hacettepe medical journal

A QUARTERLY PUBLICATION **VOLUME 17 / NO. 2 / APRIL 1984**

PUBLISHED BY HACETTEPE UNIVERSITY PRESS

SUBSCRIPTION RATES

TURKEY :	Annual subscription (four issues forming one volume including postage)	1500.00 TL.
	Special annual rate for students, interns and residents	500.00 TL.
	Single issue (including postage)	500.00 TL.
FOREIGN :	Annual subscription (including postage)	$ 20.00 or 50 D.M.
	Special annual rate for students, interns and residents	$ 10.00 or 25 D.M.
	Single issue (including postage)	$ 6.00 or 15 D.M.

Inquiries, articles, reprints and subscriptions should be forwarded to:

HACETTEPE TIP DERGİSİ/HACETTEPE MEDICAL JOURNAL
HACETTEPE ÜNİVERSİTESİ TIP FAKÜLTESİ DEKANLIĞI HACETTEPE-ANKARA

Printed by
Hacettepe University Press
Printing Division

VOLUME 17 / NO. 2 / APRIL 1984

hacettepe medical journal

CONTENTS

hacettepe medical journal

VOLUME 17 / NO. 2 APRIL / 1984

Comparison of Cellular Alterations in Normal and Preeclamptic Placental Cell Culture

Berrin Acar, M.D.* / Altan Günalp, M.D. / Meral Sakızlı, Ph.D.*****

Summary

Placental cell culture was done in cases of normal pregnancy and preeclampsia. An attempt was made to determine to what extent disorders in preeclamptic placental cells and their functions would be important in the etiology. The changes observed in cell cultures over a period of 15 days suggest that the alterations in the trophoblastic cells are reversible and secondary in nature.

Key Words: Placental cell culture, preeclampsia

Introduction

The placenta plays a central part in preeclampsia. It is not known whether the alterations in the placenta are of primary or secondary nature. Some authors have emphasized the fact that this event occurs as a consequence of derangement in the trophoblasts.[1,2]

Due to the fact that the placenta is a sanguine tissue, and infection may readily occur there in, and also because of technical difficulties, placental cell cultures have been rarely carried out. Furthermore, one fails to encounter any studies demonstrating placental cell culture growth

* Assistant Professor in Department of Obstetrics and Gynecology, Faculty of Medicine, Dokuz Eylül University, İzmir, Turkey.

** Professor in Department of Pediatrics, Faculty of Medicine, Hacettepe University, Ankara, Turkey.

*** Associate Professor in the Child Health Institute. Hacettepe University, Ankara, Turkey.

in preeclampsia. An attempt was made to investigate whether there are differences at the cell culture level between normal and preeclamptic placental cells, and examine the manner of their growth under the same conditions.

Materials and Methods

Placental cell culture was carried out in 21 cases, 10 of which were instances of normal pregnancy and 11 preeclampsia. On the vitality test given on the second day with 1 % trypan blue, the placental cells were found to be viable at a rate of 90 %. The cells within the medium were examined under a light microscope.

In addition, placental cell culture was done in 8 cases, 4 of which were instances of normal pregnancy and 4 preeclampsia. Upon completion of the experiment performed with 1 % trypan blue, the cells were found to be viable at a rate of 90 %. The cells were observed in the viable state for 15 days following growth in cover slips, petri dishes or Leighten tubes. Some of the cover slips were examined following staining with Haematoxylin and Eosin after fixation with 10 % formalin at varying times.

The terms of pregnancy of the subjects varied from 39 to 41 weeks, being cases delivered normally through the vaginal route. The preeclamptic cases had blood pressure of at least 140/100 mm Hg, and oedema and proteinuria.

Cell culture was carried out by the methods of Fox[3] and Winkel,[4] modified according to the laboratory conditions. Pieces obtained from the placenta after birth were placed in cold sterile Hanks' solution. Then the material was freed from the basal plate, septa and vascular tissue and washed in Hanks' solution 7-10 times in an effort to discard the red blood cells. The material was cut into 1-2 mm pieces. The tissue prepared in this way weighed approximately 40 g. This tissue was transferred into an Erlenmeyer flask containing 100 ml of 0.5 % tripsin (supplied by BDH Biochemical) at pH 7.5. The material was shaken in a water bath at 37°C for 10 minutes and the supernatant was discarded in an effort to dispose of the red blood cells. 200 ml of 0.5 % tripsin was added and the material was shaken under the same conditions for 35-50 minutes. Next, the experimental material was kept in a water bath for 10 minutes for the precipitation procedure. The supernatant was decanted through double-folded gauze. It was centrifuged at 800 rpm for 8 minutes. After centrifugation, the supernatant was discarded, and 4 ml of medium 199 (supplied by Flow Laboratories) at pH 7.4 was added to each tube. After centrifugation again at 800 rpm for 8 minutes, the supernatant

was disposed of, and medium 199 containing 20 % fetal calf serum (supplied by Gibco Europe) was added so that 1 ml of the material would contain 5 x 10^5 cells, and was placed in an incubator at 37°C. The medium was changed every 72 hours.

Results

Upon examination immediately after staining with Haematoxylin and eosin, the normal placental cell culture was seen to contain, among profuse red blood cell aggregates, round epitheloid cells, multinucleated giant cells and intermediate cells. The round epitheloid cells varied in size, with smooth edges. Most of the cells contained a single large central nucleus, although some were binucleated. Of the nuclei, most were round, some ovoid in form and all basophilic. The cytoplasm was scanty in amount, exhibiting a somewhat eosinophilic characteristic. The multinucleated giant cells varied in shape, being more strongly basophilically stained. Their cytoplasmic content was scanty, being more darkly stained and granular in appearance. They started to adhere to the surface of the cover slip within 2-3 hours after the completion of the experiment. On the third day, the monolayer formed. On the sixth day the free multinucleated giant cells were seen to detach from the cover slip, being followed by cytotrophoblastic hyperplasia. On the 13th day, the epitheloid cells were seen to make up aggregates here and there with new multinucleated cells forming. On the 15 th day, reduction in the number of the epitheloid cells, to the extent of being almost non-existent, and an increases in multinucleated cells were observed.

In the suspension of preeclamptic placental cell culture stained with Haematoxylin and eosin, it was observed that round epitheloid cells had increased two fold in number while multinucleated giant cells were reduced at the same rate when compared to the normal placental cell culture (Figure 1). Preeclamptic placental cell nuclei were pyknotic with the cytoplasm being more scanty. The borders of the round epitheloid cells were undulated in a lacy fashion and the cells did not exhibit any early adherence to the cover slip. On the third day, they adhered to the slip more weakly than the normal placental cells (Figure 2). There were black, dotted formations in the epitheloid cells, indicating cytoplasmic membrane derangement. Besides exhibition by the epitheloid cells, a perinuclear halo was another distinctive feature. On the fourth day, the monolayer formed, but adherence to the cover slip was still weak. In addition, growths of different preparations were observed resembling multinucleated giant cells but devoid of the cytoplasmic portion and consisting of nuclear masses. These were interpreted as being syncy-

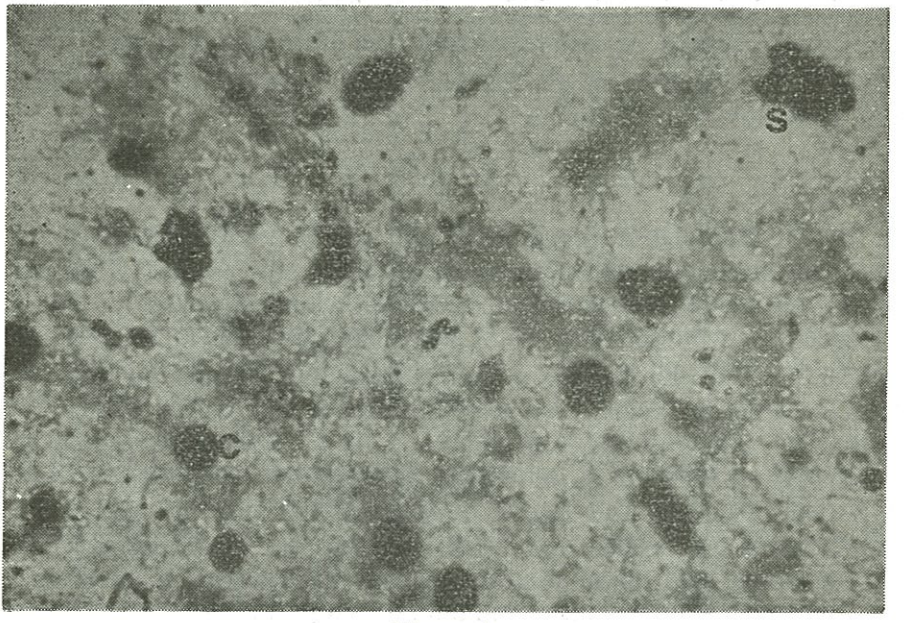

Figure 1
Haematoxylin and eosin stained preeclamptic placental cell suspension. X 500
S: Syncytiotrophoblast, C: Cytotrophoblast

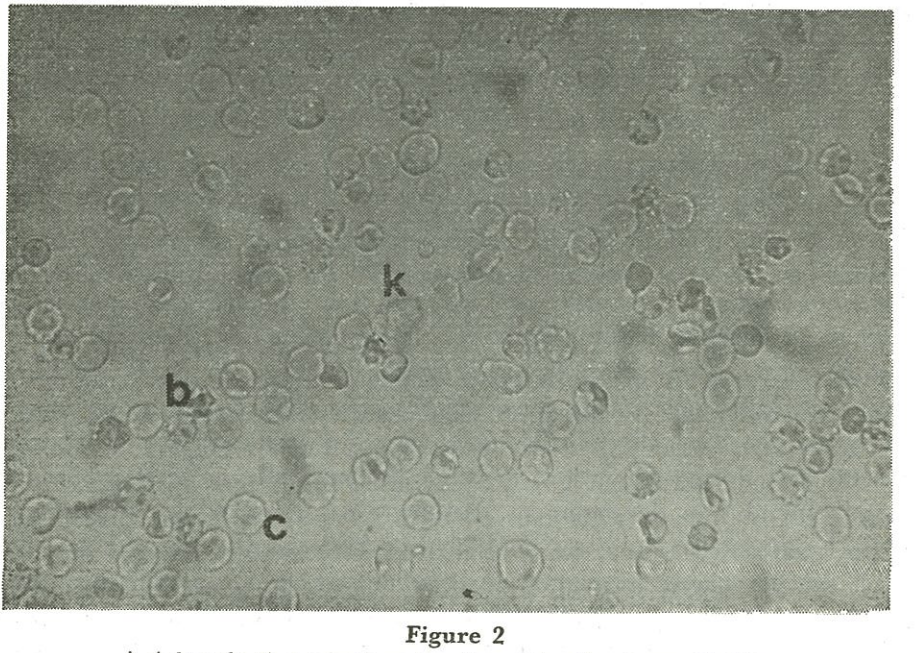

Figure 2
A 4-day-old live preeclamptic placental cell culture. X 500
CO: Cytotrophoblast, K: Syncytial kont, b: Black dotted formations.

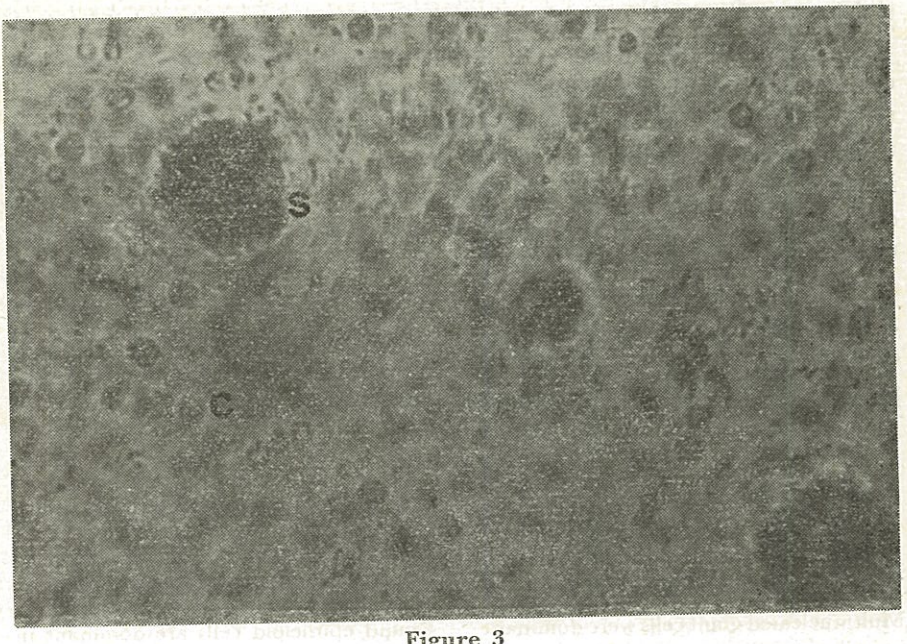

Figure 3
A 10-day-old live preeclamptic placental cell culture. X 500
S: Syncytiotrophoblast, C: Cytotrophoblast.

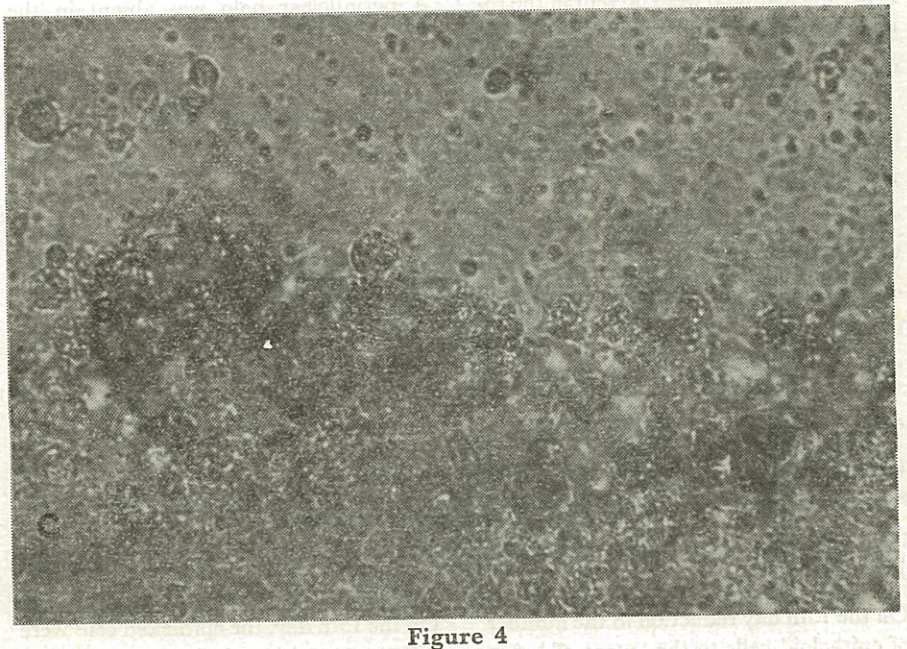

Figure 4
A 12-day-old live preeclamptic placental cell culture. X 500
S: Syncytiotrophoblast, C: Cytotrophoblast.

tial knots (Figure 2). On the sixth day, the multinucleated giant cells were seen to detach from the cover slip, and profuse round epitheloid cells to exist with improvement in the cytoplasmic membrane degeneration. On the tenth day new multinucleated giant cells were observed to form (Figure 3). It was a striking observation that more round epitheloid cells were present than in the simultaneous normal placental cell culture. On the 12th day, the epitheloid cells were observed to adhere to each other forming large masses, and more multinucleated giant cells formed (Figure 4).On the 15th day, the epitheloid cells were still present, although they were reduced 4 fold in number, while multinucleated giant cells were increased at the same rate. Differences between normal and preeclamptic placental cell cultures are listed in Table I.

TABLE I

DIFFERENCES BETWEEN NORMAL AND PREECLAMPTIC PLACENTAL CELL CULTURES

Normal Placental Cell Culture	Preeclamptic Placental Cell Culture
Multinucleated giant cells were dominant in cell suspension	Round epitheloid cells are dominant in cell suspension
The nuclei of cells were pyknotic	The nuclei of cells were not pyknotic
A perinuclear halo were present in the round epitheloid cells	A perinuclear halo was absent in the round epitheloid cells
The cytoplasm of cells was scanty	The cytoplasm of cells was more scanty than the normal placental cells
The borders of the round epitheloid cells were smooth	The borders of the round epitheloid cells were undulated in a lacy fashion
There were black dotted formations in the epitheloid cells	There were no black dotted formations in the epitheloid cells
The cells started to adhere to the cover slip on the first day	The cells started to adhere to the cover slip on the third day
The monolayer formed on the third day	The monolayer formed on the fourth day
Adherence to the cover slip was strong	Adherence to the cover slip was weak
Hyperplasia of the epitheloid cells was seen at the beginning of the second week	Hyperplasia of the epitheloid cells was present in the first week
New multinucleated cells formed on the 13th day	New multinucleated cells formed on the tenth day
On the 15th day reduction in the number of epitheloid cells to the extent of being almost non-existent	On the 15th day, the epitheloid cells were still present, although they were reduced by 4 fold in number

Discussion

It is said that preeclampsia results from alterations in the placenta. Herting[2] has maintained that the endothelial defects in the spiral arteries are repaired by the trophoblasts in cases of normal pregnancy, which is not the case with gestosis where occlusion develops and thrombi form as a result of derangement in the vascular walls. He has also emphasized the fact that this event occurs as a consequence of derangement in the trophoblasts. Therefore, it is necessary to determine the nature of the derangement in trophoblasts and whether it is of primary of secondary nature.

In the present study, two principal types of cell were observed in normal and preeclamptic placental cell cultures. Multinucleated giant cells were regarded as syncytiotrophoblasts, round epitheloid cells as cytotrophoblasts, and other types of cell as intermediate cells. This is in agreement with the findings of Winkel et al.[4]

Many findings obtained for the normal placental cell culture in the present study were similar to those of Fox and Kharkongor.[3] However, although these authors have maintained that the fibroblasts form on the 15th day, it was found in the present study that the epitheloid cells had decreased to the extent of being almost non-existent, and that the multinucleated cells dominated the picture. This suggests that new syncytiotrophoblasts form from the existing cytotrophoblasts and that the life span of the trophoblastic cells forming in the culture medium is longer.

In both cell cultures, by the end of the first week, the syncytiotrophoblasts terminating their life span were seen to be degenerated. It was considered that in the beginning of the second week of the normal placental cell culture cytotrophoblastic hyperplasia, which is present in a long period of preeclamptic placental cell culture and in greater amount, was a consequence of an attempt to form new syncytiotrophoblasts. Formation of syncytiotrophoblasts during the second week in both cultures but somewhat earlier with preeclampsia was proof of this. Disapperance of the cytotrophoblasts from the normal placental cell culture on the 15th day, and their persistence in the preeclamptic one, was only natural. The reason here was the existence of many fewer cytotrophoblasts in the normal placental culture than in the preeclamptic cell culture, and their forming syncytiotrophoblasts. The unavailability of a previous investigation related to preeclamptic cell culture renders a comparison impossible.

In conclusion, it can be said that the trophoblastic changes seen with preeclampsia are not primary and irreversible in nature. Occur-

rence in the culture medium of improvement in the derangement cell membranes within the second week and regression in cytotrophoblastic hyperplasia with formation of many new syncytiotrophoblasts suggest that abnormal cellular alterations with preeclampsia may result from undernourishment due to insufficiency in uteroplacental circulation.

REFERENCES

1. Stark J, Kaufmann P. Regressive placentaveranderungen und syney-plasma polypen. Bei Gestosen, 1973; 214: 78-80.
2. Herting W. Tagung der niederche inischen -West Jal ischen Gesellschalf für Gynakologie und Geburtstülfeem 26/27.6.1976 Köln Geberts N Frauenhe ilh 1977; 37: 67-71.
3. Fox H, Kharkongor F N. Morphology and enzyme histochemistry of cells derived from placental villi in tissue culture. J Path. 1970; 101: 267-76.
4. Winkel CA, Snycler JM, MacDonald PC, Simpson ER. Regulation of cholesterol and progesterone synthesis in human placental cells in culture by serum lipoproteins. Endocrinology. 1980; 106: 1054-60.

Hacettepe Medical Journal
Volume 17 / No. 2 / April 1984 / pp. 67 – 75

The Aid of Computerized Tomography in the Diagnosis of Multiple Meningioma*

M. Memet Özek, M.D. / M. Necmettin Pamir, M.D.*** / Tunçalp Özgen, M.D.**** / Aykut Erbengi, M.D.*****

Summary

The features of 7 cases of multiple intracranial meningiomas and the pertinent literature are reviewed and the value of computerized tomography is emphasized as a diagnostic procedure.

Key Words: Multiple meningioma, Computerized tomography.

Introduction

Among brain tumors, "multiple meningiomas"have always attracted the interest of neurosurgeons. Meningiomas comprise 13.4-19 % of all brain tumors; multiple meningiomas are very rarely observed.[1-6] In this report multiple meningiomas which had surgical intervention and histopathological confirmation are discussed. Furthermore, the value of computerized tomography (CT) as a method in the diagnosis of multiple meningiomas is compared with the literature.

Among 352 meningioma cases only seven were conformable to the definition of "multiple meningioma".[7,8] None of these seven patients had cafe au lait spots, cutaneous tumors, or a history of von Recklinghausen's neurofibromatosis.

* From the Neurosurgery Department of Hacettepe University School of Medicine Ankara, Turkey.

** Resident in Neurosurgery.

*** Instructor of Neurosurgery.

**** Associate Professor of Neurosurgery.

***** Professor of Neurosurgery.

Case Reports

Case 1: A 35 year-old-male was admitted because of convulsive disorder and weakness in the right arm. Neurological examination disclosed bilateral papilledema and hemiparesis on the right side. Brain scintigraphy was used as the only neurological diagnostic procedure and only one spot of radioactive uptake was found 7 cm apart from each other, two separate tumors (4x5x3 cm and 6x8x4 cm) of the falx were totally excised. Microscopic examination revealed that the tumors were meningocytic meningioma with angioblastic components. During the follow-up of 11 years the neurological examination remained within normal limits.

Case 2: A 47-year-old woman was admitted because of headache and memory defect. Examination demonstrated mild right hemiparesis and papilledema. Brain scintigraphy revealed the presence of a single left temporoparietal mass. A left temporoparietal craniotomy disclosed 3 separate tumors; two in the left parietal and one in the left temporal convexity. (4x5x5 cm; 2x1x2 cm and 3x3x3 cm). Histological examination revealed calcified meningiomas. 9 years later the neurological status was normal.

Case 3: A 42-year-old woman was admitted with unsteadness of gait, twitching of the right side of the face and right hemiparesis. Computerized tomography disclosed evidence of multiple nodules in the left parasagital region. Seven separate tumors were totally removed from the left parietal convexity, with a left temporoparietal craniotomy (One 6x5x4 cm., the others 2x2x2 cm).

Case 4: A 40-year-old male was admitted suffering from nausea, vomiting, weakness of the right extremities and a right visual field defect. Examination demonstrated right hemiparesis and papilledema. Left carotid arteriography and brain scintigraphy revealed only one mass lesion. Nevertheless CT demonstrated two separate masses, one in the left frontal, the other in the left parietal region. He underwent a frontoparietal craniotomy with total removal of the two meningiomas which upon histologically examination proved to be fibroblastic meningiomas (5x6x6 cm and 3x4x4 cm) (Figure 1,a, b, c, d).

Case 5: A 47-year-old man was admitted because of headache, memory deficit and visual blurring. Neurological examination revealed only papilledema. CT showed two masses, one in the right frontal, the other in the left parietal region. The tumors were removed with two separate craniotomies. He was discharged in a normal neurological status. The tumors were confirmed histologically to be meningocytic and fibroblastic meningiomas (Figure 2).

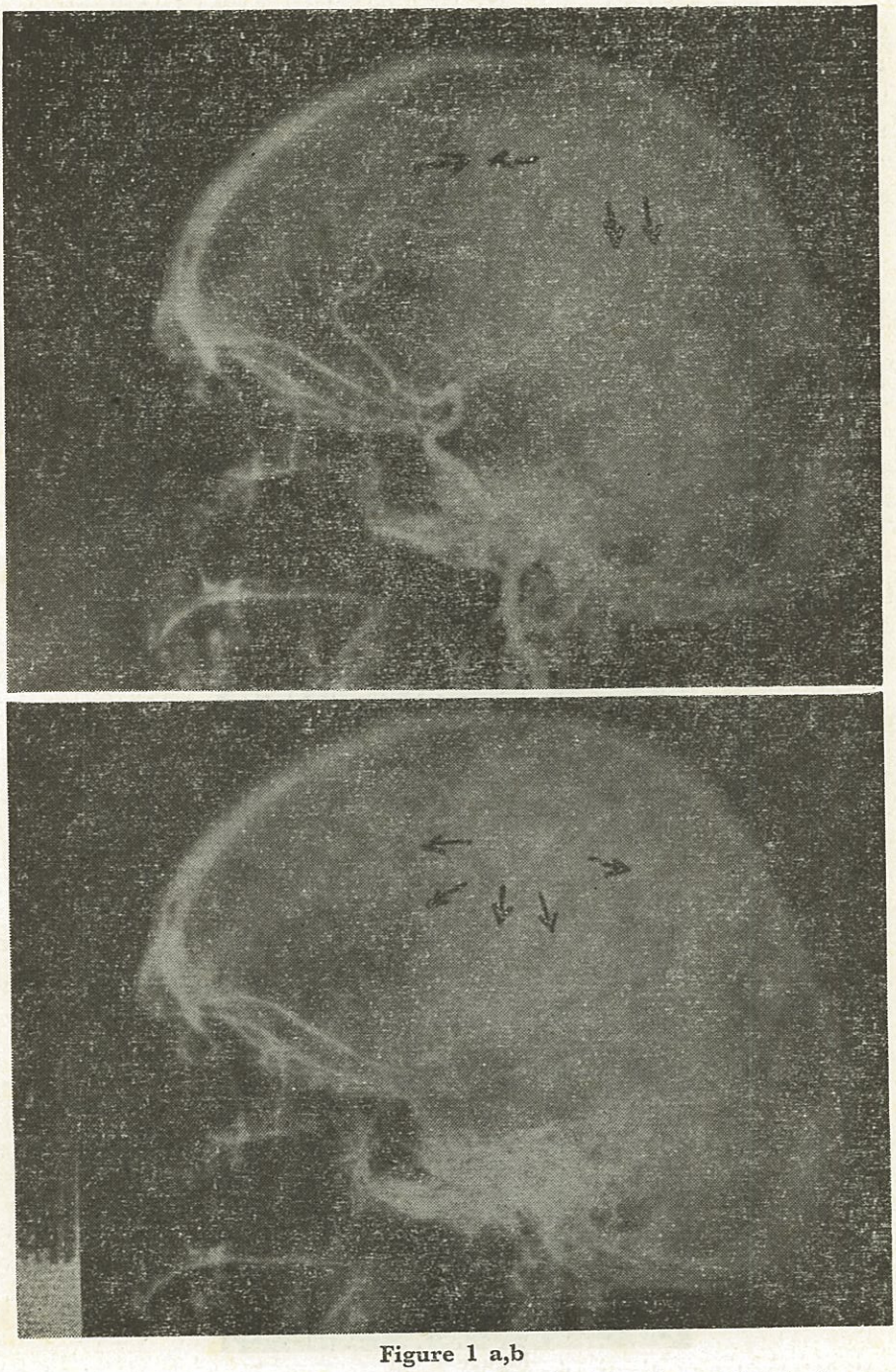

Figure 1 a,b

Fig. 1a and Fig. 1b shows angiography of Case 4. Angiography reveals a single mass effect.

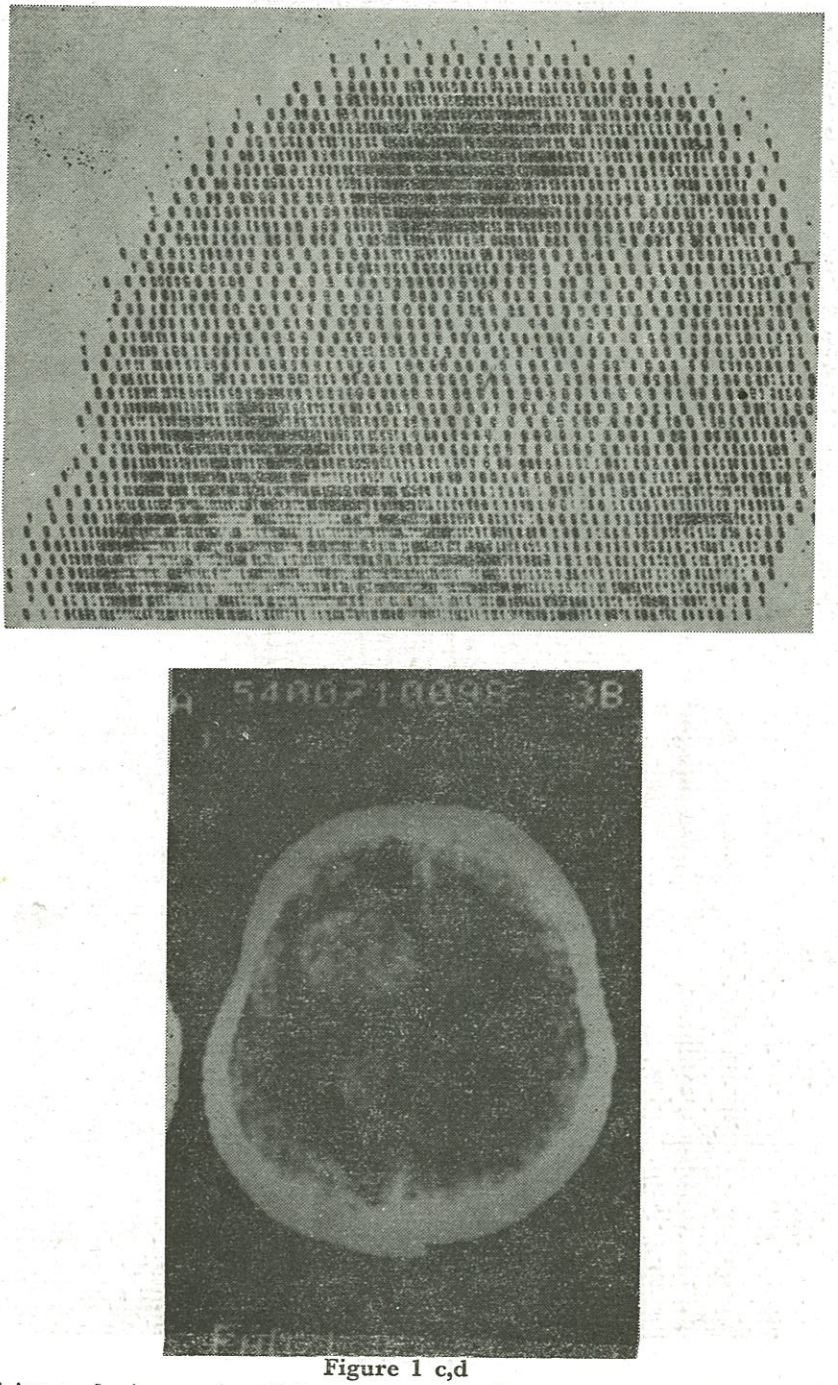

Figure 1 c,d

Radioisotope brain scanning of the same case reveals a huge mass localized in frontoparietal region (Fig. 1c). CT revaled two separate meningiomas (Fig. 1d).

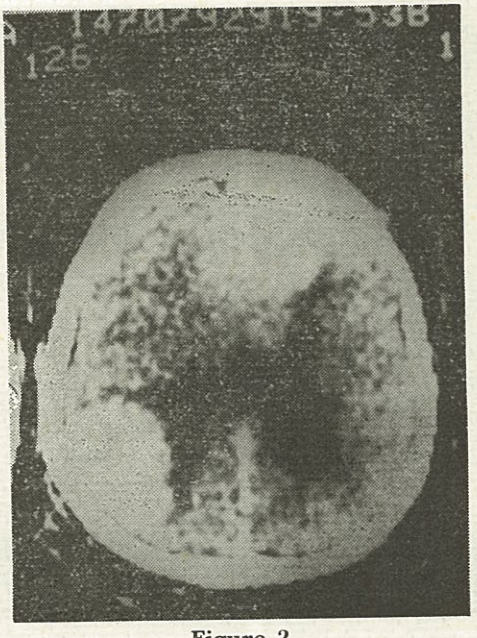

Figure 2

CT of Case 5 shows two separate meningiomas with enhancement.

Case 6: A 51-year-old woman had headache, disorientation and focal motor seizures on the right side. Examination demonstrated papilledema and a mild right hemiparesis. CT revealed multiple small mass lesions in the left hemisphere. A left side craniotomy disclosed 5 nodules under the parietal dura (2x3x2 cm), two separate tumors in the left temporal covexity (5x2x3 cm and 3x3x3 cm), a nodule (6x3x4 cm) under the frontal dura and again two separate nodules in the left parasagittal region.

Case 7: A 26-year-old woman was admitted with right sided focal seizures. Neurological examination disclosed a righ hemiparesis and papilledema. 7 years before the admission a retrobulber meningioma had been removed. An arteriogram of the left common carotid revealed a large mass in the left temporoparietal region. The brain radionuclide scanning demonstrated also only one spot of radioactive uptake in the same region. At surgery two separate masses (6x6x6 cm and 3x2x1.5 cm) were found 5 cm. apart from each other. Histologically the larger tumor was meningocytic meningioma and the smaller was fibroblastic meningioma (Figure 3a, b. c, d).

All of the patients are still alive and show no stigmata of von Recklinghausen's disease.

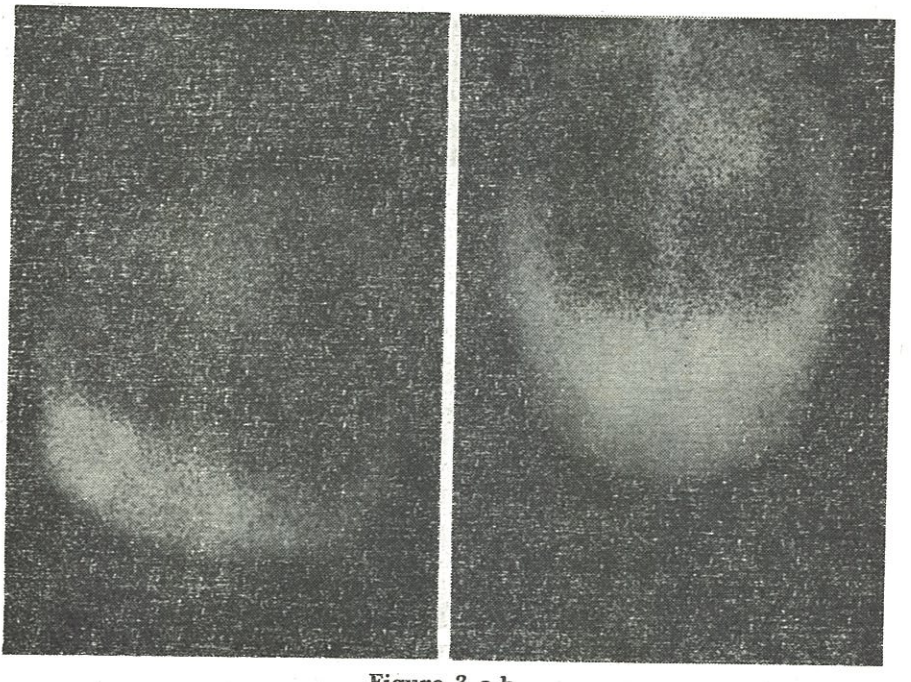

Figure 3 a,b

Radioisotope brain scanning of case 7. Left side (Fig. 3a) and anteroposterior (Fig. 3b) view shows only one area of accumulation.

Discussion

Meningiomas, known as benign tumors, comprise 13.4-19 % of all brain tumors. Cushing and Eisenhart applied the term "Multiple Meningioma" to a condition in which a patient has more than one meningioma. Meningiomas and meningiomatosis associated with von Recklinghausen's neurofibromatosis are not included in this definition.[1, 2, 6, 7] Reports on multiple meningiomas are rare.[1, 2, 9, 10] The first report on this subject was by Amfimow and Blumenau in 1889.[11] In the literature not only intracranial meningiomas but also others that were in various neuroaxial locations have been reported.[2, 6, 12] There are also cases in which meningiomas were found with other intracranial tumors.[2, 6] Multiple meningiomas have been reported as 1.3-5.9 % of all intracranial meningiomas.[2, 7, 8, 12] The seven cases that we present here constitute 1.95 % of our meningioma cases which had surgical intervention during the same period. Inclination to unilateral localization which is reported as an interesting feature of multiple meningiomas in the literature is also one of the characteristics of our cases, except one (Case 5).[6]

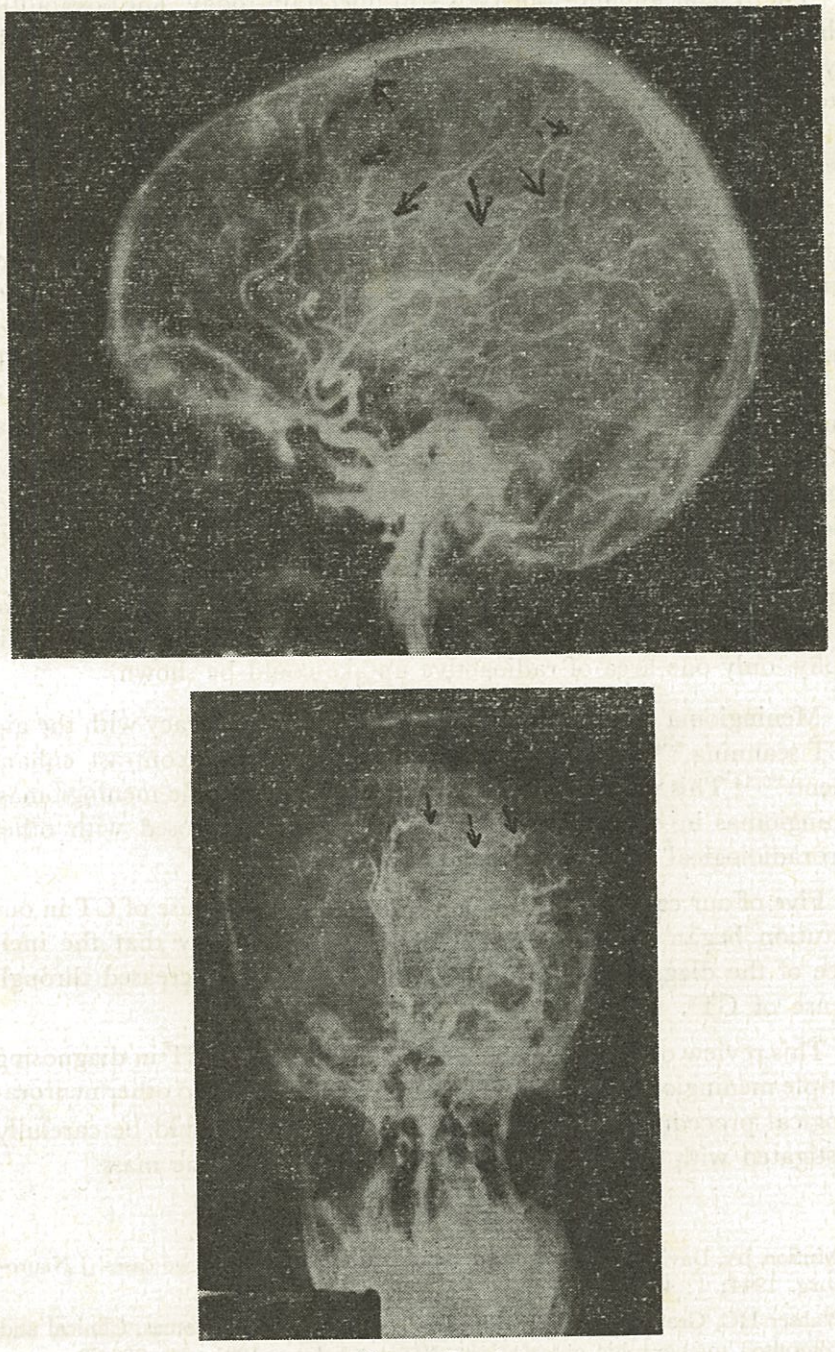

Figure 3 c,d
Left carotid angiography verifies a parasagital meningioma (Fig. 3c and Fig. 3d). Two separate masses could not be distinguished.

The resaon for multiplicity is still uncertain today. The possibilities include multicentric foci, spreading along the cerebrospinal fluid pathways and venous transmission.[6, 8] Another possibility may be hereditary factors. According to this thesis, a disorder of the formation in mesodermal germ layers would be the factor in multiple meningioma pathogenesis.[6, 8]

In recent years, with the increasing use of CT scanning in neurosurgery, important steps have been taken in the diagnosis of multiple meningiomas. Although the value of cerebral angiography cannot be denied, the accuracy of meningioma diagnosis for even single nodullary meningiomas is 83 %.[3, 14] The accuracy rate in cases with more than one nodule is quite low. As a matter of fact in our case 4, carotid angiography demonstrated only a single mass in the left parietal region (Figure 1a and Figure 1b), and two separate masses were visualized with CT scanning (Figure 1d). Also in case 7, a single nodule in the left temporoparietal region is demonstrated with left carotid angiography, but two nodules were excised during the surgical intervention. The possibility of correct diagnosis of meningiomas is only 31 % with the aid of radioisotop brain scintigraphy.[3] In the four cases (1,2,4,7) in wich we used brain scintigraphy, only one area of radioactive uptake could be shown.

Meningioma cases are diagnosed with 84.5 % accuracy with the aid of CT scanning.[3, 4] This percentile reaches 96.3 % with contrast enhancement.[3-5, 14] This point is especially important in multiple meningiomas. Meningiomas in our cases which could not be diagnosed with other neuroradiological methods were visualized by CT.

Five of our cases (72 %), were diagnosed after the use of CT in our institution began in 1976. This also supports the view that the incidence of the diagnosis of multiple meningiomas has increased through the use of CT[2].

This review of our cases has shown that the use of CT in diagnosing multiple meningiomas is much more effective compared to other neuroradiological procedures. Therefore meningioma cases should be carefully investigated with CT for the evidence of more than one mass.

REFERENCES

1. Mufson JA, Davidoff LM. Multiple meningiomas. Report of two cases. J Neurosurg. 1944; 1: 45-7.
2. Nahser HC, Grote W, Löhr E, Gerhard L. Multiple meningiomas. Clinical and computed tomographic observations. Neuroradiology. 1981; 21: 259-63.
3. New PFJ, Aranow S, Hesselink J. Evaluation of computed tomography in the diagnosis of intracranial neoplasms. Radiology. 1980; 136: 665-75.

4. Pullicino P, Kendall B, Jakubowski J. Difficulties in the diagnosis of intracranial meningiomas by computed tomography. J Neurol Neurosurg Psychiatry. 1980; 43: 1022-9.
5. Vassilouthis J, Ambrose J. Computed tomography scanning appearences of intracranial meningiomas. J Neurosurg. 1979; 50: 320-7.
6. Waga S, Matsuda M, Shintani A, Honda H, Matsushima M. Multiple meningiomas occupying separate neuroaxial compartments. J Neurosurg. 1970; 33: 216-20.
7. Cushing H, Eisenhardt L. Meningiomas. Their classification, regional behavior, life history and surgical results. Springfield III: Charles C Thomas. 1938; 45-59.
8. Levin P, Sidney WG, Leonard M, Kirschenbaum AH, Hollin S. Multiple intracranial meningiomas. Surg Gynecol Obstet. 1964; 119: 1085-90.
9. Kendall P, Pullicino P. Comparison of consistency of meningiomas and CT appearances. Neuroradiology. 1979; 18: 173-6.
10. Vestergaard E. Multiple intracranial meningiomas. Acta Psychiatr Neurol Kbh. 1944; 19: 389.
11. Amfimow J, Blumenau L. Ein Fall multipler Geschwülste in der Schaedelhöhle. Neurol Zentrbl. 1889; 8: 585.
12. Zervas NT, Koller B, Berry G. Multiple meningiomas. Report of four cases. J Neurosurg. 1972; 37: 348-55.
13. Horrax G. Meningiomas of the brain. Arch Neurol Psychiatry. 1939; 41: 140-57.
14. Sauer J, Piebach O, Otto H. Comparative studies of cerebral scintigraphy, angiography and encephalography for diagnosis of meningiomas. Neuroradiology. 1971; 2: 102-6.

Hacettepe Medical Journal
Volume 17 / No. 2 / April 1984 / pp. 76 – 80

Hydatid Disease of the Thyroid in Childhood

Mehmet Ali Altın, M.D.* / Akgün Hiçsönmez, M.D.**
Nebil Büyükpamukçu, M.D.**

Summary

The localisation of hydatid cyst in the thyroid gland is rare and even rarer in childhood. In the literature, only 155 adult cases are reported, and not more than 10 cases in childhood. 4 out of our 77 thyroid patients requiring surgical treatment are diagnosed to have hydatid cysts.

The most accurate method for determining the nature of the thyroid nodule is by ultrasonography. We believe this is the way to obtain a definite diagnosis for this disease preoperatively.

Key Words: Hydatid cyst, Thyroid gland.

Introduction

Hydatid cyst disease is seen all over the world but it is in countries of the Mediterranean and South America that this entity is most often diagnosed. In a review of the literature the organ selection of hydatid cyst in descending order of preference is found to be the liver, lungs, abdomen, spleen, cranium, bone, muscle and thyroid gland.

Hydatid cyst is rarely seen in thyroid tissue. Among the 77 thyroid patients operated on between 1970-1982 in Hacettepe University Pediatric Surgery Department, 4 were found to have hydatid cysts peroperatively. Childhood hydatid disease of the thyroid is discussed and compared with the literature.

Clinical Data

Case 1: A girl 8 years old was admitted to the hospital because of a cervical mass that had existed for a long time and had recently begun to enlarge.

* Instructor, Department of Pediatric Surgery, Hacettepe University Medical School Ankara, Turkey.
** Professor, Department of Pediatric Surgery, Hacettepe University Medical School.

Physical examination showed a mobile mass 5X5 cm. in the right cervical region. The other systems were normal.

In laboratory examination, T_3 and T_4 tests were normal; there was a hypoactive nodule in the right lobe of thyroid scintigraphically.

The patient was explored with a preoperative diagnosis of noduler goitre. The mass was found to be cystic. Hydatid cyst was diagnosed and an operation of excision and capitonage was performed, without any per or postoperative complication.

Case 2: A boy 6 years old was admitted because of a left cervical mass.

In physical examination, there was a mobile mass 3X4 cm. in the left thyroid region.

T_3 and T_4 were normal; there was a hypoactive nodule in the left lobe of thyroid gland scintigraphically.

The patient was operated on because of his noduler goitre. There was a cystic mass in the left lobe of thyroid. "Spring water" was aspirated and hydatid cyst was diagnosed during surgery. Without any per or postoperative complication, excision and capitonage of the hydatid cyst was performed.

Case 3: A girl 11 years old was admitted to the hospital for a mass in her cervical region that had existed for 7 months and had recently begun to enlarge.

There was a mobile mass 5X6 cm. in the left thyroid region.

T_3-T_4 were normal; there was a hypoactive nodule in the left lobe of the thyroid scintigraphically.

When operated on, the patient was found to have a hydatid cyst in the left lobe of the thyroid. Excision of the cyst was performed without any complication.

Case 4: A girl 9 years old was admitted with a complaint of a mass in her cervical region existing for 4 months.

There was a mobile mass 3X4 cm. in size between the two lobes of the thyroid.

T_3-T_4 were found to be normal. The area between the two lobes of the thyroid gland was hypoactive scintigraphically.

The patient was operated with a clinical diagnosis of nodular goitre, a hydatid cyst was found, and total excision without any complication was performed.

TABLE I

ANALYSIS OF CLINICAL AND LABORATORY FINDINGS

Case	Symptom	Sign	Preop Dx.	Thyroid Scan	Postop. Dx
1	Cervical mass	3x4 cm. right lobe	Noduler goitre	Hypoactive nodule	Hydatid cyst
2	Cervical mass	3x4 cm left lobe	Noduler goitre	Hypoactive nodule	Hydatid cyst
3	Cervical mass	5x6 cm. left lobe	Noduler goitre	Hypoactive nodule	Hydatid cyst
4	Cervical mass	3x4 cm. isthmus	Noduler goitre	Hypoactive nodule	Hydatid cyst

Discussion

The thyroid gland is a rare localisation for hydatid disease in children. In review of the literature it is noticed that the disease was first reported in 1704 by Liteaud and soon after this there came Oser's and Descerac's 12, Shalkeas' and Sechas' 12, von Eiselberg's 21 cases in series.[1] The total number of cysts of the thyroid gland reported does not exceed 155, most of which are adults in South American countries.[2]

The first case of hydatid cyst in childhood was reported by Gattiin 1913.[3] There are not more than 10 cases reported in the literature of hydatid disease localised in thyroid in children.

Nacif and Perinetti reported a rate of 0.38 % for a hydatid cyst to be located in the thyroid gland.[4] In our series this rate is 3.4 % of thyroid operations performed at our center. This high rate is most probably due to our country being an endemic area for this disease.

Enlargement of the thyroid gland in childhood has a spectrum of 1-6%[5] in regions of endemic goitre, this number increases.[6] Hydatid disease in the thyroid is very rare. We can explain the etiology of implantation of hydatic cysts in thyroid tissue by the life cycle of Echinococcus Granulosus. This parasite can settle in the thyroid gland passing the liver and lungs. The blood flow rate in thyroid tissue is high, 6 ml/gr of thyroid tissue per minute. This amount is 50 times the flow rate of other parts of the human body.[7] But it is hard to correlate this high amount of blood flow with such a small number of incidence. This could be explained by lodging of the parasite in the liver and the lungs.

When the clinical data is overviewed, the common finding is a solitary cervical mass in the thyroid gland.

Hydatid cysts localised in the thyroid are reported by Meilleen and coll in 5 out of 607 cases with isolated thyroidal nodules, Soustelle and coll. in 11 out of 275, Cousales and coll. in 4 out of 211.[8,9] The chronic cervical mass palpated as a solitary isolated thyroidal nodule must be kept in mind as being a possible hydatid cyst in differential diagnosis.

In hydatid cysts of the thyroid gland, both the physical and laboratory findings must be evaluated together.[10,11] Thyroid scan does not differentiate whether the lesion is cystic or solid; there is no case diagnosed by thyroid scanning in the literature.[12,13,14] The T_3-T_4 values are normal in our cases, in correlation with the literature.

The best method for determining the nature of the isolated solitary nodules of the thyroid gland is ultrasonography.[15,16] It can certainly differentiate whether the lesion is cystic or solid. Some authors tried aspiration of the nodule but this carries the risk of contamination.

Our patients were all diagnosed preoperatively, congruent to the literature.[17] The treatment of choice for our patients was excision of the cyst. Marsupialisation is of no value in hydatid cystic disease of the thyroid gland.[18,19] No recurrences were seen in our series or in the literature.

REFERENCES

1. Skaleas GD et Sechas MN. Echinococosis of the Thyroid gland. JAMA. 1967; 200: 178-9.
2. Timlioğlu B, Acar İ, Kayabalı İ. Kystes hydatiques de la tyroide. AÜ Tıp Fakültesi Mec. 1979; 32: 519-22.
3. Vironque C Gausert J. Le Kyste hydatique du corps thyroide de I'enfant. Ann Chir Infant. 1968; 9: 51-3.
4. Nacif J, Perinetti H. Hidatiaosis tiroides. Rev Med Valparaisc. 1969; 22: 28-30.
5. Reiter EO. Childhood thyromegaly. Recent developments. J Pediatr. 1981; 99: 507-8.
6. Koloğlu, S, ve Koloğlu B. Türkiye'de endemik guatre. A Ü Tıp Fak Mec. 1966; 19: 319-21.
7. Davis-Christopher. Textbook of Surgery. Thyroid diseases. 1980; 2: 174-5.
8. Gonzalez Gonzalez M, Martinez Diez M, Juste SM. Kystes Hydatiques de la thyroid. Lyon Chir 1982; 78: 196-7.
9. Granado A, Granado MA, Fraga J. Hydatidose primitive de la thyroide. Lyon Chir. 1982; 78: 193-6.
10. Julien JP, Legond G. et Lapilled. Kyste hydatique de la thyroide une observatione. Nouv Presse Med. 1979; 8: 1667-9.
11. Kocaoğlu H. Kyste hydatique du corps thyroide. J Chir. 1961; 81: 383-6.
12. Prakash A, et Chandra T. A case of hydatid cyst of thyroid. 1965; 52: 235-7.
13. Lepille D. A propos d'un cas de kyste hydatique de la glande thyroide. Thise de Méedecine, 1978 Rouen juin.

14. Grosbeck HP. Evalution of routine Scintiscanning of nontoxic Thyroid nodules, Cancer. 1959; 12: 1-3.

15. Walfish PG. Hazani E, Harry TG. A prospective study of combined ultrasonography and needle aspiration biopsy in the assessement of the hypofunctioning thyroid nodule. Surgery. 1977; 82: 474-6.

16. Caroli J, Dannet P, Demenlenare L. Kyste hydatique e Double Localisation pancreatique et Thyroide. Difficulte's Diaqnostixnes Med Chir Dig. 1977; 6: 555-7.

17. Yaıcı M, Hammoudi F, Hartan M. Echotomotoqraphie et hydatitoze Abdominale XXI congres int I'hydatidolaqie, 1981; 5: Alger.

18. De Montis G, Ricud D, Rossier A. Kyste hydatique de la thyroide chez I'enfant Arch Fr Pédiatr. 1972; 29: 900-2.

19. De Montis G, Cervetti F, Dicaud D. Le Tanvinh, Rossier A. Kyste hydatique de la thyroide. Revue de la littérature a proposd'un cas. Sem Hop. 1973; 49: 901-3.

Hacettepe Medical Journal
Volume 17 / No. 2 / April 1984 / pp. 81 – 86

Segmental Sclerosing Cholangitis

Atilla Engin, M.D., Ph.D.* / Yılmaz Sanaç, M.D.**

Summary

This is a case report of a 26-year old female who presented with acute abdominal pain and jaundice. Operative cholangiogram demonstrated an obliterated segment involving about 1.5 cm of the proximal common hepatic bile duct during the surgical intervention. Pathophysiology, clinical manifestations and an appropriate treatment of this rare condition were discussed.

Key Words: Sclerosing cholangitis.

Introduction

Chronic fibroinflammatory stenosis of the hepatic duct junction is an unusual variety of segmental sclerosing cholangitis.[1,2] It has been emphasized that the preoperative diagnosis of this condition is practically impossible because the symptoms resemble obstructive jaundice or recurrent cholangitis. After the demonstration of a narrow segment by the intraoperative cholangiography under high pressure,[2] the following criteria have been proposed as a prerequisite for diagnosis.[10]

1- Absence of biliary stones,

2- No prior biliary tract surgery.

3- Absence of biliary tract malignancy as determined by a reasonably long follow-up,

4- No evidence of primary biliary cirrhosis as determined by liver biopsy,

5- Absence of associated systemic granulomatous disease.

* Associate Professor in the Department of General Surgery, Faculty of Medicine, Gazi University Ankara, Turkey.

** Professor in the Department of General Surgery, Faculty of Medicine, Hacettepe University, Ankara, Turkey.

This case report demonstrates the complete surgical and roentgenologic properties of segmental sclerosing cholangitis.

Case Report

GK, a 26-year old woman, was admitted to the Department of Surgery of Hacettepe University Hospital on 16 April 1974, with a 15-day history of jaundice and right upper quadrant abdominal pain. She had noticed the presence of dark urine and light stools. There was no past history pertinent to biliary tract or gastrointestinal disease. Abdominal examination revealed mild tenderness without rigidity in the right upper quadrant. The liver was palpable 3 cm below the right costal margin with a sharp nontender edge. Her total bilirubin level was 17.5 mg. percent with a 14.5 mg percent direct component. The tentative diagnosis was obstructive jaundice secondary to choledocholithiasis.

On April 16 th, the patient underwent emergency abdominal exploration. Exploratory laparotomy revealed an obliterated segment involving about 1.5 cm of the proximal common hepatic bile duct. The smallest Bakes dilator could barely be passed into the right and left hepatic ducts because of extreme stenosis. There was no evidence of calculi in the extrahepatic biliary system. A cholecystectomy was performed and a small T-tube was inserted into the opened common bile duct. The proximal limb of the tube was succesfully placed into the stenotic segment. Operative cholangiogram showed an abnormal dilatation of the biliary system above the obliterated common hepatic duct (Figure 1 A and B). E. coli was isolated from bile and she received large doses of ampicillin and chloramphenicol.

The patient had an uneventful postoperative period and serum bilirubin and alkaline phosphatase returned to normal levels within 34 days. The liver biopsy taken during surgery revealed cholangitis. The patient was discharged on prednisone 10 mg daily.[10] She did well for the next five months during which time she was entirely asymptomatic and the T-tube was left in place.

On 24 October 1974, she was readmitted to the Hacettepe Hospitals with a one week history of right upper quadrant pain and jaundice. The liver function tests showed serum bilirubin of 4.5 mg per cent and alkaline phosphatase of 21.7 K. A. u. T-tube cholangiogram revealed some narrowing of the common hepatic and left hepatic ducts (Figure 2). Pyocyaneus was isolated in the bile culture and she was treated with large doses of gentamycin and penicillin. With the continued lack of improvement in her condition (Figure 3), a cholangiojejunostomy was performed at a point where, the right hepatic duct appeared normal in the interlobar

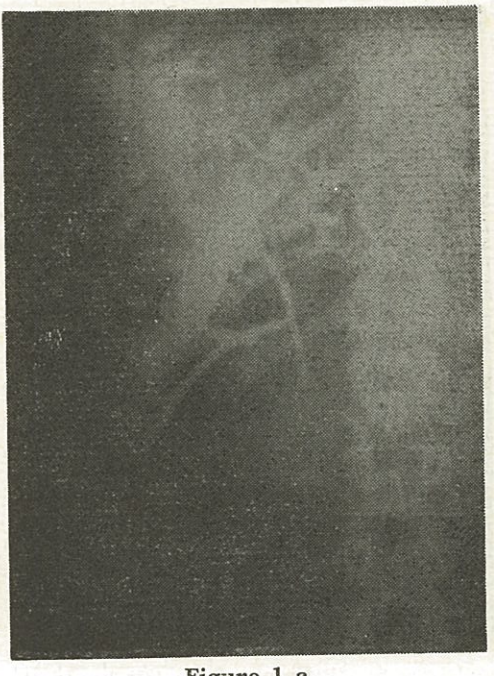

Figure 1 a

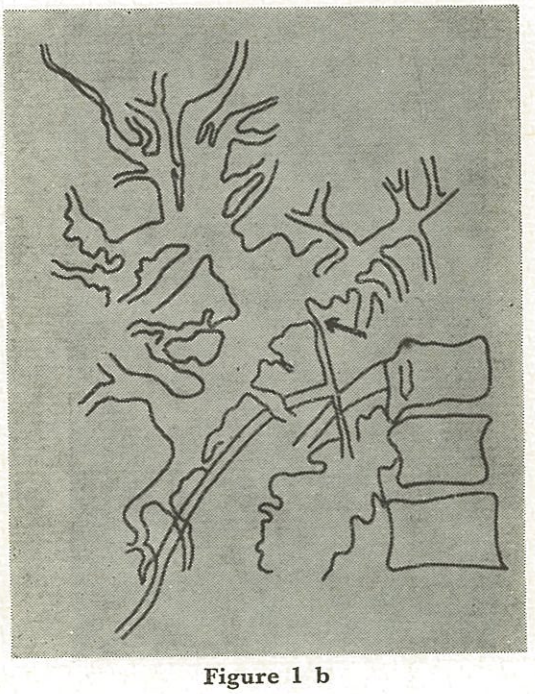

Figure 1 b

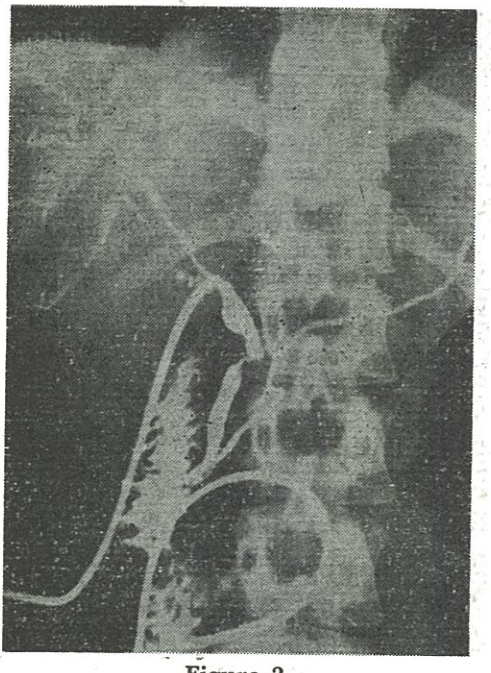

Figure 2

Figure 3

region and a biopsy was taken from the most thickened area of the proximal common hepatic duct wall. The pathological evamination revealed severe chronic fibrosis without any evidence of malignancy, with a cholangiolytic hepatitis in the liver biopsy. The patient was discharged on January 15, 1975. She continued to do well for the next five months. She was again readmitted to the surgical service with an incomplete obstruction of the cholangiojejunostomy anastomosis. At operation, the stoma was dilated gradually by Bakes dilators. Operative cholangiogram showed an abnormal dilatation of the intrahepatic biliary system with the exception of the left hepatic duct. The liver biopsy on this occasion showed histologic changes consistent with obstructive cholangitis.

She developed cardiopulmonary failure in the immediate postoperative period. She gradually became more icteric, showed evidence of additional liver failure and died.

Discussion

The cause of sclerosing cholangitis remains obscure. Although a genetic factor may be operative,[1] congenital biliary stenosis seems unlikely due to onset in the third decade of life. The symptoms of segmental sclerosing cholangitis are indistinguishable from the obstructive biliary tract disease. Our patient presented a picture of obstructive jaundice showing elevated bilirubin and alkaline phosphatase without marked elevation of enzymes. Recognition of this condition is almost impossible unless an operative cholangiography is done under high pressure.[2] This radiologic picture was quite distinctive in our case. Thorpe et al. have emphasized that there are short focal strictures with proximal areas of slight dilatation in the biliary tract in sclerosing cholangitis.[3] However a similar appearance of the intrahepatic biliary tree with a normal extrahepatic biliary system may be observed in ulcerative colitis, postnecrotic hepatic cirrhosis and pericholangitis.[4]

Marked dilatation is rare in diffuse sclerosing cholangitis due to the surrounding fibrosis, but most frequently occurs proximal to a malignant stricture of the bile ducts.[5] The clinical picture of the slow-growing scirrhous carcinomas of the biliary system is also similar to that produced by segmental sclerosing cholangitis; even at surgery, the diagnosis may be missed because the site of involvement is inaccessible as in our patient.[6,7] The definite diagnosis in our case was made by careful documentation of the lesion by operative cholangiography and pathological examination of the liver and the stenotic segment of the hepatic duct junction. Surgical exploration is essential for the diagnosis and treat-

will be dead on arrival at the hospital[2] and 34 to 57 per cent of the patients who reach the hospital alive and are surgically treated will subsequently die.[2-8] Penetrating and blunt abdominal trauma can be responsible for these serious injuries. We recently dealt with a case which can be regarded as an obstetrical complication. Since we have not encountered such an interesting obstetrical complication in the literature, we wish to report this case.

Case Report

A twenty-two year old female entered the emergency room on April 10, 1983 in the middle of the night, complaining of generalized weakness, dizziness, nausea and vomiting. Since she had a cloudy consciousness, information was given by her husband about her recent history. He stated that she had delivered a term infant normally and spontaneously at the Manisa Maternity Hospital approximately 10 hours before the admission and had not had excessive postpartum vaginal bleeding. Two hours after the delivery she had begun to feel ill, anxious, faint and pale. Primary care including 1000 cc of dextran solution had been given at the Manisa Maternity Hospital because of her reduced and clouded consciousness and decreased systolic blood pressure. However, she had not improved and was sent to the Aegean University Medical Faculty Hospital for further investigation and treatment.

On arrival at the obstetrics and gynecology clinic her systolic blood pressure was 50 mm Hg, and pulse was filiform. Her axillar temperature and respiration rate were 36 °C and 48 per minute respectively. She looked ill and pale, and her skin was covered with cold sweat. Her extremities were cold and pale. Breathing sounds were equal bilaterally but tachypneic. Abdominal examination revealed that the fundus of the uterus was two centimeters below the umblicus and contracted. On the right side and behind the uterus there was a hard mass which extended to the right upper quadrant of the abdomen. On admission hematocrit was 20 per cent. Large caliber intravenous cannulas were immediately placed bilaterally to the upper extremities and Ringer's lactate solutions were administered. At the same time blood was sent for type and cross match. The uterine cavity was investigated manually to rule-out uterine rupture and found to be intact. After surgical consultation we decided to perform exploratory laparotomy. She was given 4 units of compatible whole blood before the operation. At surgery she was found to have an extensive retroperitoneal hematoma especially at the right side of the columna vertebralis; the hematoma extended posteriorly from the pelvis up to the level of the costal margin. There was no pulse

in it. Uterus and adnexial region were observed to be normal for the the postpartum period. The posterior parietal peritoneum was dissected and massive retroperitoneal hematoma was evacuated, and a complete rupture at the vena cava inferior was observed below the renal vein. Just as we had placed vascular clamps at the proximal and distal ends of the ruptured vein, cardiac arrest developed. Before and during the operation a total of 7 units of compatible whole blood was transfused to the patient. Exploration of the entire abdomen revealed no vascular-or nonvascular-associated injuries.

Discussion

Prior to 1965, there were very few reports of successful management of major abdominal vascular injuries. Since then, more of these patients are being salvaged compared to the past, presumably because of early recognition of their vascular injury with more effective resuscitation and vascular control.

A proper patient management program may be instituted if the diagnosis of major abdominal vascular injury is considered. But it is probably inevitable that, in our case, in some instances the diagnosis of major vascular injury will be made only during operation. This was to the patient's disadvantage. One of the other disadvantages was the presence of hemorrhagic shock on admission. As previously reported, those arriving in the emergency room not in shock had, in general, a good prognosis whereas patients arriving in hemorrhagic shock had an exceedingly high mortality rate.[9-11] Another disadvantage of our case was that she was referred to the emergency center ten-and-a-half hours after the injury, probably because of the difficulty to consider the occurrance of such a major vascular injury at delivery. As a result, on admission to the emergency center she was in shock. We know that, as previously reported, the survival of these patients also depends on the early recognition of their vascular injury, followed promptly by a logical and well organized plan for management.[10, 11]

Injury was at the infrarenal region of the vena cava inferior: this was to her advantage, as we know that supra renal region is the more difficult to manage portion of the vena cava inferior.[9-11] Another advantage of our case was the absence of associated injuries. We know that additional factors adversely influencing survival include increasing numbers of associated injuries. This of course not only increases the probability of postoperative complications, but adds significantly to the overall blood loss.[11]

An interesting point of our case was that this injury occurred at delivery probably as a result of excessively and wrongly performed Kristeller maneuver by the midwife, as there was no vascular abnormality seen upon surgery. Because the perivascular connective tissues and intact abdominal wall potentially were able to provide a significant tamponade effect, she stayed alive after the injury up to the operation. This tamponade effect was suddenly lost when anesthesia or laporatomy was begun, and ischemic cardiac arrest occurred.

The present study reviews the factors that appear critical to patient survival. Hopefully results in the future will be better than we have been able to report at this time.

REFERENCES

1. Cheek RC, Pope JC,Smith HF,et al. Diagnosis and management of major vascular injuries: A review of 200 operative cases. Am Surg. 1975; 41: 755-60.
2. Ochsner JL, Crawford ES, DeBakey ME. Injuries of the vena cava caused by external trauma. Surgery. 1961; 49: 397-405.
3. Duke JH Jr, Jones RC, Shires GT. Management of injuries to the inferior vena cava. Am J Surg. 1965; 110: 759-63.
4. Quast DC, Shirkey AL, Fitzgerald JB, Beall AC Jr, DeBakey ME. Surgical correction of injuries of the vena cava: an analysis of sixty-one cases. J Trauma. 1965; 5: 1-10.
5. Weichert RF III, Hewitt RL. Injuries to the inferior vena cava: report of 35 cases. J Trauma. 1970; 10: 649-57.
6. Bricker DL, Morton JR, Okies JE, Beall AC Jr. Surgical management of injuries to the vena cava: Changing patterns of injury and new techniques of repair. J Trauma 1971; 11: 725-35.
7. Burns GR, Sherman RT. Trauma of the abdominal aorta and inferior vena cava: Am Surg. 1972; 38: 303-6.
8. Allen RE, Blaisdell FW. Injuries to the inferior vena cava. Surg Clin North Am. 1972; 52: 699-710.
9. Turpin I, State D, Schwartz A. Injuries to the inferior vena cava and their management. Am J Surg. 1977; 134: 25-32.
10. Graham JM, Mattox KL, Beall AC Jr, DeBakey ME. Traumatic injuries of the inferior vena cava. Arch Surg. 1978; 113: 413-9.
11. Halpern NB, Aldrete JS. Factors influencing mortality and morbidity from injuries to the abdominal aorta and inferior vena cava. Am J Surg. 1979; 137: 384-8.

Hacettepe Medical Journal
Volume 17 / No. 2 / April 1984 / pp. 91 – 96

Werner's Syndrome

A Case Report

Fikret Kölemen, M.D.* / Nazif Kürkçüoğlu, M.D. / Sevinç Akkaya, M.D.*** / Tülin Akan, M.D.***

Summary

A case of Werner's syndrome is presented and the pertinent literature is reviewed.

Key Words: Werner's syndrome, cataract, malignancy.

Introduction

Werner's syndrome is a rare disorder which is transmitted as an autosomal recessive trait. The number of cases of Werner's syndrome reported to date approaches 200.[1] Parental consanguinity and occurrence of this condition in siblings have been reported frequently.[1] The sex distribution is equal and cases have been described in all races.[1]

The clinical picture includes short stature, acromicria, premature canities, baldness, hypotrichosis in the axillary and pubic regions, trophic ulcers, scleroderma-like skin changes, bilateral anterior and posterior subcapsular cataracts, hyperkeratosis on bony prominences and soles, hypogonadism, high-pitched voice, beaked-shaped nose, tendency to diabetes mellitus, premature atherosclerosis, myocardial infarction, congestive heart failure, calcification of blood vessels and soft tissues (especially on the Achilles tendon), osteoporosis, osteomyelitis, aged appearance of the face, hyper- and hypopigmentation and a high frequency of neoplasms.[2-5]

Case Report

A 26-year-old man was referred to us for evaluation of ulcers and hyperkeratosis on bony prominences and soles. His medical history disc-

* Associate Professor in Department of Dermatology, Hacettepe University, Faculty of Medicine, Ankara-Turkey.
** Instructor in Department of Dermatology, Hacettepe University Faculty of Medicine.
*** Professor in Department of Dermatology, Hacettepe University Faculty of Medicine.

losed that he had been suffering from these lesions for the last ten years. He had been hospitalized on several occasions and treated under the diagnosis of scleroderma. Three years ago cataract of the left eye was removed.

One sister, 36 years old, was of short stature, and appeared prematurely aged.

On physical examination the patient appeared to be prematurely aged. Blood pressure was 140/130 mm Hg, pulse rate 96 beats/minute. His weight was 42 kg, height 1.65 m. There was poor muscle development of the extremities.

There was pronounced atrophy of the skin of the face, as well as pseudoexophtalmos. The nose was sharp, the lips were thin and tightly stretched. There was polyosis. The subcutaneous tissues and muscles were underdeveloped. Armpit and pubic hairs were sparse. The testes were of prepubertal size. On the dorsal aspect of both feet, the skin was smooth and tightly bound to the underlying structures. There were atrophic ulcers, and hyperkeratosis in the ankle regions. The toenails were dystrophic. The skin temperature of the toes was 35.1°C. Ophtalmological examination disclosed cataract of the right eye (Figures 1, 2, 3).

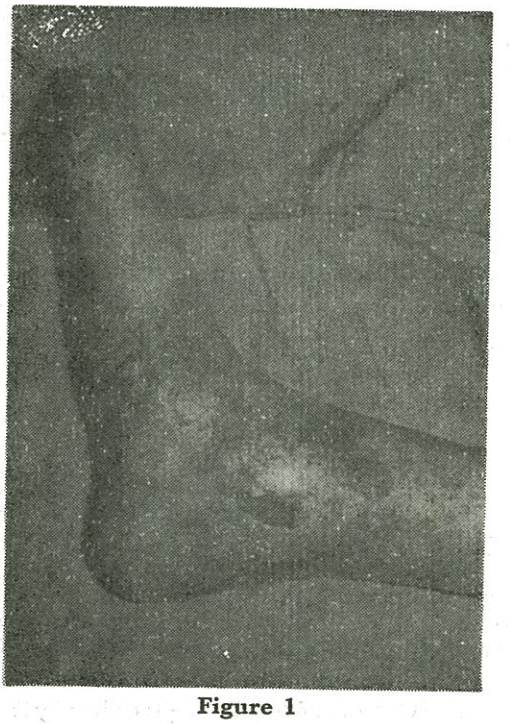

Figure 1

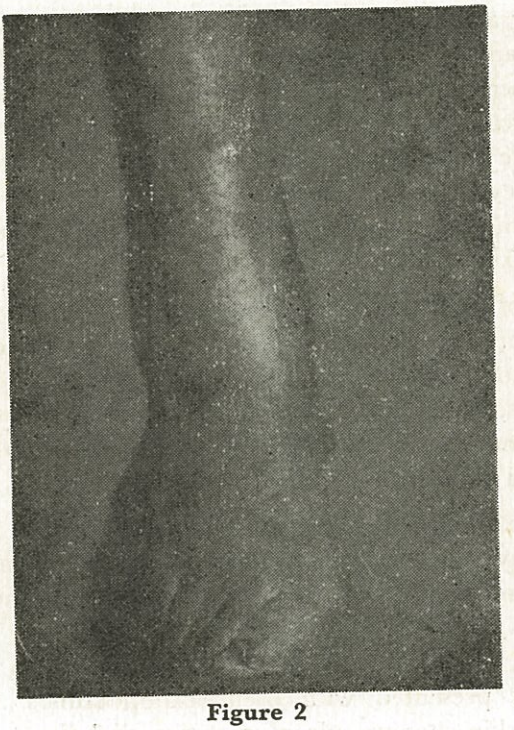

Figure 2

Figure 3

Roentgenographic survey of the bones revealed osteoporosis and neurotrophic changes in the bones of the feet. The maxillary bone scan disclosed increased osteoblastic activity. Chest X-ray showed calcifications. Left ventricular hypertrophy was detected on electrocardiographic examination. The erythrocyte sedimentation rate was 30 mm/hour. The fasting glucose level was 110 mg/dL, the 30-minute glucose level 210 mg/dL, the 60-minute glucose level 256 mg/dL, and the 120-minute glucose level 225 mg/dL.

The results of the following laboratory examinations were all normal or negative: complete blood cell counts, serum electrolyte levels, blood urea nitrogen, total plasma proteins, urinalysis, liver function tests, total serum lipids, cholesterol, uric acid, serologic test for syphilis, intravenous pyelogram, gastrointestinal tract series with barium, scans of liver, spleen, and thyroid, and T_3-T_4 levels.

Histologic examination of the skin biopsy specimen demonstrated epidermal atrophy and lack of rete ridges, increased melanin pigment in the basal layer and sclerosis of the collagen bundles in the dermis.

Discussion

Our patient presented with pseudoexoophtalmos, beaked nose, scleroderma-like skin changes, ulcers, cataract, diabetes mellitus, testicular atrophy, and osteoporosis. On the basis of our clinical and laboratory findings, this case can be diagnosed as Werner's syndrome.

In 1904, Werner described this rare, autosomal recessive connective-tissue disorder.[1] Consanguinity among parents is common and more than one sibling may be affected.

Cessation of physical growth begins between 10 and 18 years of age, resulting in small size and thin limbs. The most consistent features are short stature, acromicria, aged-appearance of the face, high-pitched voice, beaked-shaped nose, diabetes mellitus, premature atherosclerosis, metastatic calcifications, osteoporosis, osteomyelitis, vascular calcifications, gonadal atrophy, premature cavities and baldness.[1-5]

Cutaneous changes are more severe toward the acral points of the face, forearms and hands, and especially the legs and feet. On bony prominences hyperkeratosis and ulcers may develop. The sclerotic skin is restrictive of the motion of joints, and may cause deforming of digits.[1] The nails are remarkable for dystrophic changes.

Other features of Werner's syndrome are posterior cortical and subcapsular cataracts, keratoconjunctivitis, chorioretinitis, blue sclera, proptosis, nystagmus, and retinitis pigmentosa.

In about 10 % of patients with Werner's syndrome, malignant tumors may develop which are chiefly of mesenchymal origin.[6] These tumors include malignant fibroxanthoma, melanoma, mediastinal fibrosarcoma, leiomyosarcoma, spindle cell sarcoma, nerve sheath sarcoma, atypical hemangiolipoma, liposarcoma, osteogenic sarcoma and uterine myosarcoma.[2, 6, 7, 8] Many nonmesenchymal tumors have been reported[1, 2, 7, 8] in Werner's syndrome as well, which are as follows: adenocarcinoma of hepatic duct origin, breast adenocarcinoma, papillary adenocarcinoma of the thyroid gland, hepatoma, basal cell epithelioma, paraganglioma, meningioma, thyroid adenoma, adrenal adenomas, acute myeloid leukemia, papillary cystadenocarcinoma of the ovary, and prostate carcinoma. Many of these tumors are fatal. The average age at death is 47 years. The cause of death is most often cardiac decompensation, a cerebrovascular accident, or a malignancy.[1, 6]

Roentgenography reveals osteoporosis, calcification of soft tissues, osteoarthritis of peripheral joints and flexion or extension deformities of toes and fingers, neurotrophic changes in the bones of the feet, and spondylosis deformans of dorsal and lumbar spine.[1]

Endocrine assays reveal abnormalities in glucose tolerance tests. Hypercholesterolemia, hyperlipemia, and hyperuricemia may also be present.

In Werner's syndrome, DNA repair function is reportedly unimpaired.[9, 10] Cell-mediated immunity seems to be normal.[11] Patients with this syndrome have certain immunologic abnormalities of aging. Cultured fibroblasts have disclosed decreased life spans, and other abnormalities.[12]

Werner's syndrome should be differentiated from scleroderma, ectodermal dysplasia, myotonic dystrophy, lipoatrophic diabetes, Rothmund's syndrome, progeria with nanism, and Turner's syndrome.

Since this condition is hereditary, genetic counseling may be advisable. Treatment of the recurrent ulcers of the feet and legs is difficult. Autografts may have a fair chance of success. Diabetes mellitus can be treated by proper diet and oral antidiabetic agents. Cataract surgery should be undertaken with special caution, for it is often complicated by corneal degeneration, secondary glaucoma, and consequent total loss of vision.[13]

Early recognition of this syndrome may contribute to early diagnosis of the associated malignant tumors which constitute a common cause of death in these patients.

REFERENCES

1. Leider M, Selamonowitz VJ. Werner's syndrome (Progeria of the adult), in Demis DJ, Dobson RL, McGuire J (eds): Clinical Dermatology. Hagerstown, Md, Harper and Row Publishers Inc, vol 1, units 4-30, 1978; 1-5.
2. Björnberg A. Werner's syndrome and malignancy. Acta Derm Venereol. 1976; 56: 149-50.
3. Defresne C, Adam C. Syndrome de Werner. Dermatologica. 1982; 165: 612-4.
4. Degreef H. Werner Syndrome Dermatologica. 1971; 142: 45-9.
5. Fleischmajer R, Nedwich A. Werner's syndrome. Am J Med. 1973; 54: 111-8.
6. Hrabko RP, Milgrom H, Schwartz RA. Werner's syndrome with associated malignant neoplasms. Arch Dermatol. 1982; 118: 106-8.
7. Zalla JA. Werner's syndrome. Cutis. 1980; 25: 275-8.
8. Epstein CJ, Martin GM, Schultz AL. Werner's syndrome: A review of its symptomatology, natural history, pathologic features, genetics and relationship to natural aging process. Medicine. 1966; 45: 177-221.
9. Nakao Y, Kishihara M, Yoshimi H. Werner's syndrome: In vivo and in vitro characteristics as a model of aging. Am J Med. 1978; 65: 919-32.
10. Furukawa F, Taniguchi S. Werner syndrome: Report of a case. Dermatologica. 1979; 74: 175-80.
11. Salamon T, Bogdanovic B, Lazovic-Pepavac O. Werner's syndrome and the cellular immune reactions. Acta Derm Venereol. 1978; 58: 543-4.
12. Norwood TH, Hoehn H, Salk D. Cellular aging in Werner's syndrome: A unique phenotype? J Invest Dermatol. 1979; 73: 92-6.
13. Petrohelos MA. Werner's syndrome: A survey of three cases with a review of the literature. Am J Ophtalmol. 1963; 56: 941-3.

Hacettepe Medical Journal
Volume 17 / No. 2 / April 1984 / pp. 97 – 112

New Developments in Cyclo-Oxygenase Metabolites of Arachidonic Acid*

R. Kazim Türker, M.D.**

Recent studies in the field of arachidonic acid (AA) metabolism has led to the discovery of two new classes of compounds, thromboxanes (TX) and prostacyclin (PGI_2) by the action of Prostaglandin (PG) -synthetase and leukotriens (LTs) by the action of lipooxygenase. The interaction of these metabolites with cardiovascular and immune systems has opened up an exciting area of research which in addition to its basic physiological implications also has a great clinical importance for the treatment and prevention of thromboembolic and immunological disorders. This review will focus on the developments of the biosynthesis of unstable metabolites of AA and their role and functions in cardiovascular system. An attempt will also be made to review, up to date, other endogenously occurring bioactive substances and drugs which largely alter the production and degradation of PGs interacting with different levels of AA metabolism.

The first metabolites of AA discovered almost 24 years ago, were the stable group, PGE_2, $PGF_{2\alpha}$ and others.[1] These PGs have extensively been studied[2, 3-13, 14-26] and it has been established that all these species are formed by the cyclooxygenase pathway of AA metabolism.[27] These stable metabolites arise from unstable intermediates, PGG_2 and PGH_2, the PG-cyclic-endoperoxides.[28] Cyclic-endoperoxides of AA also undergo enzymatic formation to other unstable products, TXA_2 and PGI_2. The balance between these two unstable metabolites of AA is extremely important for the regional vascular homeostasis and any little change in this balance results in some previously unexplained thromboembolic and vascular disorders.[29-31]

* This work was supported by a grant from Turkish Scientific and Technical Research Council (TAG-480).

** Department of Pharmacology, Faculty of Medicine, University of Ankara, Ankara, Turkey.

PGs are not stored; in response to different stimuli (mechanical, chemical, nerve), they enter to the extracellular space upon synthesis which is reflected in elevated levels in plasma and other biological fluids. After cessation of the these stimuli, PG levels rapidly reduce as a result of metabolism in the biological environment.[2, 3-12, 21-24, 32-38] PGs are derived from 20-Carbon polyunsaturated fatty acids, eicosotrienoic, eicosotetraenoic and eicosopentaenoic acids.[31, 39, 40] Eicosotetraenoic acid (arachidonic acid) is the most abundant and usually found in low concentrations a free acid but mainly in bound form to cell membrane phospholipids. This precursor is brought about by a group of enzymes, acylhydrolases, such as phospholipase A_2 and triglyceride lipase.[31, 41, 42] Many stimuli including some hormones, antigen challenge, thrombin and collagen cause the release of PGs by stimulating acylhydrolases which liberates AA in first step from its bound form in cell membrane phospholipids. Among tissue hormones, kinin-peptides and angiotensin-peptides are well known PG-releasers, so far described, which promote PG-synthesis.[5-8, 21, 24, 37, 44] Besides phospholipase A_2, other enzymes can also cause the release of AA from membrane phospholipids. In the ovary the presence of high concentration of cholesterol arachidonate, can cause the liberation of AA by cholesterol esterase stimulated by LH leading an increase of PG-synthesis.[45] Another cascade enzymatic mechanism may be involved in the release of AA from platelet membrane by the stimulation of thrombin. An alternative mechanism is based on the initial stimulation of phospholipase C with subsequent phosphorilation of diglycerides resulting in the formation of phosphatidic acid. Phosphatidic acid is the potent activator of phospholipase A_2 which liberates AA in platelet[46] as well as in kidney and vascular wall.[47]

The conversion of AA into stable and unstable PGs occurs in two steps. In the first step AA is catalysed by cyclooxygenase (PG-synthetase) which is present in all mammalian cells. This results in oxygenation and cyclization of AA, forming the unstable intermediates, the cycloendoperoxides.[48] In the second step the catalyzation occurs by tissue specific enzymes, TXA_2-synthetase in platelets and prostacyclin synthetase in blood vessels.[28-31, 49-53] PG-synthetase has partially been purified in many tissues which converts AA to PGG_2 and PGH_2.[28-30] PGG_2, PGH_2 and PGE_2 are formed variably depending on the tissue, physiological states and pathological conditions. Number of adjacent cells can influence the generation of one of these metabolites. A particular type of cell has been studied indicating that the rate of formation of PGI_2 by the sinusoidal cells of the liver can be influenced by contigous parenchymal cells, hepatocytes, through an effect on cyclic nucleotid levels in the sinusoidal cells.[54]

Glucocorticoids reduce the formation of PGs by inhibiting phospholipase activity.[41, 42] Similar inhibition has been obtained with mepacrine, an antimalaric drug.[28] The antiphospholipase activity of glucocorticoids is highly correlated with their antiinflammatory potency.[42] The inhibitory effects of steroids on phospholipase activity appeared to be the result of changes in protein synthesis since several hours were required after administration of glucocorticoids before the effect was evident.[28]

The discovery of the inhibitors of cyclooxygenase, antiinflammatory drugs, such as aspirin, indomethacin, contributed largely on the development and progress of PG research.[55] These drugs inhibit PG-synthetase and therefore prevent the formation of PG-endoperoxides resulting in decreased generation of the final products, stable and unstable PGs.[56]

The role of unstable PGs (TXA_2, PGI_2) in thromboembolism and prevention of the generation of these metabolites by antiinflammatory drugs have opened a new approach to use these drugs in such clinical disorders. In this context, aspirin-like drugs are largely investigated for the prevention and treatment of thromboembolic vascular diseases.[57-62] A major objection to this therapeutic approach is the prevention of endoperoxides which are the precursor of TXA_2, a potent aggregating agent, as well as PGI_2, a potent antiaggregating PG. However, clinical use of aspirin gave a lot of improvement in the prevention of vascular thrombosis. This point is further elucidated by large experimental studies. It has been shown that production of PGI_2 in the vascular wall is less affected by aspirin-like drugs than that of the platelet to form TXA_2.[62] Very low doses of aspirin are used to inhibit TXA_2 formation by platelets in order to prevent thrombosis in patients at risk. The selective inhibitory effect of aspirin-like drugs on platelet cyclooxygenase is due to irreversible acetylation by aspirin of the enzyme for life of the platelet.[60, 62, 63] In contrast, the vascular wall continuously generates cyclooxygenase probably due to the high and rapid synthesis of new protein.[62] The results of extensive clinical studies indicate that the dose of aspirin is about 200 mg every third day is sufficient to suppress platelet formation of TXA_2 by more than 90 %. The higher doses of aspirin, however, can inhibit cyclooxygenase in both platelet and vascular wall and therefore should be considered non-beneficial for the prevention of vascular thrombosis.

For the prevention and treatment of vascular thrombosis there are a few exciting approaches which will largely be discussed later. However, another approach has been made for the prevention of vascular thrombosis. It is possible to alter AA metabolism using other polyunsaturated fatty acids as precursor. In a series of recent studies it has been suggested

that it might be possible to modify the development of vascular diseases through diet.[53, 59] An important difference between Greenland Eskimos and Danes has been observed in the incidence of atherosclerosis and myocardial infarction. Eskimos have an extremely low incidence in thromboembolic diseases when compared with Danes. The clinical studies clearly indicate that the principal polyunsaturated fatty acid in the lipid fraction of Eskimos blood is eicosopentaenoic acid while it is AA in Danes. Eicosopentaenoic acid differs from AA (eicosotetraenoic acid) gives rise to products having theee double bonds as designated by the subscript TXA_3 and PGI_3.[39, 40, 53] TXA_3 unlike TXA_2 which arises from AA, has been observed to be unable to cause platelet aggregation.[31] However, the vascular unstable metabolite of eicosopentaenoic acid, PGI_3, possesses potent antiaggregatory activity. It has been shown that eicosopentaenoic acid is readily incorporated into platelet phospholipids and released simultaneously with AA by acylhydrolases. Although eicosopentaenoic acid is a poor substrate for cyclooxygenase, it competes effectively with AA for metabolism by this enzyme, resulting in a reduced formation of TXA_2 in the platelet.[40, 53] In addition, eicosotrienoic acid (dihomo-gammalinoleic acid) again has been considered as a diet factor or a provitamin which generates the production of PGE_1. This stable PG has anti-aggregatory and vasodilator actions therefore should be beneficial for the prevention and treatment of vascular thrombosis.[28, 59]

Thromboxanes and Prostacyclin

It should be noted that biological techniques and bioassay have contributed a lot to the development on the field of PGs.[56] Both TXA_2 and PGI_2 have been first determined depending on their biological activities before their chemical identifications. Without given a detailed information I just would like to emphasize in this review the importance of "blood bathed assay organ techniques"for the identification and discovery of the unstable metabolites of AA.[64] Some sophisticated chemical methods, such as gas chromatography and mass spectrophotometry have been developed later for the detection and quantification of PGs.

The first exciting observation was the release of an unknown substance by antigen from isolated artificial salt solution-perfused sensitized guinea-pig lung which causes a powerful contractile effect on the isolated venous return superfused spirally cut rabbit aorta.[38] This unknown substance has been called "Rabbit aorta Contracting Substance" = RCS which also has a powerful aggregating activity.[38] The half life of this substance was about 1 min. After many years, a non-PG metabolite of PGG_2 or PGH_2 have been identified and called TXA_2,[30, 50] The half

life of TXA_2 was 30 sec and had a potent aggregating activity so far described. This letter substance was absolutely identical to RCS. I think this observations clearly indicate that the biological activity is extremely important for the identification of active materials from biological fluids and overcome chemical determination because of the rapid degradation of the substance during extractional operations. On the other hand, this observation also clearly indicates that the formation of TXA_2 occurs not only in platelets but also in some regional vascular beds, like pulmonary vessels.

In vitro incubation of AA with platelet rich plasma produces about 90 % TXA_2 indicating that the major metabolite of AA in platelet is TXA_2. This unstable metabolite quickly loses its activity and turns to an inactive metabolite, TXB_2. The measurement of TXB_2 by radioimmunoassay can reflect the rate of production of TXA_2 in a particular tissue. It is highly possible that the generation of TXA_2 in the vasculature could explain the vasoconstriction which immediately follows cutting of a small vessel.[31, 49, 50]

Microsomes prepared from platelets contain an enzyme which causes the generation of TXA_2 from PGG_2 and PGH_2. This enzyme has been solubilized and seperated from cyclooxygenase. It has been shown that biosynthesis of TXA_2 from AA is associated with intracellular membrane component known as dence tubular membrane.[48] A number of cells has been shown to be capable of synthetizing TXA_2, including polymorphonuclear leukocytes, macrophages and lung fibroblasts.[28] Some tissues such as spleen, iris, conjunctiva, lungs and kidneys can also synthetize TXA_2. The location of TXA_2-synthetase in these tissues is not known. However, in some pathological conditions, like hydronephrotic kidney, the generation of TXA_2 synthesis increases indicating that the tissue damage in some unknown way activates TXA_2-synthetase. Certain vascular tissues such as human umblical artery, pulmonary artery and cultured bovine endothelial cells are capable of producing TXB_2.[30, 49]

Considerable attention has been paid to find a compound which selectively inhibits TXA_2-synthetase. Such a specific inhibitory agent against TXA_2-synthetase can prevent the generation of TXA_2 and therefore can inhibit the formation of platelet aggregation which can theoretically be beneficial for the treatment of vascular thrombosis. In this connection, many compounds have been synthetized. Imidazole is a selective but weak inhibitor for TXA_2-synthetase. However, N-substitution with alkyl[65] or arylalkyl groups[66] markedly increases the potency and selectivity for TXA_2-synthetase. Among these derivatives, 2-cyclopropyl-3-(1-imidazolylmethyl) indol is the most powerful inhibitor for TXA_2

synthetase having an IC_{50} value of 10^{-10} M. However, this compound also has an inhibitory effect on PGI_2-synthetase in vascular wall having an IC_{50} value of $8.4x10^{-7}$ M indicating its pecularity as a non-beneficial drug for the treatment of vascular thrombosis. A convenient therapeutic value has been obtained with 2-isopropyl-3-(1-imidazolmethyl) indol and 3-(1-imidazolmethyl)indol which showed a complete selectivity against TXA_2-synthetase in vascular wall.[66] 5-methyl-7-diethylaminol S-tria(1,5-a)pyrimidine (Trapidil) is also a potent inhibitor of TXA_2-synthetase.[67] An interesting compound has also been synthetized having a chemical structure of 4-(2-(1-imidazole-1-yl)benzoic acid, Dazoxiben, as the most promising novel candidate for clinical development.[68]

A series of experiments was started in England in 1975 which based upon the biological activity of an unknown substance (PGX) generated in vascular wall incubated with cyclic-endoperoxides or AA.[28, 31, 56, 69] Later, it has been established that *in vitro* incubation of AA or PGH_2 with arterial slices produces a substance which causes the relaxation of isolated vascular strips and vasodilatation when given intravenously.[91] In addition, a potent anti-aggregating effect of this unknown substance has also been described.[53] The chemical structure of PGX is further elucidated and renamed as prostacyclin with abbreviation of PGI.[53, 56] PGI_2 is the main metabolite of AA in all vascular tissues.[28, 53, 56] Large vessel wall synthetizes PGI_2 especially at the intimal surface and progressively decreases toward the adventitia.[53] The effective production of PGI_2 by vascular endothelial cells is also shown in tissue cultures.[31, 53, 56] The enzyme which causes the transformation of cyclic-endoperoxides to PGI_2 has been shown to be localised in the microsomal fraction of blood vessels endothelial cells.[31, 58] The ability of blood vessels to produce PGI_2 seems to be essential in prevention of platelet aggregation and deposition in endothelial surfaces. This mechanism might be an important event for the prevention of vascular thrombosis and atherosclerosis.[29, 53, 56, 70] In some regional vascular areas PGI_2 might also be an endogenously occurring humoral vasodilator for vascular tone.[56]

It has been described that fetal blood vessels have the greatest capacity to produce PGI_2, a property that might be related to the low peripheral resistance of the fetal circulation.[49, 54, 71] PGI_2 is also a major metabolite of AA in utero-placental tissues and its deficiency should be the cause of hypertension during pregnancy.[72] PGI_2 is an extremely labile metabolite of AA in vascular wall having one minute half-life in the biological environment. Spontaneous hydrolysis of PGI_2 forms 6-keto-$PGF_{1\alpha}$ which differs from 6-keto-PGE_1 in the substituent at C-9. The enzyme, 9-hydroxyprostaglandin dehydrogenase is probably

responsible for transforming the hydroxyl group to a ketone. Alternatively 6-keto-PGE_1 may be formed from PGI_2 through an unknown intermediary pathway.[73] PGI_2 has been shown to escape from pulmonary circulation while other stable PGs such as PGE_2, $PGF_{2\alpha}$, are metabolised in pulmonary circulation by an enzyme, 15-hydroxyprostaglandin dehydrogenase.[31] It is therefore considered that PGI_2 is a circulating as well as a local hormone. The measurement of PGI_2 level in biological fluids is based upon the radioimmunoassay of its stable metabolic product, 6-keto-$PGF_{1\alpha}$.[49, 53, 72, 74]

Many endogeneously occurring bioactive humoral factors can increase or inhibit the generation of PGI_2 in the vascular wall. Lipidperoxide derivative of AA, 15-hydroperoxyeicosotetraenoic acid (15-HPAA), is the well known inhibitor of PGI_2-biosynthesis in vascular wall.[75] The control of the biosynthesis of PGI_2 by 15-HPAA is very important and should be taken into account the possibility of the high production during long-term use of nonsteroidal analgesic anti-inflammatory drugs, Since AA is the substrate of both cyclooxygenase and lipooxygenase the inhibition by these drugs of cyclooxygenase may increase the substrate available for lipooxygenase.

Angiotensin II and bradykinin are the well known peptides which increase the generation of PGI_2 in different vascular beds especially in coronary circulation.[13, 25, 67] Both peptides also increase other stable PGs in many tissues especially in the vascular wall by a mechanism through phospholipase A_2 and cyclooxygenase.[2, 5-8, 10, 25, 26]

PGI_2 disperses platelet aggregates in vitro[59] and in the circulation of man.[53] Moreover it inhibits experimental thrombus formation.[59] In rabbits i.v. injection of AA produces "sudden death" probably due to platelet clumping which has been shown to be prevented effectively by PGI_2.[53, 77]

The antiaggregant effect of PGI_2 is shown to be mediated through the increase of cAMP levels in platelets.[45] PGI_2 also increases cAMP levels in cells other than platelets.[28, 50] In this respect PGI_2 is much more potent than either PGE_1 or PGO_2 in rising cAMP especially in platelets. Besides its stimulating effect on adenylate cyclase, PGI_2 also inhibits phospholipase and cyclooxygenase[50, 53] in platelets. PGI_2 increases cAMP in vascular endothelial cell itself, suggesting a negative feedback control for PGI_2 generation by the endothelium.[31, 53]

PGI_2 has a cytoprotective activity as studied in gastric ulcers[56] and in myocardial infarction.[78] In myocardial infarction PGI_2 reduces infarct size,[29] arrhythmias[79, 80] and the release of lysosomal enzymes

from infarcted myocardium.[70, 78] It has also a beneficial effect against endotoxin shock and improves the pertubated splanchnic circulation during the shock.[53, 59, 77] An interesting effect of PGI_2 on platelet viability has been described. It has been shown that platelet in normal in vitro conditions shows for about 6 hours functional activity. However, when prepared with the addition of PGI_2 they remain functional for more than 72 hours.[52, 57, 60, 69] In vitro long-lasting viability of platelets in the presence of PGI_2 is not accompanied by a prolonged increase in cAMP level. This clearly indicates that increase in functional viability of platelet by PGI_2 is not related with its antiaggregant activity.[28, 52, 60]

As cited above, lipid peroxides, such as 15-HPAA, are potent and selective inhibitiors of the generation of PGI_2 in the vascular wall.[39, 51, 53, 81, 82] It has also been shown that lipid peroxides tremendously increase in atherosclerotic vascular lesions.[28, 59] The increased lipid peroxidation has been observed in vitamin E deficiency, ageing process and hyperlipidemia accompanying atherosclerosis.[56, 75] Deposition of lipid peroxides (15-HPAA) in atheromatous plaque could predispose to thrombus formation because of its inhibitiory effect against the generation of PGI_2 without altering that of TXA_2.[31, 53] Human atheromatous plaques do not produce PGI_2.[53] This has also been described in experimental atherosclerotic rabbits.[28, 53] In normal rabbits PGI_2 formation in aorta is abolished by de-endothelization and progressively recovers with re-endothelization over a period of about 70 days. However, this recovery does not occur when the rabbits are made hypercholesterolemic by diet.[23, 53, 69] All these findings clearly indicate that there is a close relation between atherosclerosis and PGI_2 formation in arterial wall. Lipid peroxides, as a potent and selective inhibitor of PGI_2 formation, should have a very important role in the development of atheresclerosis. On the other hand, these findings have opened up a new approach for the prevention and treatment of atherosclerosis. Since the inhibition of the generation of 15-HPAA might result in an increase in the biosynthesis of PGI_2 in vascular wall. Vitamin E acts as an antioxidant and perhaps its empirical use in arterial diseases in the past,[56] had, in fact, a biochemical rational.[56] After the discovery of TXA_2 and PGI_2 and their functional homeostatic role in cardiovascular regulation, the explanation of the disorders related with this system became understandable and many therapeutic approaches are raised. It is very clear that the inhibition of the biosynthesis of PGI_2 may cause the initiation of atherosclerotic cardiovascular diseases. It should be learned whether or not all drugs used in therapeutics have any effect on PGI_2 and TXA_2 generations and how these drugs can influence the ratio of TXA_2/PGI_2. In

addition, the drugs which act through the generation of lipid peroxides (15-HPAA) should also be taken into consideration for the development of such a disorder. It is therefore obvious that chronical use of a known or a newly synthetized drug should be undertaken into the search for understanding their possible side effects acting through PGI_2 and TXA_2 systems.

Besides a few examples, we do not really know how we alter unstable metabolites of AA, using the drugs for the treatment of various diseases. This unproved speculation, may be one of the causes of the increasing incidence of cardiovascular disease in many western countries.

For almost a century, the hazardous effect of nicotine on cardiovascular system have extensively been studied. Many statistical studies clearly indicated a highly significant increase in the incidence of cardiovascular diseases among cigarette smokers. Until recently the hazardous effect of nicotine has been attributed to its classically known action on autonomic nervous system. After the discovery of labile metabolites of AA, a very important side of action of nicotine has been described. Nicotine is a very specific and potent inhibitor of the biosynthesis of PGI_2 in vascular wall.[83, 84] Moreover, some new evidences have been presented indicating the stimulating effect of nicotine on TXA_2 synthesis.[53] Now it is apparent how nicotine increases the incidence of cardiovascular diseases. In addition, nicotine also inhibitis the effects of some drugs which particularly act through the increase of PGI_2 biosynthesis. Inhibition by nicotine of some cardiovascular effects of bradykinin,[25] angiotensin II[26] and propranolol[85] have been described.

An interesting relationship between labile metabolites of AA and widely clinical used drug, heparin, has been observed. It is well established that thrombocytopenia is a recognised complication of heparin therapy.[86] A heparin-dependent serum platelet aggregating factor has been described. This factor has been shown to induce heparin-dependent increases in TXB_2 level. On the other hand, the antagonistic effect of heparin against PGI_2 biosynthesis has also been defined.[87, 88] Studies on extracorporal circulation indicate that PGI_2 potentiate the effect of heparin.[89] A low indirect anticoagulant effect of PGI_2 has also been observed which is due to the inhibition of stimulated platelets by PGI_2. In platelet rich plasma addition of kaolin or collagen to the medium produces a shortening of clotting time which could effectively be inhibited by further incubation of PGI_2 into the medium.[53, 59] Platelets also release an antiheparin substance which reduces the anticoagulant effect of heparin in vitro. PGI_2, by inhibiting the release of this substance can enhance the action of heparin by as much as 100 %.[53, 56] All these in

vitro observations support the beneficial effect of PGI_2 in extracorporal circulation. Long term use of heparin in the therapy is complicated in some patient by thrombocytopenia and thromboembolic episodes. It is worthy to note here that heparin-induced platelet aggregation is not inhibited by cyclooxygenase inhibitors, such as aspirin, but inhibited by substances which elevate plasma cAMP level.[53, 59]

Many antihypertensive and vasodilator drugs, partially act through the increased biosynthesis of PGI_2 in tissues. A series of exciting observations have been published recently indicating PGI_2 releasing effect of propranolol, a non-selective beta-adrenoceptor blocker. It has recently been described that cyclooxygenase inhibitors such as aspirin lessened the fall in blood pressure induced by propranolol in hypertensive patients suggesting that the antihypertensive effect of the drug may be associated with PGs.[90] Recently the evidences have been presented indicating that propranolol can cause the release of PGI_2 from kidney which may contribute to a direct antihypertensive action of this beta adrenoceptor blocking agent.[85] An antiarrhythmic effect of PGI_2 has also been described in different arrhythmias models.[79, 80] It is highly possible that the antiarrhythmic effect of propranolol might be partially mediated through the increase of the biosynthesis of PGI_2 in myocardium.[79]

So far, PGI_2 is the most potent inhibitor of all forms of aggregation, and potent vasodilator. This fact clearly suggests that the future of antithrombotic and vasodilator therapy lies in the development of compounds with "PGI_2" type of action, long acting and orally active.

During last six years PGI_2 (Eporostenol^R) has been available experimental studies in humans and it has been tested in a wide range of disorders. Its beneficial effect is established in extracorporal circulation such as cardiopulmonary bypass, charcoal haemoperfusion and haemodialysis.[59, 91] Other application for this compound include peripheral arterial diseases,[82] acute and chronic artery insufficiency,[82] haemolytic uremic syndrome,[59, 82] thrombotic thrombocytopenic purpura,[56, 82] hypertension in pregnancy,[92] pulmonary hypertension,[53, 56, 59] Raynaud's disorder[82] and persistent foetal circulation.[92] A few side effects have been reported during the therapy with Epoprostenol. Facial flushing, headache, tachycardia and decrease in diastolic pressure are the most common side effects. Erythema over the venous infusion site, sudden bradycardia, palor and sweating are rarely reported side effects seen during Epoprostenol therapy. In addition, restlessness, abdominal discomfort, nausea and drowsiness are reported in a few cases.[91]

Most recently a new chemically stable analogue of PGI_2 has been synthetized. This new compound, having the chemical structure, 5-((E)-1S, 5S, 6R, 7R)-7-hydroxy-6-((E)-(3S, 4RS)-3-hydroxy-4-methyl-oct-1-en-6yn-yl)-bicyclo (3.3.0)-octan-3-yliden) pentonoic acid (ZK 36 374) has been shown to have a profile of action similar to natural PGI_2 in various pharmacological *in vitro* studies.[93, 94] The PGI_2-like activity of ZK 36 374 has been found to be more potent and long-lasting when compared with PGI_2 in both *in vitro* and *in vivo*. Recent studies also indicate that this compound also has a potent antiarrhythmic effect against digoxin induced ventricular extrasystoles.[95] A beta-adrenoceptor blocking effect of ZK 36 374 has also been described.[85]

Continuous i.v. infusion of ZK 36 374 at the dose of 50 ng/kg/min causes a fall in systolic blood pressure ranging from 4 to 12 mm Hg which disappears within a few min after the cessation of infusion.[95] The hypotensive effect of ZK 36 374 seems to be less than that of Epoprostenol and therefore some of the systemic side effects might be expected to be lower than Epoprostenol. Although the clinical studies with ZK 36 374 is not yet complete, but according to the results of the published experimental observations, ZK 36 374 is promised to be the most effective stable analogue of PGI_2 so far described.

AA and related polyunsaturated fatty acids are also metabolised by lipooxygenases to generate hydroperoxy derivatives. In mammalian systems the hydroperoxy fatty acids may be further metabolized to leukotriens[75] Recently considerable studies have been carried out to elucidate the chemical structures, possible physiological significance and possible participations of leukotriens to pathological conditions. Collection of the contributions made in this particular metabolic pathway of AA should be considered another subject of a review article.

Acknowledgements

I acknowledge the splendid assistance of Dr. Hakan Zengil, Assistant Professor of Pharmacology, Department of Pharmacology, Faculty of Medicine, Gazi University, Ankara, in the preparation of this manuscript.

REFERENCES

1. Bergström S. Isolation, structure and actions of prostaglandins, in Prostaglandins Proceedings of the Second Nobel Symposium, Eds. S. Bergström and B. Samuelsson Wiley, New York, London, Sydney. 1966; 21-30.
2. Dusting GJ. Angiotensin-induced release of a prostacyclin-like substance from the lungs, J Cardivas Pharmacol. 1981; 3: 197-206.

3. Ercan ZS. Changes induced by angiotensins and PGE_2 on the release of transmitter from isolated perfused rabbit kidney during periarterial stimulation, Arch. Int Physiol Biochim. 1975; 83: 799-807.
4. Ercan ZS and Türker RK. Potentiation of the effect of histamine by PGE_2 in the isolated perfused rabbit kidney and rat lung, Experientia. 1975; 31: 333-4.
5. Ercan ZS and Türker RK. A comparison between the prostaglandin releasing effect of angiotensin II and angiotensin III. Agents and Actions. 1977; 7: 569-72.
6. Ercan ZS, Türker RK and Torunoğlu M. The difference between prostaglandin-mediated myotropic effects of angiotensin II and angiotensin III in the rabbit aorta, Arch Int Physiol Biochim. 1978; 86: 569-75.
7. Ercan ZS, Ersoy FF and Türker RK. The relaxing effects of angiotensin II and angiotensin III on canine isolated tracheal muscle, J Pharm Pharmacol. 1978; 30-452-3.
8. Ercan ZS, Bökesoy TA and Türker RK. Role of endogenous prostaglandins on the conversion of angiotensin I to angiotensin II in the pulmonary circulation, Prost Med. 1979; 2: 343-52.
9. Ercan ZS, Bor NM and Türker RK. The role of endogenous prostaglandins in the renal response to clonidine, Arch Int Pharmacodyn. 1979; 239: 319-25.
10. Ercan ZS, Torunoğlu M and Türker RK. Eleboration of prostaglandin-like material by angiotensin II in the isolated perfused rabbit spleen, NI Cont Clin Sci. 1980; 13: 3-8.
11. Ercan ZS.Prostaglandin-mediated contractile effect of impromidine and dimaprit in the isolated rat stomach fundus, Experientia. 1981; 37: 1092-3.
12. Ercan ZS. Prejunctional alpha-Adrenoceptor mediated prostaglandin-reasing effect of clonidine in the isolated perfused rabbit kidney, Arch Int Pharmacodyn. 1983; 265: 138-49.
13. Ercan ZS. Zengil H, Akar F and Türker RK. Possible prostacyclin-mediated vascular effect of angiotensin II in the isolated perfused rat lung, Prost Leuk Med. 1983; 12: 77-83.
14. Türker RK, Khairallah PA, Kayaalp SO and Kaymakçalan Ş. Nictitating membrane and angiotensin, Prostaglandin E_1, Eur J Pharmacol. 1969; 5: 173-9.
15. Türker RK and Khairallah PA. Prostaglandin E_1 action on the isolated canine tracheal muscle, J Pharm Pharmacol. 1969; 21: 498-501.
16. Türker RK and Kıran BK. Interaction of PGE_1 with oxytocin on the mammary gland of the lactating rabbit Eur J Pharmacol. 1969; 8: 377-9.
17. Türker RK, Kaymakçalan Ş and Ayhan İH. Effect of PGE_1 on the vascular responsiveness to norepinephrine and angiotensin II in the anesthetized rats, Arz-Forsch. 1971; 18: 1310-12.
18. Türker RK and Özer A. Effect of PGE_1, bradykinin in normal and depolarized isolated duodenum of the rat, Agents and Actions, 1970; 1: 124-7.
19. Türker RK, Kıran BK and Vural H. Dual action of PGE_1 on the isolated papillary muscle of the cat, Arz-Forsch. 1971; 21: 989-91.
20. Türker RK and Onur R. Effect of PGE_1 on the intestinal motility of the cat, Arch Int Physiol Biochim. 1971; 79: 535-43.
21. Türker RK and Ercan ZS. The effects of angiotensin I and angiotensin II on the isolated tracheal muscle of the cat, J Pharmacol. 1976; 28: 298-301.

22. Türker RK and Ercan ZS. Effect of prostaglandin E_2 on the pressor response to periarterial stimulation and norepinephrine of the isolated perfused rabbit Kidney, Prostaglandins. 1975; 9(5): 695-701.

23. Türker RK and Zengil H. Release of Prostaglandin-like material from isolated cat tracheal muscle by electrical and mechanical stimulation, Arch Int Physiol Biochim. 1976; 84: 833-41.

24. Türker RK and Ercan ZS. Inhibition of transmitter release from isolated rabbit Kidney by bradykinin, Agents and Actions. 1977; 7: 453-7.

25. Türker RK, Ercan ZS, Ersoy A and Zengil H. Inhibition by nicotine of the vasodilator effect of bradykinin: Evidence for a prostacyclin-dependent mechanism, Arch Int Pharmacodyn. 1982; 257: 94-103.

26. Türker RK. Evidence for a prostacyclin-mediated chronotropic effect of angiotensin II in the isolated cat right atria, Eur J Pharmacol. 1982; 83: 271-5.

27. Samuelsson B. Quantitative aspects on prostaglandin synthesis in man, in: Advances in the Biosciences, International Conference on prostaglandins, Ed. S. Bergtröm Pergamon Press, Vienna. 1973; 7-14.

28. Moncada S and Vane JR. Pharmacology and endogenous roles of prostaglandin endoperoxides, thromboxane A_2 and prostacyclin, Pharmacol Rev. 1979;30: 293-331.

29. Bailey JM. Prostacyclins, Thromboxanes and cardiovascular diseases, Trends in Biochemical Sciences. 1979; 4(3): 67-71

30. Hamberg M, Svensson J and Samulsson B. Thromboxanes: a new group of biologically active compounds derived from Prostaglandin endoperoxides, Proc Natl Acad Sci. 1975; 72: 2994-8.

31. Mc Giff JC. Prostaglandins, Prostacyclin and Thromboxanes, Ann Rev Pharmacol Toxicol. 1981; 21: 479-509.

32. Gündoğan NÜ and Türker RK. Influence of pulmonary circulation on diuretic action of PGE_2, Pharmacology. 1974; 11: 278-86.

33. Kayaalp SO and Türker RK. Release of catecholamines from adrenal medulla by PGE_1, Eur J Pharmacol. 1968; 2: 175-80.

34. Kayaalp SO and Türker RK. Effect hemicholinium on the catecholamine releasing action of PGE_1, Eur J Pharmacol. 1968; 3: 139-42.

35. Kaymakçalan Ş, Ercan ZS and Türker RK. The evidence of the release of prostaglandin-like materials from rabbit Kidney and guinea-pig Lung by (–)-trans-delta-9-tetrahydrocannabinol, J Pharm Pharmacol. 1975; 27: 564-8.

36. Khairallah PA, Page IH and Türker RK. Some properties of PGE_1 action on skeletal muscle, Arch Int Pharmacodyn. 1967; 169: 328-35.

37. Mc Giff JC, Terragno NA, Malih KV and Lonigro AJ. Release of a prostaglandin E-like substance from Canin Kidney by bradykinin, Cir Res. 1972; 31: 36-43.

38. Piper PJ and Vane JR. Release of additional factors in anaphyloxis and its antagonism by anti-inflammatory drugs, Nature. 1969; 233: 29-35.

39. Dyenberg J, Bang HO, Stoffersen E, Moncada S and Vane JR. Eicosopentaenoic acid and prevention of thrombosis and atherosclerosis, Lancet. 1978; 2: 117-9.

40. Needleman P, Raz A, Minkes MS, Ferrendelli JA and Sprecher H. Triene prostaglandins: Prostacyclin, thromboxane biosynthesis and unique biological porperties, Proc Natl Acad Sci. 1979; 76: 944-8.

41. Flower R. Steroidal antiinflammatory drugs as inhibitor of Phospholipase A_2, in Advances in Prostaglandin and Thromboxane Research, Eds.: C. Galli, G. Galli, G. Porcellati, Raven Press, New York, v. 3. 1978; 105-12.

42. Hong SL and Levine L. Inhibition of arachidonic acid release from cells as the biochemical action of anti-inflammatory corticosteroids, Proc Natl Acad Sci. 1976; 73: 1730-4.

43. Kunze H and Vogt W. Significance of phospholipase A for prostaglandin formation, Ann NY Acad Sci. 1971; 180: 123-5.

44. Melli M and Türker RK. Reversal by acetyl salicylic acid of the captopril induced inhibition of angiotensin converting enzyme in the hindquarters of guinea-pigs, Arch Int Pharmacodyn. 1982; 257; 87-93.

45. Kuehl FA Jr. Prostaglandins, cyclic nucleotides and cell function, Prostaglandins. 1974; 5: 325-40.

46. Lapetina EG, Cuatrecasas P. Stimulation of phosphatidic acid production in platelets the formation of arachidonate and parallels the release of serotonin, Biochem Biophys Acta. 1979; 73: 394-402.

47. Speziale N, Speziale E. Guivernan M, Terragno A and Terragno NA. Phospholipase (PL) C activity in rat blood vessels wall, Kidney cortex and Medulla, Fed Proc. 1980; 39: 996, Abst.

48. Raz A, Minkes MS and Needleman P. Endoperoxydes and Thromboxanes: Structural determinant for platelet aggregation for vasoconstriction, Biochem Biophys Acta. 1977; 488: 305-11.

49. Bunting S, Moncada S and Vane JR. The Prostacyclin-Thromboxane A_2 balance: Pathopysiological and therapeutic implications, Brit Med Bull. 1983; 39: 271-6.

50. Gorman RR. Modulation of human platelet function by prostacyclin and Thromboxane A_2, Fed Proc. 1979; 38(1): 83-8.

51. Mehta J and Mehta P. Role of blood platelets and prostaglandins in coronary artery disease, Am J Cardiol. 1981; 48: 366-73.

52. Mitchell JRA. Clinical aspect of the arachidonic acid-Thromboxane pathway, Brit Med Bull. 1983; 93: 289-95.

53. Moncada S and Vane JR. Prostacyclin: Homeostatic regulator on biological curiosity, Clin Sci. 1981; 61: 369-72.

54. Tomasi V, Meringolo C, Bartolini G and Orlandi M. Biosynthesis of prostacyclin in rat liver endothelial cells and its control by Prostaglandin E_2, Nature. 1978; 273: 670-1.

55. Vane JR. Inhibition of prostaglandin synthesis and mechanism of action for aspirin-like drugs, Nature New Biol. 1971; 231: 232-5.

56. Vane JR. Advantures and excursion in bioassay: The stepping stones to prostacyclin, Br J Pharmac. 1983; 79: 821-38.

57. Czervionke RL, Smith JB, Fry GL, Hoak JC and Haycraft DL. Inhibition of prostacyclin by treatment of endothelium with aspirin, Correlation with platelet adherence J Clin Inves. 1979; 63: 1089-92.

58. Jaffe EA and Weksler BB. Recovery of endothelial cell prostacyclin production after inhibition by low doses of aspirin, J Clin Inves. 1979; 63: 532-5.

59. Moncada S and Vane JR. Prostacyclin and blood coagulation, Drugs. 1981; 21: 430-7.

60. Patrono C, Ciabattoni G, Pinca E, Puglisse F, Castrucci G, De Salvo A, Satta MA and Peskar BA. Low dose aspirin and inhibition of thromboxane B_2production in healthy subjects, Throm Res. 1980; 17: 317-27.

61. Rittenhouse-Simmous S, Indomethacin induced accumulation of diglyceride in activated human platelets, J Biol Chem. 1980; 225: 2259-62.

62. Roth GJ, Stanford NA and Majerus PW. Acetylation of prostaglandin synthetase by Aspirin, Proc Natl Acad Sci. 1975; 72: 3073-6.

63. Miyamoto T, Yamamoto S, Hayashi O. Prostaglandin synthetase system-resolution in to oxygenase and isomerase components, Proc Natl Acad Sci. 1974; 71: 3645-8.

64. Vane JR. Use of isolated organs for detecting active substances in circulating blood, Br J Pharmac. 1964; 23: 360-73.

65. Cross PE, Dickinson RP, Parry MJ and Randall MJ. 3-(1-imidazolylmethy.) indoles: potent and selective inhibitors human blood platelet thromboxane synthetase, Agents and Actions. 1981; 11: 274-80.

66. Kayama N, Sakaguchi K and Kaneko S. Inhibition of platelet aggregation by 1-Alkylimidazole derivatives, Thromboxane A synthetase inhibitors, Prostaglan dins. 1981; 21: 543-53.

67. Okniski H, Kosuzame H, Hayaski Y, Yamaguchi K, Suzuki Y and Itoh R. Effect of Trapidil on Thromboxane A_2-induced aggregation of platelets, ischemic changes in Heart and biosynthesis of thromboxane A_2, Prost Med. 1981; 6: 269-81.

68. Tyler HM. Dozoxiben: A pharmacological tool on clinical candidate, Br J Clin Pharmac. 1983; 15: 135-65.

69. Mc Giff JC. New developments in prostaglandin and thromboxane Research, Fed Proc. 1974; 38(1): 64-5.

70. Jugdutt BI. Prostaglandins in myocardial in farction: with emphasis on myocardial preservation, Pros Med. 1981; 7: 109-23.

71. Downing I, Blair I and Lewis PJ. 6-oxo-PGF_1 synthesis by human umbilical artery, in: Clinical pharmacology of prostacyclin, Eds: PJ. Lewis, JO.'Grady, Raven Press, New York. 1981; 131-3.

72. Misiani R, Remuzzi G and Mecca G. Prostacyclin generation by human umbilical and placental vessels in normal and hypertensine Pregnaney, in: Clinical pharmacology of Prostacyclin, Eds: P.J. Lewis, J. O'Grady, Raven Press, New York. 1981; 137-9.

73. Quilley CP. Wong PYK and Mc Giff JC. 6-Keto-PGE_1: A possible metabolite of prostacyclin hawing platelet anti-aggregatory effects, Hypertension. 1980; 2: 524-34.

74. Levin RI, Jaffe EA, Werksler BB and Tack-Goldman K. Nitroglycerin stimulates synthesis of prostacyclin by cultured human endothelial cells, J Clin Invest. 1981; 67: 762-9.

75. Warso MA and Lands WEM. Lipid peroxidation in relation to prostacyclin and thromboxane physiology and pathophysiology, Brit Med Bull. 1983; 39: 277-80.

76. Lippton HL, Chapnick BM, Hyman AL, Glass FL and Kadowitz PJ. The influence of indomethacin on vasodilator responses to bradykinin and nitroglycerin in the cat, Peptides. 1981; 2: 165-9.

77. Whittle BJR and Moncada S. Pharmacological interactions between prostacyclin and thromboxanes, Brit Med Bull. 1983; 39: 232-8.

78. Coker SJ and Parratt JR. Prostacyclin-induced changes in coronary blood flow and oxygen handling in the normal and a acutely ischaemic canine myocardium, Basic Res Cardiol. 1981; 76: 457-62.

79. Coker SJ and Parratt JR. Prostacyclin-Antiarrhythmic or arrhythmogenic? Comparison of the effects of intravenous and intracoronary Prostacyclin and ZK 36 374 during coronary artery occlusion and reperfusion in anaesthetized Greyhounds, J Cardiovas Pharmacol. 1983; 5: 557-67.

80. Dix RK, Kelliher GJ, Jurkiewicz N and Lawrence T. The influence of protacyclin on coronary acclusion induced arrhythmia in cats, Pros Med. 1979; 3: 173-84.

81. Halushka PV, Rogers RC, Loadholt CB and Colwell JA. Increased platelet thromboxane synthesis in diabetes mellitus, J Lab Clin Med. 1981; 97: 87-95.

82. Lewis PJ and Dollery CT. Clinical pharmacology and potential of prostacyclin, Brit Med Bull. 1983; 39: 281-4.

83. Berry CN, Umney ND and Hoult JRS. Effects of nicotine on the release and inactivation of prostaglandins in the perfused rat lung, J Pharm Pharmacol. 1981; 33: 326-8.

84. Wennmalm A. Effects of nicotine on cardiac prostaglandins and platelet thromboxane synthesis, Br J Pharmac. 1978; 64: 559-63.

85. Ercan ZS and Türker RK. Possible beta-adrenoceptor modulating effect of ZK 36 374, a stable analogue of carbacyclin, Pros Leuh Med. (in press).

86. Chong BH, Pitney WR and Castaldi PA. Heparin-induced thrombocytopenia: Association of thrombotic complications with heparin-dependent IgG antibody that induces thromboxane Synthesis and platelet aggregation, Lancet. 1982; Dec. 4: 1246-8.

87. Eldor A, Allan G and Weksler BB. Heparin-Prostacyclin interactions: Heparin does not modify the prostacyclin-induced relaxation of coronary vasculatare, Throm Res. 1980; 19: 719-23.

88. Gross M, Bush H, Mc Tigue H, Hamburger RJ and Flamenbaum W. A comparison of prostacyclin and heparin on haemodialyses in Dogs, Prostaglandins. 1981; 21: 879-88.

89. Weston MJ. Prostacyclin and extracorporeal circulation, Brit Med Bull. 1983; 39: 285-8.

90. Gillespie MN, Atkinson JE, Turbek JA and Diamond L. Propranolol and sotalol augment the coronary vasodilatory action of prostacyclin (PGI_2) in rabbit isolated heart, Eur J Pharmacol. 1981; 75: 155-8.

91. Pickles H and O'Grady J. Side effects occuring during administration of Epoprostenol (Prostacyclin, PGI_2), in man, Br J Clin Pharmac. 1982; 14: 177-85.

92. Fidler J, Ellis C, Bennett MJ, deSwiet M and Lewis PJ. Prostacyclin and Preeclamptic Toxaemia, in: Clinical Pharmacology of Prostacylin, Eds: P. J. Lewis, J. O'Grady, Raven Press, New York. 1981; 141-3.

93. Schrör K, Ohlendorf R and Darius H. Beneficial effects of a new carbacyclin derivative, ZK 36 374, in acute myocardial ischemia, J Pharmacol Exp Ther. 1981; 219: 243-9.

94. Schrör K, Darius H, Matzky R and Ohlendorf R. The antiplatelet and cardiovascular actions of a new carbacyclin derivative (ZK 36 374)-Equipotent to PGI_2 in vitro, Naunyn-Schmiedeberg's Arch Pharmacol. 1981; 316: 252-5.

95. Metin M. Dörtlemez Ö, Dörtlemez H, Akar F, Ercan ZS and Türker RK. Prevention of Digoxin-induced ventricular extrasystoles by ZK 36 374 in guinea-pig heart, Eur J Pharmacol. 1984; 98: 125-8.

Hacettepe Medical Journal
Instructions to Authors

1. Manuscripts, letters and editorial correspondence should be sent to "The Editor Hacettepe Medical Journal, Hacettepe University School of Medicine, Dean's Office, Ankara-Turkey" by first-class mail (airmail for overseas).

2. Submissions considered for publication are received with the understanding that no part of the submission has previously appeared elsewhere in any but abstract form.

3. Manuscripts should be typed double-spaced on standard-size typewriter paper with margins of at least 2.5 cm. is acceptable. This inludes references, tables, and figure legends. The original typescript and two high-quality copies of the manuscript should be submitted.

4. Number pages consecutively in order and place author(s) name, highest degree, institutional affiliations and adress below the title.

5. Hacettepe Medical Journal invites papers on original research, case reports, reviews, short communications for practical applications, letters, editorials, book reviews and announcements. The number of typewritten pages should not exceed 10 for original articles, 12 for reviews, 4 for case reports and 1 for letters.

6. Original articles and research papers should normally be divided into following sections:

   A. (1) An informative summary for not more than 200 words must be included and should appear at the beginning of the paper (2) Key Words, (3) Introduction, (4) Materials and Methods, (5) Results, (6) Discussion and (7) References.

   B. References must be typed in double spacing and numbered consecutively as they are cited. The style of references is that of the Index Medicus. List all authors when there are six or fewer; when there are seven or more, list the first three, then "et al". Sample references follow:

      1. Steward JH, Castaldi PA. Uremic bleeding: a reversible platelet defect corrected by dialysis. QJ Med. 1967; 36: 409-23.

2. Bearn AG. Wilson's Disease. In: Stanbury JB, Wyngaarden JB, Fredrickson DS, eds. The metabolic basic of inherited disease. New York: McGraw-Hill, 1972: 1033-50.

7. Tables should be as few as possible and should include only essential data. Tables should be typed in double spacing on separate sheets and provide a legend for each. Diagrams or illustrations should be drawn with black Indian ink on white paper and should be given Roman numerals. Each illustration should be accompanied by a legend clearly describing it: all legends should be grouped and type-written (double spaced) on a separate sheet of paper.
Photographs and photomicrographs should be unmounted high-contrast glossy black-on-white prints and should not be retouched. Each photograph or illustration should be marked on the back with the name(s) of the author(s), should bear on indication of sequence number and the top should be marked with an arrow. All measurements should be given in metric units.

8. Manuscripts are examined by the editorial staff and usually sent to outside reviewers. The Editor reserves the right to reject or to return the manuscript to the author(s) for additional changes if all the guidelines and requirements are not uniformly completed.

9. Proofs will be submitted to the author responsible for proofcorrection and should be returned to the Editor within 5 days. Major alterations from the text can not be accepted. Ten reprints of each paper are supplied free, additional copies can be purchased.

10. Correspondence and communications regarding manuscripts and editorial material should be sent to:

The Editor
Hacettepe Medical Journal
Dean's Office
Hacettepe University School of Medicine
Hacettepe, Ankara-Turkey

11. Subscription communications and payments should be mailed to "Hacettepe University Press Office, Hacettepe, Ankara-Turkey".