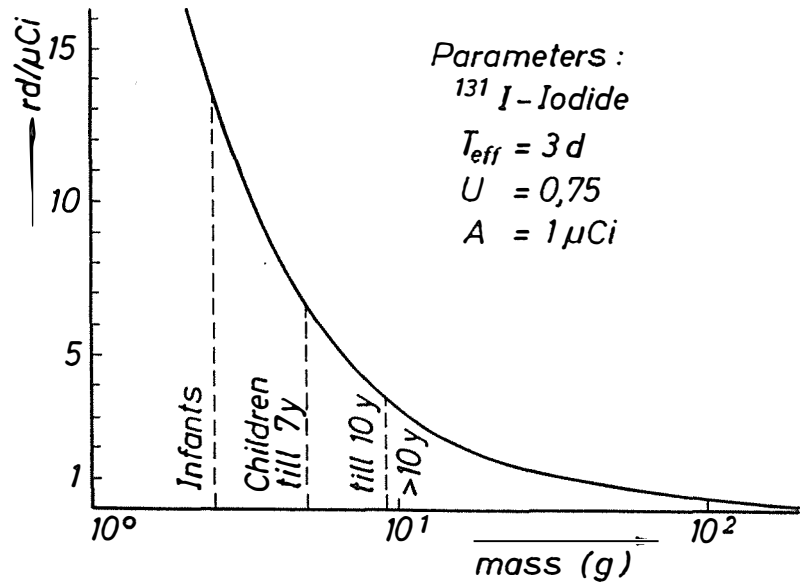

Figure 4. Thyroid dose as a function of organ mass.

It is necessary to calculate the values of ϕ for all organs of interest in age–dependence. For short-lived radionuclides, such as Tc-99 m generally recommended for use in children, variations of the biological half-life are of minor importance to the absorbed dose:

Therefore, the absorbed dose to infants and children may be calculated by adopting the biological half-lives in adults.

As an example of radiopharmaceuticals with age-dependent[2] biokinetic data, dose calcula-

Table 3. Age – dependence of the effective half–time of ^{131}I–Iodide in the thyroid

Age (years)	Effect. half–time (days)
0	5,1
0,5	6,0
1	6,1
3	6,3
5	6,3
10	6,8
15	6,9
adult	7,6

tions were performed for I-131 sodium iodide. These indicate an approximately tenfold thyroid dose to the newborn compared to the adult (Figure 4).

b) Whole-body retention studies

Whole-body profiles for the total body (Figure 5) were measured with a clinical whole-body counter and with a special measuring technique for single organs (e.g. with collimators). By means of profiles, whole-body retention was constructed with some exponential components.

In healthy persons as well as in patients with chronic pyelonephritis (Figure 5) and with renal insufficiency of different severity whole-body retention measurements were carried out up to 75 days after intravenous injection of I-131 hippurate. Whole-body retention curves of persons with healthy kidneys could be divided into two components (Table 4). The first half-life (TB1) is very short, i.e. it lasts 20 minutes.

For renal insufficiency there are three components. The last component has a half-life of up to 35 days and longer, and an extrapolated activity of 1.5 to 10% resulting from I-131 iodide split-off in vivo. Incorporation dosimetric calculations, according to the MIRD conception, allowed to determine a wholebody dose increased by the factors of 2.5 to 40 for patients with

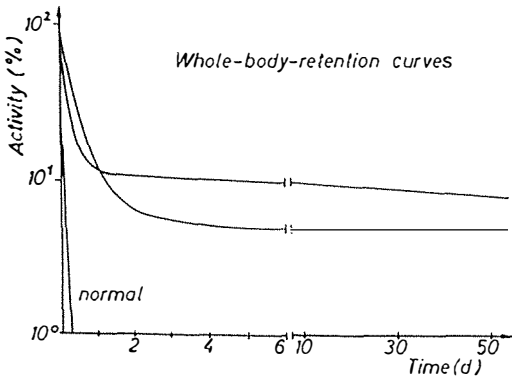

Figure 5. Long-time whole-body retention curves of I-131-Hippurate.

Table 4. Components of a whole-body retention curve (Patient: chronical Pyelonephritis).

	Components I	II	III
Activity (%)	83	7	10
Biological half-life (d)	0,15	1,25	>35
Portion of whole-body radiation dose (%)	11,5	8,5	80

Table 5. Assessment of radiation dose with ^{131}I-Hippurate for the whole-body (mrd)

	Activity	Lit.	Normal persons	Patients (Kreatinin 2–6,4 mg/100ml)
^{131}I-Hippurate (Renogr.)	20 μCi	0,2	0,15–0,4	0,4–7,7
^{131}I-Hippurate (Sequence scintigraphy)	300 μCi	3,0	2,25–6,0	6,0–116,0
Relation normal persons: patients = 1 : 2,5 – 40				
X-ray exposure pelvis	75 – 150 mrd			

renal insufficiency compared to those with healthy kidneys[3].

By in vivo splitting-off of iodide in long-time retention due to the excretion insufficiency, radiation doses were determined on the unblocked thyroid gland between 0.36 and 1.20 Sv or 36-120 rd respectively (Table 5).

Generally, it should be emphasized: The radiation dose is often a function of the serverity of disease.

c) I shall now make some summarizing remarks about *radiopharmaceuticals for clinical evaluation* of the disease of the thyroid gland with regard to radiation protection results:

These recommendations have been made by the Bureau of Radiological Health, Food and Drug Administration, Department of Health, Education and Welfare, USA.[4]

I-131 as sodium iodide should not be used any more for general examinations.

123- Iodine as sodium iodide (Table 6): for uptake measurements and for imaging the same equipments can be used as for I-131.

The following oral activities are recommended (Table 7):

Table 6. Organ doses of different radiopharmaceuticals.
Typical absorbed dose due to thyroid diagnostic radiopharmaceuticals

	A	Critical organ	D_{Co} (Actual mrd)	D_{Gonad} (mrd)
Uptake				
^{123}Iodide	10 – 20 μCi	Thyroid	110–220	M: 0,1 – 0,2 F: 0,2 – 0,4
^{131}I–Iodide	6 μCi	Thyroid	6600	M: 0,52 F: 0,84
Scan				
^{99m}Tc	5 – 10 mCi	Thyroid	1000 – 2000	M: 60 – 120
(Pertechn.)		Stomach	500 – 1500	F: 90–180
^{123}I–Iodide	100–400μCi	Thyroid	1100 – 4400	M: 1 – 4
		Stomach	22 – 88	F: 2 – 8
^{131}I–Iodide	30 μCi	Thyroid	33000	M: 2,6 F: 4,2

Table 7. Physical parameters of I–123, I–131, Tc–99 m.

	^{123}I	^{131}I	^{99m}Tc
Physical half–life	13 h	8,1 d	6 h ·
Eγ (MeV)	0,028; 0,867 0,159; 0,836 0,529; 0,11	0,030; 0,046 0,080; 0,026 0,284; 0,058	0,141; 0,883 0,143; 0,0003
n_i mean number p. disintegration		0,364; 0,820 0,637; 0,065 0,723; 0,017	
Dose constant Δnp (g · rd/μCi · hr)	0,0610	0,4085	0,0369

Measurement at 4–6 h: 370 kBq or 10 μCi
Measurement at 24 h: 740 kBq or 20 μCi

For imaging an activity within the range of 3.7–15 MBq or 100–400 μCi is recommended.

Tc-99m as pertechnetate: An imaging activity of 100-400 MBq or 3-10 mCi is generally adequate (the author's opinion: 37–50 MBq or 1–1.5 mCi should suffice). Activities of 500–750 MBq or 15–20 mCi have been used to improve visualization. At these activity levels the physician should consider the radiation dose delivered to the stomach and colon.

d) Following are some remarks about *the relation between the radiation dose from X-ray examinations and nuclear medical procedures:*

As early as 1965 Edward Smith wrote:[5] »It is not possible to compare the calculated absorbed dose in nuclear medicine with diagnostic X-ray exposures for which the exposure conditions are significantly different from those in nuclear medical procedures.«

Further differences are:
- Other clinical questions for the procedure.
- The radiation doses for healthy persons and patients are not equal.
- After completing X-ray examination, the radiation burden for the patient ends. In nuclear medicine the total radiation dose depends on the remaining radioactivity in the body after completed examination; the following parameters have an influence on the dose:

The quantities of the activity of the radiopharmaceutical – the decay scheme of the radioisotope – uptake and distribution in different organs – long – time retention and in vivo stability of the radiopharmaceutical – organ shape and mass – the age of the patient and, last but not least, the severity of the disease.

e) In conclusion, some comments about *future prospects of internal dosimetry*

The most significant objectives and goals are accuracy and reliability:

1. Extrapolation of animal distributions and retention data to man
2. Measuring technique for biokinetic data in man with ECT and PET
3. Mathematical, physical and biological models

Generally, important progress may be expected over the next years. This will be useful for a better assessment of studies with radioisotopes from the viewpoint of radiation protection and risk estimation, and for a better understanding of the distribution and retention of each new radiopharmaceutical in the human body.

Radiation dose and risk to patients by nuclear medical procedures

A new valuation of the radiation dose with the introduction of the risk concept for stochastic genetic and somatic effects was proposed in ICRP publication No. 26 (1977). This concept contains the definition of individual radiation risk and of the effective dose equivalent which is proportional to this individual risk. The effective collective dose is a further dosimetric parameter quantifying the total risk for a population undergoing radiation applications.

The optimization of the radiation protection and the justification of measures with ionizing radiation for men were demanded by ICPR publication No. 26.

The »effective dose equivalent« proposed by the ICPR estimates the total risk to individuals and the whole population by stochastic injuries. They may induce, for instance, a fatal cancer or serious genetic defects. This effective dose equivalent He is obtained by multiplying the actual organ doses Hi with their weighting factors wi and by addition of all the values wi · Hi fi of all relevant organs of the whole body.

$$He = \sum_{1} wi \cdot Hi.$$

The weighting factors wi of individual organs are proportional to their radiation sensitivity. (Table 8)

If we consider only the somatic radiation effects without the gonad dose, we obtain the somatic effective dose equivalent Hs, e. In this connection we use varying weighting factors Ws, i, because the sum of all the weighting factors must equal 1.

Table 8. Relative weighting factors Wi (ICPR report No. 26, 1977) *and* $W_{s,i}$ (quoted by Persson, 1980)

Tissue	W_i	$W_{s,i}$
Gonads	0.25	–
Breast	0.15	0.19
Red marrow	0.12	0.16
Lung	0.12	0.16
Thyroid gland	0.03	0.04
Bone surface	0.03	0.04
Remainder	0.30	0.41
	$\Sigma = 1$	$\Sigma = 1$

Table 9. Factors of risk for a single organs and the whole-body (ICRP No. 26)

Organ	a (10^{-4}·Sv^{-1} resp.10^{-6}·rem^{-1}
Breast	25
Red bone marrow	20
Lung	20
Thyroid	5
Bone surfaces	5
Other	50
Total body	125
Genetic effects	40

The somatic radiation risk R will be obtained by multiplying the risk factor a with the effective dose equivalent and with the factor for occurrence of malignant diseases m.

$R = a \cdot Hs, e \cdot m.$

The risk factors (Table 9) are the assessed additional risks for radiation–induced fatal cancer per unit of the dose equivalent of the respective tissues and organs. The recommended risk factor for the whole body except for gonads according to ICRP publication No. 26 was applied ($a = 1.25 \cdot 10^{-2}$ Sv^{-1}). These risk factors are dependent on the age and sex distributions of the irradiated persons. The reductions of the risk factors are taken into consideration by the expected manifestation of malignancies (ICRP publication No. 26, 1977).

By multiplying the somatic radiation risk with the number of patients, we obtain according to the ICRP the number of induced malignancies for different investigations.

To estimate both the effective dose equivalent and the total risk to examined patients, one needs to specify the type and number of the diagnostic procedures, including the administered radiopharmaceuticals and their activities, as well as the number, sex and age distributions of the patients

Own results

We estimated the radiation risk to examined patients in nuclear medicine in the former GDR.[6]

The calculated values of the somatic effective dose equivalent, the radiopharmaceuticals, and the administered activities for diagnostic procedure are shown in Table 10. The values for the dose equivalents for individual organs were published by other authors.

In Table 11 the frequency of routinely employed radiopharmaceuticals is shown. As expected, we found an increase in the application of Tc–99m compounds.

The results of our calculation for 1978 and 1981. are given in Table 12. In 1979 and 1981 respectively we calculated 4.4 and 2.9 possible radiation–induced fatal cancer resulting from all nuclear medical procedures performed in the former GDR.

The risk induced by nuclear medical procedures has to be compared to spontaneous cancer risk. The risk of all cancers amounts to about $2.5 \cdot 10^{-3}$ per year. That is, the average somatic radiation risk resulting from nuclear medical diagnostic procedure is about 2 orders smaller than spontaneous cancer risk. It is necessary to

Table 10. Calculated values for the somatic equivalent doses $H_{s,e}$ and the somatic risk of nuclear medical procedures.

Method.	Radiopharmaceutical	Admin. activity (MBq)	$H_{s,e}$ (mSv)	Somatic risk
Thyroid imaging	^{99m}Tc–Pertechnetate	37	0.45	4.0 E-6
Radiorenography	^{131}I–Iodohippurate	0.5	0.62	5.5 E-6
Thyroid uptake/imaging	^{131}I–Sodium iodide	0.74/3.7	31.0	2.8 E-4
Renal imaging (static)	^{99m}Tc–DMSA	74	1.17	1.0 E-5
Brain imaging (static)	^{99m}Tc–Pertechnetate	555/259	6.37	5.7 E-5
Renal imaging (dynamic)	^{131}I–Iodohippurate	5.6	4.48	4.0 E-5
Liver imaging	^{99m}Tc–S–Colloid	37	0.56	4.9 E-6
Bone imaging	^{99m}Tc–MDP	185/555	1.68	1.5 E-5
Vitamin B_{12} absorption	^{57}Co–Vitamin B_{12}	0.02	0.17	1.5 E-6
Placental imaging	^{113m}In–Colloid	55.5/9.3	0.38	3.4 E-6
Pancreas imaging	^{75}Se–Selenomethionine	9.3	39.78	3.5 E-4
Plasma volume	^{131}I–HSA	0.19	0.09	7.8 E-7
Lung perfusion study	^{99m}Tc–HSA microspheres	185	2.75	2.4 E-5
Spleen imaging	^{99m}Tc–Heat--denatured red cells	18.5	0.87	7.6 E-6
Brain imaging (dynamic)	^{99m}Tc–Pertechnetate	555	6.69	5.9 E-5
Renal clearance	^{131}I–Iodohippurate	1.5	1.19	1.0 E-5
Thyroid metastases imaging	^{131}I–Sodium iodide	37	4.86	4.3 E-5
Renal clearance (gamma camera)	^{131}I–Iodohippurate	11	8.95	7.8 E-5
Tumour imaging	^{67}Ga–Citrate/^{111}In–bleomycin	79	13.62	1.2 E-4
Myocardial imaging	^{201}Tl–Chloride	55.5	3.41	3.0 E-5
Red cell survival time	^{51}Cr–Chromate	3	0.83	7.3 E-6
Salivary gland imaging	^{99m}Tc–Pertechnetate	37	0.45	4.0 E-6
Reflux imaging	^{131}I–Iodohippurate	1.5	1.19	1.0 E-5
Bilious paths imaging	^{99m}Tc–HIDA	74	0.48	4.2 E-6
Iron kinetics	^{59}Fe–Citrate	0.9	8.36	7.3 E-5
Lachrymatory paths imaging	^{99m}Tc–Pertechnetate	3	0.03	2.6 E-7
Parathyroid imaging	^{75}Se–Selenomethionine	11	46.54	4.1 E-4

Table 11. Different frequencies of use of radiopharmaceuticals in the former GDR for 1978 and 1981.

Radiopharmaceutical	Applications(%)	
	1978	1981
^{99m}Tc–Labeled compounds	49.1	61.5
^{131}I–Iodohippurate	28.0	26.5
^{131}I–Sodium iodide	8.3	4.3
^{197}Hg–Chlormerodrine	6.5	–
^{113m}In–Labeled compounds	2.5	1.1
^{57}Co–Vitamin B_{12}	1.5	1.5
^{75}Se–Selenomethionine	1.2	0.4
^{67}Ga–Citrate/^{111}In–bleomycin	0.4	0.2
^{201}Tl–Chloride	–	0.8

point out that the very small actual radiation risk in nuclear medicine concerns only about 130 000 patients yearly in the former GDR whereas spontaneous cancer risk is valid for each member of the total population (the former GDR had about 16,7 million inhabitants).

Furthermore, we have to compare the benefits of nuclear medical examinations to the risks! Reliable epidemiological studies lead to the conclusion that a very small cancer risk from the lowest radiation dose cannot be excluded.

Nevertheless, we should look for every possibility of reducing radiation dose and risk to patient without lack of information: this may be achieved by such measures as careful indication

Table 12. Own results for risk assessment for the former GDR. Comparison of the results for the years 1978 and 1981.

Number of patients	$H_{s,e}$ (mSv)	$S_{2,e}$ (man S_v)	Somatic risk	Number of malignancies
115194	4.27	483.3	3.8 E-5	4.4
129326	2.58	336.2	2.3 E-5	2.9

for special examinations, selection of suitable radiopharmaceuticals which are stable in vivo, and their continuous quality control using highly sophisticated instruments.

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Medical care of patients injured and irradiated in a nuclear accident

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Medical Emergency Center for Radiation Injuries in Zagreb, Croatia is the only institution of that kind in this part of Europe.
At the beginning, the service was organized within the existing premises, to be later expanded and, at the time being, the Center is a three–storey building with a basement. It includes such units as: first triage and monitoring, self–decontamination, special decontamination bath for heavily contaminated or patients with combined injuries, whole body counter, alfa–, beta– and gamma–spectroscopy and sample counting, small surgery, bone marrow transplantation with nine sterile chambers, small clinical ward and even a specially designed lead shielded low temperature mortuary.
We believe that our qualified personnel, in collaboration with other clinics of our big hospital center, is able to handle most of the emergencies and radiation injuries that could result from an accident on–site at the Nuclear power plant.
In this work the organisation of our Center is explained in detail, together with the exercises, courses that we organize and our collaboration with governmental bodies and similar centers in the world.

Key words: radiation injuries, radiation monitoring, dekontamination; nuclear reactor

Introduction

Medical Emergency Center for Radiation Injuries was founded in 1981 to provide the off-site medical service as one of the basic conditions for the nuclear power plant »Krško« located about 40 km north–west of Zagreb to get the licence. The construction of »Krško« was a joint venture of Slovenia and Croatia, the one–time republics of former Yugoslavia.

The Center makes part of our Nuclear Medicine Department, which was found suitable for this purpose because of its vicinity to the Nuclear power plant »Krško« (NPP) as well as being very well equipped. Some instrumentation needed was already in use in the Department, but many more has been acquired by the help of the NPP and The Electricity Board of Croatia. The staff of the Department consists of about one hundred people of different specialities well experienced in measuring radioactivity in humans as well as in dealing with opened and closed radioactive sources in general.

Medical doctors and health physicists have attended special courses in Oak Ridge, Boston, Argonne and Paris to improve their knowledge and qualifications. All this was of remarkable help in making–up the emergency plans and

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written procedures for acceptance and triage of the people incidentally irradiated, injured and/or contaminated during an accident at the nuclear power plant. Our plans and procedures are mainly based on the experiences of world famous centers as described in the literature[1, 2], but modified for our special conditions and circumstances (e. g. after international recognition of both Croatia and Slovenia as independent countries the NPP is in one country and our Center in the other). In the treatment of patients all major international documents published by IAEA,[3] ICRP,[4] MIRD[5] etc. are respected as well as the experiences of some world experts published elsewhere.[6-9]

Table 1. Basic data about Krsko Nuclear Power Plant.

NPP KRSKO – SLOVENIA	
REACTOR TYPE	Westinghouse, PWR
THERMAL OUTPUT:	1882 MW
NET ELECTRICAL OUTPUT:	632 MWe
ANNUAL EL. POWER PRODUCTION:	4.4 TWh
NUCLEAR GENERATED ELECTRICITY IN 1990 AS A PERCENTAGE OF TOTAL GENERATION:	5.4% (EX YU) 15-20% CRO & SLO
LOW AND ITERMEDIATE RADWASTE DISPOSAL	Surface repository Proposed: landfull
AIR DISTANCE TO ZAGREB: (1 million inhabitants)	40 km

Table 2. Elementary classification of radiation accidents at nuclear powerplant site.

CLASSIFICATION OF ACCIDENTS AT NPP
– TRIVIAL INCIDENT (e.g. small leakage in containment)
– SMALL LEAKAGE IN THE ENVIRONMENT
– MISSHANDLING OF RADWASTE (e. g. defective instrumentation for controlled release of radioactive gases)
– BREAK-IN OF FISSION PRODUCTS INTO PRIMARY OR SECONDARY CIRCLE (defective cladding of fuel element or defects on steam generators or tubes)
– ACCIDENT DURING FUEL LOADING OR SERVICE (e.g. elements drop down or a heavy object falls on them)
– LOCA – »LOSS OF COOLANT ACCIDENT« (core melting containment failure, massive release of radioactivity)

What could happen?

Nuclear power plant »Krško«, constructed by »Westinghouse«, with the first self–sustained chain reaction achieved in September 1981, belongs to that family of PWRs which are highly ranked from the standpoint of nuclear safety. Basic data about the plant are given in Table 1.

All principal structures of the NPP are located on a solid reinforced concrete platform,[10] which is situated upon the Pliocene sandy–clay sediments of the Krško basin. The structures are designed and constructed to resist an earthquake of 9 degrees of magnitude according to the MCS scale without being damaged. The containment, which contains the reactor coolant systems, consists of the inner cylindrical steel shell and the outer reinforced concrete shield building. The containment airlock is equipped with sealed passage chamber with double doors while numerous pipings and cable penetrations are all double sealed. Cooling water intake structures are located on the Sava river bank, but additional cooling towers are provided for the case of exceptionally low water flow of the river.

Solid waste storage is located on the south–western border of the plant. It can temporary hold up to 6000 containers. The liquid radioactive waste is purified in the liquid waste treatment facilities consisting of filters, demineralizers and evaporators. The blow–down water from the steam generators is purified separately. The radioactivity of the water discharged into the Sava river is considerably bellow the maximum permissible concentration. The gaseous waste processing system consists of two parallel closed loops with compressors and catalytic hydrogen recombiners and of six decay tanks for compressed fission gases. Four of the tanks are used during normal plant operation while the remaining two are used during the reactor shut–down. The capacity of the tanks is adequate for more than one month gaseous waste hold–up, within

which period the majority of the short–lived fission gases will decay.

So, what could happen?

Although lots of precautions have been taken and an accident of the »Chernobyl type« and extent is excluded, still some more or less severe accidental situations must be considered and provisions regarding medical help in all these cases should be taken. Table 2 lists the accidents which could happen, classifying them according to their severity, starting from really trivial things and ending with worst situation of a LOCA accident.

Basic classification of radiation injuries is given in Table 3. General situation can be much more complicated than this because there are possible combinations of local and overall external irradiation, multiple iradiation, acute, fractionated or continuous intake of radionuclides in the body, and so on. In all these situations it is expected that the body burden and the committed dose equivalent be assessed and consequently, adequate medical countermeasures be taken.

Table 3. Possible injuries as a consequence of an accident at the NPP

TYPES OF RADIATION INJURIES
– EXTERNALLY IRRADIATED ONLY (mostly mixed non-uniform radiation)
– CONTAMINATED (externally, internally or both)
– COMBINED RADIATION INJURIES:
A) Mechanical hurts & irradiation
B) Mechanical hurts & contamination
C) Burns & irradiation
D) Burns & contamination
E) Combinations of the above injuries

SEQUENCE OF EMERGENCY ACTIONS

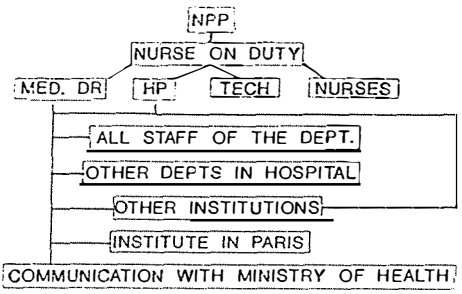

Figure 1. Notification system and order of actions after an accident has been reported.

CONNECTIONS WITH OTHER SPECIALISTS, DEPARTMENTS AND INSTITUTIONS

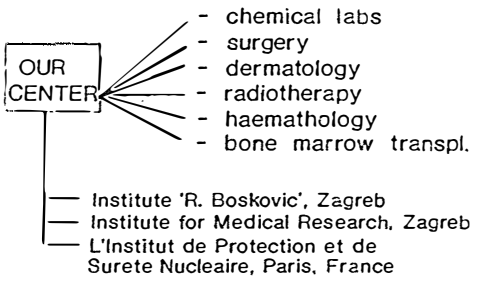

Figure 2. Connections of the Center with other hospital departments and other institutes in the country and abroad.

Organisation and functioning of the center

The specialists of the Center are grouped in expert teams, each team comprising a medical doctor, a health physicist and a chemist. Normally, the assisting staff in included too. The team on duty is available all the time by means of a pager system. There is a hot telephone line as well as a reserved radio frequency providing the 24–hour direct connection between the Center and the NPP.

First actions after an accident has happened are to be taken by the radiation protection personnel at the nuclear power plant. This will include: first aid, first decontamination (if patient's general condition permits), organization of the attended transport and notifying our Medical Emergency Center for Radiation Injuries.

The nurse on duty will fill in the prepared forms with patient as well as the accident data and immediatelly call the medical doctor who is going to be the head of the expert team and the person in charge for all activities connected with acceptance and triage of the patients. At the same time she will notify the health physicist, technologists and nurses as shown in Figure 1. If

there is only one or two not very badly injured persons, the team on duty will manage to handle them, but in the case of more patients or more severe and combined radiation injuries, the head of the team will call all needed personnel of the Department and make immediate contacts with other departments of the Clinical Hospital Centre Rebro. This means that the burns are going to be treated by a specialist for burns and other surgical cases by a highly qualified surgeon, specialist in that field.

In some complicated situations the head of the team – named the coordinator – will, after consulting the health physicist too, ask for advices or practical help from other institutions in the town (Zagreb is a famous university town and the main Croatian scientific institutes are located here), or even out of the country. The Center has developed a very good collaboration with L'Institut de Protection et de Surete Nucleaire in Fontenay–aux–Roses (Paris) whose experts under the leadership of dr Nenot have shown a lot of understanding for our possible problems. In Figure 2 the scheme of the connections with other specialists, departments and institutions is given.

The procedures for acceptance, first triage and later treatment of patients in the Center have been prepared in written form[9] explaining in details the duties of every single member of the team and giving the general rules and codex of behaviour to be respected by all the people involved in the work with irradiated and/or contaminated persons.

The Center is just being moved into a new building. It consists of four floors, when the basement is included, each one having the useful surface of about 400 square meters. The arrangement of rooms in the basement and the ground floor was carefully planned to assure that under no circumstances there should be any spread of contamination to other premises and persons in the hospital.

The reception of patients is on the ground floor. There is the first control point in the waiting room near the entrance. There, in the case of a life–threatening situation the patient is sent to the main surgery of the hospital, or in the case of heavy outside contamination with combined injuries, to the special decontamination unit in the basement of the Center (Figure 3), where he is being decontaminated by the qualified nurses. All other patients are switched to the Monitoring Room and Medical Examination Room. While talking to the patient, medical doctor and health physicist will collect many important information essential for the reconstruction of the accident and the assessment of the absorbed dose. The doctor will record the clinical simptoms which will help in the first judgement of the absorbed dose and body burden in general. In Medical Examination Room the small surgery and wound decontamination can be done too.

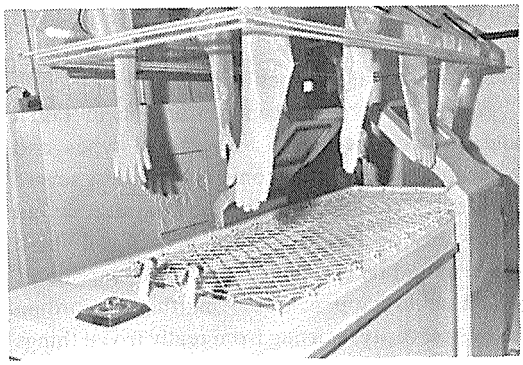

Figure 3. Special decontamination bath for patients with injuries and severe outside contamination. Note lead and lead-glass shields for personnel. Water is drained to the special liquid waste repository and left to decay.

After removing the patient's clothes which are sent for analysis by gamma spectroscopy using HPGe detectors and multichannel analyzers, the patient is sent to the shower or bath to be repeatedly monitored afterwards. When there is no significant difference between the two succeeding monitoring results, the person is considered 'clean', which means that the detected counts come from either fixed outside contamination or from internally deposited radionuclides. So, the patient is sent to the Sample Taking Room and to the Internal Decontamination Room. All samples needed for biological dosimetry are taken,

primarily blood, urine, sputum and vomitus samples, but also wipes from ears, nostrils, wounds etc., which all may be of great help to assess the body burden and the absorbed dose. Some samples are going to be taken repeatedly through a prolonged period of time to enable us to assess the committed dose equivalent in every particular case.

In the basement there are laboratories for chemical analysis connected with Biological Dosimetry and Radiotoxicology, the Special Decontamination Room, the Whole Body Counter and the Whole Body Scanner, the Computer Room and even a special lead shielded low–temperature Mortuary in which six corps can be kept for long time. In the basement there is a Counting Room also, equipped with automatic gamma counters, liquid beta counters, dose calibrators, an alpha/beta counter and a system for thermoluminiscent dosimetry.

The Whole Body Counter is the shadow shielded 'Canberra Accuscan' (Figure 4) designed especially for our Institute, (in order to have a HPGe detector in addition to the standard NaI(Tl) 10x4x4 inches crystal. This combination makes possible the gamma spectroscopy 'in vivo' as well as the measuring of internally deposited radioactivities at the very low level. Because of the lower sensitivity of the semiconductor detector and using additional slit collimators, higher activities can be measured, which enables us to use the counter for some medical retention studies too. The results obtained up till now seem to be rather reliable. For the purpose of medically controlled diagnostic radionuclide studies or in the case of internal contamination of greater extent, the distribution of radionuclides deposited in the body can be imaged by the Whole Body Scanner. Both, the Counter and the Scanner, are connected to the computer for data analysis, body burden calculation and dose assessment. There are several PCs with programs for gamma spectroscopy and dose calculations from bioassay data or repeated whole body counts.

The very new Bone Marrow Transplantation Unit occupies the first floor. It consists of six Sterile Chambers, the Room for Small Interventions, Doctor's and Nurses' Room. In addition to the three already existing sterile chambers elswhere in the hospital it makes altogether nine sterile chambers. The whole body irradiation is provided by the Radiation Therapy Department of the hospital.

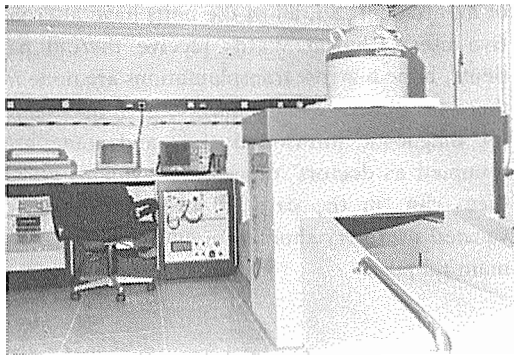

Figure 4. Shadow-shield whole body counter with sodium iodide and HPGe detectors.

On the second floor there is a small Clinical Ward consisting of six comfortable singlebedrooms with their own bathrooms assuring the possibility of really good patient separation. This is an addition to the previously existing 17 beds which now belong to the older part of the Center.

The coordinator himself will contact the Ministry of Health and Social Wellfare to inform them of the actions taken and potential help needed from any of the governmental bodies. He will also give the statements to the press or nominate the person to be the official spokesman for the Center. Normally, in the case of a major nuclear accident, an expert group will be formed for this purpose at the governmental level.

Special care has been taken for handling of radioactive waste. So, there is a big water storage, where all liquid waste is diluted and decayed before being released to the sewage. Solid waste is stored too and gases are filtered before being released to the atmosphere.

As our Hospital Centre, in general, is not an extremely rich one, all the described units, although dedicated for the above special purposes, can not be kept empty to be used only in the case

of an accident. So, all of the units have alternative uses: Clinical Wards receive thyroid patients, bone marrow transplantations are done in the cases of accute leukemias, some rooms serve for diagnostic ultrasound tests and some are occupied as doctors' offices. As evident, all of them can, in the case of an emergency, be vacated in a very short time and used for their main purpose.

Discussion and conclusion

The Medical Emergency Center for Radiation Injuries in Zagreb, Croatia is a dedicated institution built especially to provide an off-site medical emergency service for the Nuclear Power Plant Krško in nearby Republic of Slovenia.

The Center is organized according to internationally accepted norms and regulations, including all services essential to offer high level of proffessional medical help to the workers and other persons who could get incidentally irradiated, contaminated and/or injured during an accident at the NPP. The Center is, according to the detailed written procedures, able to handle most of the emergencies that could result as a consequence of such a case, but if needed the help is granted by other departments of the Hospital Centre Rebro as well as by other institutes in Zagreb and, even, outside of the country.

The preparedness of the emergency teams is periodically tested by means of practical drills with different simulated accidental situations. The equipment is checked often and, in general, the quality assurance program is considered very seriously.

In 1990, the Center, in collaboration with the Medical Faculty of Zagreb University, organized the first Course intended for the attendants from all parts of former Yugoslavia under the title 'Medical Procedures and Handling of Radiation Accidents'. The Course was disscontinued because of the war situation and the decomposition of Yugoslavia. Now, the independent Republic of Croatia is making provisions for its own international contacts in the fields of different activities, so we do expect future collaboration with the countries of Western and Eastern world too.

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An outline of the development of radiotherapy in Slovenia*

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The historical data on the development of radiotherapy (RT) in Slovenia are presented from its first use in this country in 1902 till present. The Institute of Oncology in Ljubljana (IO) was established in 1938 with the intention to provide a sound development of radium and roentgen cancer treatment. After the World War II the development of RT at IO was rather dynamic, which is evident from the data on new radiation sources in external beam therapy (accelerators, telecobalt units), in brachytherapy (various sealed radioisotopes) as well as in therapy with unsealed radioisotopes being introduced. In 1947 a Chair of Oncology and Radiotherapy was instituted at the Medical Faculty of the University of Ljubljana (with the seat at the IO). In 1955 radiotherapy and oncology was officially recognized as a separate branch of medicine, requiring a special, obligatory postgraduate residency training. Considering the size of population of Slovenia (near 2 million), it was reasonable that by the time RT became almost completely concentrated in one central institution i.e. in the IO, representing its core and cohesive activity in the multidisciplinary cancer treatment approach.

Key words: radiotherapy-history; Slovenia

Introduction

As an old-timer in radiotherapy (RT), engaged at the Institute of Oncology, Ljubljana (IO) since 1946, the data given below on the development of RT in Slovenia in the following decades have been recorded by my own knowledge. For the previous period I collected the information from our predecessors in this field, out of their dispersely published or unpublished papers or by personal communications of some of them.

For better understanding the topic, following are some relevant data on Slovenia. It is situated in the north-west part of the former Yugoslavia, covering a territory of 20 256 km,[2] and at present comprising near to 2 million population. Ljubljana is its capital (286 681 inhabitants) and the next largest city is Maribor (105 431 inhabitants). According to the data of the population-based Cancer Registry of Slovenia, the number of new cancer cases in the year 1950 was 1 795 (130 per 100 000 population),[1] whereas in the year 1987 it was 5 736 (288 per 100 000 population).[2] As noted since 1950, about 50% of cancer patients are, sooner or later in the course of their disease, treated by radiation. In the last decade around 3 000 have been treated yearly in the IO.

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History

Soon after the World War I, the interest of our physicians for RT was on the one hand enhanced by its already commonly recognised effectiveness in the treatment of cancer and also of various benign diseases, and on the other, by the increasing cancer morbidity in our population.

Roentgenotherapy of cancer and benign diseases was introduced at the Roentgen Department of the General Hospital in Ljubljana, headed by Dr. Alojzij Kunst, in 1923, two years later it was started in Maribor in a private sanatorium by a gynecologist Benjamin Ipavic[3] and presumably some years later in the General Hospital in Brežice by its chief-surgeon Josip Cholewa in frame of the activity of the Oncological Laboratory he established there in 1920.[4] In the '30s this therapy was carried out also in some other public or private roentgen stations in Ljubljana and some other towns. At that time, mainly the Siemens universal roentgen apparatus was used for both diagnostics and therapy.[3]

Before World War II, the few specialised rentgenologists that were there (altogether 6), as well as two gynecologists interested in RT, received their knowledge in this therapy mainly in the Viennese Central Roentgen Institute (headed by Dr. Guido Holzknecht), and also by visiting the relevant institutions in Prague, Berlin, Frankfurt-upon-Main, Munich and Paris.[3]

As to the *radium therapy,* it is of historic interest that in Ljubljana it was used for the first time in the years 1902-16 by Dr. Emil Bock, the then chief of Ophthalmology Department of the General Hospital, for treating skin cancer in eye region.[3] For this purpose he used a special applicator (Figure 1) containing but 4 microcuries of radium (according to present measurements). Further, from 1929 on, in the above mentioned Oncological Laboratory in Brežice a pair of »radium-points« (alloy of radium with platinum – unfiltered), cointaining 1 and 1.5 mg of radium respectively, were used for interstitial application in cancer treatment.[4] However, a year before the then Head of Otorhinolaryngologic Department of the Ljubljana General Hospital Dr. Josip Pogačnik provided for cancer treatment purposes 49 mg of radium in needles and tubes at his own expense, since he could not get the means from the government.[5] Bought from him, these were in fact the first radium sources available for the treatment in our Institute.[5,6]

For more than ten years, the physicians of various specialities, interested in cancer research and its radiation treatment, devoted strong endeavours to establishing an institution intended exclusively for cancer, and in which RT, specially radium therapy would be concentrated. Finally they succeeded, and in 1938 by the order of Slovenian government such an institution was

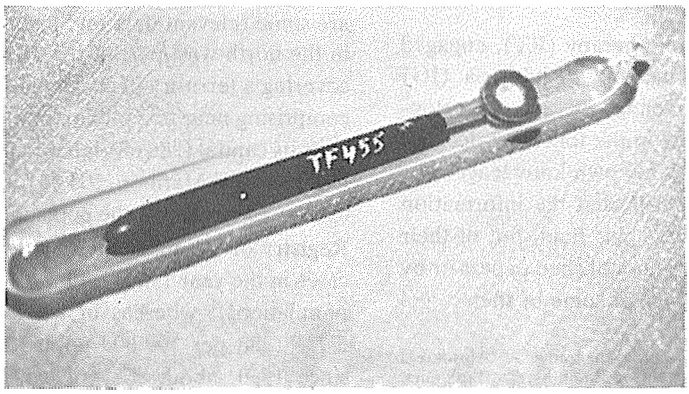

Figure 1. Applicator with ^{226}Ra (4 μCi) purchased by Dr. Emil Bock in 1902 for treatment of skin cancer in eye region at the Ophthalmology Depertment of the General Hospital in Ljubljana. Lenght 18 cm.

established in Ljubljana.[6,7] It was the embryo of our present IO. Its original name was: *Institute for Research and Treatment of Neoplasms,* and the concept of its activity as a comprehensive cancer center was already outlined, although its starting space, equipment and personnel capacities were very modest. It was situated in an adapted part of an almost 200-year old building (previously barracks) where some of its units have remained till present time. There were only 28 patient beds.[7]

The RT equipment comprised three roentgen units: one orthovoltage (Siemens Stabilivolt 180-200 kV) for deep therapy, one (according to Schaefer & Witte – 90-100 kV) for intravaginal irradiation, and one (according to Chaoul – 50-60 kV) for »contact« irradiation of superficial lesions.[6,7] Besides, a stock of altogether 410 mg of radium encapsulated in tubes and needles was available.[7]

The initial Institute's staff of 5 physicians consisted of 1 surgeon (director Josip Cholewa), 2 gynecologists, and 2 general practitioners.[7] Only 4 years later one specialized roentgenologist was engaged. In fact at that time modern radiation treatment methods of cancer and benign disease were introduced by the chief gynecologist Leo Šavnik, who had been already before, mainly at his own initiative, trained in the radiotherapy in several European (mainly German) radiotherapy centers.[3,6] Among the initial staff of the Institute there was also an electroengineer engaged part time for maintenance of roentgen equipment, and radiation planning dosimetry.[6,7]

Immediately after the World War II, during which the activity of the Institute was severely impeded, it was joined with the Roentgen Institute of the newly formed University Hospitals (from the previous General Hospital in Ljubljana), into a common *Institute of Roentgenology and Radiology.* Fortunately, this had lasted only for 8 months, as it soon became evident that such a symbiosis was unreasonable. Thus, these two institutions were separated, ours getting the present name: *Institute of Oncology,* and which in 1961 became autonomous like it had been before the World War II. Moreover, by December 1947 the *Chair of Oncology and Radiotherapy* was instituted at the Medical Faculty of the University of Ljubljana, the seat of which was entrusted to our Institute. Thus, an adequate education in this subject has been provided for the undergraduate medical students in the last terms of the curriculum.

During the first post-war decade, when the possibility to engage more physicians in the IO was opened, our endeavours were devoted mainly to catching up with the development of RT as achieved in respective institutions abroad, e.g. in Stockholm, Paris, Manchester, New York. This was enabled by ensuring adequate conditions, i. e. on the one hand in RT trained physicians, radiophysicists, and technicians, and on the other, by updating the treatment and dosimetric equipment. It is worth mentioning that by year 1955 in Slovenia *RT together with oncology was officially recognised as a special branch of medicine,* i.e. apart from roentgen diagnostics, with which it had been joined previously. From then on, for obtaining the title of specialist in this branch, a special program of residency has been required, lasting for 3 years until 1978 and for 4 years afterwards. From 1955 till now, i.e. in the last 35 years, 31 physicians have passed board examination in this branch; 8 of them have also reached doctor of science degree.

Overcoming many obstacles, specially a constant shortage of space, the development of the IO as a multidisciplinary cancer treatment, research and education centre was rather dynamic during the whole post-war time, but still in the patient treatment RT remained its core activity.[8] Although all other modalities of cancer treatment have been carried out, i.e. surgery, chemo-, endocrine-, and immunotherapy, they were and are mainly limited to those cancer sites in which they are mostly combined with RT. On the 50th anniversary of the IO, i.e. in 1988, the number of its patient beds was 365 of which 172 were assigned to patients treated by radiation. Among the total of 85 fulltime engaged physicians of various diagnostic and therapeutic disci-

plines, there were 25 radiotherapists, and among other 19 high degree professionals of other disciplines, there were 5 radiophysicists, and 2 radiobiologists; the number of radiotherapy technicians was 26. Until the end of 1990 these figures did not change essentially.

The development of RT might be evident from the *equipment and treatment techniques used.* Below, a brief review of the situation **from 1938-on** is presented with some comments.

External beam radiotherapy

Roentgen low-voltage, short source-skin distance (»contact«, superficial) therapy, as already mentioned above, has been used in the IO ever since its beginnning, and is still performed, but to a limited extent (in cancer treatment being replaced either by applications of small sealed radioactive sources or by accelerators' electron irradiation). In around 1950 it was also introduced in the General Hospital in Maribor, and somewhat later in the Dermatology Department of the University Hospital in Ljubljana. In both instances, besides for the skin cancer it has been used to a great extent for the treatment of benign skin diseases. At the Dermatology Department in Ljubljana in the '60s even the *»telesuperficial«,* i.e. a total body surface roentgen irradiation by Siemens Dermopan for the treatment of generalised dermatoses was developed.[9] Presently, the roentgen therapy of benign skin diseases has been almost completely omitted, since other effective means of their treatment are available.

Roentgen orthovoltage – deep therapy at the time when it was introduced in the IO, as also mentioned in the beginning, had already had some tradition in the Roentgen Department of the General Hospital in Ljubljana, and in that in Maribor. Since then, in the former institution it had still been carried out until 1959, mainly for benign diseases, whereas in Maribor it is still used in malignant diseases, mainly as palliative treatment, as well as in certain benign diseases, like also in the IO. In 1957 the latter obtained a new roentgen apparatus (Siemens Stabilipan) which enabled *moving irradiation,* i.e. pendulant and convergent.[10] However, we had not been using these techniques for a long time.

Supervoltage X-ray therapy we started to carry out in 1955 with a betatron 31 MeV (Brown Boveri), which was installed in the Institute of Physics »Jožef Stefan«.[11] Despite the inconvenience that this Institute was located rather far from the buildings of the IO, this accelerator had been used for the radical treatment of deep seated cancers until 1978, when a *linear accelerator* (Philips MEL 75-20 with X-ray energy 8 and 16 MeV) was installed in a new building for teletherapy of our Institute, and by which also *electron beam therapy* (5-20 MeV) was possible. Two years ago another new linear accelerator (Philips SL 75-15, X-rays 6 and 10 MeV, electrons 5-15 MeV) was installed.

Telecobalt unit was first put into operation in IO by 1962 (Siemens' Gammatron I) with initial activity of source 1000 Ci. Later on it was replaced by two new ones (AECL Theratron 80 in 1968, and Philips Telecobalt in 1979) with rather higher initial activities of sources. In 1989 the second one was replaced by the fourth (AECL Theratron 780 with initial activity of source 10 000 Ci. In fact, for almost two decades the main deep therapy load was on the telecobalt units, and just to mention, along with them a »mantle field« technique, and the total-body (TBI) and half-body irradiation were introduced. TBI for immunosuppression at bone marrow transplantation in leukemia treatment in Ljubljana was first used in 1989.[12]

Finally, it should be mentioned that during the '70s adequate modern *facilities for radiation treatment planning and control* were provided. Among these were: the transversoaxial tomograph, two simulators, treatment planning computers, body outline tracing device, apparatus for formation of individual fixation masks, and other accessories for patient immobilisation during irradiation.

Brachytherapy with sealed radioactive sources

For this kind of treatment only *radium-226* in needles and tubes was used in the IO until 1956

(with total amount of the element being near 1 gram from 1947 on). By the end of '50s and in the following decades *radioisotopes* came into use. First, *cobalt-60* was purchased in form of globules, and grains in plastic mass (»plastobalt«), but it was used only for a few years, because of certain disadvantages of its application.

During the '60s the treatment of *superficial lesions* (specialy in the eye region) was carried out also by *beta emitters (phosphorous-32* and *strontium-90* surface applicators), but not for a long time. However, since 1985, again a beta-ray eye plaques with *ruthenium-123* have been used in the treatment of chorioidal melanomas.

For the *interstitial* applications, in '60s also the *gold-198* seeds, *tantalum-182* wires (»hairpins«), and mainly *iridium-192* wires and seeds came into use. A relevant dosimetric system for implants was worked out in a cooperative study by one of our radiotherapists and radiophysicist.[13]

For *intrauterine irradiation,* in the '70s, Simon's afterload packing technique with *cesium-137* miniature sources was introduced, like it was previously performed according to Heyman with radium, and then with cobalt sources. As before, *cervical carcinoma* remains the main field of brachytherapy. Until 1953 it was performed according to so–called Paris (Regaud) technique, and since then according to Manchester (Paterson-Parker) technique. In the mid '70s, our own modified Henschke's manual after-loading application of cesium sources was developed. In 1985 a *unit for remote after-loading (CGR Curietron)* was purchased. Thus, in the last years cesium sources almost completely replaced the use of radium in the treatment of uterine cancers.

In other cancer sites the use of brachytherapy steeply decreased during the '70s. However, it seems that in the last years the interest, specially for interstitial therapy has been renewed. It is worth mentioning that in 1985 our radiotherapists introduced *interstitial hyperthermia* combined with RT, which has already shown favourable results.[14]

Radiotherapy with unsealed (fluid) radioisotopes

was first used at the Medical Department (later Department of Nuclear Medicine) of the University Hospitals in Ljubljana in the years 1954-59, i.e. by *iodine-131* in hyperthyroidism and thyroid cancer metastases, and by *phosphours-32* in polycythemia vera and chronic leukemias.[15] Later on, these kinds of treatment were introduced also in the IO, (P-32 also for treatment of bone metastases). Besides that, already from 1956 on *intracavitary therapy* with gold-198 colloid has been used in the management of peritoneal and pleural cancerous effusions. Later also colloidal Ytrium-90 has been applied for this purpose.

By the end of '80s the computer assisted data processing for cancer patients treated by RT – was developed, linked with our population-based cancer registry, and in which the detailed clinical and technical data relevant to radiation treatment methods are noticed.[16] Thus, it enables a continous follow-up of the effectiveness of particular methods and treatment techniques in cancers of specific sites and stages.

Radiotherapists of the IO have been and are steadily fulfilling *their role in the necessary interdisciplinary approach in the treatment of cancer patients,* as since 1950 they have been regularly attending, by the IO initiated and organized *multidisciplinary joint clinics* for cancers of specific sites and separately for childhood cancers. In these joint clinics the specialists of other relevant branches, either from the IO and/or from other departments of the University Clinical Centre in Ljubljana take part. Most of these clinics have been taking place weekly in the IO. Besides, our radiotherapists have been paying *regular visits as consultants to the peripheral general hospitals* for many years already. Besides, they are *engaged in teaching radiation oncology* at undergraduate and postgraduate level of medical education, as well at the school for radiology technicians and at the school for nurses.

In connection with the above activities of our radiotherapists, I consider the problem derived

from the knowledge requirement for site specific cancer treatment worth mentioning. Accordingly, the radiotherapists have developed into subspecialists, loosing the broad knowledge and experience in radiation treatment of all malignant diseases. Actually, they are separately engaged in cancer treatment of the following site regions: 1. head and neck, 2. intrathoracic organs, 3. digestive, urinary and male genital organs, 4. female genital organs, 5. breast 6. lymphatic, haematopoietic, bone and soft tissues (including pediatric malignomas). In these fields they have been cooperating in some international clinical trials concerning the problems of combined modality treatment of patients with malignant diseases.

Conclusion

From this review of the development of radiotherapy in Slovenia it can be derived that with respect to the size of its population, there has been a sound tendency to concentrate it in the Institute of Oncology in Ljubljana, as the only such institution in this country. In fact, it is its nucleus in playing a cohesion role in the comprehensive multidisciplinary cancer treatment approach.

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The history of nuclear medicine in the Republic of Slovenia – pioneering age from 1954 to 1968

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Early beginnings of the biomedical use of radionuclides in Ljubljana date back to the year 1954 when J. Satler at the Medical Clinic first used radioiodine (131-J) for diagnosis. In the '50s the institutions which used radionuclides appeared in the following sequence: In 1955 at the Institute of Oncology L. Šavnik injected 198-Au-colloid intraperitoneally for the treatment of malignant disease; at Orthopedic Clinic Thorium-X was used therapeutically; at Institute of Physics of the Medical Faculty dosimetry, and at Institute of Pathophysiology the transport of sodium and potassium ions through cellular membranes was studied by means of radioactive tracers (22-Na and 42-K).

In the year 1960 the Basic Laboratory for Work with Radioisotopes was established in Ljubljana with the aim to provide facilities and place for work as well as coordination to all five institutions which had been using radionuclides.

In fact, till 1968 only the Radium and Isotopic Laboratory of the Institute of Oncology and the Radioisotopic Laboratory of the Medical Clinic operated together in the same place. Research at the Institute of Physics found no clinical application, the therapeutic use of Thorium X at the Orthopaedic Clinic was completely abandoned and the Institute of Pathophysiology built in 1962 its own laboratory for radionuclide investigations.

During the period from 1954 to 1968 Slovenian nuclear medicine, which was in the beginning more or less research-oriented activity, gradually developed broadly into a clinically applicable science.

The year 1968 denotes the end of the pioneering period in Ljubljana and the beginning of a rapid development of nuclear medicine departments in regional hospitals out of Ljubljana.

Key words: nuclear medicine-history; Slovenia

Introduction

By the end of World War II, the use of radioactive isotopes in diagnostics and therapy which established nuclear medicine as a new medical speciality spread throughout Europe and also in Slovenia. Here, the development of this new speciality is presented from its first steps in 1954 till the beginning of rapid augmentation in 1968 which resulted in the establishment of seven nuclear medicine laboratories: two in Ljubljana and one each in the peripheral towns Maribor, Celje, Slovenj Gradec, Šempeter by Gorica and Ankaran. Further development showed that by 1974, these seven nuclear medicine departments sufficed for the needs of Slovenian health service, which was in charge of nearly two million of

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inhabitants, and since then there was no need to open any new ones.

In the first part of this presentation the pioneering age from 1954 till 1968 is described.

1952 – The Institute Jožef Stefan and The Slovenian Academy of Sciences and Arts

In 1952 The Institute Jožef Stefan and The Slovenian Academy of Sciences and Arts organized the first cycle of lectures on the use of radioactive isotopes in medicine, intended for medical doctors. These were followed by practical courses on the handling of unsealed radioactive sources, upon completion of which the attendants obtained legal rights to use these materials.

In the following years the location of these courses changed for a majority of Slovenian doctors, technicians and nurses who gained their theoretical and practical skills at the »School for Handling Radioactive Material« in The Institute Boris Kidrič, Vinča in Belgrade.[1]

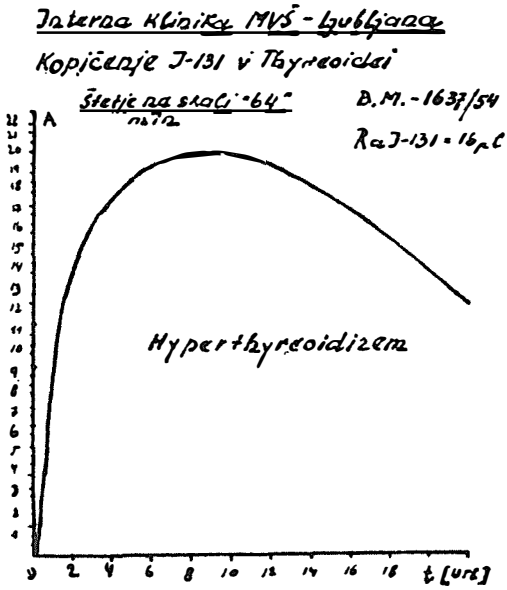

Figure 1. Time-activity curve of 131-I thyroid uptake in a patient with hyperthyrosis treated at Medical Clinic in Ljubljana in 1954 (3).

1954 – The Medical Clinic in Ljubljana

The first diagnostic application of radioiodine in a patient was performed at The Medical Clinic in Ljubljana in the year 1954 by J. Satler. He remembers:[2]

»In the spring 1954 I attended a three-month course on the use of radionuclides in medicine at the Institute Jožef Stefan in Ljubljana, and in the same year the first diagnostic applications of radioiodine (131-J) were performed. I reported about this at The Second Slovene–Chroatian Meeting in Ljubljana and had the article published by Zdravstveni vestnik in 1955. That was probably the first report[3] on the practical use of radioactive isotopes in medicine that appeared in Yugoslav medical press«.

Figure 1 taken from the above mentioned article[3] shows a diagram of 131-J accumulation in the thyroid gland of a patient with hyperthyreosis.

Between the years 1954 and 1960, when the first laboratory for nuclear medicine was opened, the pioneers of nuclear medicine in Slovenia did not have a fixed location of their own. Thus, for example, the Radioisotope Laboratory at the Medical Clinic moved in that period through four different rooms, and accordingly it had to be rearranged, reequipped, reorganized and reopened four times.[1]

J. Satler, who established nuclear medicine practice at the Medical Clinic in Ljubljana, was after some months succeeded by B. Varl while the former moved to Etiopia where he functioned as an expert of World Health Organisation. In that time nuclear medicine staff consisted of only two persons: a doctor (B. Varl) and a technician (B. Rozman). Their measuring equipment was borrowed from the Institute Jožef Stefan: a Geiger–Mueller counter which served for the radioactivity measurements of urine, plasma and erythrocytes, and a scintillation detector with binary and decade counter used for radioiodine thyroid uptake test.[1]

After the introduction of radioiodine thyroid uptake test in 1954 at the Medical Clinic, the frequency of that test had been increasing linearly until the end of 1969, when it reached the

annual number of 2400. By that time radioimmune thyroid tests appeared, and *in vitro* measurement of thyroxine in serum almost completely replaced *in vivo* thyroid radioiodine uptake test.

Besides radioiodine (131-J), the following radiopharmaceuticals were used also: radioactive chromium (51-Cr) served as an erythrocyte marker in the measurements of blood volume, whereas radioactive phosphorus (32-P) was injected for the therapy of polycythemia rubra vera and chronic lymphatic leukemia.[1]

Soon after functional radioiodine diagnostics had been introduced, B. Varl made his first attempts in localisation diagnostics which enabled imaging of radiotracer distribution in the patient's body.[4] As the Geiger–Mueller counter proved insufficient for that purpose, it was gradually replaced by a better detector, i.e. scintillation counter equipped with a specific collimator.

The simplest information on radiotracer distribution in the body was achieved by drawing the radioactivity profile of the body (Figure 2). Better, but much more complicated and time consuming was elaboration of a map of e.g. the neck map with isoactivity lines (Figure 3). The best localisation diagnostics at that time was thyroid scanning with an automatic rectilinear scanner. It was, however, available only after 1962 when the then *Basic laboratory for work with isotopes* was equipped with Nuclear Chicago scintiscanner.

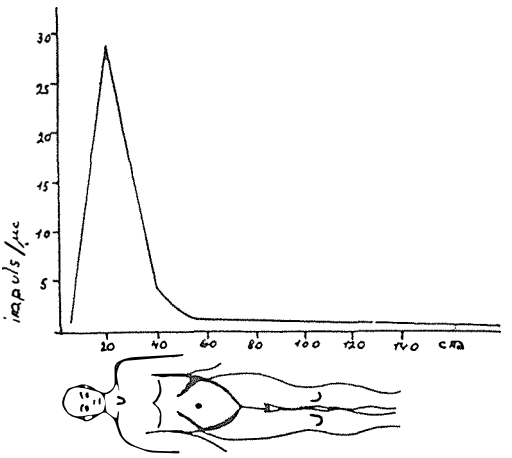

Figure 2. Radioactive prophyle of a patient treated at Medical Clinic in Ljubljana in 1957 with 131-I (4).

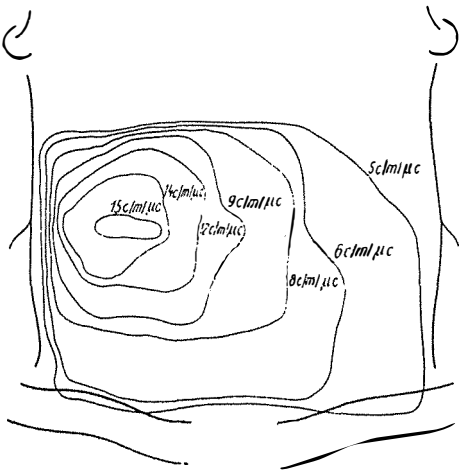

Figure 3. Isoimpulse-drawing of the 131-I uptake in the neck of a patient with anaplastic thyroid cancer – The Institute of Oncology in Ljubljana in 1958 (6).

1955 – The Institute of Oncology in Ljubljana

From its very establishment in 1938, the Institute of Oncology in Ljubljana was dedicated to the comprehensive care of cancer patients in Slovenia. The newest achievements were used in the diagnostics and therapy and therefore it is not surprising, that some of the pioneers of Slovenian nuclear medicine could be found there also.

From the very beginning, therapy with radionuclides was the most intriguing item for oncologists. First they used sealed radioactive sources such as 60-Co-seeds, later they included in their repertoire unsealed radioactive sources such as 198-Au-colloid, which was injected intraperitoneally since 1955 by L. Šavnik to some patients with disseminated ovarian cancer.[5]

Radioiodine-131 was used in patients with thyroid cancer for diagnostic and therapeutic purposes by S. Plesničar since 1957.[5,6]

Among the instruments used in the beginning, Geiger–Mueller counter intended for localization diagnostics played the main role. Initially, they measured the distribution of radiotracers in the patient's body by means of a body mould with openings arranged in rows; a Geiger–Mueller detector was sequentially inserted into the holes and the obtained measurements written on a body map.

Later on, the procedure was greatly improved by the use of scintillation detector purchased for that purpose. Figure 3 shows a drawing of radioiodine distribution in the neck of a patient with anaplastic thyroid cancer. In that time the bio-distribution of radioiodine was studied in excised specimens by means of autoradiography as well.[6]

1957 – Center for The Use of Isotopes in Medicine

This Center was established on the initiative of the Federal Commission for Nuclear Energy, as a cooperative association of institutions in order to unite and rationalize all efforts related to introducing of radioactive isotopes in biomedical research, diagnostics and therapy. The same commission founded similar centers in the capitals of all six Yugoslav republics. The institutions which had been already using or intended to use radioisotopes for biomedical research, diagnostics and therapy were also included. In Ljubljana the members were: Institute of Medical Sciences at the Slovenian Academy of Sciences and Arts, Medical Clinic, Orthopedic Clinic, Institute of Oncology, Institute of Pathophysiology and Institute of Physics at the Medical Faculty.[5]

Later development showed that this cooperation was partly accepted only by Medical Clinic and the Institute of Oncology mainly with reference to prospective room facilities made available by the building of *Basic Laboratory for Work with Isotopes.*

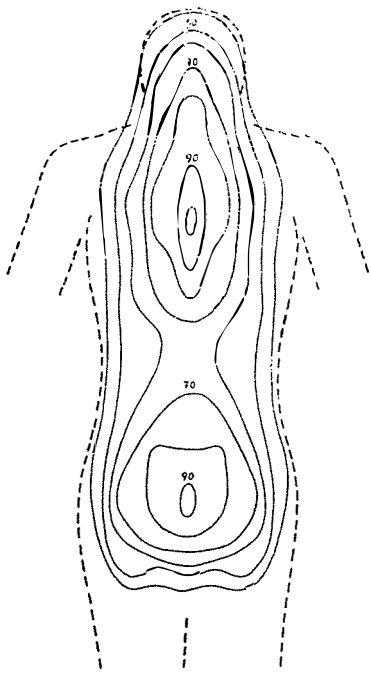

Figure 4. Isoimpulse-drawing of the 85-Sr uptake in the trunk of a patient with bone metastases – The Institute of Oncology in Ljubljana in 1961.

1960 – Basic Laboratory for Work with Isotopes in Ljubljana

In 1960, the Basic Laboratory for Work with Radioisotopes was established in Ljubljana with the aim to provide facilities together and working place as well as coordination for all five institutions of the above mentioned Center, which had begun with the use of radionuclides.

It was located in a brand new extension accomplished during one of the several reconstructions of the buildings where the Institute of Oncology was located in the adapted old Saint Peter's barrack from 1748.

In fact, only the Radium and Isotopic Laboratory of the Institute of Oncology and the Radioisotopic Laboratory of the Medical Clinic had been operating there together until they separated in 1968. The activities of other members of

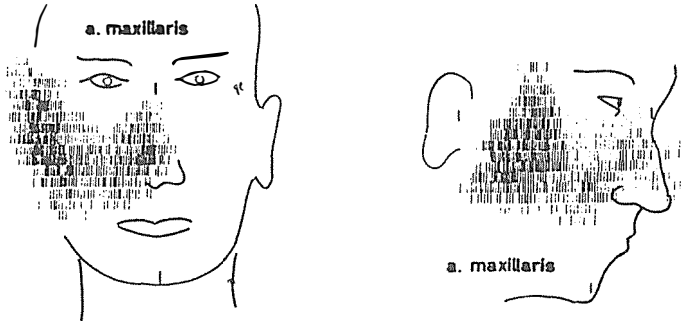

Figure 5. Scan of the area perfused through a catheter inserted into the right maxillary artery, taken after the injection of tracer dosis of macro-aggregates of radioiodinated albumin (131-J-MARA) at the Radium and Isotopic Department of the Institute of Oncology in 1968 (10).

the Center, who did not express any interest in sharing the available facilities, were as follows: in the '50s there were only a few attempts at Orthopaedic Clinic to use Thorium-X therapeutically. Later, however, this sort of therapy was completely abandoned. At the Institute of Physics of the Medical Faculty the study of dosimetry remained at academic level, and so did also the research carried out at the Academy of Science and Arts. At the Institute for Pathophysiology the transport of sodium and potassium ions through cellular membranes was studied by means of radioactive tracers (22-Na and 42-K). This studies continued and in 1962, this institute built its own laboratory.[7]

Even though medical and oncological nuclear medicine were performed in the same place using the same facilities and instruments, the collaborators from that time claim that their work was strictly separated.

Chief of medical nuclear medicine **B. Varl** described their work as follows:[1] »The staff of **Radioisotopic Laboratory of the Medical Clinic** comprised two residents in internal medicine, three technicians, a senior medical nurse, a secretary and an orderly – all of them employed full-time. For me, as chief of the radioisotopic laboratory, nuclear medicine was still a part time job.

In nuclear medicine *equipment* has always been playing a major role in comparison with other factors (e.g. available pharmaceuticals, personnel and other capacities) in determining the type, quality and quantity of operations.

The laboratory equipment was obtained gradually. First instruments were donated by the Federal Commission for Nuclear Energy and by Slovene enterprises; part of the equipment was purchased by Medical Clinic also. We had scintillation detectors with electronic scalers and printers which were used for kinetic in vivo studies. Further, we had a well-type scintillation detector, a Geiger–Mueller counter (for radioactivity measurements in feces and urine), a scanner for electrophoretic and chromatographic tapes as well as an automatic system for scintigraphy and radioactivity measurements of liquids«.

An enormous qualitative step forward in clinical nuclear medicine was made possible by the purchase of scintiscanner Nuclear Chicago; the unit was bought by the Institute of Oncology in 1961 with a loan from Boris Kidrič Foundation.[5] The device enabled automatic morphological nuclear medicine investigations that had been extremely time consuming before as they had been based on manual scanning, i.e. measurements of radioactivity in discrete points and presented as the body map of isoactive lines (Figures 3 and 4).

So, since 1961 static automatic scanning of the thyroid, liver, kidneys, spleen, and after 1967 also pancreas scanning was performed.[1]

Accordingly, a step forward in the annual num-

ber of renal examinations was noted after the purchase of renaltron in 1967.[1]

All this pioneering period was characterized by a steep increase in the annual number of diagnostic and therapeutic procedures. The total figure of annual diagnostic and therapeutic applications of radionuclides to patients in Slovenia was in 1958 between 140 and 150.[5]

In 1964, the Radioisotopic Laboratory of Medical Clinic, performed alone 1750 investigations and by 1970, the annual number at the Institute of Nuclear Medicine, which developed from the previous Radioisotopic Laboratory, increased to 7500.[1]

The time after the year 1960 was the period of first research projects in nuclear medicine based on the contracts with Federal Commission for Nuclear Energy and with the Research Council of Slovenia, the Boris Kidrič Foundation.

On the other hand, a major part of our work was dedicated to clinical and outpatient thyrology including two phase radioiodine test, first manual and afterwards automatic thyroid scanning, thyroid TSH test, thyroid suppression test, and therapy of hyperthyroidism with radioiodine«.

Investigations of other organic systems included testing of the absorption of fats, vitamin B_{12} and iron. Among the investigations performed were also other hematologic tests with radioactive chromium (51-Cr) and iron (59-Fe) as well as radionephrography with 131-I-hippurate, functional liver investigations with colloidal radioactive gold (198-Au) and 131-I-Rose Bengal.[1]

Between 1960 and 1968, the **Radium and Isotopic Department of the Institute of Oncology** shared the same rooms and facilities with the Radioisotopic Laboratory of Medical Clinic, was headed by **M. Erjavec.** He has described that period as follows:

«Regular work probably started by 1960. In that pioneering period it developed in the following six major directions:

1. *Therapy with sealed radioactive sources:* First attempts were made in 50's with 60-Co-seeds. After 1960 we have introduced artificial radionuclides in brachyradiotherapy in form of »after-load« technique which was revolutionary for that time. First we used gold seeds. Later on we developed a genuine modification of French therapy with iridium wires and original graphical dosimetry. Even later we developed our own pencil-sized apparatus for implantation of iridium seeds, which replaced Italian »wardrobe«. That pencil-sized apparatus was copied and commercially produced by the international radiopharmaceutic company Sorin.

2. *Therapy with open radioactive sources:* Treatment with 198-Au-colloid, which was injected intraperitoneally since 1955 by L. Šavnik to some patients with disseminated ovarian cancer,[5] was followed by 131-J-iodine[6] in patients with thyroid carcinoma though first in a rather simple form and not at a high professional level. The technique was upgraded only 15 years later.

Though the use of radioactive phosphorus (32-P) for the treatment of bone metastases from different tumors was introduced relatively early, this therapeutic method was soon abandoned owing to its severe toxicity. Later on it was replaced by radioactive strontium (89-Sr) in the treatment of non-curable osteoblastic metastases.

3. *Radiopharmaceutical labelling,* first with radioactive iodine (131-I) and later on with indium (113m-In) was a must if we wanted to keep abreast of the work performed elsewhere in the world.

In the beginning, radiolymphography by means of radioiodinated oils appeared very promising and therefore in 1967 we even developed our own method of production of this radiopharmaceutical. Clinical application of the method, however, was not successful, so that it was abandoned after a few years.

Actually, most of the efforts were directed into the development of labelling of radioiodinated microparticles which were initially used for lung scanning and finally for lymphography and scintigraphic monitoring of the position of intraarterially inserted catheters for later intraarterial chemotherapy application. Figure 5 shows perfusion through catheter inserted into the right maxillary artery.

4. *Skeletal scintiscanning* has always been a model achievement of our laboratory. Our first, pioneering attempts in this respect, by means of strontium (85-Sr) date back to the year 1961; not aware of the fact that two other groups from America were developing the same method, at that time we were among the beginners of those investigations. Figure 4 shows a body map of radiostrontium (85-Sr) distribution in a patient with bone metastases. Had it not been just a day to late, our report submitted for presentation at the IAEA Congress (Athens, 1964) would have been the first of the kind in the world.

5. Measuring devices have been technically upgraded and modified along with the development of skeletal scintiscanning. The first commercially available scintiscanner Nuc-Chicago was modified to such extent that even the producer could not recognize it any longer. A special collimated detector enabled imaging by means of high-energy gamma rays of 510 KeV energies emitted by radioactive strontium (85-Sr) and fluorine (18-F).

6. *Renography,* i.e. measuring of kidney clearance has always been in the first plane of our laboratory work, first as a «hobby» activity and later on because of the increased demand related to the expanding use of chemotherapy at the Institute of Oncology.

The method has been frequently changed and upgraded until it reached its ideal form in the recent years. Presently, the investigation is completely automated, blood-sample taking is unnecessary, and kidney clearance of 131-I hippurate is obtained simultaneously with standard renography«.[8]

Due to the growing scope of work, the capacities of the Basic Laboratory in Ljubljana became too small to house medical nuclear medicine and oncological nuclear medicine under the same roof.

As a result, the former activity was moved from the mutual premises back to the west wing of the old Clinic of Internal Medicine.[1] After that time The Basic Laboratory served for the needs of Radium and Nuclear Medicine Department of the Institute of Oncology only.

By that time the first nuclear medicine laboratory in a regional hospital, i.e. in the Health Center in Celje, was established.[9]

The year 1968 marked the end of the pioneering period and the beginning of a rapid development of nuclear medicine departments in regional hospitals out of Ljubljana.

Acknowledgement

In preparation of this text I was greatly assisted by B. Varl, B. Ravnihar, M. Erjavec, J. Satler, S. Plesničar, F. Fazarinc, M. Porenta, D. Sket and B. Kastelic, who were kindly willing to offer me their valuable advice as well as verbal and written information for which I am indebted. My due thanks are to O. Shrestha for her help with English translation.

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Radiol Oncol 1992; 26: 90-1.

Report from ESTRO meeting with representatives of national radiotherapy associations

As the president of Yugoslav society of radiotherapy, on March 1991 I was invited to attend – together with 22 representatives of other national radiotherapy societies of Europe – the meeting organized in Leuven under the auspices of ESTRO.

The main topic of the meeting was the proposal of a minimal program of common European specialisation in radiotherapy. The program was prepared on the basis of data on individual radiotherapy specialisation programs collected in different European countries. With reference to the legal aspects of the correct title of this common specialisation, we were assisted by an expert of the European Community. By unifying the basic program of radiotherapy specialisation in Europe, we hope to ensure an adequate level of knowledge in radiotherapy in all countries joining this program.

RECOMMENDED MINIMUM CURRICULUM FOR THE POSTGRADUATE TRAINING OF MEDICAL PRACTITIONERS IN RADIOTHERAPY (RADIATION ONCOLOGY) WITHIN EUROPE WAS ACCEPTED AND SIGNED.

Radiotherapy (radiation oncology) is the use by medical practitioners of ionising radiation, either alone or in combination with other modalities, for the treatment of patients with malignant and other diseases.

It can be practiced as an independant oncological specialty or it may be integrated into a broader medical practice.

Radiotherapy (radiation oncology) includes, in a multidisciplinary approach, responsibility for the diagnosis, treatment, follow up and supportive care of the cancer patient.

The term »radiotherapy« has been used in this document in reference to »radiation oncology« because the former term is that under which this specialised area of medicine is recognised in many countries at the present time. In particular it is the recognised term in most Member States of the European Community and is the term used in EC legislation on medical training (directives 75/362 and 75/363/EEC of June 1975).

The following curriculum outlines the minimum requirements which the representatives of responsible national societies and/or representative teaching bodies have agreed upon to serve as a basis for the training in radiotherapy. To conform with the EC directives, such training should consist of a minimum of four years full-time theoretical and practical instruction.

The responsibility for the teaching of radiotherapy (radiation oncology), as set out in this document, will lie with the local and/or national training bodies.

The curriculum

Training in radiotherapy (radiation oncology) should cover at least the following:

1. General Oncology

1.1. Cancer biology
1.2. Epidemiology of cancer
1.3. Cancer prevention, screening, early detection and education of the public
1.4. Pathology of malignant tumours and related diseases
1.5. Symptoms and signs of neoplastic diseases
1.6. Diagnostic procedures
1.7. Classification, stage grouping and prognostic factors of malignant diseases

2. Principles of cancer treatment

2.1. Treatment with surgery
2.2. Treatment with radiation
2.3. Chemotherapy and endocrine therapy
2.4. Other forms of treatment
2.5. Decision making: treatment aim and choice of modality
2.6. Follow up of patients
2.7. Supportive care
2.8. Psychosocial aspects and quality of life
2.9. Terminal care

3. Therapeutic use of ionising radiation

3.1. Biological basis of radiation effects
3.2. Response of tumours to irradiation
3.3. Early and late radiation effects in normal tissues
3.4. Optimal radiation therapy in relation to disease type and location.
3.5. Physics applied to radiotherapy
3.6. Techniques and equipment for radiotherapy
3.7. Treatment planning and dosimetry for external beam radiotherapy and brachytherapy
3.8. Therapeutic use of radionuclides
3.9. Radiation protection and safety
3.10. Quality assurance and auditing in radiation oncology
3.11. Interactions of radiotherapy with other treatment modalities
3.12. Role of radiotherapy in non-malignant diseases

4. Clinical research in Oncology

4.1. Principles and methodology of clinical research
4.2. Quantification of tumour response
4.3. Description and quantification of normal tissue reactions
4.4. Design, conduct and evaluation of clinical trials
4.5. Medical statistics
4.6. Ethical aspects

All the relevant centers of former Yugoslavia have already been informed about the common European specialization in radiotherapy, but nevertheless, it should be pointed out again that all those centers not having adjusted their programs of specialisation in radiotherapy according to the above recommendations are expected to do so as soon as possible.

So far, Slovenia and Macedonia have already submitted their adjusted programs to ESTRO. In order to provide an adequately high level of knowledge in radiotherapy and oncology to all future radiotherapists, the specialisation programs in all European countries should be unified. ESTRO will support this activity by providing text-books, and organizing the necessary courses for basic and clinical education in radiotherapy.

I am convinced that this minimum agreement on specialization in radiotherapy represents the initial, though small step toward uniform knowledge of radiotherapy in Europe, which would enable radiotherapists to perform their work anywhere in Europe.

Prof. J. Kuhelj, MD, PhD
The Institute of Oncology,
Ljubljana

Notices

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

MOLECULAR BIOLOGY FOR CLINICAL ONCOLOGIST

The 2nd postgraduate teaching course will be held in London, U.K., *July 1-3, 1992.*

Contact Dr. J. R. Yarnold, Academic Radiotherapy Unit, The Royal Marsden Hospital, Downs Road, Sutton, Surrey, SM2 5PT; or call +44 81 642 6011 Ext. 3273. Fax + 44 81 643 2272.

MOLECULAR BIOLOGY FOR CLINICAL ONCOLOGIST

The workshop will be offered in Aspen, Colorado, USA, *July 5-11, 1992.*

Contact American Assoc. for Cancer Research, Public Ledger Bldg., 620 Chestnut St., Suite 816, Philadelphia, PA 19106 3483; or call + 1 215 440 9300.

PHYISICAL TREATMENT OF LYMPHOEDEMAS

The ESO training course for non-oncologists will be offered in Monte Verita, Switzerland, *July 6-9, 1992.*

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

COLORECTAL CANCER

The ESO residential course will be offered in Orta San Giulio, Italy, *July 6-10, 1992.*

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

SCIENTIFIC WRITER AND EDITOR

The ESO seminar will take place in San Servolo, Venice, *July 13-15, 1992.*

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

HEAD AND NECK CANCER

The 3th international conference will be offered in San Francisco, California, USA, *July 26-30, 1992.*

Contact Charles W. Cummings MD, Chairman, Dept of Otolaryngology – Head and Neck Surgery, University of Washington, Seattle, WA 98195, USA.

CELL BIOLOGY

The 5th international congress will be held in Madrid, Spain, *July 26-31, 1992.*

Contact TILESA, Londres 39, 28028 Madrid, Spain.

CARCINOGENESIS

The 2nd international conference will take place in Oslo, Norway, *August 15-21, 1992.*

Contact Conference Secretariat, International Conference Service, Holbergs Plass 3a, N-0166 Oslo, Norway; or call + 47 2 11-21-90. Fax: + 47 2 36-11-44.

IMMUNOLOGY

The 8th international congress will be held in Budapest, Hungary, *August 23-29, 1992.*

Contact IPV/Intercongress, H-1068 Budapest, Dozsa Gy, ut 84/a, Hungary.

IMMUNOLOGY

The »John Humphrey Course on Tumor Immunology«, organized by the Rumanian Society for Immunology and sponsored by Gesellschaft fuer Immunologie, Germany, will be offered in Iasi, Rumania, *August 30 – September 3, 1992.*

Contact Dr. Eugen Carasevici, Spitalul Universitar »Sf. Spiridon«, Clinica Oncologica, Lab. de Imnologue Tumorala, B-dul Independentei, Nr. 1, 6600 Iasi, Romania.

11th ANNUAL ESTRO MEETING

The meeting will take place in Malmo, Sweden, *September 1 – 4, 1992.*

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

RADIOTHERAPY

The teaching courses »Detectors for Reference Dose, Dose Distribution and *in vivo* Dose Measurements« and »Methodology of clinical Trials« will be linked to Annual ESTRO Meeting and offered in Malmo, Sweden, *September 5-6, 1992.*

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.

BRACHYTHERAPY

The »7th International Working Conference« will take place in Baltimore, Washington, USA, *September 6-8, 1992.*

Contact Conference Secretariat, Jacqueline van Zetten, Nucletron International B. V., 3900 AX Veenendaal, The Netherlands; or call + 31 8385-33133.

GYNAECOLOGICAL ONCOLOGY

The ESO course will be offered in Amsterdam, Netherlands *September 6-11, 1992.*

Contact European School of Oncology, Via Venezian, 18 20133 Milan, Italy; or call + 39 2 70636923 or 2364283. Fax: + 39 2 2664662.

PAEDIATRIC HAEMATOLOGY

The »ESH Classical Study Session« will be offered in Moscow, Russia, *September 7-10, 1992.*

Contact European School of Haematology, Centre Hayem, Hopital Saint-Louis, avenue Claude Vellefaux, 1, 75475 Paris Cedex 10, France; or call + 33 1 42-06-65-40. Fax + 33 1 42-41-14-70.

ONCOGENESIS

The symposium »Zinc Finger Proteins in Oncogenesis: DNA Binding and Gene Regulation« will take place in Noordwijkerhout, the Netherlands, *September 7-19, 1992.*

Contact Conf. Dept., NYAS, 2 E. 63rd St., New York, NY 10021; or call + 1 212 838 0230.

BREAST CANCER

The international meeting will be held in Nottingham, U.K., *September 9-11, 1992.*

Contact Mrs. Wendy Bartlam, Secretary to Prof. R. W. Blamey, Professorial Unit of Surgery, City Hospital, Hucknall Road, Nottingham, NG5 IPB, U.K.

INTRAOPERATIVE RADIOTHERAPY

The »4th International Symposium on IORT« will take place in Munich, Germany, *September 13-16.*

Contact Dr. N. Willich, Linik dre Universitaet Muenchen, Abt. Strahlentherapie, Marchioninst. 15, W-8000 Muenchen 70, Germany; or call + 49 89-7095-3843. Fax: 0049 89-7095-8895.

RADIATION PHYSICS FOR CLINICAL RADIOTHERAPY

The ESTRO teaching course will be offered in Leuven, Belgium, *September 13-17, 1992.*

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.

RADIATION ONCOLOGY

The »4th International Conference on Dose, Time and Fractionation« will be held in Madison, Wisconsin, USA, *September 16-19, 1992.*

Contact Bhudatt Paliwal, Ph.D., Conference Chairman, Department of Human Oncology and Medical Physics, University of Wisconsin, 600 Highland Ave. K4/B 100, Madison, WI 53792, USA; or call + 1 608 263 8506.

CANCER & THE IMMUNE SYSTEM

The ESO seminar will take place in San Servolo, Venice, *September 21-23, 1992.*

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

GYNAECOLOGICAL ONCOLOGY

The ESO course will be offered in Prague, Tchecho-Slowakia, *September 21-24, 1992.*

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

SCRIPPS CLINIC AND RESEARCH FOUNDATION

The course »Coronary Interventions: 1992« will be offered in La Jolla, California, *September 25-26, 1992.*

Contact Scripps Clinic and Research Fdn., Dept. of Academic Affairs, Box 403C, 10666 N. Torrey Pines Rd., La Jolla, CA 92037; or call + 1 619 554 8556.

MOLECULAR GENETICS IN CLINICAL ONCOLOGY

The ESO seminar will be held in San Servolo, Venice, *September 28-30, 1992.*

Contact European School of Oncology, Via Venezian, 18 20133 Milan, Italy; or call + 39 2 70635923 or 2364283. Fax: + 39 2 26644662.

LYMPHOMAS

The ESO course will be offered in Tel Aviv, Israel, *October 1992.*

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

THE ROLE OF RADIOTHERAPY IN THE MANAGEMENT OF CANCER

The ESTRO teaching course will be held in Tuebingen, Germany, *October 4-8, 1992.*

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.

LEUKEMIAS & LYMPHOMAS

The course will be offered in Paris, France, *October 5-8, 1992.*

Contact European School of Haematology, Centre Hayem, Hopital Saint-Louis, avenue Claude Vellefaux, 1, 75475 Paris Cedex 10, France; or call + 33 1 42-06-65-40. Fax + 33 1 42-41-14-70.

BREAST CANCER

The ESO residential course will be offered in Orta San Giulio, Italy, *October 5-9, 1992.*

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

MEDICAL PHYSICS

The »Joint Annual Meeting on Medical Physics« will take place in Basel, Switzerland, *October 8-10, 1992.*

Contact Frau I. Fankhauser, Abteilung fuer Radiologische Physik, Kantonsspital, CH 4031 Basel, Switzerland; or call + 41 61 265 31 40.

NUTRITION & CANCER

The ESO seminar will take place in San Servolo, Venice, *October 12-14, 1992.*

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

SCRIPPS CLINIC AND RESEARCH FOUNDATION

The »18th Annual Lukes Lymphoma Conference« will be offered in La Jolla, California, *October 12-18, 1992.*

Contact Scripps Clinic and Research Fdn., Dept. of Academic Affairs, Box 403C, 10666 N. Torrey Pines Rd., La Jolla, CA 92037; or call + 1 619 554 8556.

BASIC CLINICAL RADIOBIOLOGY

The ESTRO teaching course will be offered in Copenhagen, Denmark, *October 18-23, 1992.*

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.

RADIOTHERAPY

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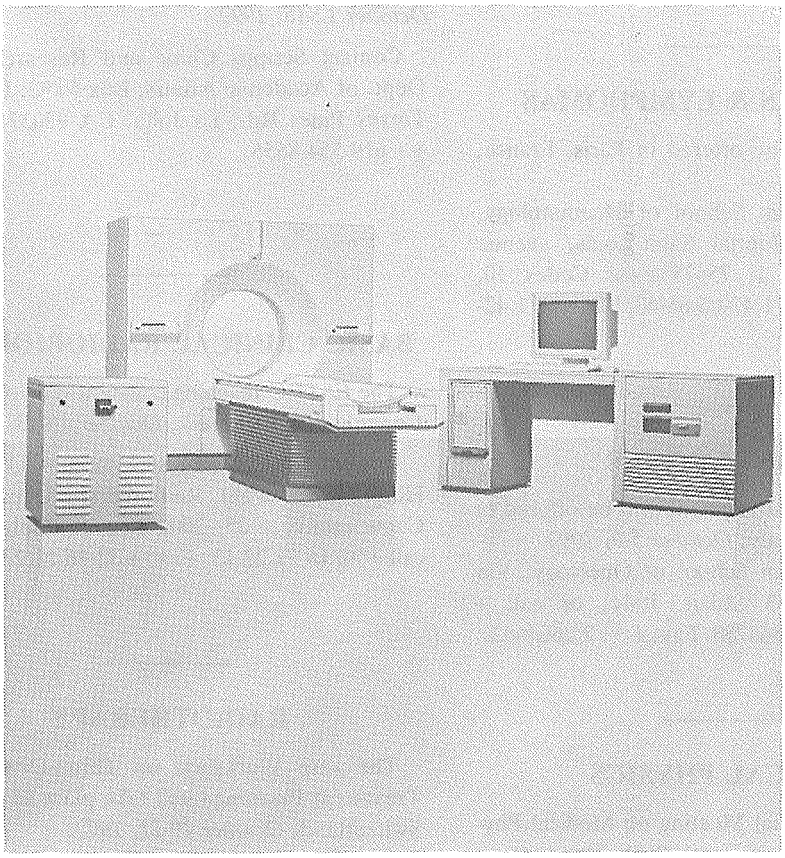

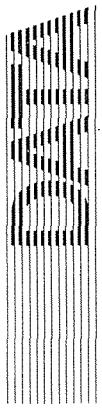

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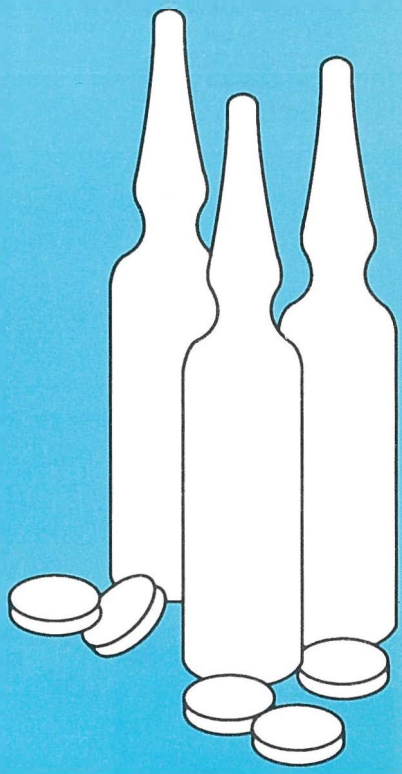

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Pefloxacin is contraindicated in patients with known hypersensitivity to quinolones, in pregnant women, nursing mothers, children under 15 years of age, and patients with inborn glucose-6-phosphate dehydrogenase deficiency.

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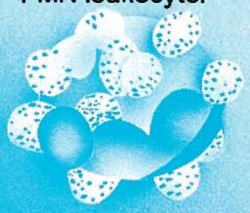

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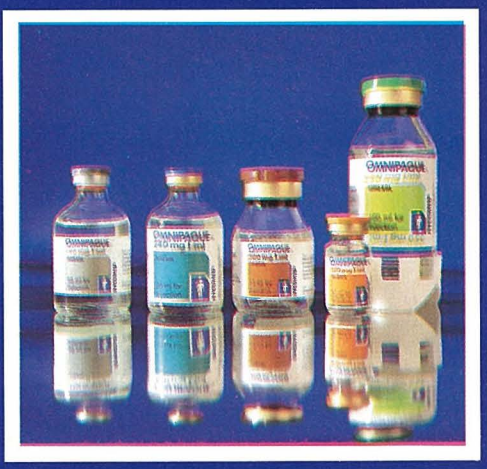

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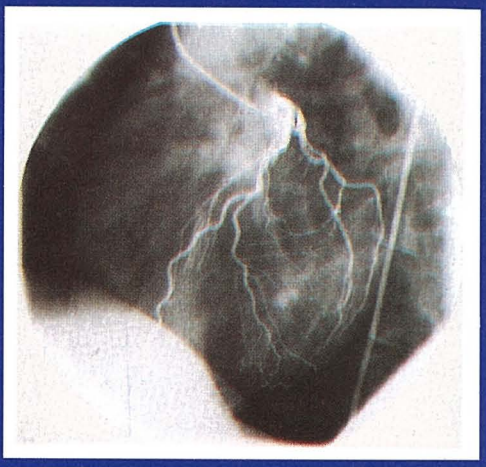

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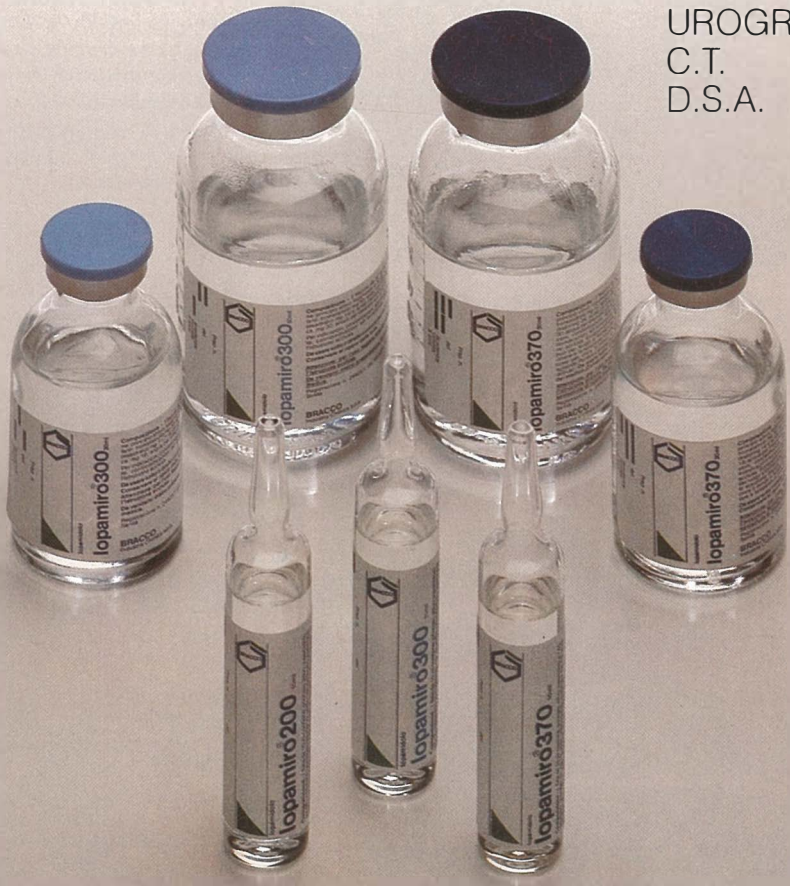

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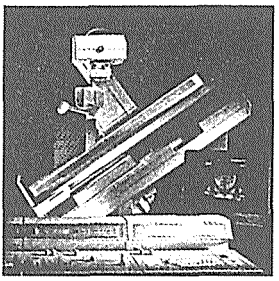

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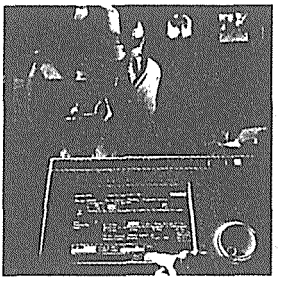

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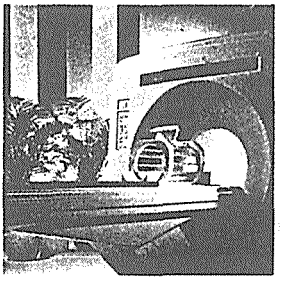

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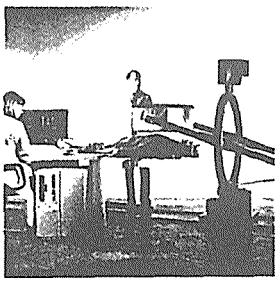

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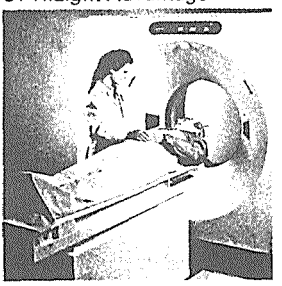

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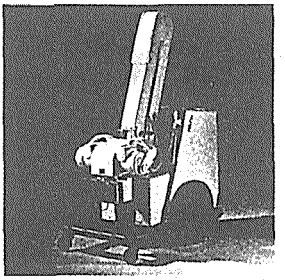

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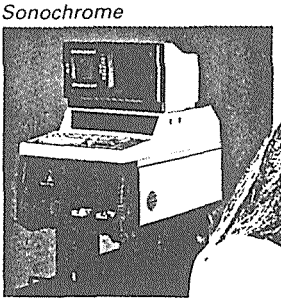

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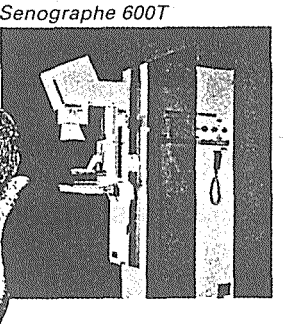

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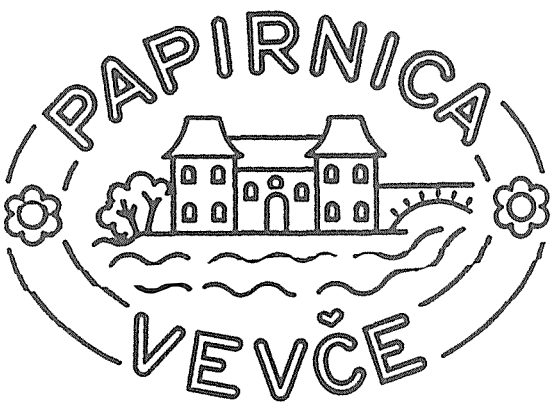

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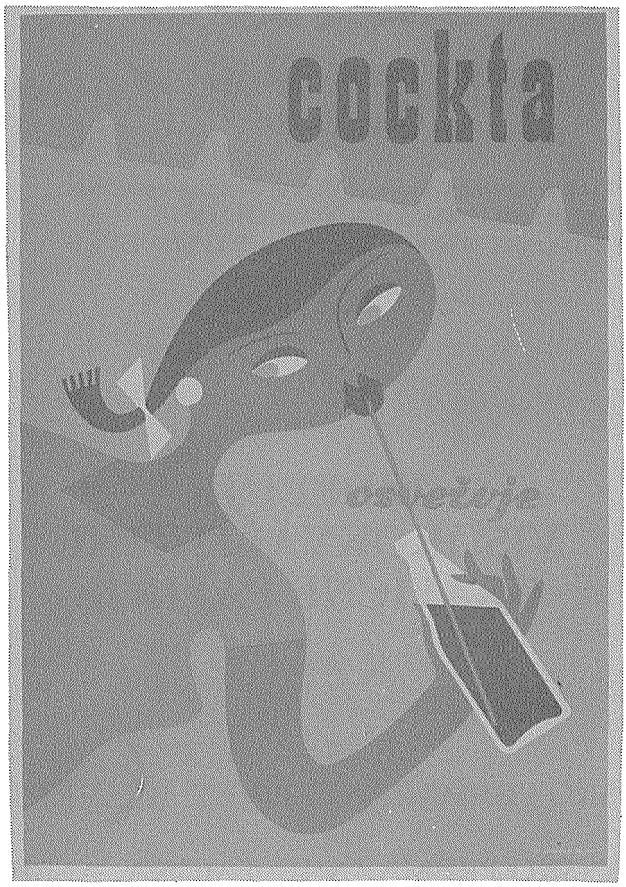

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Radiology and Oncology will consider manuscripts prepared according to the Vancouver Agreement (N Engl J Med 1991; 324: 424-8.; BMJ 1991; 302: 6772.).

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General instructions: Type the manuscript double spaced on one side with a 4 cm margin at the top and left hand side of the sheet. Write the paper in grammatically and stylistically correct language. Avoid abbreviations unless previously explained. The technical data should confirm to the SI system. The manuscript, including the references may not exceed 15 typewritten pages, and the number of figures and tables is limited to 4. If appropriate, organise the text so that it includes: Introduction, Material and methods, Results and Discussion. Exceptionally, the results and discussion can be combined in a single section. Start each section on a new page and number these consecutively with Arabic numerals. Authors are encouraged to submit their contributions besides three typewritten copies also on diskettes (5 1/4") in standard ASCI format.

First page:

- name and tamily name of all authors,
- a brief and specific title avoiding abbreviations and colloquialisms,
- complete address of institution for each author,
- in the abstract of not more than 200 words cover the main factual points of the article, and illustrate them with the most relevant data, so that the reader may quickly obtain a general view of the material.

Introduction is a brief and concise section stating the purpose of the article in relation to other already published papers on the same subject. Do not present extensive reviews of the literature.

Material and methods should provide enough information to enable experiments to be repeated.

Write the **Results** clearly and concisely and avoid repeating the data in the tables and figures.

Discussion should explain the results, and not simply repeat them, interpret their significance and draw conclusions.

Graphic material (figures and tables). Each item should be sent in triplicate, one of them marked original for publication. Only high-contrast glossy prints will be accepted. Line drawings, graphs and charts should be done professionally in Indian ink. All lettering must be legible after reduction to column size. In photographs mask the identities of patients. Label the figures in pencil on the back indicating author's name, the first few words of the title and figure number: indicate the top with and arrow. Write legend to figures and illustrations on a separate sheet of paper. Omit vertical lines in tables and write the text to tables overhead. Label the tables on their reverse side.

References should be taped in accordance with Vancouver style, double spaced on a separate sheet of paper. Number the references in the order in which they appear in the text and quote their corresponding numbers in the text. Following are some examples of references from articles, books and book chapters:

1. Dent RG, Cole P. *In vitro* maturation of monocytes in squamous carcinoma of the lung. *Br J Cancer* 1981; **43:** 486-95.
2. Chapman S, Nakielny R. *A guide to radiological procedures.* London: Bailliere Tindall, 1986.
3. Evans R, Alexander P. Mechanisms of extracellular killing of nucleated mammalian cells by macrophages. In: Nelson DS ed. *Immunobiology of macrophage* New York: Academic Press, 1976: 45-74.

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