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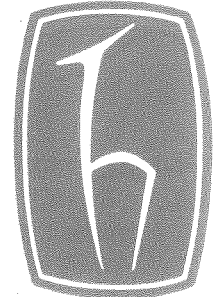
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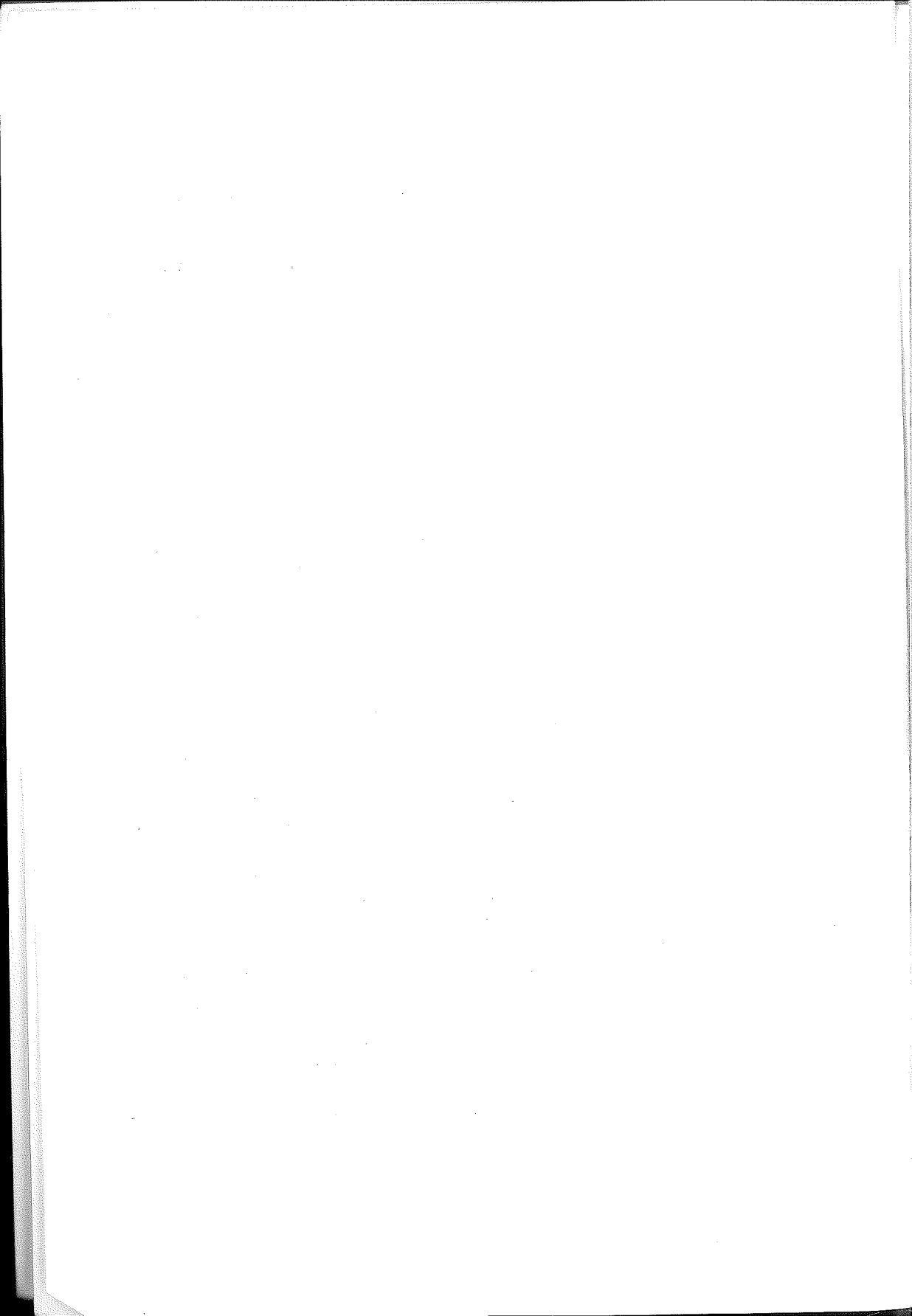
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# Ranitidine Hepatitis Potentiated by Acetaminophene in Mice

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Tevfik Tekeli, D.V.M.\*\*\* / Hüda-verdi Erer, D.V.M.\*\*\*\*

## Summary

**T**wenty male albino mice were given ranitidine at a dose of 3000 mg/kg body weight in drinking water on the first day of the study. Ten mice also received acetaminophene at the daily dose of 75 mg/kg body weight in drinking water on the second and third days. Another ten mice received only acetaminophene at the same dose and on the same days. At the end of the third day there was a striking elevation of serum aminotransferase activities ( $p < 0.01$ ) and the liver weight was lower ( $p < 0.05$ ) in animals which received both ranitidine and acetaminophene. There was no pathological sign in the light microscopic examination of the liver sections.

*Key Words:* Acetaminophene, Ranitidine, Liver toxicity.

## Introduction

Both ranitidine and acetaminophene depend on the availability of reduced glutathione for detoxification.<sup>1-6</sup> According to Proctor,<sup>4</sup> there is a theoretical basis for ranitidine-induced hepatotoxicity that may be

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potentiated by acetaminophene, but it has not yet been studied in detail. For this reason, we examined the effects of ranitidine with or without acetaminophene in liver tissue.

#### *Materials and Methods*

Thirty male albino mice weighing 30-35 g were included in this study. They were separated into three groups with ten mice in each group. Mice in the first and second groups received ranitidine at a dose of 3000 mg/kg body weight in drinking water beginning on the first day of the study. Then, acetaminophene was given to the mice in the second and third groups at a daily dose of 75 mg/kg body weight in drinking water beginning on the second and third days of the study.

At the end of the third day, blood samples were taken for determination of serum aminotransferases activities.<sup>7</sup> Serum and liver-tissue concentrations of the drugs and their metabolites were not determined. All of the animals and their livers were weighed. Sections of the liver were randomly taken from different lobes, embedded in paraffin, cut into four micron-thick sections and stained with haematoxyline and eosine for examination by light microscopy. The results were expressed as the mean  $\pm$  SEM. Student's test was used to compare the results.

#### *Results*

In animals receiving ranitidine and acetaminophene, there was a striking elevation of SGOT and SGPT activities with means of  $92.30 \pm 13.14$  U and  $72.80 \pm 17.21$  U. SGOT and SGPT activities in animals treated with only ranitidine or acetaminophene were  $56.09 \pm 9.34$  U and  $48.00 \pm 6.42$  U ( $p < 0.01$ ), and  $53.02 \pm 14.1$  U and  $51.01 \pm 12.35$  U ( $p < 0.01$ ) respectively. Although the body weights were same in three groups ( $33.24 \pm 1.54$  g,  $32.47 \pm 1.01$  g and  $31.79 \pm 2.08$  g,  $p > 0.05$ ), liver weight ( $2.12 \pm 0.14$  g and  $1.99 \pm 0.20$ , and  $1.64 \pm 0.05$  g  $p < 0.01$ ) and the percentage of liver weight to body weight ( $6.33 \pm 0.19$  % and  $5.86 \pm 0.67$  %, and  $5.09 \pm 0.17$  %,  $p < 0.05$ ) were lower in animals which received ranitidine and acetaminophene. Light microscopic examination of the liver of mice in the three groups showed no pathological findings.

#### *Discussion*

Ranitidine causes minimal and infrequent adverse effects at the therapeutic dosages. Although slight and transient increases in serum aminotransferases have been observed, their significance and the causes are pathogenesis presently unknown. Hepatitis has also been reported in several cases.<sup>1-4</sup>

Ranitidine is chemically distinct from cimetidine by virtue of having a furan ring instead of imidazole ring. Some of the side effects of ranitidine may be related to the metabolism of the structure of the aminoalkyl furan ring. Several furan compounds and drugs cause injury, such as to the liver, that varies patly with the endogenous availability of reduced cytochrome P450 activity.<sup>1, 2</sup>

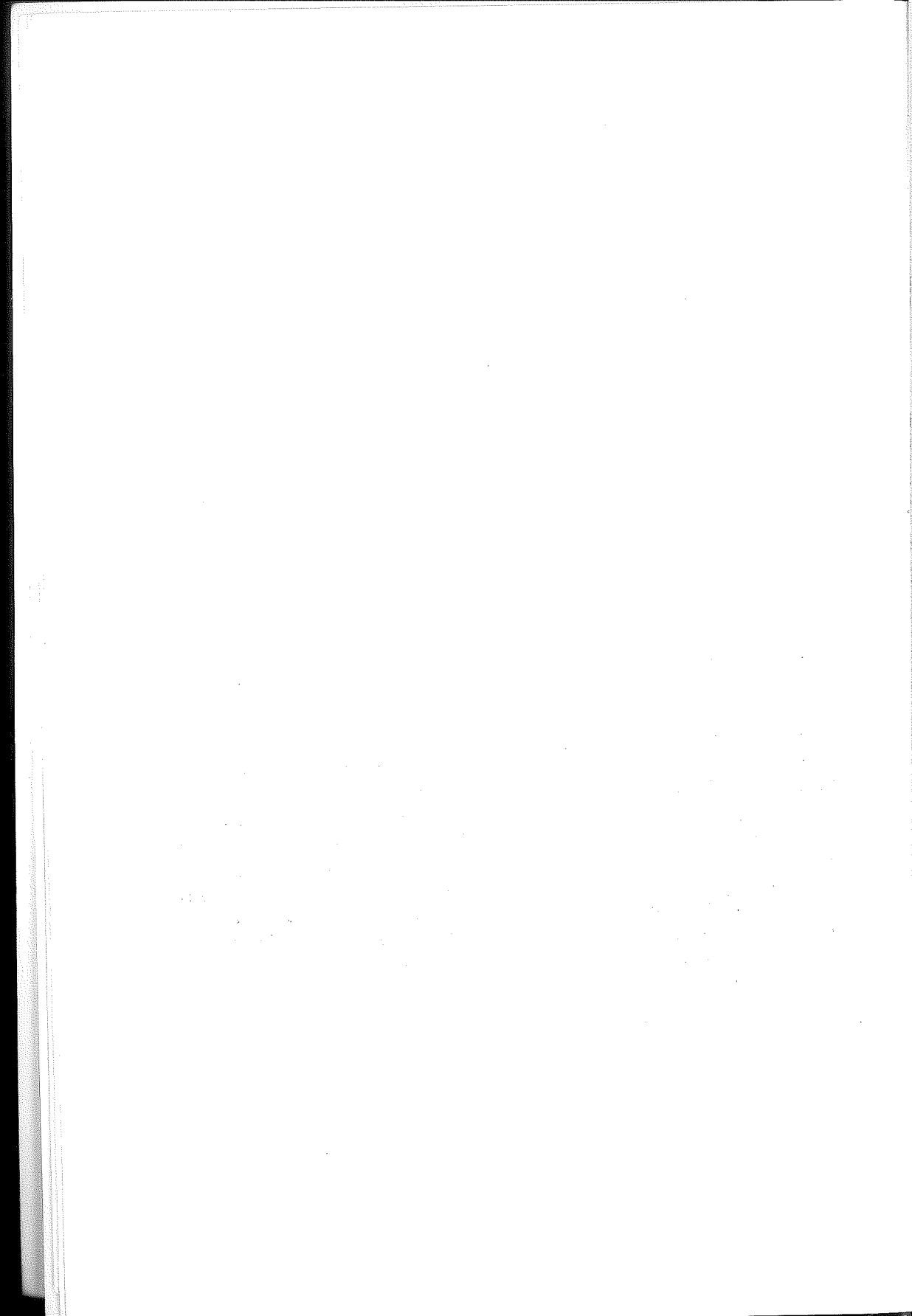
Acetaminophene is eliminated only if it is administered in therapeutic doses along with glucronate and sulphate. Only a small amount of the toxic metabolite is formed by cytochrome P450-mediated oxidation of acetaminophene; and this product is usually conjugated with glutathione which renders the compound nontoxic.<sup>5</sup> Ranitidine does not inhibit the hepatic cytochrome P450 enzyme system.<sup>6</sup>

In summary, reduced glutathione is very important for detoxification of both ranitidine and acetaminophene. There is a potential competitive inhibition between ranitidine and acetaminophene in the body. When these drugs are used together in high doses, reduced glutathione can not meet the requirement for the detoxification reactions and accumulates in the body; may cause liver damage according to the suggestions of Proctor<sup>4</sup> which is supported by this study.

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# The Value of Fiberoptic Endoscopy in Clinical Diagnosis

Halis Şimşek, M.D.\* / Hasan Telatar, M.D.\*\* /  
Şükran Karacadağ, M.D.\*\* / Burhan Kayhan, M.D.\*\*

## Summary

Five thousand upper gastrointestinal (GI) fiberoptic endoscopies were performed at the Hacettepe University Hospital, Ankara from January 1980 to December 1984. One thousand four hundred eight-five (34 %) of the patients had normal endoscopy, 14 % duodenal ulcer, 7 % hiatal hernia. Pyloric stenosis and duodenal polyps were more common in men than in women. The male/female ratio was 15.6/1 respectively. The diagnostic accuracy of radiology was 68 % when compared to endoscopy, whereas the accuracy of endoscopy was 93 % compared to surgery. The results of 184 patients with acute upper gastrointestinal bleeding (UGIB) were reviewed, and the diagnostic accuracy was found to be 93 %. Peptic ulcer disease (PUD) accounted for 42 % of the bleeding sites. Endoscopic complications occurred in 6 out of 5000 patients (0.12 %).

*Key Words:* Endoscopy, Gastric ulcer, Duodenal ulcer, Bleeding.

## Introduction

Upper GI endoscopy, using the flexible fiberoptic gastroscope is an accepted, reliable and widely practiced method.<sup>1, 2</sup> The superiority of the fiberoptic endoscopy over the barium meal examination has been well established in the diagnosis of GI diseases<sup>2</sup> and for determining the site of the bleeding.<sup>3</sup> This paper reviews our experience of upper gastrointestinal fiberoptic endoscopy and compares it with radiological and sur-

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gical findings. The other purpose of this report is to demonstrate the pattern of various diseases of the upper GI tract discovered by endoscopic examination in this hospital.

### *Patients and Methods*

Five thousand patients were examined in the Hacettepe University Medical Center between January 1980 and December 1984. The patients ranged from 17 to 81 years of age and included 3222 males and 1778 females. One hundred eightyfour out of 5000 patients had emergency endoscopy examinations for acute UGIB. Examinations were performed by trained endoscopists using the forward-viewing panendoscope, Olympus Model GIF D<sub>3</sub>. The procedure was performed after an overnight fast. Five-ten mg of intramuscular diazepam was injected 15-20 minutes prior to the procedure. Local anesthesia was applied with 2 % lidocaine spray ("Citanest") 10 minutes before the procedure and 20-440 mg of hyoscine butylbromide ("Buscopan") was administered intravenously to some of the patients after the instruments passed through the pylorus. In acute UGIB, endoscopy was performed within 24 hours of the initial bleeding episode. If the patient's condition was unstable, the examination was delayed until an adequate blood transfusion was given. The initial examinations were performed without saline lavage. If bleeding was too brisk or if the stomach was full of blood clots, lavage was carried out with an ewald tube.

Upper GI barium meal examination was performed on all patients except those with acute UGIB, and the results were compared with endoscopic examinations.

Indications for endoscopy were based on radiologic diagnosis and/or clinical manifestations.<sup>4</sup> Diagnosis of hiatal hernia, esophagitis, gastritis, and duodenitis were established by endoscopic examination and were confirmed by biopsy. Histology was essential for the diagnosis of benign gastric ulcers, polyps, intestinal metaplasia and carcinomas.

### *Results*

As indicated in Table I, 1485 patients were found to have normal endoscopic examinations. Three hundred and thirty-one had hiatal hernia, which was the most common type of lesion seen in the esophagus and 224 (68 %) had co-existing esophagitis. Varices were diagnosed in 261 (5 %) patients and graded according to the in severity. Ninety-seven patients had esophagitis of which 12 % had candidal esophagitis, 6 % gastritis and 9 % gastric ulcer. Two percent of the patients with gastric

carcinoma had co-existing intestinal metaplasia and 12 patients had duodenal as well as gastric ulcer. The incidence of gastric and duodenal lesions are also shown in Table I. Thirty-eight (7 %) out of 540 patients with duodenitis had co-existing esophagitis and/or hiatal hernia.

TABLE I  
ANALYSIS OF 5000 ENDOSCOPIES

	Total Number (%)	M/F	Mean Age in Years
Normal endoscopy	1685 (34)	927/760	31 (18 - 81)
Esophageal disease			
Varices	261 (5)	179/82	46 (18 - 80)
Esophagitis	97 (2)	59/38	44 (21 - 68)
Hiatal Hernia	331 (7)	204/127	46 (20 - 80)
Carcinoma	105 (2)	84/21	55 (28 - 81)
Achalasia	18 (0.4)	8/10	41 (22 - 59)
Diverticula	16 (0.3)	10/6	50 (26 - 67)
Stomach Disease			
Gastritis	489 (10)	331/168	45 (17 - 71)
Carcinoma	183 (4)	124/59	55 (22 - 81)
Polyps	55 (1)	21/34	47 (30 - 72)
Ulcer	151 (3)	108/43	47 (27 - 76)
Post-surgery	286 (6)	210/76	43 (22 - 68)
Duodenal diseases			
Ulcer	714 (14)	549/165	35 (19 - 70)
Duodenitis	540 (11)	342/198	40 (18 - 72)
Pyloric stenosis	50 (1)	47/3	50 (30 - 68)
Polyps	15 (0.3)	14/1	39 (30 - 70)
Diverticula	4 (0.1)	3/1	49 (33 - 62)

Before endoscopy, upper GI barium meal examination was performed on 4816 patients. Radiological diagnosis was confirmed in 3275 patients by endoscopy. The overall diagnostic accuracy of radiology was 68 % compared to endoscopy.

Upon endoscopic examination 152 (53 %) of the postsurgical patients were found to have definite abnormalities, as indicated in Table II. In comparing x-rays to endoscopic examination of the 286 patients, the overall diagnostic accuracy was found to be 27 %. Endoscopic examination was established as the most helpful method in diagnosing postsurgical patients. Radiology showed the correct diagnosis in only 27 % of the patients in which mucosal abnormalities and marginal ulcers were the most prominent findings.

TABLE II  
ENDOSCOPIC FINDINGS IN POSTSURGICAL PATIENTS

	No. of Cases	Percent
1. Gastritis	94	33
2. Anastomotic ulcer	44	15
3. Esophagitis	6	6
4. Intestinal metaplasia.	4	1
5. Hiatal hernia	2	1
6. Gastric carcinoma	2	1
7. Normal	134	45
Total	286	

Table III shows the correlation between endoscopic examination and surgical diagnosis. The diagnostic accuracy of endoscopy was 96 %. Of the ten patients who had different findings at surgery, three had gastric carcinomas, four duodenal ulcers, one pancreatic carcinoma, one choledochal carcinoma and one had marginal ulcer.

TABLE III  
ENDOSCOPIC DIAGNOSIS IN PATIENTS WHO UNDERWENT SURGERY

No. of Cases	Endoscopic and Surgical Diagnosis	
	Same	Different
	251	10
Percent	96	4

*Analysis of the Cases with UGIB:* Endoscopy was successfully performed on 184 patients. Two hundred-twenty lesions were identified in 171 of the patients, with a diagnostic accuracy of 92.9 %. Table IV indicates the sites of bleeding. In 13 patients no bleeding site was found. Peptic ulceration accounts for 77 patients with 171 bleeding sites. Fifty-one (28 %) patients had erosive gastritis, which was the second most common bleeding site. Two gastric hemangiomas were present in this series.

In our series, forty-nine (27 %) patients had associated lesions which were as follows: 28 patients with gastritis, 12 patients with esophageal varices, 6 patients with hiatal hernia and 3 patients with duodenal ulcer.

Endoscopic complications occurred in 6 patients. This represents 0.12 % of all 5000 endoscopies. As indicated in Table V two patients died; a 42 year old cirrhotic female who had abnormalities in both platelet count, and prothombin time, and who had a deep neck infection and hematoma as a major complication died 6 days later. Another patient, a 65 year old woman, had nonspecific electrocardiogram, suffered from

acute UGIB and died of cardiac arrest during the endoscopy. Additionally a patient with abnormalities in the platelet count developed hematoma on her neck following endoscopy.

TABLE IV  
BLEEDING SITE IN 184 PATIENTS

	Total Number (%)	M/F	Mean Age in Years
Duodenal ulcer	68 (37)	52/16	36 (20 - 68)
Erosive gastritis	51 (28)	34/17	47 (19 - 64)
Esophageal varices	29 (16)	21/8	30 (18 - 72)
Gastric ulcer	9 (5)	7/2	44 (27 - 71)
Gastric carcinoma	8 (4)	6/2	52 (26 - 80)
Esophageal carcinoma	2 (1)	2/0	50 (37 - 63)
Gastric polyps	2 (1)	2/0	42 (37 - 45)
Gastric hemangioma	2 (1)	0/2	46 (35 - 58)
No lesion	13 (7)	9/4	33 (20 - 80)
Total	184 (100)	133/51	

TABLE V  
ENDOSCOPIC COMPLICATIONS IN 5000 ENDOSCOPIES

	No. of Cases
1. Cardiac arrest	1+
2. Deep neck infection and hematoma	1+
3. Hematoma	1
4. Pseudo acute abdomen	2
5. Mandibular dislocation	1
+ Death	

### Discussion

We conclude that endoscopy is a reliable method of diagnosing upper gastrointestinal diseases which were seen in the Hacettepe University Hospital. Hiatal hernias were more common in this series than in Europe<sup>2</sup> and Africa.<sup>3</sup> The frequency of gastric ulcer was higher in this series than in Sudan.<sup>5</sup> The low incidence of gastric ulcer has been reported from India<sup>6</sup> and Kuwait<sup>7</sup> and it is recognized that the incidence of gastric ulcer disease is much lower in most parts of the developing world. Our ratio of duodenal to gastric ulcer (7/1) was less than in Africa (33/1),<sup>8</sup> but higher than in the United States (1/11).<sup>9</sup>

Comparison of endoscopy with the barium meal examination has demonstrated that endoscopy misses fewer lesions.<sup>10</sup> Most of the missed lesions are found high in the gastric fundus, between large gastric folds

or in a scarred duodenum. In our study, the majority of diagnostic errors by x-ray examinations occurred with gastritis, primarily due to the lack of detection of atrophic or erosive gastritis. In Montagne's series<sup>11</sup> from 20 % to 40 % of lesions seen with endoscopy, were missed on single contrast studies. Endoscopic examination of the upper gastrointestinal tract is superior to standard radiologic examination.

Satisfactory evaluation of the patient with post-gastrectomy complaints is a potentially difficult situation for a gastroenterologist. The traditional modes of evaluation by x-ray techniques are frequently inadequate. The results of this study clearly indicate that an adequate evaluation cannot be considered to be complete until flexible fiberoptic endoscopic examination of the upper GI tract has been carried out. The creation of post-surgical artifacts and the lack of a definition of mucosal details limit the use of x-ray series. On endoscopy, gastritis was the most common lesion seen in post-surgical patients in this series. After gastric resection<sup>12</sup> gastritis was more common in the stoma than in the proximal stomach. This problem is being recognized with increasing frequency following gastric procedures which either obviate or interfere with the pyloric mechanisms.

Hirschowitz and Luketic<sup>13</sup> found radiologic results to be positive in only 36 % 111 patients with marginal ulcer, and negative in 90 % of those with significant findings on endoscopy. In our series, only a 27 % accuracy rate was found in post-gastrectomy patients with x-ray. The accuracy of barium radiology in diagnosing ulcers in patients who have had gastric surgery remains a matter of debate. Suture and plication deformities produce shadows that may on occasion be impossible to differentiate from tumors and, therefore, endoscopy and biopsy are necessary with such patients.

The importance of early endoscopy in UGIB is emphasized by Hunt and colleagues from Australia.<sup>14</sup> Endoscopy is diagnostically superior to the upper GI series in UGIB. For this reason, we prefer to use only endoscopy in the initial diagnosis of these patients. We were able to identify the source of bleeding in 93 % of the cases. Our results are comparable with those reported by Gilbert, et al. from Seattle<sup>15</sup> and Al Nakib, et al. from Kuwait.<sup>7</sup> The etiology of UGIB is expected to vary from one geographical region to another. Duodenal ulcer was the most common source of bleeding in our series (37 %), which is equal to the 39.3 % reported from Kuwait.<sup>7</sup> The ratio of duodenal to gastric ulcer was 7.6/1 in this series, which differs from 0.86/1 to 6.22/1 in some reports.<sup>2, 16</sup> Gastritis was the most common associated lesions in our series, which is in agreement with Webb's report.<sup>17</sup>

It is still a controversial issue as to whether early endoscopy affects mortality and morbidity.<sup>3,18</sup> Endoscopy, however, is a very beneficial method, in that it can distinguish between peptic ulcer, gastritis and varices as the source of bleeding of which management and treatment are different. It is interesting to note that a nonbleeding visible vessel in the peptic ulcer bed has had the greatest prognostic importance since it rebleeds about 56 % of the time.<sup>19</sup>

Diagnostic and therapeutic indications of endoscopy were expanded with improved technology of fiberoptic instruments and the literature including complications of endoscopy has been growing.<sup>20</sup> Submandibular and parotid swelling, aspiration pneumonia, perforation, hemorrhage and electrocardiographic changes were established during endoscopy.<sup>21</sup> Large volumes of air were introduced during endoscopy, leading to the occurrence of a pseudo-acute abdomen. EKG changes during panendoscopy are relatively common, although usually transient and not life-threatening. Cardiac arrest and acute myocardial infarction are rare, but when they occur, are often fatal. In the survey of 211410 procedures,<sup>22</sup> there were eight patients with cardiac arrest or ventricular fibrillation, four of whom died. Logical recommendations to minimize untoward events include: obtain baseline EKG in all patients who had cardiac disorders or severe active bleeding. Full resuscitative care should be available. Coagulation data should be checked for prevention of hemorrhage at endoscopy. Mandibular dislocation was an interesting endoscopic complication in this series.

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# Suprapubic Transvesical Prostatectomy Versus Retropubic Prostatectomy

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## Summary

In this retrospective study a comparison of 30 retropubic and 72 suprapubic transvesical prostatectomies is presented. It was concluded that retropubic prostatectomy is superior to suprapubic transvesical prostatectomy with regard to peroperative bleeding control and is more cost effective due to a shorter hospital stay.

*Key Words:* Suprapubic transvesical prostatectomy, Retropubic prostatectomy, Benign prostatic hyperplasia.

## Introduction

Each surgeon usually develops a favorite method of prostatectomy that provides a low morbidity and therefore becomes the predominant operation in his practice; the most widely accepted procedure in this decade is transurethral prostatectomy (TUR). Most urologic surgeons are comfortable doing a TUR for adenomas up to 60 grams. Other limiting factors are large bladder calculi, bladder diverticula, reflux, urethral strictures, contracted bladders and ankylosis of the hips interfering with the lithotomy position.<sup>1</sup> The result of this is that in approximately 10 % of adenomas, an open enucleation procedure is used.<sup>2</sup>

We present a comparative retrospective study of 102 open enucleation procedures performed by either suprapubic transvesical or retropubic route.

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### *Materials and Methods*

The material of this study is based on 30 patients who were operated by retropubic and 72 patients operated by suprapubic transvesical route in the Urology Department of Medical Faculty of Hacettepe University between 1982 and 1984.

Patients with incidental prostatic carcinoma, impaired renal function, neuropathic bladder and previous operations on the lower urinary tract were excluded from the study.

The mean age for the retropubic prostatectomy (RPP) group was 67.50 years (50-84 years). RPP was performed in the classical procedure as described by Millin.<sup>3</sup> For the suprapubic transvesical prostatectomy (SPTVP), the group mean age was 68.09 (range 54-88 years) years. SPTVP was performed as described by O'Connor.<sup>2</sup> The mean ages of the two groups were not statistically different ( $p > 0.05$ ). All operations were performed by the chief residents under the supervision of a member of the teaching staff.

The mean weights of the adenomas enucleated did not differ significantly in the RPP and SPTVP groups (58.26 grams versus 48.73 grams respectively) ( $p > 0.05$ ).

The hospital records were reviewed for early complications (septicemia, epididymoorchitis, bleeding, the need for a second operation for uleeding and for persistent urinary leakage) and any need for blood transfusions.

The patients were assessed in the outpatient clinic for late complications at one month and three months postoperatively, especially with regard to urinary tract infection, urethral stricture and incontinence.

The hospitalization period is defined as the time between operation date and discharge date.

Students t test, Chi square and Exact Chi square tests were used in evaluating the differences.

### *Results*

*Hospitalization period:* The mean hospitalization period was 9.4 (range 4-23 days) days and 12.83 (range 7-52 days) days for RPP and SPTVP groups respectively. Statistical analysis revealed that the differences between the two groups were significant ( $p < 0.05$ ).

*Blood transfusions:* In RPP group, 13 patients (peroperatively) and one patient (postoperatively), required one unit (500 ml) blood transfusion. Only one patient needed six units of whole blood transfusions (postoperatively) in this group.

In SPTVP group, 27 patients had blood transfusions (17 patients had unit, 10 patients had two units) peroperatively. In the postoperative period, eight patients required transfusions (three patients had one unit, three patients had two units, two patients had four units and one patient had five units).

Statistical analysis revealed that the differences between the two groups with regard to the need for transfusions were not significant ( $p > 0.05$ ), however the need for more than one unit of blood was significantly higher in SPTVP group ( $p < 0.05$ ).

*Early complications:* In the RPP group, ordinary measures to control bleeding were adequate; but in the SPTVP group, six patients (8.33 %) required packing during the operation (in addition to the classical measures) and three patients in the SPTVP group underwent secondary operations for immediate abundant bleeding (Table I).

TABLE I  
COMPARISON OF EARLY COMPLICATIONS IN TWO GROUPS

	RPP	SPTVP	Statistical Analysis
Mortality %	3.33 (1)*	2.77 (2)	$p > 0.05$
Orchitis %	3.33 (1)	6.94 (5)	$p > 0.05$
Septicemia %	3.33 (1)	1.38 (1)	$p > 0.05$
Wound complications %	10.00 (3)	12.50 (9)	$p > 0.05$
Need for secondary operation for immediate abundant bleeding %	- (-)	4.16 (3)	$p > 0.05$
Prolonged urinary leakage %	- (-)	6.94 (5)	$p > 0.05$

\* Number of patients.

Although none of the patients in the RPP group suffered from prolonged urinary drainage, this complication was observed in five patients in the other group. The statistical analysis, however, was not significant (Table I).

Mortality due to septicemia in two patients and myocard infarction in one patient was not statistically different in the two operative procedures (Table I).

*Late complications:* The incidence of urethral stricture, osteitis pubis, urinary incontinence and persistent urinary tract infection is listed in Table II. The differences between the two groups were insignificant.

TABLE II  
COMPARISON OF LATE COMPLICATIONS IN TWO GROUPS

	RPP	SPTVP	Statistical Analysis
Urethral Stricture	-	2.77 % (2)*	p > 0.05
Osteitis Pubis	3.33 % (1)	-	p > 0.05
Persistent Incontinence	3.33 % (1)	1.38 % (1)	p > 0.05
Persistent urinary tract infection	23.33 % (7)	19.44 % (14)	p > 0.05

\* Number of patients.

#### Discussion

Despite the current popularity of TUR, a critical examination of the long-term results and the sequelae of the operations shows that the clean enucleation of the hypertrophied tissue in an enlarged prostate gives a more satisfactory outcome than TUR, even when this is carried out by the best resectionists.<sup>4</sup> The most important factor which made the TUR the most popular technique is its cost effectiveness. Hospital-stay data show that the inpatient period for those undergoing TUR is almost half that for open procedures.<sup>5</sup> In our study RPP seemed to be more cost effective as far as hospital stay is concerned. This finding was also reported by Cooper,<sup>6</sup> but Harrison and Poutasse did not observe any difference in hospitalization periods.<sup>7</sup> The shorter hospitalization period in RPP may be attributed to the absence of prolonged suprapubic leakage.<sup>8</sup> Although we did not find a statistically significant difference between the two operations in regard to prolonged urinary drainage, all of the prolonged leakages occurred in SPTVP patients.

Similar to the reports in the literature,<sup>1</sup> the percentage of patients who needed blood replacement was not significantly different in the two groups, but the need for more than one unit blood replacement in the SPTVP group was found to be higher than in the RPP group; this was statistically significant (p > 0.05). The main advantage of RPP is its good anatomical approach to the prostate and good exposure of the operation site which affords an excellent view of the interior of the prostatic cavity for the detection of residual tissue and bleeding points.<sup>4</sup> The difficulty in controlling the bleeding in the prostatic fossa in SPTVP has resulted in eight packing procedures in that group; this might be also the

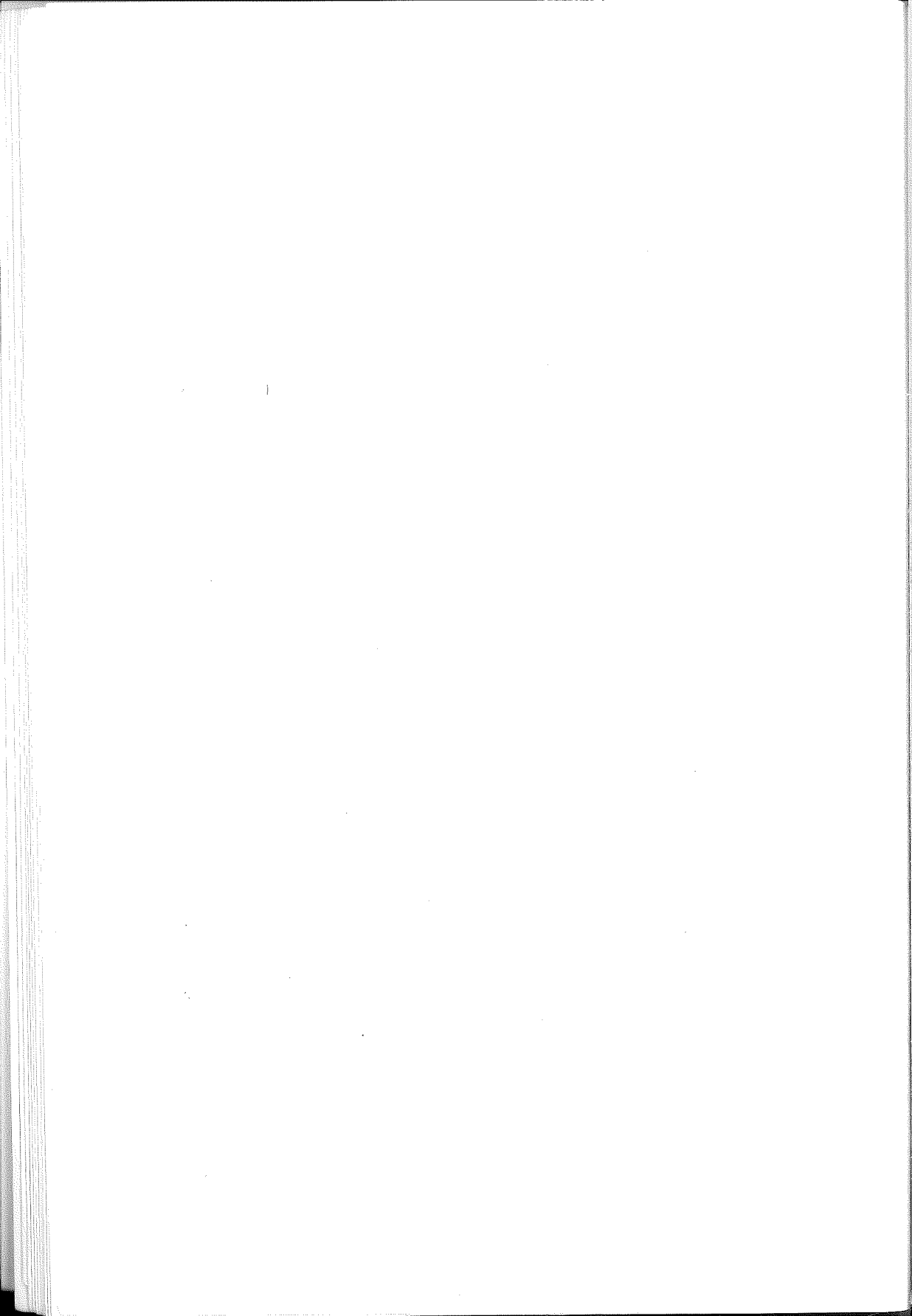
most important factor in the longer hospital stay, the higher incidence of suprapubic prolonged urinary leakage and the need for more than 500 ml of blood.

For the other parameters concerning the late and early complications of this study there is no difference between the two groups, and the incidence of the parameters evaluated is comparable with the previous studies about this subject.<sup>9-11</sup>

In conclusion, RPP is superior to SPTVP, both with regard to peroperative bleeding control and cost effectiveness due to its shorter hospital stay.

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# Spontaneous and Enhanced Expression of Chromosome Fragile Site 10q25

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## *Summary*

30 individuals were examined for the BrdU requiring fragile site at 10q25. Only one female and her mother had the fragile site at 10q25. Expression of this fragile site was spontaneously found to be 3 % in the proband and increased by addition of BrdU to the medium. Maximum expression of the fragile site 10q25 was observed in the 40  $\mu$  gr/ml BrdU dilution.

*Key Words:* Fra (10) (q25), bromodeoxyuridine, heredity fragile site, chromosome 10.

## *Introduction*

Heritable fragile sites have been defined and provisionally classified according to their expression under different conditions of tissue culture.<sup>1,2</sup> Expression of the 10q25 fragile site is induced by addition of BrdU to the culture medium.<sup>3,4</sup> Recently a few researchers reported a spontaneous and an enhancement of the fragile site 10q25 on chromosomes.<sup>5-8</sup> We report here data indicating spontaneous and enhanced expressions of the fragile site at 10q25.

## *Materials and Methods*

Sister chromatid exchange (SCE) studies were carried out on 70 workers of a ferro-chrome factory, and also on 30 smokers and 30 healthy

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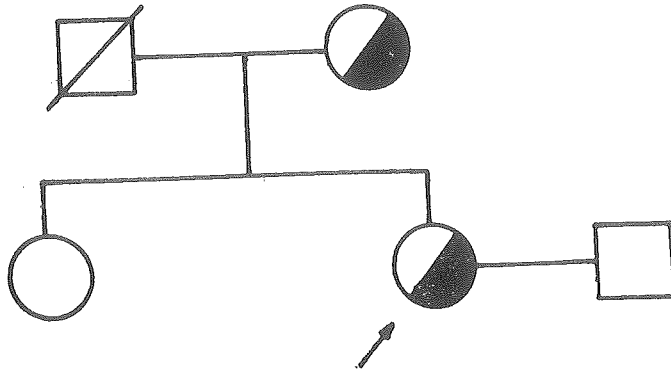
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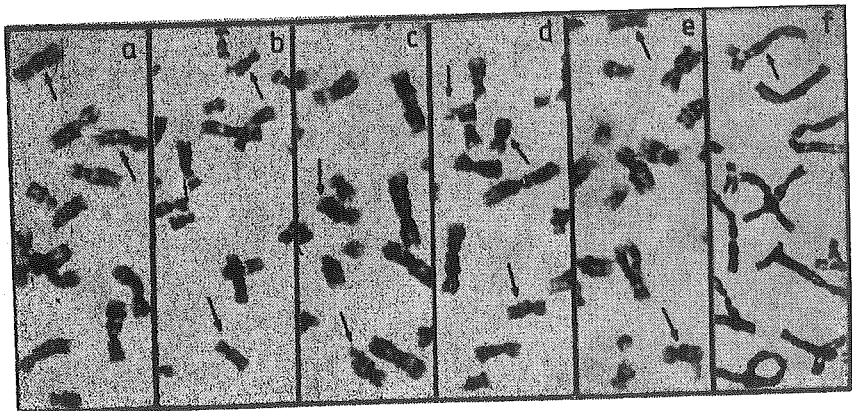


controls, as part of another project. In the same groups we also examined the existence of the fragile site at 10q25.

Peripheral blood lymphocytes were grown in Mc Coy's 5A supplemented with 15 % fetal calf serum. 10  $\mu$  gr/ml BrdU was added to the culture medium. The chromosomes were banded by Trypsin-Giemsa technique. Furthermore, different BrdU concentrations were tested in our single case with fragile 10q25 (10  $\mu$  gr/ml, 20  $\mu$  gr/ml, 40  $\mu$  gr/ml, 60  $\mu$  gr/ml and 80  $\mu$  gr/ml). Mc Coy's 5A lacking BrdU was used to study the existence of the spontaneous fragile 10q25. The proband was a 28 year old female with endometriosis and an ovarion cyst. She was married for 9 years and had no children.



**Figure 1**  
Family pedigree.



**Figure 2**  
Fragile site at 10q25. a, b, c: proband, d, e, f: mother.

*Results*

130 individuals were examined for the BrdU requiring fragile site at 10q25. Only one female in the smokers group had the fragile site at 10q25. Later, her family was also studied and the same fragile site was found in her mother. Her sister had no apparent fragile site (Figure 1). Mc Coy's 5A without BrdU was used to show possible existence of the spontaneous fragile 10q25 in this family. The 10q25 fragile site frequency was 3 % in the proband and 0 % in her mother. 10  $\mu$  gr/ml, 20  $\mu$  gr/ml, 40  $\mu$  gr/ml, 60  $\mu$  gr/ml dilutions of BrdU was used in the culture medium to demonstrate maximum expression of the fragile site 10q25 in the proband. One hundred cells were evaluated for each dilution. Maximum expression of the fragile site 10q25 was observed in 40  $\mu$  gr/ml dilution (Table I). Mono-chromatid and di-chromatid breaks and fragments were observed between 43 % - 60 % in heterozygous forms on the chromosomes of both individuals (Figure 2). To test the possible effect of duration in BrdU, 10  $\mu$  gr/ml BrdU was added in the cultures at the beginning, at the 24<sup>th</sup> hour and at the 48<sup>th</sup> hour of culture. We couldn't find any apparent difference related to the incubation period in 10q25 fragile site forms of proband and her mother (Table II).

TABLE I  
EFFECT OF VARIOUS CONCENTRATION OF BrdU ON EXPRESSION  
FRA (10)q25 FROM THE PROBAND

Concentration ( $\mu$ gr/ml)	Frequency of Fra (10)
10	45/100
20	50/100
40	62/100
60	60/100
80	56/100

TABLE II  
DIFFERENT FORMS OF THE FRAGILE SITE EXPRESSION IN THE CASES

Forms of expression (%)	Mother			daughter		
	0h	24h	48h	0h	24h	48h
mono-chromatid break	18	17	19	21	19	18
di-chromatid break	5	5	2	15	14	15
fragment	11	15	17	9	8	10
Quadraradial	1	-	-	-	-	-
Normal	65	63	62	55	59	57

*Discussion*

The fragile 10q25 site is present in a heterozygous form in 1 in 40 Australians.<sup>9</sup> There is no phenotypic effect in heterozygote and homozygote children.<sup>10</sup> Sutherland concludes that this fragile site may be polymorphic for this population.<sup>8</sup> We found only one female with the fragile 10q25 among 130 individuals. The same fragile site was found for the mother. The number of cases is certainly not enough to say that there is no polymorphism in the Turkish population. Our proband fragile site 10q25 was BrdU sensitive, but not in the dependent group.<sup>11</sup> Without induction of BrdU it was rarely observed spontaneously (3% in the proband and 0% in her mother). The expression frequency of the fragile 10q25 was enhanced, when 10  $\mu$  gr/ml BrdU was added in the tissue culture medium (proband 45%, mother 35%). The 10q25 fragile site was BrdU sensitive in the mother. The expression frequency was not significantly enhanced in the different BrdU dilutions and different incubation periods in BrdU Table I. Susanne et al, Taylor and Bundey have reported spontaneous expression of the fragile site 10q25 and an increase by adding BrdU to the tissue culture medium.<sup>5, 7</sup> But there was no BrdU dependent increase in the cases reported by Petit and Fryns.<sup>6</sup> We believe that it is too early to reach a conclusion about the spontaneous expression of fragile 10q25 with these insufficient number of reports. However, the media containing BrdU can be useful in the detection and further understanding of this heritable fragile site on the chromosome of man.

The fragile site 10q25 has been observed in both homozygous and heterozygous states in the normal healthy individuals in the Australian population.<sup>9, 10</sup> However different researchers have reported different patients with fragile sites.<sup>3, 5, 7, 8</sup> Our proband is phenotypically normal but has some gynecological problems. She had endometriosis and an ovarian cyst and she was married for 9 years but had no children. Fragile 10q25 cases other than the frequent Australian polymorphism, may be causing non specific clinical findings. Our report supports the findings of other authors about the relationship between spontaneous and BrdU inducible fragile site 10q25. Reports of more cases are required to be able to substantiate if the fragile site 10q25 leads to clinicopathologic disorders or polymorphism in people of the countries other than Australia.

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# The Connection Between Estrogen Receptors and Thyroid Functions in Breast Cancer

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## Summary

A possible relationship between estrogen receptors and thyroid function was investigated. The plasma TSH, T<sub>3</sub> and T<sub>4</sub> levels were measured in women with breast cancer. Estrogen receptors were also studied in the tumor tissues of these patients. Thyroid function was compared with those of two control groups. The first control group consisted of women without any cancer, the second control group consisted of women who had cancers of various organs other than the thyroid gland and the breast. No differences were found between the mean TSH, T<sub>3</sub> and T<sub>4</sub> levels of the three groups. Thyroid functions were not influenced by the estrogen receptor status of breast cancer. The results did not support a relationship between breast tumor estrogen receptors and the thyroid gland.

*Key Words:* Estrogen receptors, thyroid functions, breast cancer.

## Introduction

In 1836, Cooper<sup>1</sup> announced that breast tumor size was influenced by the menstrual cycle. This was the first observation pertaining to a

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connection between breast cancer and the ovaries. Beatson,<sup>2</sup> who claimed that oophorectomy caused regression of breast cancer metastases, supported this view. Beatson<sup>2</sup> also suggested the use of thyroid extract as an adjuvant to oophorectomy in the treatment of advanced breast cancer, and started the search for a possible relationship between the thyroid gland and breast cancer. The results of different workers were contradictory; thyroid functions were found to be decreased,<sup>3,6</sup> unchanged<sup>7-11</sup> or increased<sup>12-15</sup> in breast cancer. Generally, studies based on establishing the presence of gross, clinical thyroid disease in breast cancer have not always been able to establish a relationship (for example, Kalache et al<sup>16</sup> found no association with any kind of thyroid disease. Consideration of the changes in thyroid functions which were sometimes only subtle, have been more rewarding, but not in universal agreement. Using free thyroxine as a thyroid function index and finding a mean value below normal controls in breast cancer with the lowest levels in anaplastic and the highest in well differentiated tumors, Thomas et al<sup>17</sup> have reasoned that thyroid hormones may be involved in tumor cell differentiation. The relationship between the thyroid gland and breast cancer has been the subject of other recent investigations.<sup>18, 19, 20</sup> Mittra<sup>3</sup> attempted to explain this relationship and hypothesized a hypothalamo-pituitary-prolactin axis in breast cancer. He stated that feedback mechanisms operating in hypothyroidism and causing TRH to rise would result in an elevation of the serum levels of prolactin as well as TSH. (Jacobs and Synder<sup>21</sup> had demonstrated that an amplification of the TRH level caused an increase of serum prolactin). Mittra<sup>3</sup> argued that such an increase could end up with breast cancer as a result of the continuous stimulation of breast ductal epithelium by prolactin; in addition hyperplasia of the hypophysis (to provide the necessary increase of TSH), elevation of the levels of the hypophyseal gonadotropins, and estrogenic stimulation of breast ductal epithelium could occur, consecutive by, in hypothyroidism. Sommers,<sup>22</sup> who found changes in both the ovarian and thyroid glands in women who died from breast cancer, strengthened these thoughts. But, McMahan<sup>23</sup> showed that a rise of the serum prolactin level did not have any pathologic effect on the human breast epithelium, Mittra and others<sup>3, 24, 25, 26</sup> found that the serum prolactin level did not show a significant change in breast cancer. After these findings, the role of estrogen in breast cancer became the focus of growing interest. Luft and Olivecrona<sup>27</sup> found that estrogen could influence the development of breast cancer even after hypophysectomy and oophorectomy. The source of this effect is thought to be the conversion of androstenedione into estrogen.<sup>28</sup> In 1971, Jensen<sup>29</sup> demonstrated that breast cancer was sensitive to 17- $\beta$  estradiol. Mc Guire<sup>30</sup> stated that estrogen had direct

impact on estrogen receptor-positive breast tumors. The importance of estrogen and estrogen receptors in breast cancer has been extensively studied.<sup>31-34</sup>

Burke<sup>35</sup> and Cerbon<sup>36</sup> found thyroid hormone receptors in the nuclei of breast cancer cells. This may, in the future, provide the basis of an explanation of the role of thyroid hormones in breast cancer.

Although the mechanisms remain to be awaiting elucidation, there is considerable evidence pointing to relationships between thyroid function and breast cancer, estrogen and estrogen receptors-positive breast cancer. We hypothesized that there could be a connection between thyroid function and estrogen and estrogen receptors in breast cancer. We searched for a significant correlation between thyroid function and the estrogen receptor status of breast cancer.

#### *Materials and Methods*

Forty women with breast cancer were studied. None of them had clinical evidence of thyroid disease. After confirming the diagnosis of breast cancer with incisional biopsy and frozen section, we searched for estrogen receptors in fresh tumor tissue with the fluorescent antibody-labeling technique. Serum  $T_3$ ,  $T_4$  and TSH levels were also measured in breast cancer patients. The results were compared with two control groups.

The first control group (Control Group I) consisted of forty women awaiting surgery for problems unrelated to any kind of cancer and breast disease. A second control group (Control Group II) was composed of forty women who were suffering from cancer of various organs other than the thyroid gland and the breast. The patients in the control groups had no prior history of thyroid or breast diseases. Women who had been administered iodine containing dyes and hormonal drugs were excluded from the study. No medicine was allowed for seven days before the performance of the tests included in the study.

#### *Methods :*

A) *Determination of Serum  $T_3$ ,  $T_4$  and TSH:* Blood samples were taken from all of the patients at 8-10 A.M., the serum was separated and stored at  $-20^{\circ}\text{C}$  until analysed. Serum  $T_3$  levels were determined by radioimmunological methods using the RIA-mat  $T_3$  test.<sup>37</sup> With this method, the normal range of serum  $T_3$  was 0.2-0.4 ng/ml. Serum  $T_4$  levels were determined with the same test and the normal range was 4-12  $\mu\text{g}/100$  ml. Serum TSH level were assayed using indirectly coupled antibodies. The normal range of serum TSH was 0-5  $\mu\text{U}/\text{ml}$ . Serum  $T_3$ ,  $T_4$  and TSH levels were measured at the Radioisotope Laboratory of Hacettepe University.



*B) Determination of Estrogen Receptor (ER) Status:* Fresh breast tumor tissue was homogenized in saline solution buffered with phosphate to contain  $10^6$  cells/ml and was incubated with 17 FE [1 t-(N)-fluoresceinyl-estrone-thiosemicarbazone] at  $37^\circ\text{C}$  for 60 minutes. After labeling the cells with fluoresceinyl-estrone, the mixture was examined using fluorescence microscopy and 500 cells were counted. If the cells staining with fluoresceinyl-estrone were less than 10 %, the tumor was accepted as ER negative; otherwise the tumor was regarded as ER positive<sup>38</sup>. The estrogen receptor studies were carried on in cooperation with the Hacettepe University Oncology Institute.

*C) Statistical Analyses:* Comparison between the three groups were statistically tested by use of variation and multiple regression analyses.

### Results

The mean age was 50.2 years in the Breast Cancer Group, 46.4 in Control Group I and 48.4 in Control Group II. There was no difference between the mean age of the three groups (Table I).

TABLE I  
THE MEAN AGE OF THE PATIENTS

Group	Mean	Age	Range
Breast Cancer	50.2	1.9	24 - 77
Control Group I	46.4	2.1	24 - 70
Control Group II	48.4	2.3	25 - 85
	F : 0.825	p > 0.05	

We found 52.5 percent of the breast cancer patients to be ER (+), 47.5 percent of the breast cancer patients were ER (-) (Table II).

TABLE II  
THE ESTROGEN STATUS IN THE BREAST CANCER PATIENTS

ER Status	Patient Number	%
ER (+)	21	52.5
ER (-)	19	47.5
Total	40	100.0

Serum  $T_3$ ,  $T_4$  and TSH levels were within normal limits in all three groups. Furthermore, thyroid functions were not shown to be influenced by the estrogen receptor status of breast cancer (Table III).

TABLE III  
THE MEAN VALUES OF SERUM T<sub>3</sub>, T<sub>4</sub> AND TSH IN THE PATIENTS

Group	Patient Number	Serum T <sub>3</sub> ng/ml	Serum T <sub>4</sub> μg/dl	Serum TSH μU/ml
RE (+) Breast Cancer	19	1.16 ± 0.09	2.85 ± 0.27	1.7 ± 0.32
ER (-) Breast Cancer	21	1.13 ± 0.20	8.42 ± 0.35	1.5 ± 0.31
Control Group I	40	1.04 ± 0.05	8.45 ± 0.24	1.9 ± 0.26
Control Group II	40	1.03 ± 0.15	8.03 ± 0.30	2.4 ± 0.41
	F : 1.08		p > 0.05	

### Discussion

The role of hormones and hormone receptors in breast cancer has interested many investigators. Studies concerning the relationships of thyroid hormones and diseases to breast cancer have not given uniform results, however considerable evidence pointing to a connection between thyroid hypofunction and breast cancer has accumulated.<sup>3, 4, 5, 6, 17, 39</sup> Steroid hormones, especially estrogen and their receptors have been widely researched.<sup>27, 29-33, 40</sup>

Under the guidance of the results gained from previous investigations, we hypothesized that the effect of thyroid functions on breast cancer could be related to estrogen. This idea was also proposed by Mitra<sup>3</sup> but was not tested. We accepted that to provide for the increase of TSH obligated by the elevated TRH levels in hypothyroidism, hyperplasia of the anterior hypophysis could occur. This could bring an augmentation of the levels of the gonadotropins which are also secreted by these cells. This could cause estrogen to increase. As estrogen is thought to be effective upon estrogen receptor-positive breast tissue, primary hypothyroidism could initiate continuous estrogenic stimulation of estrogen receptor-positive breast tissue and could therefore be related with estrogen receptor-positive breast cancer. The practical consequence of this reasoning would be a significant correlation between thyroid hypofunction and an estrogen receptor-positive status in breast cancer.

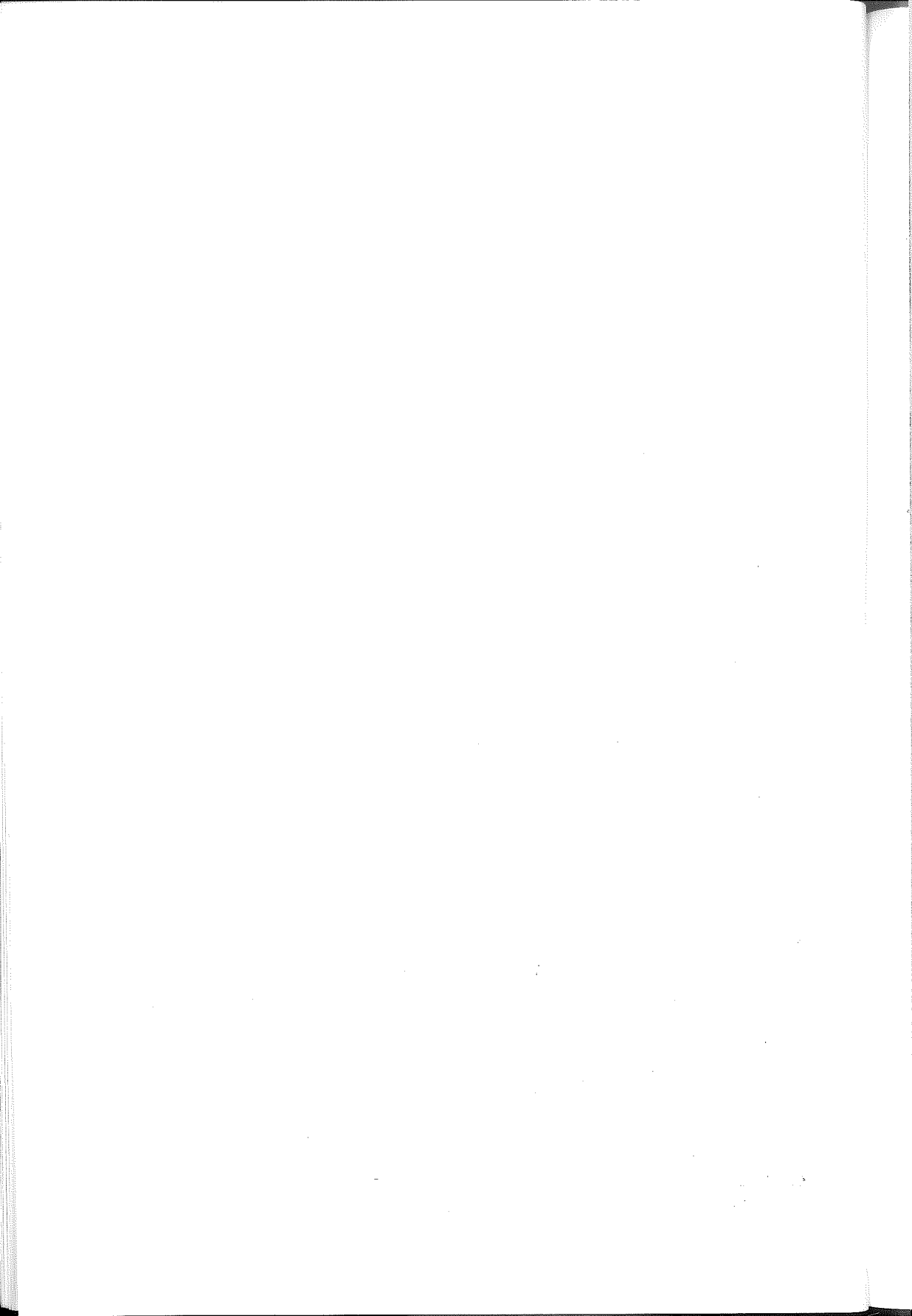
We searched for a correlation between thyroid function and the estrogen receptor status in breast cancer tissue. No correlation was found. We believe that a more extensive study including the hypophyseal gonadotropin levels of patients with breast cancer and also, randomized and prospective studies of normal women with comparison of those who eventually evolve breast cancer with the others are needed. Bulbrook et al<sup>39</sup> have found a significant degree of subclinical hypothyroidism in pre-cancer cases who also had a family history of breast cancer in their

prospective study. Similar and more extensive studies, including investigation of the full biochemical spectrum of thyroid function assays as proposed by Thomas et al<sup>17</sup> and also, hypothalamic, hypophyseal, adrenal and ovarian functions will be necessary before a conclusion can be reached.

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# Microcytic Anaemia Does Not Predict Aluminium Bone Disease in Chronic Renal Failure

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## Summary

Twenty patients with chronic renal failure (CRF) and histologic evidence of aluminium osteomalacia, and twenty four patients with aluminium toxicity were investigated to determine whether the severity of hypochromic microcytic anaemia could predict aluminium toxicity. The diagnosis was confirmed by bone biopsy in all patients. The mean corpuscular volume (MCV) value was  $88.8 \text{ um}^3/\text{red cell}$  (range: 65-103) in all patients with aluminium osteomalacia and  $91.8 \text{ um}^3/\text{red cell}$  (range: 84-107) with aluminium toxicity. Mean serum aluminium level was  $3.46 \text{ umol/l}$  in patients with aluminium osteomalacia and  $3.1 \text{ umol/l}$  in patients with aluminium toxicity around the time of bone biopsy. Hemoglobin levels were also recorded. The number of blood transfusions ranged between 0 to 4 units with a mean of 0.9 units during the two months period prior to the bone biopsy. Our findings suggest that MCV is not a reliable predictor of aluminium toxicity or bone disease. In addition we have found that microcytic anaemia is not a frequent finding in aluminium osteomalacia as has been previously suggested.

**Key Words:** Aluminium bone disease, Microcytic Anaemia.

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### *Introduction*

The development of microcytic anaemia in patients with CRF is often the first clinical manifestation of aluminium intoxication.<sup>1, 2</sup> O'Hare and Murnaghan have shown the reversal of aluminium-induced hemodialysis anemia by low-aluminium dialysate.<sup>3</sup> The improvement of MCV with desferrioxamine therapy in aluminium induced microcytic anaemia has been reported previously.<sup>4</sup> Physicians have apparently recognized microcytic anaemia with increased frequency.<sup>5</sup> Some authors put forward that microcytic anaemia is an early haematological manifestation of aluminium intoxication and it is a useful index to detect affected patients.<sup>6</sup> A severe microcytic anaemia is occasionally associated with serious aluminium-induced conditions, dialysis encephalopathy.<sup>7</sup> Hemoglobin values in some encephalopathic patients fell progressively during the year prior to the development of neurological symptoms.<sup>1, 8</sup> Also regression of the iron-unresponsive anaemia has been observed prospectively across a changeover from inadequate to rigorous water treatment.<sup>3, 7, 9</sup> Hewitt et al suggest that aluminium is incorporated in the red cells during their development in the bone marrow.<sup>10</sup>

### *Materials and Methods*

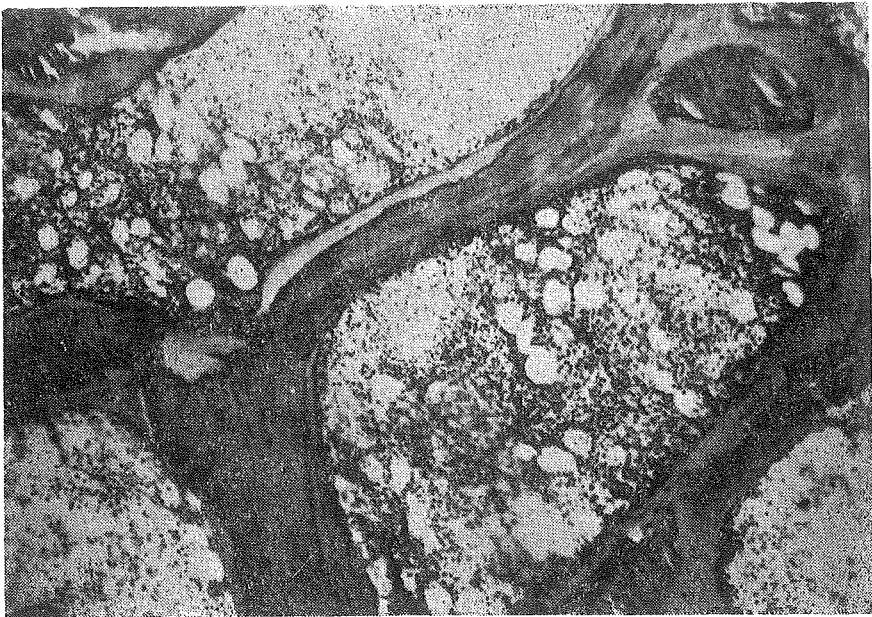
Twenty patients (15 M; 5 F) aged between 20 and 60 with CRF had intermittent haemodialysis (HD) in the Western Infirmary Glasgow between 1980 and 1984. They were diagnosed and followed-up as aluminium osteomalacia, a total of 51 bone biopsies were taken. The mean duration of HD in this group was 47.8 months.

Twentyfour patients (13 M, 11 F), aged between 20 to 63, who had CRF showing aluminium staining in their bone biopsies in association with aluminium toxicity were also included in this study. A total of 30 biopsy specimens were obtained from these 24 patients. The mean duration of haemodialysis in this group was 47.4 months for each patient. Biopsy specimens were evaluated by the same pathologists. The diagnosis of aluminium osteomalacia and aluminium toxicity was based on histochemical staining which has now replaced neutron activation analysis and electrothermal atomic absorption spectrophotometry.<sup>11, 12, 13</sup> The total number of blood transfusions during the month period prior to the bone biopsy ranged between 0 to 4 with a mean of 0.9 unit. Routine haematological parameters were recorded at the time of bone biopsy included. Serum folate levels were in the normal range in all patients and there was no iron deficiency based on ferritin levels. None of the patients were on azathioprine nor on desferrioxamine therapy.

### Results

Twenty patients with chronic renal failure and histologically proven aluminium osteomalacia had a mean haemoglobin level of  $8.1 \pm 1.65$  g/dl (range: 5.1-11.2 g/dl). The mean MCV of these patients was  $88.8 \pm 8.0$   $\mu\text{m}^3$ /red cell (range: 65-103  $\mu\text{m}^3$ /red cell). Two patients had MCV and mean corpuscular hemoglobin (MCH) values below the normal range. Serum aluminium levels of these patients were  $3.46 \pm 1.63$   $\mu\text{mol/l}$  (range: 1.3-6.9  $\mu\text{mol/l}$ ) during the biopsy periods. Figure 1 shows an example from this group of patients with aluminium related osteomalacia where the osteoid is increased in extent and thickness with reduced staining of calcification fronts.

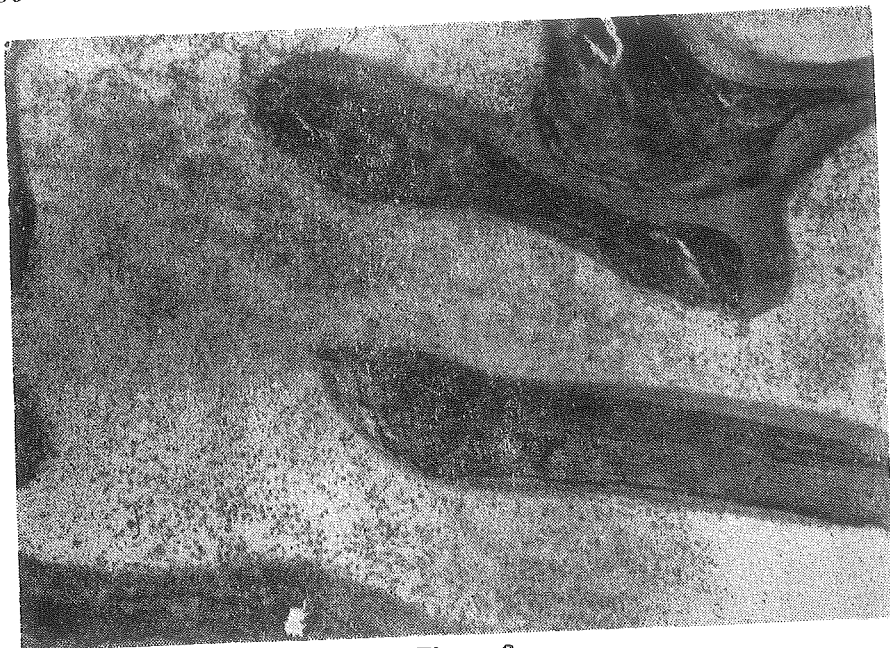
Twentyfour patients with chronic renal failure and histological evidence of aluminium toxicity had a mean MCV of  $91.8 \pm 6.1$  (range: 84-107  $\mu\text{m}^3$ /red cell). All these patients showed positive aluminium stain in their bone biopsies. The mean serum aluminium in this group was  $3.1 \pm 1.3$   $\mu\text{mol/l}$  (range: 1.1-6.1  $\mu\text{mol/l}$ ). Figure 2 shows a bone biopsy from this group of patients with aluminium accumulating at the interface between calcified bone and osteoid in the mineralisation front. In the control patients there was no stainable aluminium at the calcification fronts or at the cement lines.



**Figure 1**

Bone biopsy from aluminium related osteomalacia; the osteoid is increased in extent and thickness with reduced staining of calcification fronts.





**Figure 2**  
Bone biopsy from aluminium toxicity patients; aluminium accumulating at the interface between calcified bone and osteoid in the mineralization front.

Twentyseven patients with aluminium bone disease had renal transplantation from aluminium osteomalacia and aluminium toxicity groups randomly. Pre-operative mean MCV values were  $89.6 \pm 8.2 \mu\text{m}^3/\text{red cell}$  and rose to a mean of  $97.4 \pm 6.3 \mu\text{m}^3/\text{red cell}$  at the mean of 4.8 months in the post-operative period in this group.

Six patients had desferrioxamine (DFO) therapy in the osteomalacia group. The mean MCV was  $87 \pm 7.5 \mu\text{m}^3/\text{red cell}$  (range:  $81-96 \mu\text{m}^3/\text{red cell}$ ) at the pre-DFO period and increased to a mean of  $99.5 \pm 8.7 \mu\text{m}^3/\text{red cell}$  (range:  $89-116 \mu\text{m}^3/\text{red cell}$ ) five months after starting DFO therapy. In the DFO treated group the mean serum aluminium rose from  $2.9 \pm 1.0 \mu\text{mol/l}$  to  $12 \pm 3.4 \mu\text{mol/l}$  after DFO therapy. The mean serum aluminium in the 3 microcytic patients was  $3.1 \pm 1.2 \mu\text{mol/l}$  before DFO and rose to  $16.3 \pm 3.2 \mu\text{mol/l}$ . This increase was from  $2.6 \pm 1.1 \mu\text{mol/l}$  to  $8.0 \pm 2.4 \mu\text{mol/l}$  in normocytic 3 patients after DFO therapy.

#### *Discussion*

Anaemia is a universal complication of end-stage renal disease, but it is normocytic and normochromic. It has been recognized that worsening of the anaemia of uremia may be the first clinical evidence of

aluminium toxicity. The possible causal relationship between anaemia and aluminium intoxication was first described by Elliott et al.<sup>1</sup> In our study also, twentyfour aluminium-related osteomalacia patients were found to be anaemic, but their mean MCV values were within normal levels at  $88.8 \pm 8 \mu\text{m}^3/\text{red cell}$  (Normal values:  $90.1 \pm 4.8$  and  $90.4 \pm 4.8 \mu\text{m}^3/\text{red cell}$  in males and females subsequently).<sup>14</sup> Surprisingly only two of the patients had low MCV values in the twenty osteomalacia patients. Serum aluminium levels were found to be high in all these patients during biopsy periods. These patients had only received a mean of 0.9 Unit/per patient blood transfusion in the two months period before bone biopsy; this did not effect blood composition. In the twentyfour CRF patients with aluminium toxicity, MCV values were in the normal range slightly higher than the osteomalacia group. Serum aluminium levels were also found to be high in this group. After renal transplantation and DFO therapy MCV values rose slightly, although they were in the normal range in the pre-transplant and pre-DFO therapy state. Of the six DFO treated patients, 3 were microcytic in which serum aluminium rose more than the normocytic 3 patients after DFO therapy. Our results suggest that there is not a good correlation between microcytic anaemia and aluminium bone disease, and that microcytic anaemia is not a good predictor of aluminium bone disease.

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# Nonmetastatic Hepatic Dysfunction Associated with Renal Cell Carcinoma

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## Summary

This study includes 60 patients with renal cell carcinoma treated at the Hacettepe University Department of Urology between 1977 and 1987. 15 patients without the evidence of hepatic metastases had abnormalities of 2 or more liver function tests. There was a close association with the presence of raised erythrocyte sedimentation rate (ESR) in this group of patients compared with those whose liver function tests were normal ( $p < 0.05$ ). Time to first recurrence and survival rates were again poorer in nonmetastatic hepatic dysfunction group ( $p < 0.005$ ).

*Key Words* : Renal cell carcinoma, nonmetastatic hepatic dysfunction, erythrocyte sedimentation rate (ESR).

## Introduction

It is well known that many patients with renal carcinoma do not present with urological symptoms, and that a variety of other presenting symptoms and signs are due to the nonspecific "toxic" effects of the tumor.<sup>1</sup> Non-metastatic hepatic dysfunction (NMHD) is one such anomaly which is also known as paraneoplastic syndrome. It was first described in 5 patients with renal carcinoma who had developed hepatomegaly

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and abnormal liver function without the evidence of hepatic metastases.<sup>2</sup> Although an incidence of 4 to 15 % had been reported in the literature<sup>3-7</sup> the importance of this condition had never been fully understood until 1981.<sup>8</sup>

The aim of the present study was to document the incidence of hepatic dysfunction in 2 group of patients with renal cell carcinoma and to determine its prognostic significance.

#### *Patients and Methods*

The clinical records of 60 patients with renal cell carcinoma who had presented to us between 1977 and 1987, have been retrospectively reviewed. The symptoms, signs, laboratory investigations and ESR levels, which were recorded, were evaluated. Hepatic function was determined by serum transaminases (ALT and AST), serum alkaline phosphatase, the ratio of albumin to globulin, and protrombin time. The diagnosis of nonmetastatic hepatic dysfunction was made on the basis of abnormalities of two or more of these tests, and the exclusion of hepatic metastases by liver scan and surgical findings.

All of the patients had been treated surgically; and radical or simple nephrectomy had been carried out. The histopathological diagnosis in all of our cases was renal cell carcinoma. Robson's modification of the system of Flocks and Kadesky<sup>9</sup> was employed as the staging system. The patients were followed for median sixteen months (6-96 months). Survival data were analysed by Gehan test;<sup>10</sup> and ESR levels and the clinical features were compared by the Chi-Square test with Yates's correction for small numbers.

#### *Results*

The mean age, sex distribution and the stage of the disease was found to be not statistically different in both groups ( $p > 0.05$ ) (Table I).

TABLE I

Stage	Nonmetastatic Hepatic dysfunction		Control group	
	No.	%	No.	%
I	3	20	13	28
II	3	20	11	24
III	5	33	13	28
IV	4	27	8	20
	15	100	45	100

( $p > 0.05$ )

Alkaline phosphatase was abnormal in 9 of 15 patients (60 %). None of these patients had radiological or histological evidence of bone metastases.

Significant clinical and laboratory features of renal cell carcinoma in patients with and without nonmetastatic hepatic dysfunction are shown in Table II. Although there were no differences between two groups, the occurrence of raised ESR was more commonly associated with hepatic dysfunction ( $p < 0.05$ ).

TABLE II  
SYMPTOMS, SIGNS AND ESR LEVELS

	NMHD group		Control group		
	No.	%	No.	%	
Classical triad	2	13	7	15	$p > 0.05$
Pain	6	40	23	51	$p > 0.05$
Haematuria	11	73	34	75	$p > 0.05$
Palpable mass	5	33	20	44	$p > 0.05$
Fever	1	6	3	6	$p > 0.05$
Anemia	3	20	5	11	$p > 0.05$
Weightloss/malaise	2	13	1	2	$p > 0.05$
Raised ESR levels	12	80	26	57	$p < 0.05$

Time to first recurrence are shown in Figure 1 and survival rates in Figure 2. During their median follow up, 6 patients died in the control group (13 %) and 8 in NMHD group (53 %) ( $p < 0.05$ ).

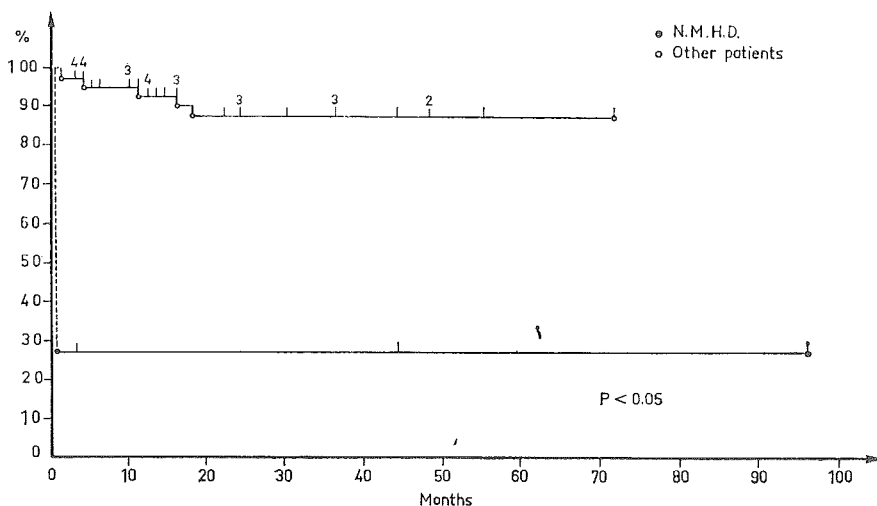
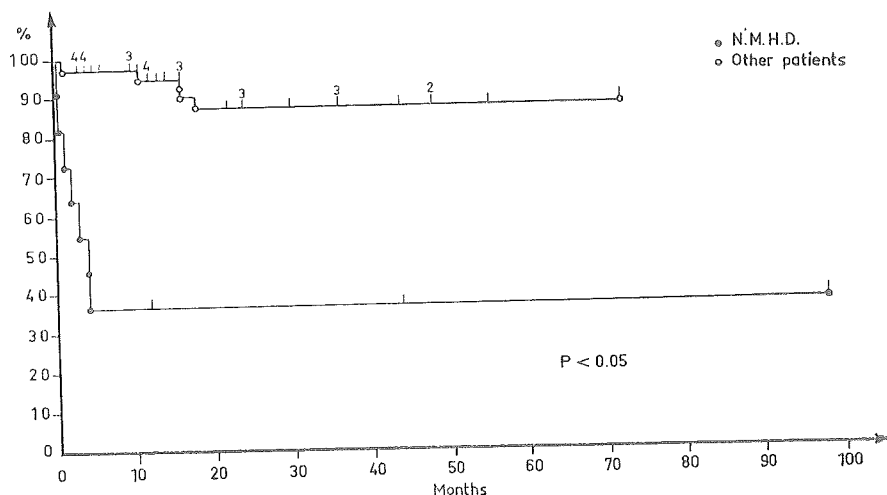


Figure 1  
Time to first recurrence.



**Figure 2**  
Survival Curves in both groups of renal carcinoma.

### Discussion

Although the incidence of NMHD was reported between 4 and 15 % in the literature<sup>3-7</sup> this figure was found to be 25 % in our study. When the presenting symptoms of our group were to be analysed, NMHD was found to be one of major presenting symptom and signs, especially if compared to 15 % of the classical triad.

Although there are many reports in the literature investigating the association between fever, anemia, weight loss and NMHD,<sup>11</sup> we couldn't find any statistical support for these findings. However, there was a significant association between raised ESR levels and NMHD. This finding may be part of the syndrome, and probably the combination of raised ESR and NMHD could be a better prognostic sign in patients with renal cell carcinoma. The most consistent abnormality in this and the other series was an elevated alkaline phosphatase.<sup>12</sup> A variant of this enzyme has been found to be released from neoplastic tissue, and it has been suggested that ectopic production by the tumor may be an explanation for this occurrence.

The etiology of this syndrome remains speculative. According to Utz, a humoral substance was responsible for this dysfunction,<sup>13</sup> but it was not proved by experimental studies. The consistent finding of abnormal globulin suggests that the syndrome may have an immunological basis, but few studies of immunoglobulins have been reported in detail.

Whatever the cause is, NMHD in renal cell carcinoma, shortens the period of time to first recurrence, and patient survival. It is our view that the continuing abnormal liver function test, after nephrectomy would be a better prognostic indicator in these patient. However this needs to be further evaluated with studies using larger groups.

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# Antenatal Diagnosis of Sacrococcygeal Teratoma

A Report on Two Cases

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## Summary

Two cases of sacrococcygeal teratoma, where prenatal diagnosis was made with ultrasonographic examination, were reviewed. Clinical, pathologic, sonographic and postmortem characteristics were sought in accordance with the recent literature.

*Key Words:* Sacrococcygeal teratoma, Antenatal diagnosis, Ultrasound.

## Introduction

Sacrococcygeal teratoma (ST) is a congenital tumour arising from all three germ layers.<sup>1</sup> It has an incidence of 1-2/40000 deliveries.<sup>2</sup> Prenatal diagnosis is important in many ways: (a) Ten percent of these tumours may be malignant at delivery. (b) They may attain a large size and cause dystocia. (c) Prenatal diagnosis allows a decision as to the best way of delivery without compromising the life of the fetus.<sup>3</sup> In the present paper, we review two cases of sacrococcygeal teratoma whose prenatal diagnosis was made with ultrasonographic examination.

## Case Reports

**Case 1 :** A 22 year old pregnant woman gravida 3 abortus 2 was referred to the University of Hacettepe Department of Obstetrics and Gynecology because of hypertension, nausea, vomiting and jaundice. Her bilirubin and liver enzyme levels were elevated. The sonographic examination performed at the local hospital had revealed a fetus which was small and which had a suspected partial mole hydatiform.

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The woman was hospitalized. She was 26 weeks pregnant according to her last menstrual period. Her blood pressure was 140/90 mmHg and she had ++ pretibial edema. Urinalysis showed + proteinuria. Her hemoglobin was 8.60 gm/dl. Her biochemical profile revealed BUN: 38 mg/dl, fasting blood sugar: 94 mg/dl, Na: 135 mmol/L, K: 3.9 mmol/L, Cl: 109 mmol/L, ALT: 14 IU/L, AST: 29 IU/L, Creatinine: 1.5 mg/dl, AP:165 IU/L. Thrombocytes were normal and the PT was 13 seconds. Ultrasonic examination was performed with a real-time linear scanner using a 3.5 mHz probe; and the fetus was found to be dead in utero. The sonogram demonstrated a 13 x 15 cm. mass containing solid and cystic components beside the fetus and a polyhydramnios (Figure 1).

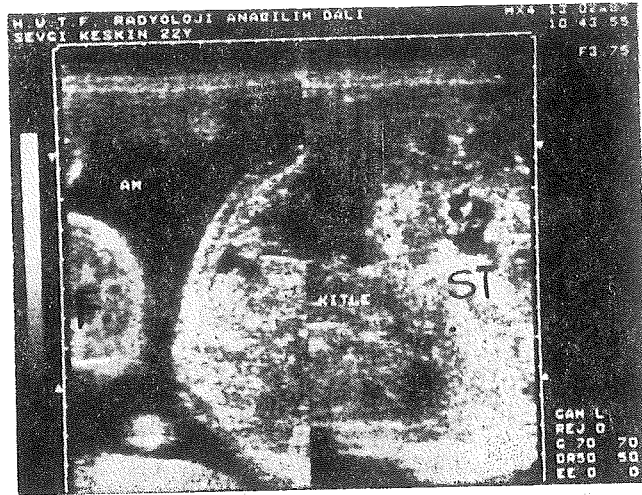
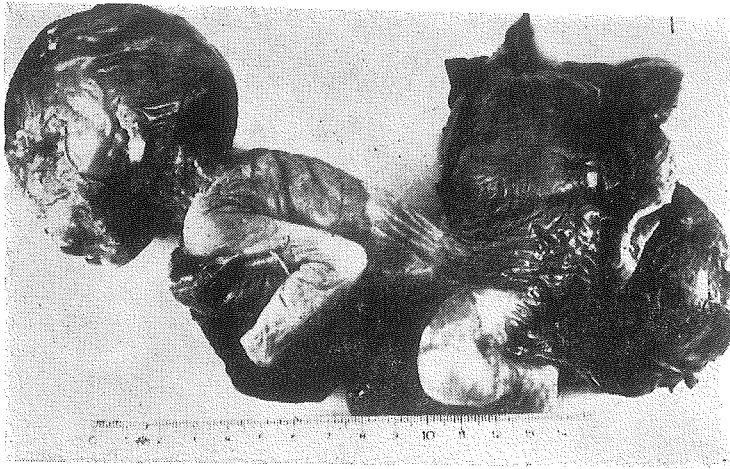


Figure 1

Real-time sonographic demonstration of the sacrococcygeal mass. (Case 1). AM: Amniotic fluid, F: Fetus, ST: Sacrococcygeal teratome.

Induction of labour with oxtocin was started. During labour her blood pressure rose to 150/100 mmHg. and  $MgSO_4$  was administered. The labour came to an arrest at 90 percent effacement, at 3 cm. of dilatation and with the presenting part floating. A caesarean section was performed at week 27 of gestation and a 2000 gm. dead female fetus was delivered with a large tumoral mass (15 x 15 cm.) arising from the fetal rump (Figure 2,3). The placenta was large and bulky and more than 2 litres of amniotic fluid was drained.

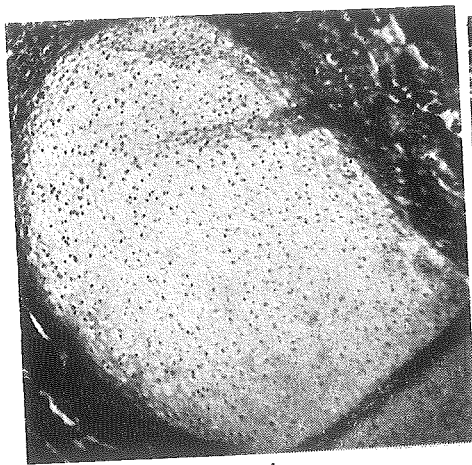
The patient was diagnosed as a second trimester pre-eclampsia with a possible HELLP syndrome. Her post-operative course was uneventful. The liver enzymes returned to their normal levels, jaundice disappeared and the patient was discharged on her ninth post-operative day.



**Figure 2, 3**

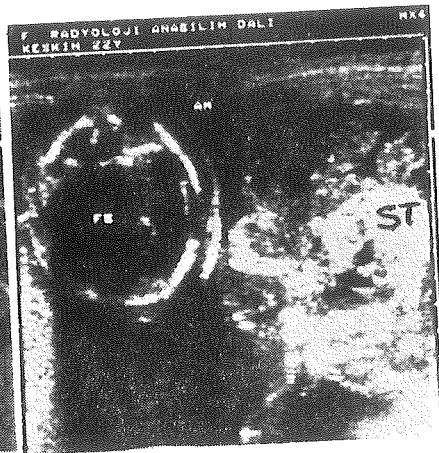
Anteroposterior and lateral view of the fetus after delivery (Case 1).

At autopsy the infant weighed 1600 gm, the placenta weighed 600gm. and was 4 cm. thick. A large lobulated mass which measured 13 x 15 cm. was covered with skin projecting posteriorly and inferiorly from the fetal rump which distorted the buttocks. A section of the mass showed soft tissue which resembled the texture of brain with small and large cavities and a foci of necrosis and calcification. The histological sections contained neuroglia, striated and nonstriated muscle, cartilage and irregular lymphoid tissue (Figure 4). No malignant cells were found. A diagnosis of sacrococcygeal teratoma was made in a dead fetus, with polyhydramnios, placentomegaly and pregnancy induced hypertension.



**Figure 4**

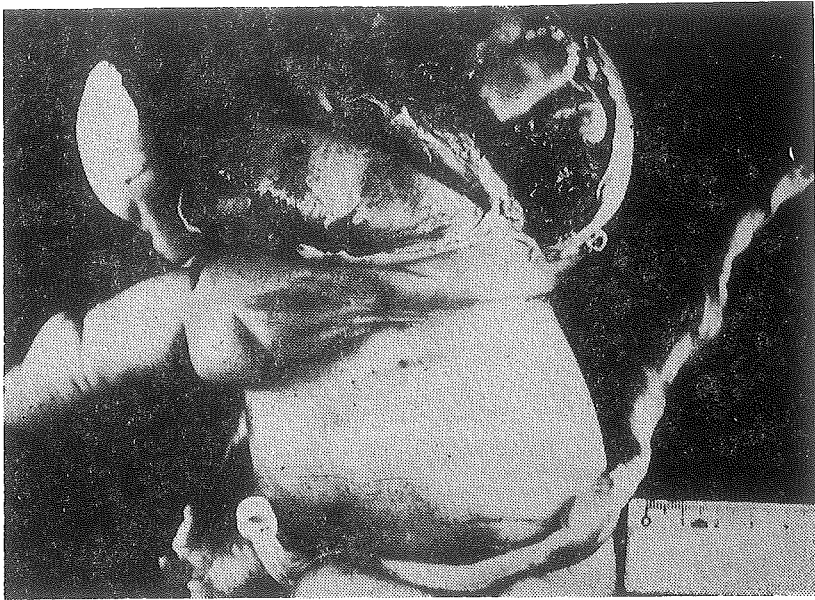
A histologic section of the tumor demonstrating cartilagenous tissue.



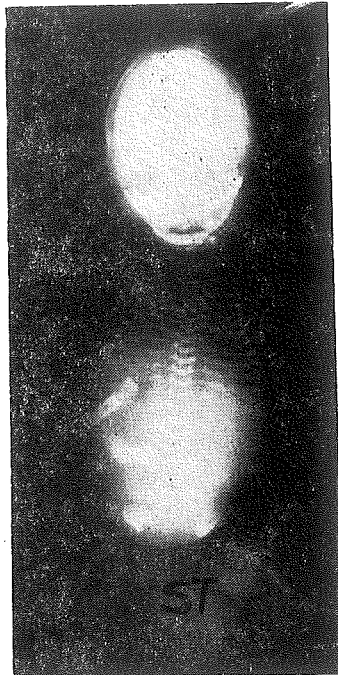
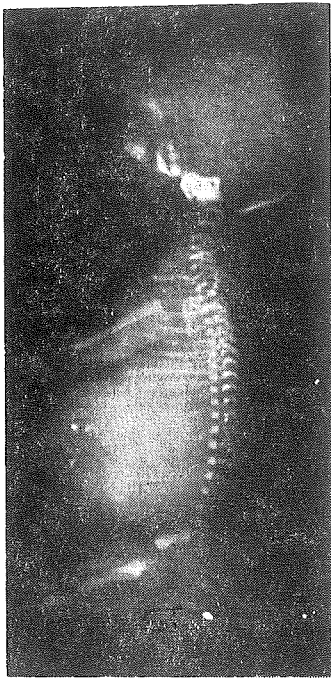
**Figure 5**

Real-time sonographic demonstration of the sacrococcygeal mass (Case 2).  
 FB: Fetal head, AM: Amniotic fluid,  
 ST: Sacrococcygeal teratoma.

**Case 2:** A thirty year old pregnant woman gravida 5 para 2 was hospitalised at 27.5 weeks of gestation (according to her last menstrual period) because of a blood pressure of 140/90, ++ pretibial edema and + proteinuria with a fundal height larger for dates. Her biochemical profile was unremarkable. The sonogram revealed a large mass arising from the fetal rump and a diagnosis of sacrococcygeal teratoma was made (Figure 5). The amniotic fluid was abundant. The ovaries were measured 8x8 cm. and containing multiple cysts. Four days after hospitalisation the patient went into spontaneous labour and delivered a 1540 gm female infant with an Apgar score of 1 in caesarean section, (Figure 6,7,8). The indication for abdominal delivery was failure to progress. The post-operative course was uneventful, her blood pressure declined gradually and she was discharged on her 7th post-operative day. At autopsy the infant weighed 1500 gm, and the placenta weighed 900 gm, The tumoral mass located at the fetal rump measured 10x7x7 cm. Macroscopically the tumour was soft and contained multiple small and large foci of necrosis and calcifications. Rudimentary limbs and fingers were observed in the tumour (Figure 6). Histological sections revealed tissue samples from the GI system, pancreas, liver, kidneys, adrenal and salivary glands and cartilage (Figure 9). The tumour also contained differentiated and undifferentiated neural tissue (Figure 10). The undifferentiated neural tissue resembled neuroblastoma and ganglioneuroblastoma.



**Figure 6**  
Fetus is seen with the tumor attached to the rump (Case 2).



**Figure 7, 8**  
Radiologic views of the fetus born with sacrococcygeal teratome (Case 2). ST: Sacrococcygeal teratoma.



**Figure 9**

Histologic sections of the tumor revealing gastrointestinal mucose.



**Figure 10**

Histologic sections of the tumor revealing neural tissue.

### *Discussion*

Sacrococcygeal teratomas are rare congenital anomalies.<sup>1,2</sup> They arise from the mesodermal streak and contain all three germ layers. They are skin covered masses localised in the fetal rump. Few extend into the pelvis<sup>4</sup> They are more frequent in the female infants (75 to 80 percent) and one third have been reported to be malignant.<sup>5</sup> Infants with this congenital anomaly have been reported to have an increased incidence of other anomalies.<sup>6</sup> Polyhydramnios and hydrops fetalis have been found in association with sacral teratomata.<sup>7</sup>

Calcification and soft tissue masses can be detected on a plain radiography of the abdomen of pregnant women<sup>5</sup> (Figure 7,8). Alpha-feto-protein and acetylcholine esterase have been reported to be elevated in the amniotic fluid, especially in the second trimester.<sup>8</sup>

Sonography is a very accurate method of prenatal diagnosis and management of ST.<sup>3,4</sup> In this paper, we represented two cases of ST diagnosed ante nately by ultrasonic examination. The findings in these two pregnancies complicated by ST, placentomegaly, hydramnios and pregnancy induced hypertension suggest a high-output congestive fetal

heart failure. The same conclusion has been reported before by Cousins et al.<sup>9</sup> The tumour acting as a large arterio-venous fistula may be responsible for cardiac failure.

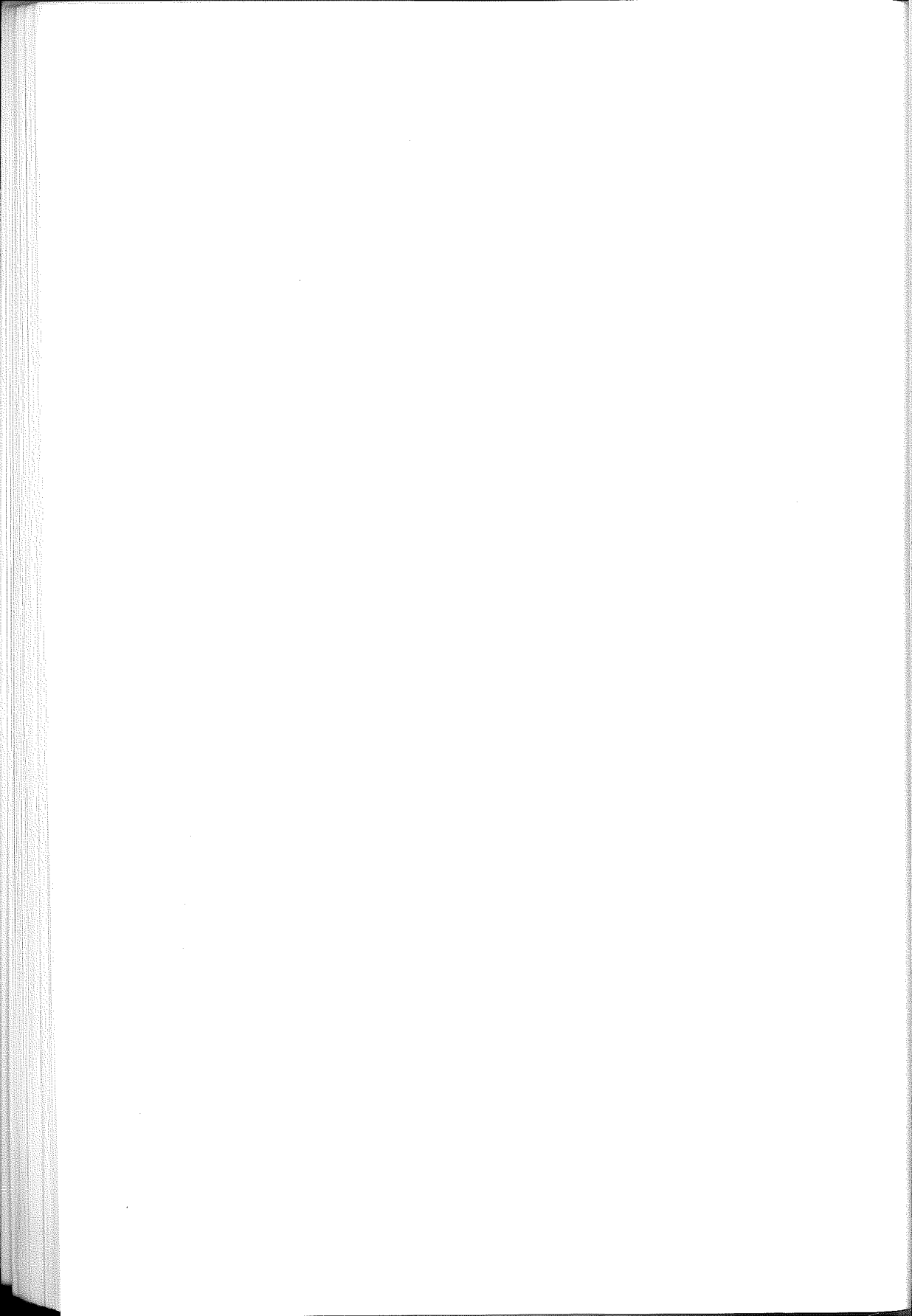
Both infants were delivered by the abdominal route because of failure to labour progress of. It is suggested that the tumours larger than 5 cm. are better handled by caesarean section.<sup>10</sup>

For fetuses with these tumors which are diagnosed by prenatal sonography, a careful search should be made for other anomalies. If no other anomalies are found, patients should be kept under close supervision with serial sonography and should be delivered in a tertiary centre where neonatal surgery is readily available.<sup>12</sup>

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# A Giant Ureteral Stone

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## Summary

Generally, ureteral stones originate in the renal collecting system and pass into the ureter. Tuberculosis as a cause of ureteral stone is not common. The incidence of urinary lithiasis in urinary tuberculosis has been reported as 10 % in clinical practice.

The case presented here is an interesting and rare one, because of its relationship with tuberculosis and the stone dimension of 16 by 3 cm, which is among the largest ureteral stones reported.

*Key Words:* Giant, Ureter Stone.

## Introduction

Most of the ureteral stones originate in the kidney and become lodged in the ureter. On the other hand, primary stone formation in the ureters is possible in cases of ureteral stricture, ureterocele and ureteral diverticulum.<sup>1</sup>

Although most of the ureteral stones are smaller than 0.5 by 0.5 cm, and therefore pass spontaneously, nearly 30 % of ureteral stones are bigger in size and can be arrested in the ureter. For such stones, surgical or endoscopic manipulation is indicated. Ureteral stones bigger than 1 by 2 cm are rarely seen.<sup>2 3</sup>

The typical symptom of an ureteral stone is its colicky, agonizing pain. If infection is supervened on the obstruction, then flank pain, fever and chills are also been encountered. Although ureteral stones have these prominent symptoms, they rarely have a silent progression and rarely reach such unusual sizes.

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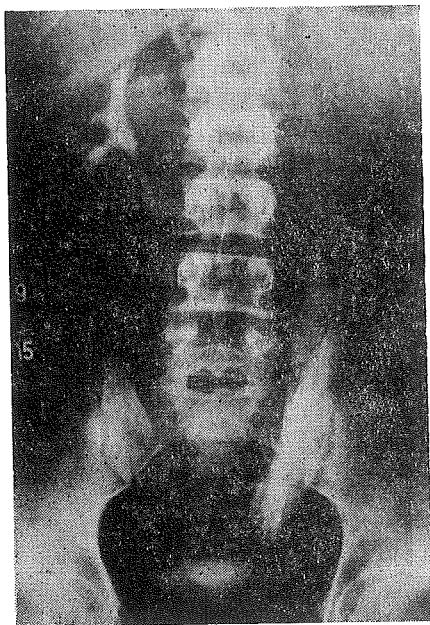
We here, report a ureteral stone of 3 by 16 cm which gave the patient only minimal symptoms.

### *Case Report*

An 18 year old, male patient was admitted to our clinic because of a dull left flank pain. He did not have any other urological complaints. Physical examination revealed costovertebral tenderness, and a palpable left renal mass. As an unusual finding, a hard, longitudinal, left abdominal mass was also palpable.

Although, 10-12 pus cells were noted in urinalysis, urine culture was negative. Acid fast stains of concentrated urine sediment and tuberculosis cultures of urine were also negative.

The plain abdominal X ray, showed a giant radioopacity of approximately 3 by 16 cm extending from the level of the fourth lumbar vertebra to the middle of the bony pelvis. Excretory urograms (Figure 1) revealed, right renal compensatory hypertrophy with a non-functioning left kidney. The ultrasonic study demonstrated a left hydroureteronephrosis with a giant ureteral stone extending from the lower pole of the kidney to a level 1.5 cm above the bladder (Figure 2).



**Figure 1**



**Figure 2**

A left nephrectomy with excision of the ureter distal to the stone was performed. The subsequent histopathologic examination revealed the specimen as tuberculosis.

### *Discussion*

Ureteral stones, causing a clinical entity, are mostly impacted in the lower third portion of the ureter (73.5 % - 77 %). These impacted stones are usually removed by surgical or endoscopic manipulation.

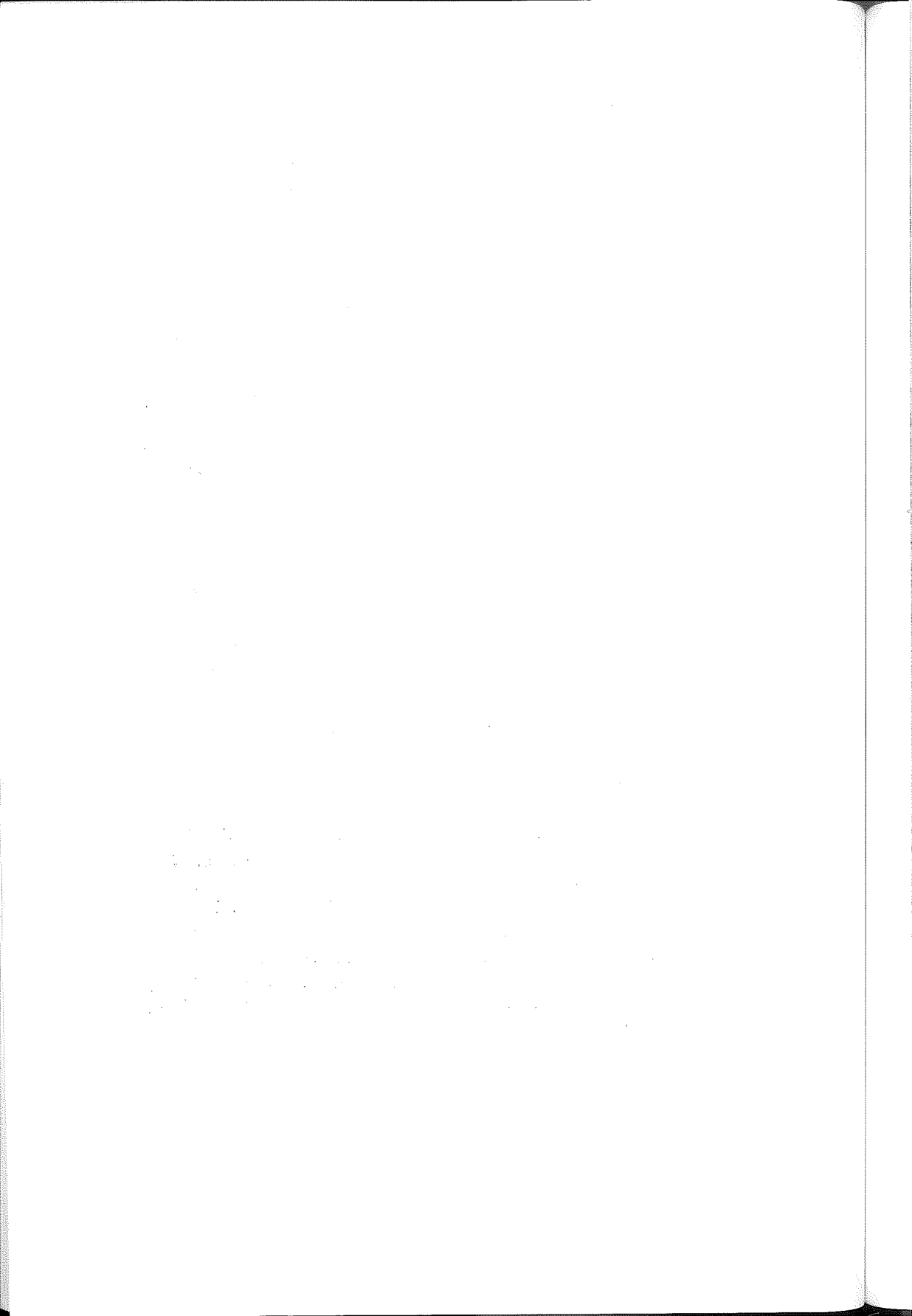
It is unusual for a ureteral stone to have a size greater than 1 by 2 cm. In 1922, Heath<sup>4</sup> removed a calculus 2.5 by 1.5 cm that weighed 65.8 gm. In 1924, Tennant<sup>5</sup> removed a ureteral stone that weighed 66 gm and Drach<sup>6</sup> cited one case reported by Federof in which the calculus weighed 52 gm. When compared with these reported giant stones, our stone was even larger, and had a dimension of 3 by 1.6 cm and weighed 71.4 gm (Figure 2).

The incidence of urinary stone in urinary tuberculosis is 10 %, but the incidence of primary stone formation in the ureters is very low. As scarring of the ureter with stricture formation is one of the typical lesions of tuberculosis, our giant stone might be a primary ureteral stone due to tuberculosis stricture.

This case is presented because of its rarity and association with urinary tuberculosis.

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# Torsion of the Spermatic Cord in the Neonate of Four Days Old

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## *Summary*

Torsion of the spermatic cord in the neonate is very rare and is usually observed during the first 24 hours after birth. A case of spermatic cord torsion observed on the four-day old neonate and in which management prednisolone was applied to protect the contralateral testis was presented.

*Key Words:* Spermatic cord.

## *Introduction*

Torsion of the testis in older children is much more common than that in neonates and occurs within the tunica vaginalis (intravaginal). In contrast, neonatal torsion usually involves the entire spermatic cord and its tunics (extravaginal).<sup>1</sup>

## *Case Report*

A healthy mother of 30 years old delivered a baby through vaginal route without complications. Routine physical examination of the boy showed no abnormalities. In the morning of the fourth day, the mother noticed a scrotal swelling. It was observed that skin of left hemiscrotum was cyanotic, the left testis was 3 times the size of the right testis; and of was also hard. It did not transmit light. Exploration through an inguinal

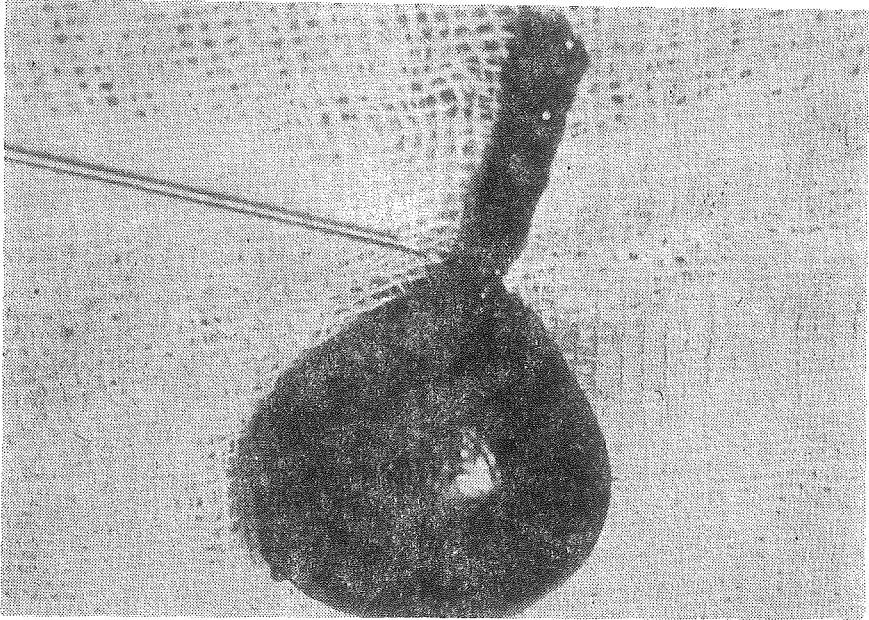
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approach revealed a hemorrhagic infarction of the left testis, secondary to extravaginal torsion. Orchiectomy was performed Figure 1; and a prophylactically contralateral orchiopexy and prednisolone injection (3 mg/kg for 10 days) were given. Histological examination of the testis revealed a coagulative necrosis.



**Figure 1**  
Typical appearance of extravaginal torsion.

### *Discussion*

Only a few cases of spermatic cord torsion (after 24 hours of birth) has been reported.<sup>2</sup> Our case was an extravaginal cord torsion in a neonate of 4 days old. One reason for the cause of this problem may be that fixation of the testicular tunics to the scrotum is not completed before 4 days after birth. However, the actual time by which the attachment is completed is not known.

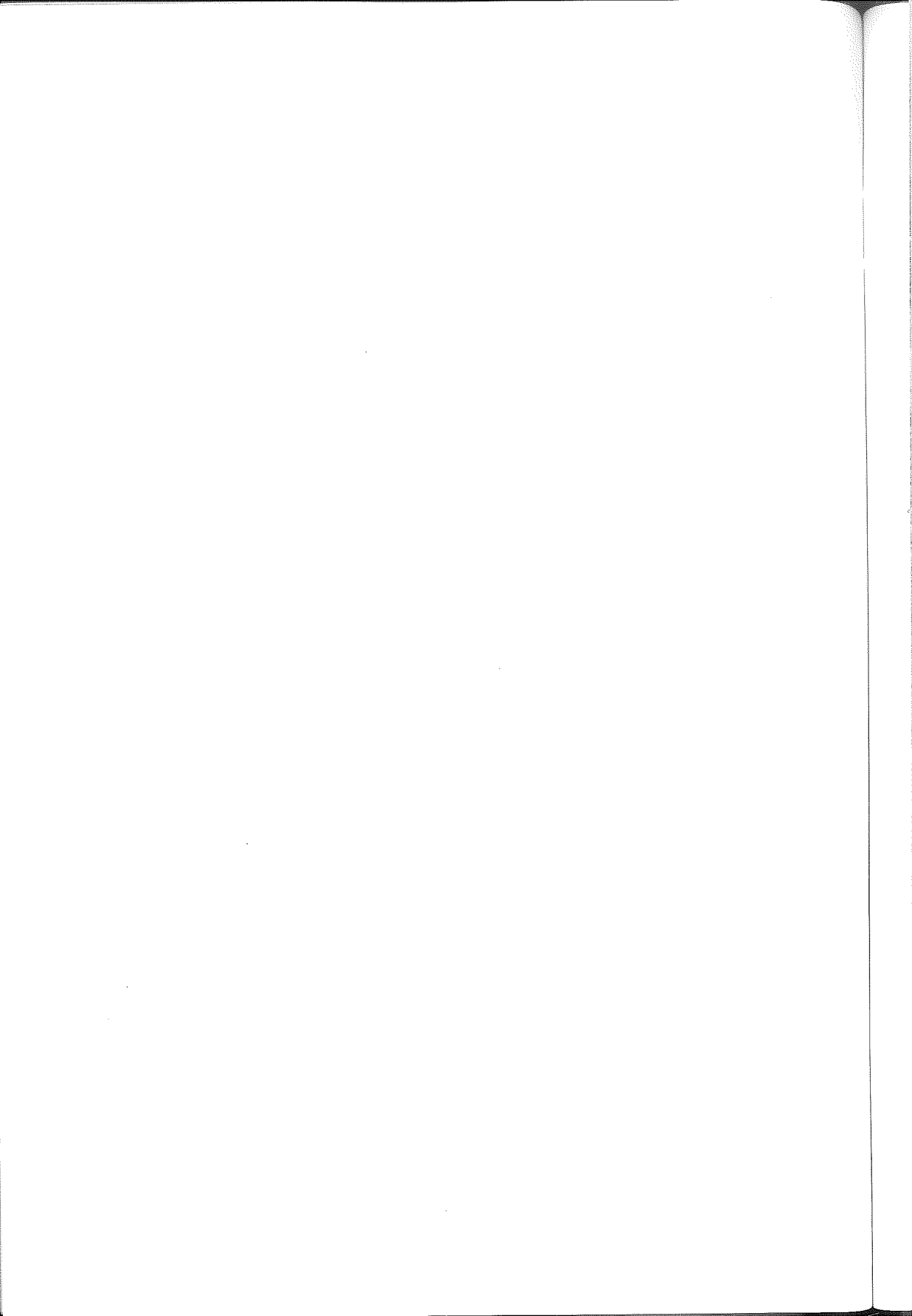
Certain controversial questions include whether contralateral orchiopexy and immunosuppression should be performed,<sup>3</sup> and what surgical approach should be used. We believe that it is necessary to rule out the risk for contralateral torsion and the potential effect on the remaining testis with the current interest in the immunology of testicular necrosis. The differential diagnosis includes tumor, hemocele, torsion of the testicular or epididymal appendages, incarcerated hernia, scrotal abscess

and torsion of the spermatic cord. All of these require immediate surgical exploration through an inguinal approach for an accurate diagnosis and an appropriate therapy.

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# Calcified Pituitary Adenoma

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## *Summary*

This report presents an unusual example of massive calcification of pituitary adenoma in a young man. The adenomatous tissue was characterised by extensive replacement of calcium deposits which was diagnosed by CT-scan and confirmed by surgery and by histology.

*Key Words:* Pituitary adenoma, Calcification, CT-scan.

## *Introduction*

Calcifications are rarely observed in pituitary adenomas. When it does occur, it may be found either in the central portion or in the wall of the tumor.<sup>1</sup> The presence of recognizable intrasellar or suprasellar calcifications are the most commonly encountered in craniopharyngioma. Calcified aneurysms of the circle of willis and calcified gliomas of the hypothalamic area are also to be considered in the differential diagnosis of calcified lesions of the hypophysial region.<sup>1</sup> Therefore, the presence of calcification may be misleading because it occurs so much more frequently in lesions other than pituitary adenomas.

Case reports and studies on calcifications of pituitary adenomas usually describe small or scattered calcium deposits; and to our knowledge, no such extensive pituitary adenoma calcification has been reported.

## *Case Report*

After suffering an increasing loss of vision during a twenty day period, a 24-year old man with a history of headaches and retarded development of the secondary sexual characteristics and impotence was

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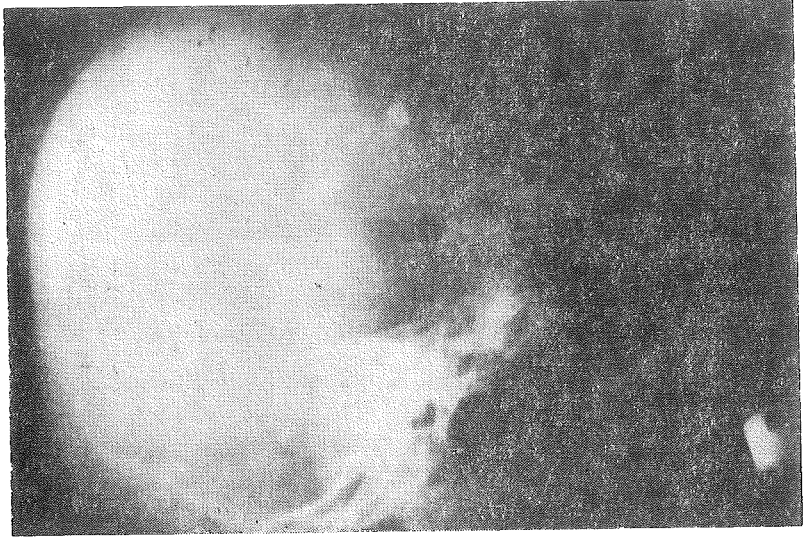
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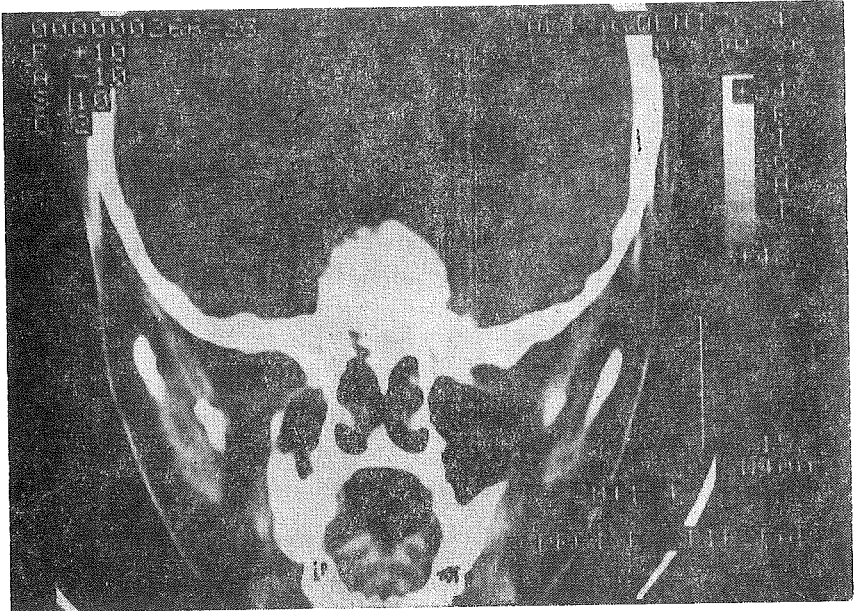
\*\*\* Professor of Pathology.

admitted to our clinic. The physical and neurological examination revealed signs of gonadal insufficiency and partial bitemporal field defects. Endocrine studies showed low levels of testosterone (110.6 ng/100 ml, normal 360-990 ng/100 ml), FSH (2.9 mIU/ml, normal 0-20 mIU/ml),



**Figure 1**

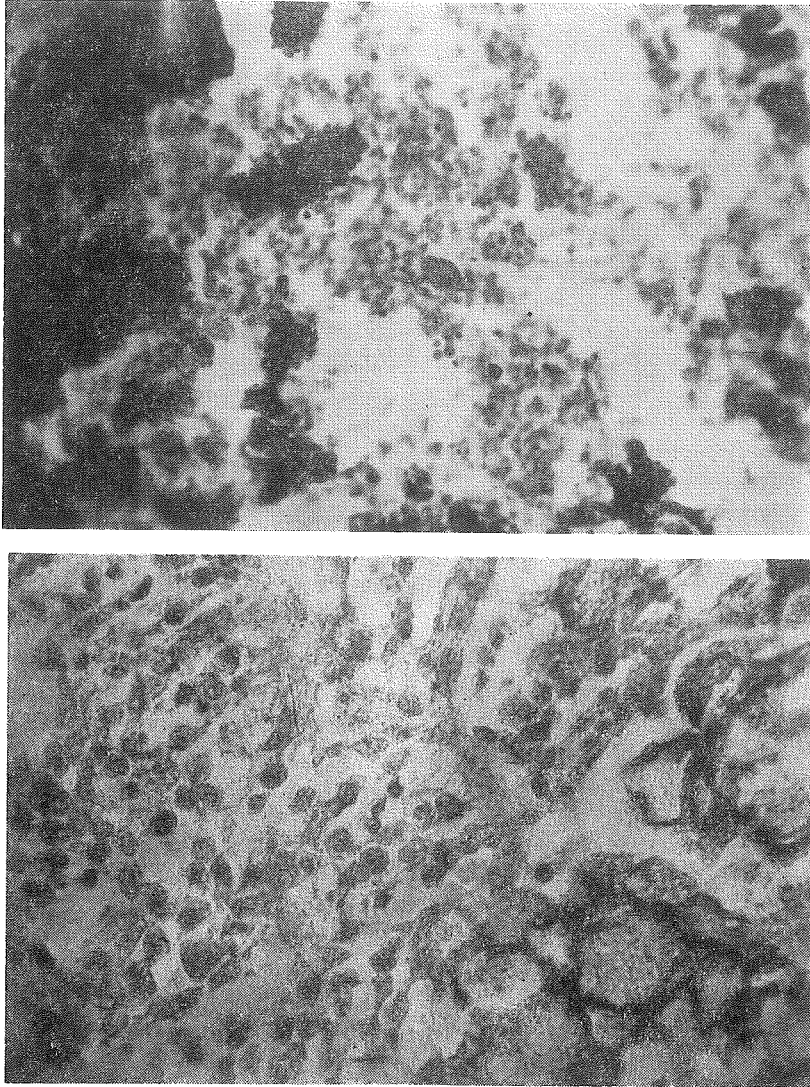
Craniogram shows dense intra and suprasellar calcification.



**Figure 2**

CT-scan shows an almost completely calcified mass in the pituitary region.

LH (3.7 mIU/ml, normal 5-25 mIU/ml), and GH (0.717 ng/ml, normal 0-5 ng/ml). X-ray examinations revealed an increase in the size of the sella turcica and dense intra and suprasellar calcification (figure 1). The CT-scan showed an almost completely calcified mass in the pituitary region (figure 2).



**Figure 3**

Photomicrographs of the calcified adenoma.

A- The tumor is replaced extensively by calcifications (HE $\times$ 160).

B- Irregularly shaped calcium deposits are dispersed in the adenoma tissue (HE $\times$ 450).

At craniotomy a solid calcified tumor was found in the pituitary fossa. The tumor felt like normal bone cut with rongeur and could not be removed by curettes or disc rongeurs. After removal of the solid exterior part of the tumor by a fine bone rongeur, the central portion was exposed; this which consisted of calcium deposits and tumor cells forming a substance like the substantia spongiosa of bone. The tumor tissue was totally removed using a micro-operative technique. Following the operation, the patient had transient diabetes insipidus that lasted for several days, but the postoperative course was otherwise uneventful.

Microscopical examination of the lesion showed a dense accumulation of uniform cells with regular nuclei showing occasional intranuclear vacuoles and nucleoli. The cells had sharply delineated cytoplasmic borders and contained numerous eosinophilic granules. No mitoses were found. The cells did not show a particular type of arrangement. Irregularly shaped calcium deposits were dispersed in the adenoma tissue. Some parts of the tumor consisted almost exclusively of calcium deposits with a concentric structure. The foci of calcification was scattered and did not show a tendency to grow together (figure 3).

#### *Discussion*

Calcifications of the pituitary adenoma are rather rare. In a study of 285 of Cushing's verified adenomas, Deery found 19 (7 %) adenomas with radiologically demonstrated calcifications.<sup>1</sup> Some investigators observed this incidence to be even less.<sup>1,2</sup> Landolt and Rothenbühler<sup>3</sup> found a total of 42 cases in the literature. The calcium deposits were usually described as starlike or psammoma bodies. Curvilinear calcification seen with chromophobe adenomas occurs in the capsule of the tumor or in the wall of the cyst,<sup>4</sup> and calcium in the capsule may extend well above the sella turcica in a conical form.<sup>1</sup>

Calcifications may occur in eosinophilic adenomas as calcareous deposits or bone formation within the sella turcica called "pituitary calculi".<sup>1,4</sup> Calcification and bone formation also can rarely be seen in the normal pituitary.<sup>3</sup>

Factors that determine the tendency of a pituitary adenoma to calcify remains as an unanswered question. No constant factors were found which might influence this calcification process, such as the type of adenoma, the age of the patient, the size of the tumor, or the duration of symptoms.<sup>1,3</sup> It has been suggested that local factors and the type of hormone secreted may play a role in the calcification pattern of pituitary adenomas. Landolt and Rothenbühler,<sup>3</sup> in their report on the ultrastructural

examination of pituitary adenoma calcification, stated that the calcium deposits in pituitary adenomas are immediately surrounded by apparently healthy cells engaged in active hormone synthesis, and only single degenerating cells are transformed into calcified masses. Contrary to this, the lime deposits of the majority of other dystrophic calcifications, eg, craniopharyngiomas, are usually localized in large areas of tissue necrosis and separated from the living tissue by larger distances. They also suggested that substances liberated by the dying cells may be involved in the process considering that all calcified adenomas of their series secreted prolactin and in some cases also growth hormone. However, endocrine levels in our case were below normal which might suggest that the type of hormone secreted, is also of no importance.

Calcifications seen on the lateral views of the craniograms are not necessarily localized within the pituitary adenomas. They may be situated in the walls of the adjacent intracranial arteries or in the mesothelial connective tissue on the surface of the pituitary.<sup>9</sup> In our case, the CT-scan showed the extensive replacement of the adenomatous tissue by calcified bodies. This was confirmed during surgery.

Although a few cases of pituitary adenomas with extensive calcifications appear in the literature<sup>6, 9</sup> no such case with an almost totally calcified adenoma diagnosed by CT-scan has been reported previously.

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1890

Jan 1st

Feb 1st

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# Intracranial Solitary Plasmacytoma of the Base of the Skull

Case Report Including Immunohistochemical Features

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Mahir Tevrüz, M.D.\*

## *Summary*

A solitary intracranial plasmacytoma involving the ethmoid cells, partially in the right orbita, half of the right frontal sinus, and the brain parenchyma in the frontal lobe, is reported. The CT scan findings are demonstrated. The immunohistochemical study confirms that the tumor is monoclonal, producing only kappa light chain and IgG heavy chain immunoglobulins.

*Key Words:* Intracranial plasmacytoma, plasmacytoma, immunohistochemical features of.

## *Introduction*

Solitary plasmacytomas may occur in either bones or soft tissues. The most frequently involved bone is the vertebral column; this is followed by ribs, skull (calvarium), pelvis, femur, clavicle and scapula. Extrasosseous lesions usually occur in the lungs, oronasopharynx or nasal sinuses.<sup>1</sup> Solitary plasmacytomas occurring in the cranial cavity are rare lesions,<sup>2-4</sup> and they may involve meninges and parenchymal nervous tissue, or the bones at the base of the skull.<sup>4</sup>

The following report concerns a considerably large solitary plasmacytoma which occupied the region of the ethmoid cells, partially the right orbita, half of the right frontal sinus, the brain parenchyma in the anterior frontal lobe and infiltrating the overlying meninges and dura mater.

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*Case Report*

A 45 years old female was admitted to the Haydarpaşa Numune Hospital İstanbul on December 24, 1985 complaining of headaches, in the frontal region, which radiated to both sides. The headaches had begun one year previously, and had gradually increased in severity. She also suffered from a loss of equilibrium and urinary incontinence during the last months. Two weeks prior to the admission she was noticed to talk garrulously. Examination revealed that she was disoriented in time and place. Her ability to co-operate was poor. She was euphoric and there was logorrhea. Her deep tendon reflexes were hyperactive. Babinski's sign and Achilles clonus were positive on the right side. A severe degree of ataxia was present. The fundus oculi was normal. A routine biochemical analysis did not show any pathological problems. Skull X- Rays revealed a lytic area in the fronto-parietal region (Figure 1). A CT scan before and after contrast injection was performed: A bulk of soft tissue mass occupying the right ethmoid cell region was present at the level of the base of the skull. This lesion had destroyed the right ethmoid lamina, displaced the right medial rectus and partially filled the orbita (Figure 2). It enlarged upwards, destroyed the right half of lamina cribriformis, crossed the mid-line at the gyrus rectus, and formed a large mass in the frontal pole (Figure 3). The posterior wall of the frontal sinus was also destroyed and the lesion occupied the right half (Figure 4). The meninges were infiltrated by the tumour in the fronto-parietal region. A wide area of edema was present around the lesion. Lateral ventricles were displaced backwards and towards the left side.

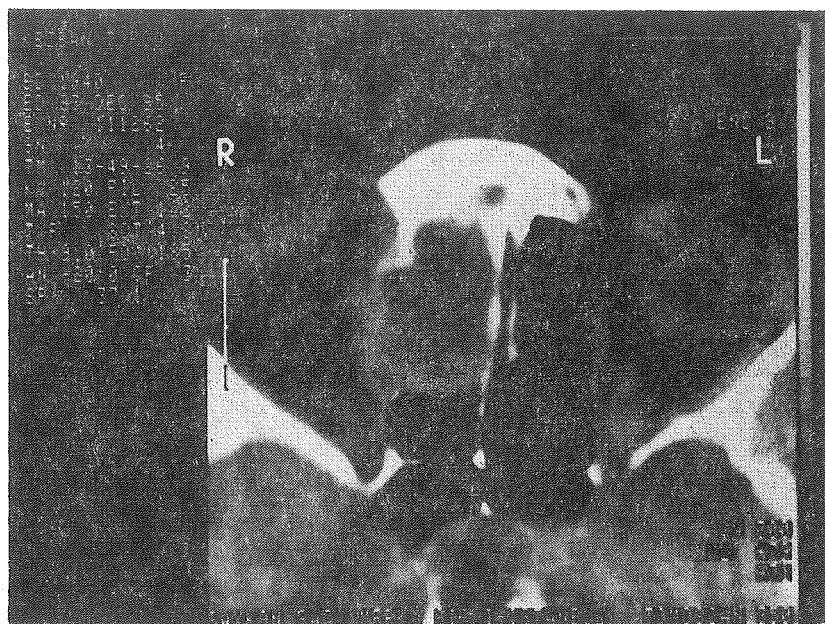
In December, 1985, surgery through a bifrontal craniectomy was performed. The bone at the frontal region was very thin. This was due to pressure atrophy and there was no tumor infiltration within the bone. Removal of the bone revealed a soft, friable pinkish tumor measuring approximately 5x8 cm. It had infiltrated the dura mater, superior sagittal sinus and falx. At the inferior border, the tumor was tightly adherent to the base of the frontal fossa so it could only be removed partially. The extirpation included the anterior one-third of the superior sagittal sinus as well.

Following the histopathological diagnosis of the plasmacytoma, a complete skeletal X-Ray survey was undertaken, but no abnormality was detected. The serum protein electrophoresis was within normal limits (alb.:47 %, alpha 1: 5 %, alpha 2: 12 %, beta 10 %, gamma 26 %). Urine analysis for Bence-Jones protein was negative. The bone marrow aspirate was normal; an increase of plasma cells was not observed. In



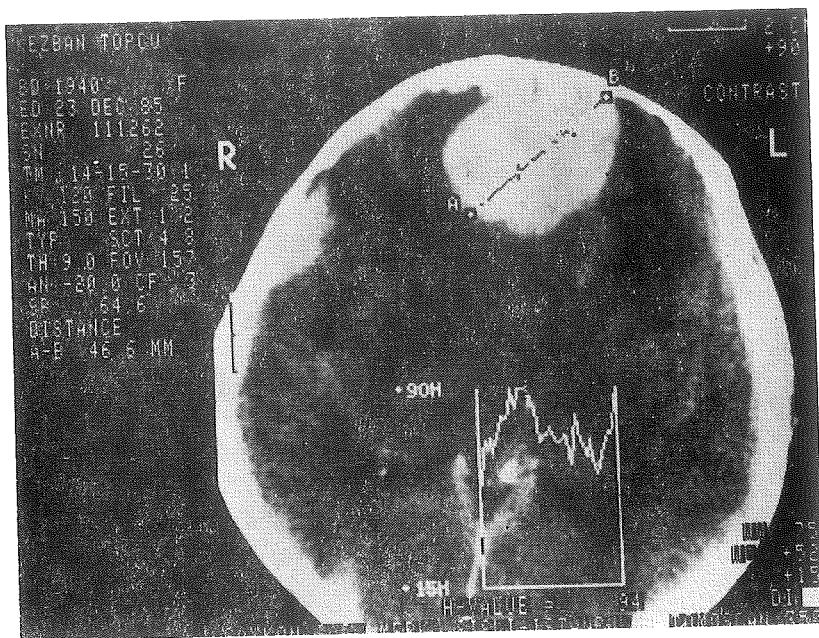
**Figure 1**

Lateral X-Ray of the skull showing a lytic area in the fronto-parietal region.



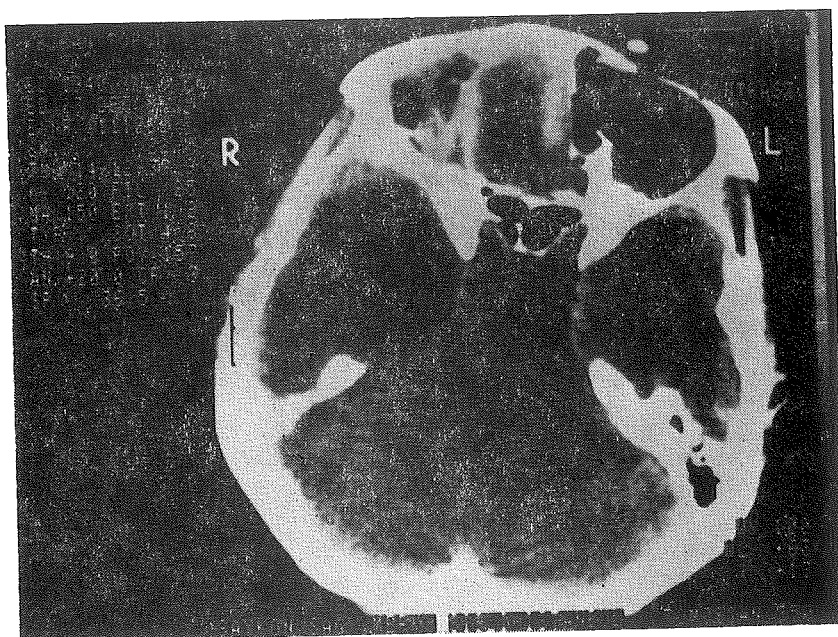
**Figure 2**

CT scan: The right ethmoid lamina is destroyed, the right medial rectus is displaced and the tumor is partially occupying the orbit.



**Figure 3**

CT scan: A large mass is present in the frontal pole.



**Figure 4**

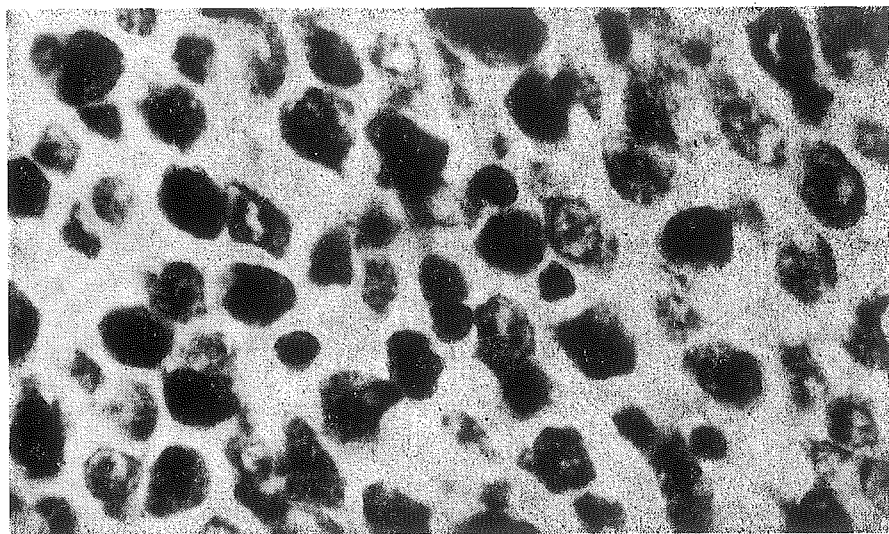
CT scan: The tumor is destructing the posterior wall and the right half of the frontal sinus.

the postoperative period the neurological symptoms disappeared. The patient remained well and was discharged for radiotherapy on the 16th postoperative day.

#### *Pathologic Findings*

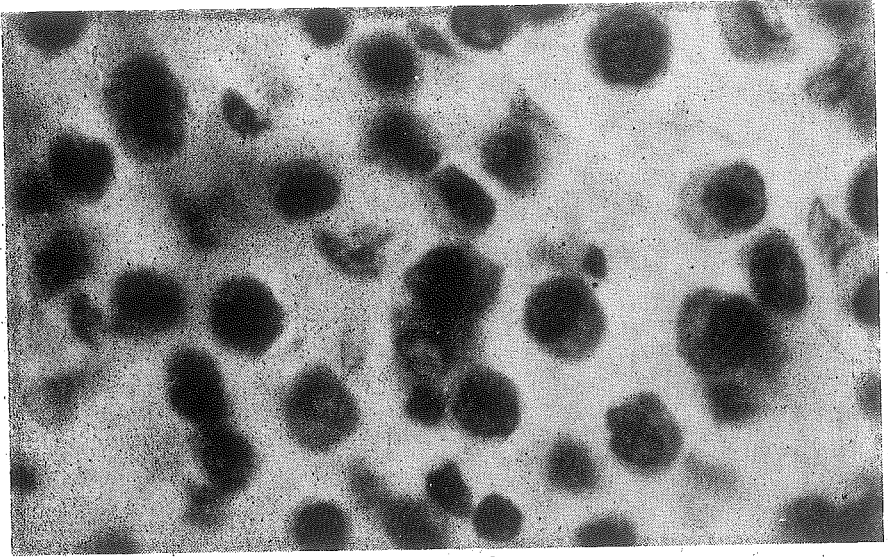
Segments of the tumor tissue were fixed in 10 % formalin. Following the routine processing, they were embedded in paraffin, sectioned and stained with hematoxylin-eosin. The histologic picture showed a tumor which was composed of a diffuse proliferation of mostly mature plasma cells with round nuclei, chromatin which had a configuration with a clock-face appearance, and abundant eosinophilic cytoplasm. Mitotic figures were not present. In areas where the tumor infiltrated dura, lymphocytes and sparse histiocytes were intermingled with plasma cells. For the demonstration of the intracytoplasmic immunoglobulins, the unlabeled antibody enzyme peroxidase-antiperoxidase technique (PAP) according Taylor<sup>5</sup> was performed. Specific rabbit antihuman antisera (DAKO) was used in dilutions of 1: 500 (kappa and lambda) 1: 100 (IgM and IgA), 1: 200 (IgG). The PAP complex was diluted 1: 200. Swine anti-rabbit antisera (SWAR) was diluted 1: 60; and normal swine serum was diluted 1: 20.

Sections stained by using normal serum absorbed with insolubilized human proteins instead of the specific antiserum served as controls. Positive staining for kappa light chain and IgG heavy chain was observed, while staining for lambda light chain, IgM and IgA was negative (Figures 5, 6, 7).



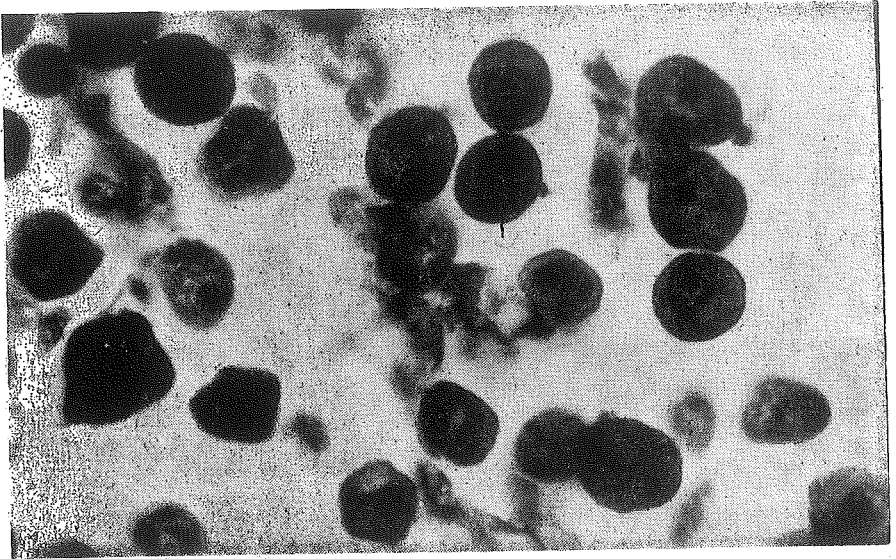
**Figure 5**

PAP: positive staining for kappa light chain. ( 1250)



**Figure 6**

PAP: No staining for lambda light chain. (x 1250)



**Figure 7**

PAP: Positive staining for IgG heavy chain (x 1250)

#### *Discussion*

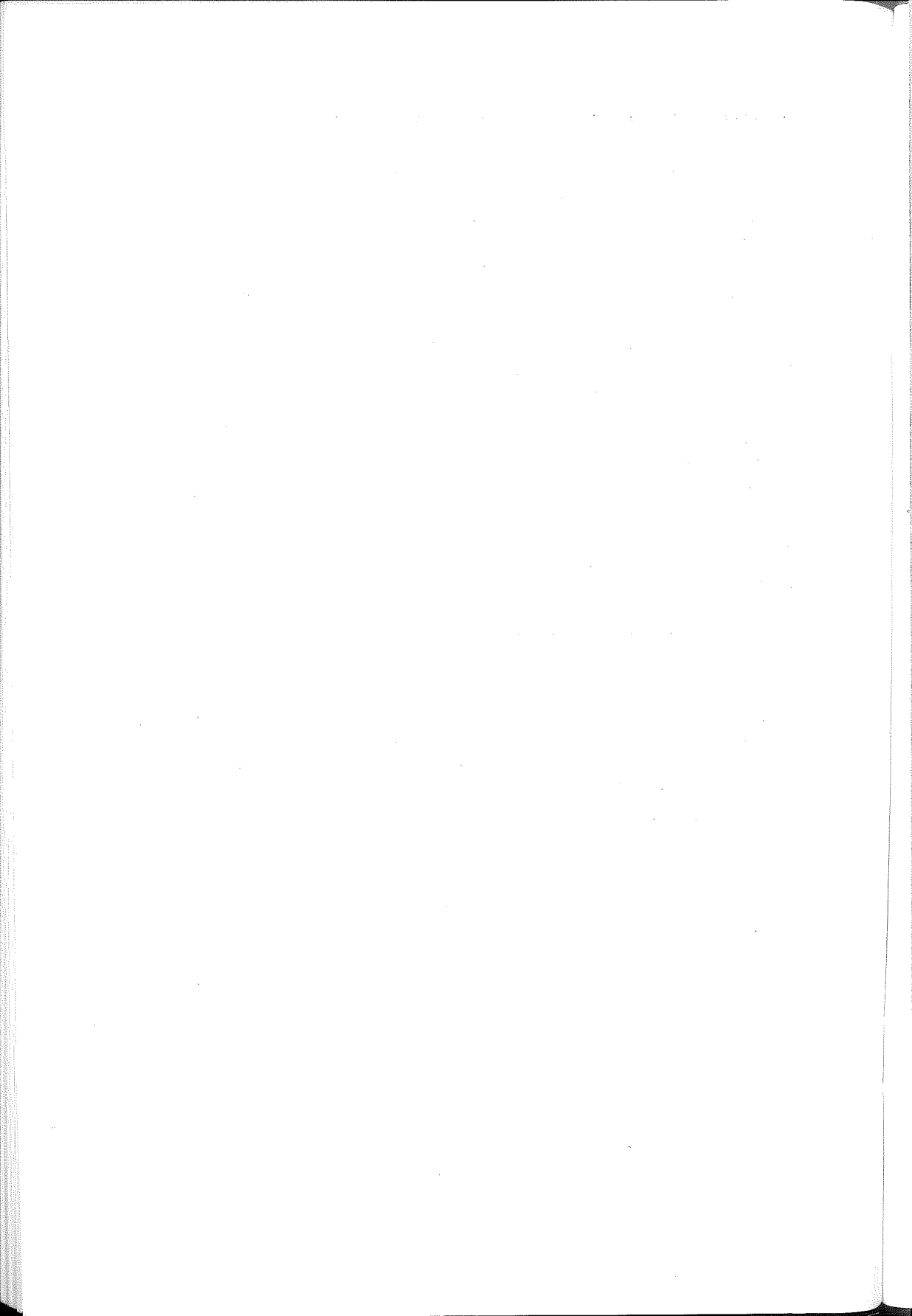
An intracranial lesion made up mainly of well-differentiated plasma cells may belong to one of the three pathologic entities, namely plasma cell granuloma, meningioma with a conspicuous plasma cell-lymphocytic

component and plasmacytoma. In the current case the absence of histiocytic granulomas or meningotheliomatous elements among plasma cells rule out the former two possibilities morphologically, and the monoclonal staining pattern (kappa and IgG only) allows for a definite plasmacytoma diagnosis to be made. Although bone scintigraphy is the most reliable method to determine if a plasmacytoma is solitary or not,<sup>3</sup> this method could not be used in our case due to technical reasons. However, we presume that the tumor is solitary and not merely an expression of multiple myeloma because there is no clinical and radiographic evidence of another tumor in any part of the body. The serum protein electrophoresis was normal. There were no Bence-Jones proteins in the urine. And the marrow aspirate was normal.

The present case appears to be distinct from the previously reported cases by two features: 1- Most of the solitary plasmacytomas originating from the bones at the base of the skull occupy the middle or posterior fossae (the body of the sphenoid bone and the apex of the petrous bone being the most common sites;<sup>3,4</sup> whereas, the frontal fossa was the tumor site in our case. 2- The current tumor is one of the largest intracranial solitary plasmacytomas ever reported.<sup>2,4</sup>

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# Colonic Varices

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## *Summary*

The diagnosis of colonic varices, a rare cause of gastrointestinal hemorrhage, may be exceedingly difficult. Because of the apparent extreme rarity of the condition and for general medical interest a case of varices of the colon is reported here. A discussion of probable etiological conditions and aids in diagnosis and treatment of this disease are also presented.

*Key Words:* Varices, Colon.

## *Introduction*

Varices of the colon are rare causes of lower gastrointestinal hemorrhage. Since the first case report in 1954 33 patients with colonic varices have been reported in the medical literature.<sup>1-4</sup> Feldman, et al found only two cases in 2912 consecutive adult autopsies.<sup>5</sup>

We report a patient, who was diagnosed by colonoscopy and angiography, and who is now the fourth idiopathic case in literature.<sup>6</sup>

## *Case Report*

A 25-year-old woman admitted to the Hacettepe Medical Center in 1986, because of chronic intermittent hematochezia frequently associated with diarrhea. She had first noted these symptoms in 1977. She had been evaluated at another institution 2 years previously for a similar episode. At that time she underwent a sigmoidoscopy and barium enema; the evaluation were inconclusive.

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There was no history of any other bleeding disorders or peptic ulcer disease or of taking any medications such as aspirin-containing products.

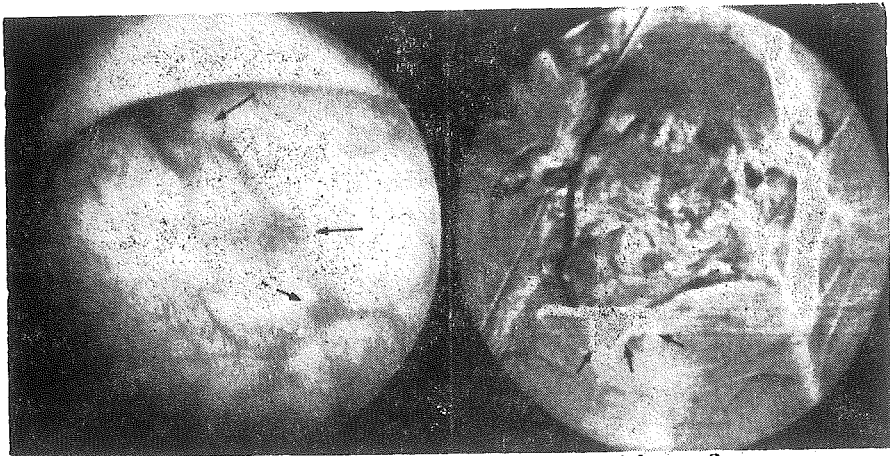
*Physical examination:* She was pale with a blood pressure of 120/70 mmHg and a pulse rate of 80/min. She had an oral aphthous lesion and the spleen was minimally enlarged.

*Laboratory findings:* Hemoglobin was 10.90 g/dl, white blood cell count was 7000/mm<sup>3</sup> with normal differential and normal platelet count. BUN was 11 mg/dl and serum creatinin of 1.3 mg/dl. The rest of the serum biochemistries showed a serum bilirubin of 1.3 mg/dl, an SGOT of 35 U/l, an alkaline phosphatase of 49 IU/l, a total serum protein of 6.2 g/dl with a serum albumin of 3.7 g/dl. HBsAg, Antinuclear antibody and Anti-DNA antibody were negative. Carcinoembryonic antigen was also negative.

Diagnostic procedures revealed a normal upper gastrointestinal series and no esophageal varices. A barium enema showed a swollen mucosal pattern throughout the colon.

Colonoscopy revealed tortuous, bluish varices along the left half of the colon, but there was no visible bleeding (Figure 1). Abdominal aortography by intravenous digital subtraction angiography demonstrated no evidence of arterial bleeding. The venous phase of injection revealed large clusters of dilated veins in the areas of both the ascending and the sigmoid colon (Figure 2). CT scan of the abdomen was normal.

The patient remained stable with no further therapy and was discharged from the hospital.



**Figure 1**

Dilated tortuous vein in the descending colon at colonoscopy (arrows).

**Figure 2**

Venous phase of inferior mesenteric angiogram, demonstrating varices over descending colon and retroperitoneum (arrows).

*Discussion*

Varices of the colon have rarely been diagnosed as a cause of gastrointestinal bleeding. Since the first case report in 1954, 33 patients with colonic varices have been reported in the medical literature.<sup>1-4</sup> Feldman, et al listed four main causes: Congenital anomaly, portal hypertension, mesenteric vein obstruction, and congestive heart failure.<sup>5</sup>

Portal hypertension, due to cirrhosis, is the most accepted cause of colonic varices.<sup>3,7</sup> Because of rare congenital and anatomic variations, the colonic area is more vascularized and will carry most of the shunted blood, thus causing colonic varices.<sup>3, 8</sup>

The patient reported by Levy et al had an additional venous anomaly in that the vein draining the varices of the cecum and the ascending colon was joined to the left gastric or gastroepiploic vein via the omentum and gastrocolic ligament.<sup>9</sup>

Why colonic varices bleed is difficult to answer. The fact that some of the patients have ulceration on the surface of the varices may explain bleeding at least in some cases. It is possible that the varix erodes into the mucosa and stretches it. Capillary blood flow to that area may be reduced and sloughing of the mucosa may occur. The varix ruptures either from internal pressure or from abrasion due to hard stool. This may account for sigmoid and rectal variceal bleeding.<sup>3</sup> The clinical presentation is light to bright red bleeding from the rectum. The rectal bleeding varies from very small quantities to torrential life threatening.<sup>3, 8</sup>

The diagnosis of colonic varices has been made using both radiographic and endoscopic techniques.<sup>1, 2, 3, 5, 9, 10, 11</sup> Barium enema generally lacks sensitivity for this lesion and the findings (including segmental narrowing, polypoid masses and nodular filling defects) are easily misinterpreted.<sup>3, 5, 10, 11</sup> With the use of colonoscopy, the diagnosis of colonic varices has been easier.

The primary way of diagnosing varices is endoscopy.<sup>1, 3, 7</sup> It must be remembered that excessive air insufflation will collapse the varices.<sup>3</sup>

Selective superior or inferior mesenteric arteriography is helpful in finding colonic varices. Feldman, et al were unable to demonstrate colonic varices by splenoportography.<sup>3, 5, 7, 8, 11, 12, 13</sup>

Three types of therapies have been tried in these patients: Conservative, colonic resection, and portocaval shunt. Conservative therapy

consists only the follow-up and no other measure is applied. It seems that portocaval shunting is safer in the short-term management of massive variceal bleeding, but no long-term follow-up study has been reported.<sup>3, 8, 14, 15</sup>

Our patient's long history of intermittent hematochezia points out the pitfalls involved in the diagnosis and management of colonic varices. Despite evaluation by numerous physicians over a 9-year period, colonic varices were not considered. As described above, colonoscopic examination was diagnostic. There was no evidence of cirrhosis or portal hypertension or congestive heart failure and mesenteric vein obstruction. Our patient would probably fit the last main cause, congenital varices; this was demonstrated by selective mesenteric arteriography at venous phases.

With the conservative therapy, the patient stopped bleeding and, up to date (10 months), has not had further bleeding episodes.

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