ISSN 1015-0870

May, 1995
Vol. 13, No. 2

# Journal of Bangladesh College of Physicians and Surgeons

Official Journal of the
Bangladesh College of Physicians
and Surgeons

# JOURNAL OF BANGLADESH COLLEGE OF PHYSICIANS AND SURGEONS

**Vol. 13, No. 2, May, 1995**

Official Publication of the Bangladesh College of Physicians and Surgeons
Mohakhali, Dhaka-1212





**Published by :** Dr. Syed Kamaluddin Ahmed, on behalf of the Bangladesh College of Physicians and Surgeons

**Printed at** : Asian Colour Printing, 130, DIT Extension Road (Fokirapool), Dhaka-1000, Bangladesh Phone : 407656

**Address for Correspondence:** Editor-in-Chief, Journal of Bangladesh College of Physicians and Surgeons BCPS Bhavan, Mohakhali, Dhaka-1212. Tel : 885005-6, Fax : 02-888928

**Annual Subscription** : Tk 300/- for local and US $ 30 for overseas subscribers

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# JOURNAL OF BANGLADESH COLLEGE OF PHYSICIANS AND SURGEONS

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## EDITORIAL

# Asthma Care in the Community

Bronchial Asthma is a chronic lung disease affecting people of all ages and social classes. It produces great concern for both the patients and the physicians as it causes much morbidity leading to restricted life activity, unhappiness in the family and loss of working hours.

The prevalence and incidence of asthma is difficult to assess with certainty because of the lack of reliable population based information using uniform diagnostic criteria. It has been estimated that approximately five percent of adults and seven to 10 percent of children in the United States have this disorder[1]. There is also evidence that the prevalence and severity of asthma are rising. Though we have no population based study, our experience suggest that this disorder is very common in our country. It is suspected that approximately 10 million people in this country have been suffering from bronchial asthma.

The outlook for the management of asthma has been changed in the last few years with the introduction of newer anti-inflammatory drugs and its sophisticated delivery system. Time has come to think to do something more for our asthmatics keeping in pace with the modern concept of asthma therapy and self-management plan. The British Thoracic Society issued some guidelines for management of asthma[2]. It is difficult for our physicians to follow such guidelines for many reasons and we do not have any guideline of our own.

In our community, we ignore the real situation with bronchial asthma as well as its effective management with the available resources. It is true that over use of bronchodilators and under use of anti-inflammatory drugs like steroid, sodium chromoglycate is common although sometimes these anti-inflammatory drugs, particularly steroids are misused. Administration of anti-asthma drugs through inhalation is not popular in this country. In one study it was shown that only 17 percent of asthamtic patients used Salbutamol Metered Dose Inhaler. But most disappointing was that only 20 percent of users could demonstrate the technique of inhalation properly[3]. There are also misconceptions about the inhaler amongst the patients. Prescription of inhaler without adequately instructing the patient is nothing but wastage of time and resources. We feel that every physician and paramedic dealing with asthma should play a vital role in patient education and motivation regarding the proper use of inhaler, which will definitely improve the asthma care in the community to a great extent.

Peak flow meter now-a-days is a vital component of asthma care. Not only the physicians but the patients should have their own peak flow meter to monitor improvement or deterioration of asthma. If we can manitor blood pressure with a sphygmomano meter routinely, why can't we monitor asthma with a peak flow meter? Most of the hospitals in our country still use parenteral aminophylline for acute attacks of bronchial asthma which has got a narrow therapeutic window and its use is obsolete in many countries. Nebuliser should be supplied to each hospital so that high dose of salbutamol can be administered through this apparatus safely to cope with severe acute attacks.

There are many misconceptions regarding asthma in our community. Failing to get cured, people move from one doctor to another, from allopathic medicine to homoeopath, kabiraj and other traditional healers after

being attracted by lucarative advertisement in different mass media and some traditional healers use steroid in powder form to give temporary benefit. But the patients ultimately becomes victims of complications. We should do something for them. People should be taught regarding the chronic nature of this disease and they should be motivated for self-management of this disease. Scope for continuous liason between the asthma patients and the physicians would definitely improve the asthma care in the community.

Asthma Society of Bangladesh can take up the leadership of asthma care in this country. We hope the asthma patients, interested physicians in this field and over and above people from all corners should come forward to strengthen the Society so as to fulfil the commitment.

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*(J Bangladesh Coll Phys Surg 1995; 14: 38–39)*

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# Indications of Exploration of Common Bile Duct —Experience at IPGMR

MM HOSSAIN, FCPS[a], G RASUL, FRCS[b]

**Summary :**

A considerable proportion of patients suffering from gall stone disease also have stones in the common bile ducts (CBD). Removal of CBD stone is regarded essential to avoid complications arising from their presence. Various indicators have been used to predict presence of CBD stones. In a series of 91 explorations of common bile ducts ten such indicators were evaluated. Results show consistent high predictability of some clinical findings and laboratory investigations.

*(J Bangladesh Coll Phys Surg 1995; 13: 40-44)*

## Introduction :

About six to 20% of the patients suffering from gall stone disease are reported of have stones in their common bile ducts[1-4]. Most surgeons accept the view that both symptomatic and silent stones in the CBD bears significant risk to health because of the various known complications it can produce. Anticipation of presence of stone in the CBD prior to surgical exploration is therefore essential. A systematic and thorough search to detect and remove any stone in the CBD is considered mandatory during initial cholecystectomy[5,4]. Exploration also is attended by complications and higher rates of mortality and morbidity[6]. Therefore, decision to open the duct preoperatively or at operation should be firmly based so as to avoid unnecessary exploration. Clinical findings, investigative findings and findings during laparotomy all may indicate possible presence of stone in the duct. Different criteria have been formulated based on the experience of the surgeons[6,7,8]. While predictability of any one of them varies, combination of these criteria constitute a rliable guide to explore the CBD.

This report is based on a prospective study carried out at the Institute of Post-Graduate Medicine and Research (IPGMR). In a series of 91 choledochotomies, efforts have been taken to identify the presence of some criteria taken as indicators of presence of stone in the CBD and also to determine the reliability of these criteria in predicting possible presence of CBD stones.

## Materials and method :

Materials of this study comprises of 91 patients who had exploration of common bile ducts in one surgical unit of IPGMR from July 1987 to February 1993. These patients were screened for the presence of ten pre-selected criteria indicative of possible choledocholithiasis.

Information were collected and recorded in a prescribed format. Data were analysed to determine the positive predictive value of each criteria.

## Results :

During this study period, six hundred patients had cholecystectomy. Amongst them, 86 patients had exploration of common bile duct due to different indications. Five other

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Received : November 16, 1994; Acepted : May 8, 1995

patients who had cholecystectomy done previously also had exploration of the CBD as a second operation. These 91 patients were subjects of this study. Seventy four out of the 91 patients had stones in the duct, positive yield being 81.3%. A summary of these findings is presented in Table-II.

**Table-I**

*Criteria selected as indicators of choledocholithiasis*

A. Pre - operative presenting features :
1. Biliary colic only
2. Jaundice or past history of jaundice
3. Biliary colic with jaundice
4. Triad of biliary colic, jaundice and fever

B. Investigative evidence :
5. Ultrasonographic finding of stone and/or dilatation of the CBD
6. IVC
7. ERCP/PTC

C. Peroperative findings :
8. Palpable stone
9. Dilated common duct
10. Dilated cystic duct with small stones

**Table-II**

*Summary of operation and operative findings*

| Operation | Total no. of patients | Positive finding of stone in duct | Incidence |
|---|---|---|---|
| Exploration of CBD | 91 | 74 | 81.3% |
| Exploration of CBD at second laparotomy | 5 | 3 | 60% |
| Exploration of CBD during initial laparotomy | 86 | 71 | 82.5% |
| Cholecystectomy | 600 | 71 | 11.83% |

There were 49 female patients and 42 males. The youngest patient was 12 years old and the oldest 70 years. Half of the patients were within 30 to 50 years age range. Break up of patients according to their age and sex is shown in Table -III

Three common features of presentation were evaluated as indicators for the presence of stone in CBD : biliary Colic, jaundice or a reliable past history of jaundice, a combination of pain and jaundice, and typical Charcot's triad of intermitten fever, fluctuating jaundice and biliary colic.

Biliay colic with jaundice was by far the largest group. However, Charcot's triad was

**Table-III**

*Age and sexwise distribution of patients who had choledochotomy*

| Age range (years) | Male (%) | Female (%) | Total | Percentage of total |
|---|---|---|---|---|
| Below 30 | 9 (21.4) | 7 (14.3) | 16 | 17.5 |
| 31-40 | 11 (27.2) | 15 (30.6) | 26 | 28.5 |
| 41-50 | 8 (19.2) | 12 (24.5) | 20 | 21.9 |
| 51-60 | 7 (16.6) | 10 (20) | 17 | 18.6 |
| 61-70 | 3 (7.1) | 4 (8) | 10 | 7.6 |
| 70+ | 4 (9.5) | 1 (2) | 5 | 5.5 |
| Total | 42 | 49 | 91 | |

most consistant among the presentation criteria with positive findings at exploration. Table-IV shows the predictability of presenting features.

Ultrasonography (USG), IVC, ERCP and PTC were done to diagnose choledocholithiasis or a dilated extrahepatic biliary tree. Though USG was done in all cases, others were done in selective cases and when the facilities were available. For the purpose of this study, common bile ducts of more than 10 mm diameter were taken as dilated ducts.

When investigative findings were matched with operative findings, USG was found less reliable. ERCP, PTC and IVC on the other hand had a reliability of more than 80%. These findings are presented in Table–V.

**Tabe–IV**

*Presenting feature and operative findings with predictive value*

| Presenting features | No. of patients | Stone present in CBD | PPV* |
|---|---|---|---|
| Biliary colic | 21 | 11 | 51 |
| Jaundice | 13 | 6 | 46 |
| Biliary colic and jaundice | 49 | 31 | 63 |
| Charcot's triad | 8 | 8 | 75 |

* PPV - Positive predictive value

At laporatomy three criteria were looked for as evidence of choledocholithiasis–palpable stone, dilated CBD and dilated cystic duct with small stones in gall bladder. A systematic search of extrahepatic biliary tree was carried out. Kocher's manoeuvre was done whenever felt necessary. Stone was palpable in 37 cases of which 31 had positive yield. On the other hand 11 patients out of 27 had stones in their ducts which appeared dilated. Exploration was also done in otherwise "normal" CBD on the basis of pre-operative suspicion. Out of 20 such explorations nine were positive for stones. Findings are presented in Table–VI.

**Table–V**

*Showing positive findings of different predictive investigation with positive operative findings and positive predictive value*

| Investigative findings | No. of cases with positive finding | Positive findings at operation | Positive predictive value |
|---|---|---|---|
| Stone in CBD on USG | 26 | 9 | 34.6 |
| Dilated CBD on USG | 31 | 12 | 38.7 |
| IVC | 12 | 9 | 75 |
| ERCP | 15 | 13 | 86.3 |
| PTC | 7 | 6 | 85.7 |

**Table–VI**

*Intraoperative indications and operative findings*

| Indications | No. of cases | Positive findings | PPV |
|---|---|---|---|
| Palpable stone | 37 | 31 | 83.7 |
| Dilated CBD | 27 | 11 | 40.7 |
| Dilated cystic duct and small stone | 7 | 3 | 42.8 |
| Normal duct | 20 | 9 | 45 |

**Discussion :**

There are several indications for choledochotomy. The protocol followed at different centres vary. To these, newer indications are added and adopted in an efort to reduce the rate of overlooked or unsuspected stones[9]. However, in an effort to do so, positive findings in choledochotomies were around 50% implying that half the choledochotomies

performed were unnecessary[10]. Careful scrutiny of each indication is therefore essential to reduce negative exploration on one hand and to improve reliability of indications being used on the other.

A history of typical biliary colic is a common feature, but in itself is not a very reliable indication for exploration of the CBD. In this series 52% patients had stone in the CBD. Hasmonai et al[10] had comparative findings in a series of 477 patients. In most of these patients other indications were also present. Therefore, accuracy of biliary colic as a single indication could not be ascertained. However, any single indication has positive findings in the range of 11-19% in different series reported by Colcock and Perey[7], Hasmonai et al[10] and Nullen et al[11]. On the other hand, presence of multiple factors raise the predictability even upto cent percent[9].

Presence of jaundice at the time of operation consistantly points to the possibility of presence of stones. Positive findings were reported in upto 70% cases by Kokos[12], Muillen et al[11] and Hasmonai et al[10]. However, probability of choledocholithiasis drops when a history of jaundice is considered as an indication. In our series, positive findings were found in 46% cases as compared to 40% reported by Hasmonai et al[10]. This may be due to that the stone had passed by the time exploration was done followed by disappearance of jaundice.

Jaundice and history of biliary colic in combination should raise the suspicion of presence of stone in the CBD. In our series there was 64% positive yield. On the other hand, when all three components of Charcot's triad was present, the predictibility increased to 75%.

Evidencing of stone in the bile duct is possible by various methods. In this study, we have done IVC, PTC and ERCP in 34 patients in addition to USG. Ultrasonography, as a non-invasive procedure, has gained acceptance. Also, it is economical and associated organs like liver, pancreas and other abdominal structures can be scanned at the same time. But the predictability remains low. In our series stone was found in only nine of 26 cases suggested by sonologist to have stone in CBD. Earlier reports also showed similar findings in relation to choledocholithiasis[13,14].

Predictive value of three other investigations were more than 80% (28 out of 34 positive findings). Using similar indications, positive findings were reported in 84% and 86% by Kokos et al[12] and Hashmonai et al[10] in their studies respectively.

Dilated CBD as evidenced either by IVC or USG is also taken as indication for exploration. In this series stones were found in less than 40% explorations. Hashmonai et al[10] found positive yield in 53% of cases when the CBD was found dilated on IVC and in 55% cases when dilatation was found at operation without a palpable stone. One reason for comparatively low positive exploration could be that assessment of diameter of CBD was inaccurate in some cases. The oedematous or thick wall of the CBD might also give a false impression of dilatation. Another possibility is that any small stone present was expelled by the time the patient was investigated or operated.

Among the per-operative indications, palpable stone is the most consistant indication of exploratin with high positive yield. Colcock et al[7] had 100% success. Bartlett and Wandall[15] had 99% positive finding when the patient had jaundice and 89% of cases without jaundice. In our series we had 84% positive finding. Difficulty in palpating biliary tree due to adhesions with surrounding structures and a closed foramen of Winslow or inadequate mobilisation of the duodenum may lead to confusing and puzzling situations and prompt exploration of the duct in some cases. But more commonly, an enlarged lymphnode or a nodule in the pancreas gives the false impression of stone in the CBD.

A wide cystic duct, more than 5 mm in diameter, and presence of small stones in the gall bladder have also been regarded as indications of bile duct stone. Positive findings in these group of patients remain around 45%[10,11]. In our experience also positive yield was similar.

Among other features that may indicate presence of stone, age has been considered significant. Hashmonai et al[10] have shown that the probability of presence of stone increases with age. Duration of biliary disease is also taken as indicator of choledocholithiasis. Glenn[4] reported higher chances of finding stones in patients presenting with a long history of the disease.

Pre-operative cholangiogram has been efficiently used to detect stones in the bile ducts. Though there is controversy over its use as routine, rational use in selective cases undoubtedly raises the reliability. This facility and choledochoscopy were not available consistantly, and could not be evaluated during our study.

Careful consideration of different indications to explore the CBD remains the basis of efficient management of stones with reduction of negative explorations. Some indicators consistantly have high predictive value and should be considered as absolute indicators. Other less predictable indicators when present in combination may give a strong clue to the presence of stones in the CBD.

In a good proportion of cases, endoscopists are now able to remove the stones using Dormia basket, baloon catheter or choledochoscopes. Gall stones are detected and removed earlier with the introduction of ultrasonography. It is expected therefore that the pattern of indications will be changed in near future. Also, introduction of laparoscopic technique demands more reliable methods of preoperative detection of stones. Surgeons should now prepare themselves for these new challenges.

**Acknowledgement :**

We are grateful to the Director, IPGMR and the Director P.G. Hospital for allowing us to publish this article. We are also indebted to all the doctors who worked with us during this study.

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Journal of Bangladesh College of Physicians and Surgeons
Vol. 13, No. 2, May 1995

# Cytofluorometric DNA Analysis of Hepatocellular Carcinoma

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**Summary :**

The nuclear DNA content was measured cytofluorometrically in 15 patients after hepatic resection for hepatocellular carcinoma (HCC) to develop a method for measuring the DNA content, to investigate the correlation between DNA content and clinicopathological behaviours, to investigate the relationship between DNA content and survival after hepatic resection, and to evaluate whether or not it had prognostic value. Cell disaggregation was obtained successfully. Adequate number of intact isolated nuclei were frequently found to have low background fluorescence. The DNA distribution pattern was categorized into low and high ploidy according to the degree of dispersion of cells on the histogram. A significant relationship was found between the DNA patterns and intrahepatic metastatic lesions ($P < 0.02$). The presence of high ploidy indicates worse prognosis than do low ploidy tumours. There was a statistically significant difference in survival rates between the patients with low and high ploidy tumours ($P < 0.01$). This study suggests that the cytofluorometric nuclear DNA ploidy analysis is an important biological parameter in evaluating cells. The DNA pattern did not relate to the clinicopathological behaviours of tissues. The DNA pattern significantly correlates with the intrahepatic metastatic lesions and survival rates of patients with HCC, and appeared to be a valuable indicator of treatment outcome.

*(J Bangladesh Coll Phys Surg 1995; 13: 45–51)*

## Introduction :

Hepatocellular carcinoma (HCC) is one of the most malignant fatal tumours. In 1984, the liver cancer study group in Japan[1] reported that in resectable cases the patients survived longer than in nonresectable cases. The survival time was longer after partial or segmental resection than after massive resection and in those without cirrhosis than those with cirrhosis. A few reports have investigated the correlationship between DNA content of HCC and clinicopathological parameters and stressed that the DNA pattern was closely correlated with the morphological grading and age of the patients, and also to the biological characteristics of the growth pattern without any relatinship with prognosis[2]. Fujimoto reported that the nuclear DNA content has an important prognostic value in HCC[3].

Cytofluorometric nuclear DNA ploidy analysis is a very simple, sensitive, accurate, and important biological parameter in evaluating cells for diagnostic purposes, histological assessments, prediction of clinicopathological behaviour of tissues, and for assessing prognosis. The purpose of this study was to develop a cytofluorometric method for measuring the nuclear DNA content of HCC, to investigate the relationship between DNA content and clinicopathological behaviours, to investigate the relationship between DNA content and survival after hepatic resection, and to evaluate whether or not it had prognostic value.

## Materials and method :

Formalin fixed paraffin embedded 23 liver tumour blocks were obtained from 15 patients after hepatic resection for HCC in the First Department of Surgery, The University Hospital of Tokushima, Japan. There were 12 men and three women with a mean age of 57.86 years (range, 42 to 72 years). From eight patients two samples were taken from

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Received : October 9, 1994; Accepted : May 8, 1995

two different sites of the main tumour. Eleven cases had associated liver cirrhosis, and according to the TNM classificaion[4], two cases were of stage I, 11 cases stage II, and two cases stage III malignancy. Formalin fixed paraffin embedded non-tumour non-cirrhotic non-hepatitic normal liver blocks were also prepared to make a standard control histogram. The case records of each patient were reviewed.

*Cytofluorometric DNA analysis :*

Two 50 µm thick sections were cut from each block. Nuclei were isolated according to the method of Hedley[5] with some modifications in the procedure. Sections were placed on microscopic glass slides and was then deparaffinized and rehydrated in the following sequence : xylene (twice), ethanol 99.5% (twice), 80% (once), 70% (once), 50% (once), and distilled water, 10 minutes in each solution. The target tumour tissues were collected from the sections placed on glass slides by scrapping off nonrelevant areas with a scalpel and than minced. The tissues were incubated (Taiyo Personal incubator, Taitec, Tokyo, Japan) for 120 minutes at 37°C in 6-8 ml of 0.14% collagenase type I (Sigma Chemicl Company, St. louis, USA) in Hanks balanced salt solution (Gibco Laboratories, Grand Island, N.Y., USA) per gram of tissues. The collagenase treated tissues were passed forcefully through an 18 gauze needle during incubation for one to two minutes. The samples were then filtered through a stainless steel mesh no. 150. A single cell suspension was prepared by repeated centrifugation at 377 x g for 10 minutes in RPMI 1640 medium (Sigma). Cell layers on membrane filters were produced by adding 0.2% fetal bovine serum in phosphate buffered saline on layered cells, with filter unit (Always membrane filter unit, Japan Membrane Technology, Tokyo, Japan) and fixed in methanol for five minutes. The fixed dried filters were stained with 4,6 - diamidino-2-phenylindole dihydrochloride (DAPI, Wako Pure Chemical Industries Ltd., Japan) for 60 minutes at 4°C[6]. The final concentrations of reagents in the staining solution were 50 mg/ml DAPI, 9.74 mM Tris (hydroxymethyl) aminomethane (Sigma), 9.83 mM EDTA (ethylenediaminetetraacetic acid, disodium salt; Wako), 0.10 mM cysteamine hydrochloride (2-aminoethanethiol hydrochloride; Wako), and 1M NaCl (pH 7.4). Immediately after the staining the DNA measurements were performed after irradiation at an excitarory wave length of 385 nm with a Nikonoptical-XF-EFD epifluorescence cytophotometer system[6].

A fixed slide of normal liver cells and few slides of tumour, hepatitis, and cirrhosis liver cells were stained at the same time. For each slide, 100 intact isolated nuclei were randomly counted to determine their nuclear DNA content.

*Classification of DNA histogram :*

The diploid (2C) value was determined by the mean fluorescence value of 100 normal liver cells which serves as a standard control histogram. The histogram of the DNA content relative to the control was determined. According to degree of dispersion of cells in the histogram, the distribution patterns were categorized into low ploidy and high ploidy pattern[6], which are shown from the direct copy of the computer output in Fig. 1a-c. The distribution patterns are as follows :

a) Low ploidy pattern : The dispersion of cells exceeding 6C and not surpassing 10% is referred to as low ploidy pattern of histogram.

b) High ploidy pattern : The dispersion of cells exceeding 6C and surpassing 10% is referred to as high ploidy pattern of histogram.

*Statistical analysis :*

Statistical analysis was performed using *chi-square* test. Survival was analyzed by Kaplan Meirs method. The survival rate was statistically analyzed using the generalized Wilcoxon test.

**Results :**

The relationship between the nuclear DNA ploidy and clinicopathological parameters is shown in Table-I. A high incidence of high ploidy were detected in patients less than 50 years of age, with hepatitis B surface antigen positivity, serum alpha-fetoprotein (AFP) levels over 20 ng/ml and tumour size more than 5 cm in diameter, but the difference was not statistically significant.

A low incidence of high ploidy was noted in patients associated with accompanying liver cirrhosis and high incidence in those without liver cirrhosis. There was no statistically significant relationship between DNA ploidy and presence or abscence of liver cirrhosis. DNA analysis was also performed in three different liver cirrhosis and three different chronic hepatitis without tumour patients to show their ploidy pattern. High ploidy was shown in two and low in one of both categories.

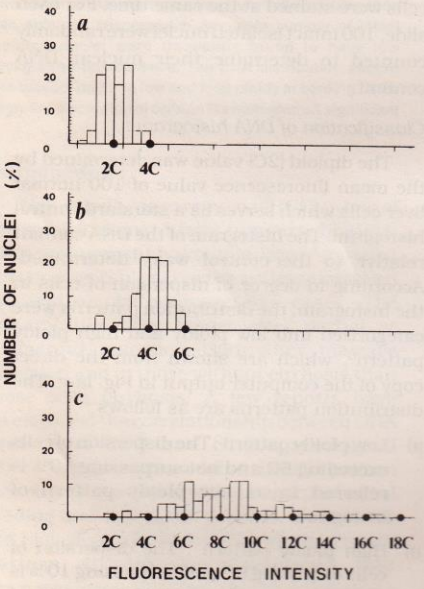


**Fig-1:** *Representative histograms of the nuclear DNA content. (a) histogram of the normal liver tissue. Diploid (2C) value was determined from the mean fluorescence value of 100 liver cells. The nistogram of the DNA content relative to the control was determined; (b) Low ploidy pattern of histogram; (c) High polidy pattern of histogram*

**Table-I**

*DNA ploidy and clinicopathological parameter*

| Variable | Number of patients | Number of low ploid (%) | Number of high ploid (%) |
|---|---|---|---|
| Age (years) : | | | |
| Less than 50 | 3 | 0 | 3 (100%) |
| More than 50 | 12 | 6 (50%) | 6 (50%) |
| Hepatitis B antigen : | | | |
| Positive | 3 | 1 (34%) | 2 (66%) |
| Negative | 12 | 5 (42%) | 7 (58%) |
| Alpha-fetoprotein (ng/ml) : | | | |
| Less than 20 | 4 | 2 (50%) | 2 (50%) |
| More than 20 | 11 | 4 (36%) | 7 (64%) |
| Tumour size : | | | |
| Less than 5 cm | 12 | 5 (42%) | 7 (58%) |
| More than 5 cm | 3 | 1 (34%) | 2 (66%) |
| Associated liver cirrhosis : | | | |
| Present | 11 | 6 (54%) | 5 (46%) |
| Absent | 4 | 0 | 4(100%) |
| Histological grade : | | | |
| I | 3 | 1 (34%) | 2 (66%) |
| II | 10 | 4 (40%) | 6 (60%) |
| III | 1 | 0 | 1 (100%) |
| IV | 1 | 1 (100%) | 0 |
| TNM stage : | | | |
| I | 2 | 2 (100%) | 0 |
| II | 11 | 3 (27%) | 8 (73%) |
| III | 2 | 1 (50%) | 1 (50%) |

The cytological features of the tumour were classified into four grades according to Edmondson and Steiner[7]. Among the 15 specimens, grade II was seen in 10, grade I in three, grade III in one, and grade IV in one. A

high incidence of high ploidy was noted in specimens of grades I, II and III. But the relationship was not statistically significant.

The DNA ploidy was also analyzed from two different sites of the same tumour in eight patients. No difference of ploidy pattern was observed in six cases but in two cases the ploidy pattern varied in two different sites of the same tumour (Fig. 2a-d).

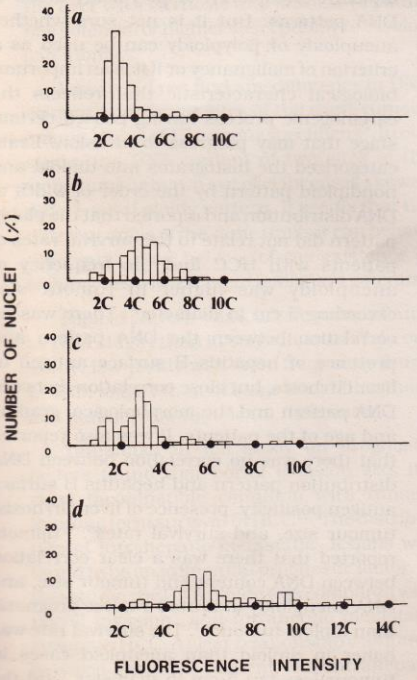


**Fig-2:** *Representative histograms of the nuclear DNA content. Diploid (2C) represents the standard DNA control. a-b) Low and high ploidy pattern from two different sites of the same tumour respectively in case no. 8; c-d) Low and high ploidy pattern from two different sites of the same tumour respectively in case no. 12.*

A high incidence of low and high ploidy was noted in TNM stage I and II patients respectively. In stage III, 50% patients showed low and 50% high ploidy. There was no statistically significant relationship between the DNA pattern and TNM stages.

V positive patients are those where the tumour thrombi are found macroscopically in the branches of vessels including the portal vein, hepatic vein, and bile duct. A high incidence of high ploidy was noted in patients having positive Vp factor, and abscence of intrahepatic metastatic lesions (IM-O). The relationship was not statistically significant in the case of Vp factor but was significant in the case of intrahepatic metastatic lesions ($P<0.02$) (Table - II).

The DNA ploidy pattern was compared with the prognosis in patients with HCC. Follow-up was continued until death or December 1991. In all 15 cases, low ploidy was noted in six (40%) and high ploidy in nine (60%). All of the low ploidy patients are surviving with a range from 14 to 30 months. Among the nine high ploidy cases, three (33%) died from liver failure, and six (67%) are

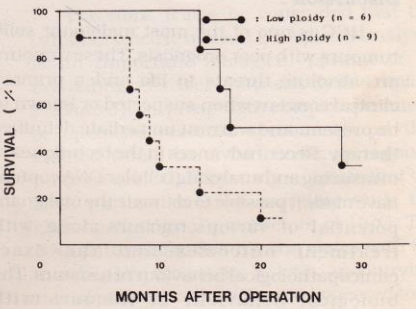


**Fig-3:** *Survival of patients with low ploidy and high ploidy of DNA pattern. There is a statistically significant difference in survival rates between patients with low and high ploidy tumours.*

surviving with a range from seven to 22 months. The 24 and 12 months survival in the six patients with low ploidy tumours were 50% each respectively. The 24 and 12 months survival in the nine patients with high ploidy tumours were zero and three (33%) respectively. The mean survival time was 22.5 months. The survival rate of 15 patients is shown in Fig. 3. There was a statistically significant difference in survival rates between patients with low and high ploidy tumours (P<0.01)

**Table-II**

*DNA ploidy and metastatic invasion*

| Variable | Number of patients | Number of low ploid (%) | Number high ploid (%) |
|---|---|---|---|
| Vp factor : | | | |
| Negative | 12 | 6 (50%) | 6 (50%) |
| Positive | 3 | 0 | 3 (100%) |
| IM factor * : | | | |
| IM-O | 12 | 3 (25%) | 9 (75%) |
| IM-1 | 3 | 3 (100%) | 0 |

* (P< 0.02)

**Discussion :**

HCC is one of the most malignant solid tumours with poor prognosis. These tumours are absolute threats to life and a primary clinical concern when suspected or known to be present, and warrant immediate definitive therapy. Recent advances in the techniques of measuring and analyzing cellular DNA content have made it possible to estimate the malignant potential of various tumours along with treatment outcomes and the exact clinicopathological behaviour of tumours. The biological behaviour of tumours with prognostic information is of great importance for evaluating the optimal treatment of the diseases. In this study, the specimens were fixed in 10% formalin for six to seven days and then embedded in paraffin. According to the method used in this study, single cellular suspension was prepared , in which adequate numbers of intact isolated nuclei were frequently found to have low background fluorescence. Cell disaggregation was obtained successfully. By using cytofluorometry, it is very difficult to differentiate between malignant and non-malignant cells after cell isolation.

Until now, many authors have analyzed suspected tumours and also histologically proven benign or malignant tumours, and predicted that the histograms behave like diploidy, aneuploidy, or polyploidy mode of DNA patterns. But it is not sure whether aneuploidy or polyploidy can be used as a criterion of malignancy or if it is an important biological characteristic that reflects the carcinogenic process having passed certain stage that may progress to invasion. Ezaki categorized the histograms into diploid and nondiploid pattern by the order of width of DNA distribution and reported that the ploidy pattern did not relate to the survival rates of patients with HCC and the frequency of aneuploidy was higher in tumour size exceeding 5 cm in diameter[2]. There was no correlation between the DNA pattern and presence of hepatitis B surface antigen or liver cirrhosis, but close correlation between DNA pattern and the morphological grading and age of the patients. It was also reported that there was no correlation between DNA distribution pattern and hepatitis B surface antigen positivity, presence of liver cirrhosis, tumour size, and survival rates[8]. Fujimoto reported that there was a clear correlation between DNA content and tumour size, and DNA aneuploidy indicated a worse prognosis than diploid tumours[3]. The survival rate was hgher in diploid than aneuploid cases in tumour less tan 5 cm in diameter, and the aneuploidy was frequently detected in tumour exceeding 5 cm in diameter[9]. Some authors categorized the histograms into low and high ploidy mode of DNA patterns and the prognosis was always worse in high than low ploidy mode which had an uneven postoperative course with no recurrence in early gastric

carcinoma[10]. In this study, we failed to show any statistically significant relationship between DNA patterns and clinicopathological behaviours of tumours. Koike reported that DNA content was widely distributed in the noncancerous part of the cirrhosis liver containing HCC[11]. In our study, the DNA content was also widely distributed in different non-tumour cirrhotic and hepatitic liver. The widely distributed DNA high ploidy in cirrhotic and hepatitic liver is a question which can not be clearly clarified. But we may assume that the liver with cirrhosis and chronic hepatitis has potential or highler susceptibiliy to develop carcinoma.

Ishizu did not find any difference in DNA content in different sites of the same tumour among 16 out of 17 tumour specimens[9]. In our study, the DNA content of two sites of the same tumour in two out of eight cases showed difference of ploidy pattern. It seems that the different areas of the same tumour can behave differently, may be due of the existence of some clones with different malignant potential.

Diploid pattern was more frequently found in TNM stage I than in stage III and IV[9]. In our study, low ploidy was more frequently found in TNM stage I than in stage II and III without any statistically significant difference.

Yamanaka in his study on prognostic factors found that portal invasion was the most incompatible condition with tumour free long term survival in HCC[12]. The distribution of intrahepatic metastatic lesions was found to be an influential prognostic factor. In this study, the DNA ploidy was compared with portal invasion and intraheptic metastatic lesions in HCC. A clear relationship was found between the DNA content and intrahepatic metastatic lesions.

The ploidy study in other words is an indirect way to measure quantitative changes in chromosome complement by measuring nuclear DNA content. It is not clear whether the DNA ploidy pattern is stable or not. Many reports concluded in favour of both stable and unstable ploidy pattern[13,14]. Comparing our study with the study of Ezaki[2], the discrepency was observed and that may be due to the differences in patient selection. In their report, patients undergoing various surgical prodedures, such as hepatic resection, hepatic arterial ligation, and cannulation were included. Many other controversial reports appeared in respect of DNA content with clinicopathological behaviours and prognosis[3,8,9]. The discrepency may be due to the differences between microspectrophotometric, cytofluorometric, and flow cytometric analysis, in patient selections, and also due to differences of method of histogram interpretation. In our series, hepatic resection was done in all the cases. Tumour recurrence was absent. DNA low ploid patients showed favourable and high ploid unfavourable outcome. The survival rate was higher in low than high ploidy cases. In this series, the presence of DNA high ploidy indicates a worse prognosis than do low ploidy tumours in HCC. The DNA ploidy pattern significantly relates to the intrahepatic metastatic lesions and survival rates of the patients. But there was no statistically significant relationship between DNA ploidy and clinicopathological behaviours of the patients.

Therefore, it can be concluded that the cytofluorometric nuclear DNA ploidy analysis is an important biological parameter in evaluating cells. It can be precisely and rapidly evaluated from preoperative biopsy specimens or operative resected specimens and this method would be of benefit for therapeutic purpose in HCC. This study suggests that the DNA pattern did not correlate with the clinicopathological parameters of HCC. The DNA pattern significantly correlates with the intrahepatic metastatic lesions, and survival rate of patients with HCC, and appeared to be a valuable indicator of treatment outcome.

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Journal of Bangladesh College of Physicians and Surgeons
Vol. 13, No. 2, May 1995

# Prevalence and Spectrum of Bronchial Asthma in School Children of Sylhet Town

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**Summary :**

**All children from play group to grade ten of schools in Sylhet town were screened for respiratory distress first by a questionnaire and then by selective clinical assessment. Prevalence of asthma was 6.39% in four to 15 years age group school children. Highest (23.47%) number of attacks was recorded at seven years of age. About 80% of asthmatic children had onset of wheeze by seven years and 40% within first two years of life. Male children suffered more (58.39%) compared to their female counter part (41.61%). Most of the children (85.60%) suffered during winter months and recurrence or persistence of symptoms was noted in 9.59% of cases.**

*(J Bangladesh Coll Phys Surg 1995; 13: 52–55)*

## Introduction :

Prevalence of asthma in childhood varies widely[1]. Robertson et al reported varying prevalence of wheeze in different age groups in government and nongovernemnt schools in greater Melbourne area of Australia[2]. In north Tyneside, 9.3% of seven years old children were found asthmatic[3]. Another study done by Strachan and Ross showed that the prevalence of childhood asthma was 11.1% in 1978 and 12.8% in 1991[4]. Childhood bronchial asthma is a common problem in our country also. This study is designed to find out the prevalence of the disease, its common symptomatology, precipitating factors and seasonal trends for better understanding of this common problem.

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Received : April 28, 1995 Accepted : May 8, 1995

## Materials and method :

A total of 9,144 students from play group to grade ten of schools in Sylhet town were screened for respiratory distress during winter months of the year 1991-92. Five government and five nongovernment schools were selected randomly. A questionnair was prepared for the purpose. All students, and in case of younger ones, their parents were asked whether the child ever had attacks of wheeze. Parents were told that wheezing meant noisy breathing with whistling quality coming from the chest and not just the throat and asked to answer 'yes' or 'no' or 'not sure'. Only those who answered 'yes' were included in this study.

Nine hundred and fourteen students were found to be symptomatic on the basis of positive response to questions on spontaneous wheeze. Of them, 136 were excluded because they had only a single attack or had other ailments such as tonsillitis, adenoids, upper respiratory tract infections or were lacking differentiation by the parents between wheeze and snoring, stridor and dyspnoea. Exclusion was done by examining each child and monitoring the response to bronchodilators of those who were experienicing episodic wheeze. Only those children who had convincing past medical records and those who were found to be asthmatic during screening were included in the analysis of data.

After indentifying the children who responded positively to questions on spontaneous wheeze, they were taken to a separate room. Detail history from the children or their parents were taken. History included the age of onset, frequency of attack, average duration of each attack, allergens and precipitating factors and family history of asthma. Their past medical records were also reviewed. A thorough physical examination was done. A complete blood count with total circulating eosinophil, chest X-ray, and routine stools investigation were done for those who were not investigated before.

**Results :**

A total of 584 children were diagnosed as having bronchial asthma. Three hundred and forty one of them were male and 243 female (Table-I).

**Table-I**

*Sex distribution of children with bronchial asthma*

| Sex | Number | Percentage |
|---|---|---|
| Male | 341 | 58.39 |
| Female | 243 | 41.61 |
| Total | 584 | 100.00 |

Students aged between four and 15 were included in the study. Age distribution is shown in Table-II.

**Table-II**

*Age distribution of children with bronchial asthma*

| Age (years) | Number | Percentage |
|---|---|---|
| 4—7 | 159 | 27.22 |
| 8—11 | 249 | 42.64 |
| 12—15 | 176 | 30.14 |

It appears that most of the children suffered from their first attack of bronchial asthma by seven years of age as shown in Table-III.

**Table–III**

*Age of onset of bronchial asthma in children*

| Age (years) | Number | Percentage |
|---|---|---|
| 1—3 | 185 | 31.68 |
| 4—7 | 208 | 35.62 |
| 8—11 | 178 | 30.48 |
| 12—15 | 13 | 2.22 |

Allergens were responsible in 40.80% cases. Among them, dust allergens in 41.18% cases, pollen in 9.8%, food in 27.45% and multiple allergens in 21.57% cases.

Most (85.61%) of the children suffered during winter season, only 0.8% in summer and another 13% children gave history of attacks in all seasons.

Night waking due to asthmatic attack was found in 18.4% children. A group (18.4%) of children suffered breathlessness at least once a week, and a small percentage (5.3%) of them missed school two or more times in a year because of breathlessness.

**Discussion :**

In this defined age group school children survey, a total of 584 out of 9,144 that is 6.39% were found asthmatic. Prevalence of asthma varies in different parts of the world. The prevalence of asthma in our study is far lower than that is found among Australian children. They showed that 34% of their children were asthmatic[5]. By seven years of age 23.47% of our children were asthmatic, which is similar to findings of a United Kingdom study where 19.4% of their children were asthmatic by age seven years[6], and a New Zealand study showing 29.4% prevalence in the same age group[7]. Table-IV shows the

prevalence of asthma in different age groups of children reported by different authors over past six years[3].

**Table–IV**

*Shows the prevalence of asthma in different age groups of children reported by differenct authors over past six years*[3]

| | | Age of children (years) | | |
|---|---|---|---|---|
| | | 7 | 12 | 15 |
| Southamton | 1986 | 11.9 | 12.30 | - |
| Dunidin | 1987 | 19.5 | - | - |
| Tyneside | 1987 | - | - | 8.60 |
| Cavicleff | 1988 | - | 15.20 | - |
| Melbourne | 1990 | 23.1 | 21.70 | 18.60 |
| Sylhet | 1992 | 23.47 | 10.45 | 2.74 |

The prevalence of wheeze fell with increasing age in all studies including the current one.

About 80% of asthmatic children usually have onset of wheeze by seven years of age and 40% within first two years of life[8]. In our study 57.2% children had onset by seven years and 28.25% became asthmatic by two years of age.

Overall incidence of asthma in boys and girls is same[8]. In our study 58.39% children were male and 41.61% female, although the number of female children in total surveyed population was slightly higher (51.71%). Most of the students (85.6%) included in this study suffered during winter months, only 0.8% suffered during summer. The seasonal trend grossly differs from studies done in other countries. Carswell et al found a fewer admissions in winter, rising in spring and early summer and reaching peak in autumn[5]. Admission in Royal Alexandria Hospital for Sick Children, Brighten and South-East Thames region showed similar picture[9]. In our country, winter months are dry and more dusty. So it is likely that temperature change, fungal spores, air pollutants and house dust mites are important factors for the seasonal variation.

Very frequent or persistent symptoms were found in 9.59% of the children which was slightly higher than what had been found in other countries[8]. But White et al reported breathlessness at least once a week in 47% of their sample and night waking at least once a week in 30% of cases[10] which is very high compared to our study. Turner and Warwick also showed similar picture that is 73% of a large sample of patients with symptoms of asthma were waking at least once a week and 39% every night[11]. Probably availability of treatment facilities and climatic condition is responsible for this difference. Atopy was found in 40.8% of our children while 63% of children were atopic in Tyneside study[3]. The finding needs further exploration.

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Journal of Bangladesh College of Physicians and Surgeons
Vol. 13, No. 2, May 1995

# Routine Histopathology of Tonsils after Tonsillectomy—A Study of 100 Cases

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**Summary :**

**Out of 100 tonsillectomies, the routine histopathological examination of the resected tonsils revealed that 94 (94%) patients had chronic tonsillitis, two (2%) tubercular tonsillitis, three (3%) non-Hodgkin's lymphoma and one (1%) had squamous cell carcinoma. Tuberculosis and malignancy were not suspected in any of these cases on clinical and radiological assessment. This indicates the importance of considering tuberculosis and malignancy as possible tonsiller pathology needing tonsillectomy in our clinical practice and all surgically removed tonsils should be subjected to routine histopathological examination.**

***(J Bangladesh Coll Phys Surg 1995; 13: 56–59)***

## Introduction :

Tonsillectomy is one of the commonly performed operations in our country as it is in many other countries. There is a lot of debate over the indication of tonsillectomy but there are some universally accepted indications. In our country, we perform tonsillectomy operation on the basis of clinical diagnosis and mostly after repeated attacks of tonsillitis. But after tonsillectomy, histopathological examination of the tissue removed may at times reveal pathology like tuberculosis[1], lymphoma[2] and squamous cell carcinoma[3]. In order to find out the exact pathology of the resected tonsils, histopathology of 100 random cases were done and is discussed in this paper.

## Materials and method :

For the purpose of the study, patients were collected from ENT out patients department and ENT ward of Institute of Postgraduate Medicine and Reseacrh (IPGMR) Hospital and Dhaka Medical College Hospital, Dhaka, from January 1990 to December 1990.

One hundred patients from three to 55 years of age belonging to different socio-economic groups were included in this study. The average age was 17.59 years with a sex ratio M:F of 5.7:4.3.

The diagnosis of chronic tonsillitis, tubercular tonsillitis and malignancies were established on the basis of history, clinical, haematological, bacteriological, radiological findings and histopathological examination of the resected tonsils.

## Results :

In 100 patients included in the study the lowest age at presentation was three years and the highest 55 years with a mean of 17.59 years. The maximum number of patients (39%) were in the age group of 11 to 20 years. The series composed of 57 males and 43 females with a male to female ratio of 5.7: 4.3.

The age and sex incidence is shown in Table-I and II. Chronic tonsillitis was the commonest indication for tonsillectomy . The clinical diagnosis on the basis of which tonsillectomy was done in this series is shown in Table-III.

The histopathological diagnosis of the tonsillectomy specimens is shown in Table -IV

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Received : June 06, 1994; Accepted : May 08, 1995

and the correlation between clinical and histopathological diagnosis is shown in Table-V.

**Table—I**

*Age and sex incidence of the patients (n=100)*

| Age (years) | No. of patients | % | Sex distribution M | F |
|---|---|---|---|---|
| 0-11 | 29 | 29 | 15 | 14 |
| 11-20 | 39 | 39 | 19 | 20 |
| 21-30 | 20 | 20 | 15 | 5 |
| 31-40 | 7 | 7 | 4 | 3 |
| 41-55 | 5 | 5 | 4 | 1 |
| Total | 100 | 100 | 57 | 43 |

**Table–II**

*Mean and average age and sex ratio*

Mean age in years for male- 17.28 years
Mean age in years for female- 17.79 years
Average age in years - 17.59 years
Sex ratio (M:F)- 5.7: 4.3

**Table—III**

*Indication for tonsillectomy (n=100)*

| Indication | No. of patients | % |
|---|---|---|
| 1. Chronic tonsillitis | 88 | 88 |
| 2. Peritonsillar abscess | 3 | 3 |
| 3. Enlarged tonsils | 4 | 4 |
| 4. Unilateral enlargement with and without ulceration | 5 | 5 |

Histological findings were consistent with clinical diagnosis in 98.95% of cases of chronic tonsillitis, whereas those in unilateral tonsiller enlargment were consistent in 80% of cases.

**Fig-1:** *Photomicrograph of chronic tonsillitis showing hyperplasia of lymphoid tissue with interstitial infiltration of lymphocytes, plasma cells and macrophages. There is increase in reticular and collagen fibres (fibrosis) (H and E X 330).*

**Fig-2:** *Photomicrograph of tuberculosis of tonsil showing mutiple tubercle formation with epithelioid cells, Langhan's giant cells sorrounded by lymphocytes and fibrous tissue with central caseation ( H and E X 330).*

**Table–IV**

*Postoperative histopathological examination findings (n=100)*

| Histopathological diagnosis | No. of patients | % |
|---|---|---|
| 1. Chronic tonsillitis | 94 | 94 |
| 2. Non-Hodgkins lymphoma | 3 | 3 |
| 3. Tubercular tonsillitis | 2 | 2 |
| 4. Squamous cell carcinoma | 1 | 1 |

**Table—V**

*Clinical diagnosis and corresponding histopathological findings (n=100)*

| Group | Clinical Diagnosis | No. of patients | Histopathological diagnosis | No. of patients |
|---|---|---|---|---|
| A. | Chronic tonsillitis | 88 | Chronic tonsillitis | 94 |
| | Peritonsillar abscess | 3 | Tubercular tonsillitis | 1 |
| | Enlarged tonsil causing difficultly in swallowing | 4 | | |
| B. | Unilateral enlargement with and without ulceration | 5 | Non-Hodgkins lymphoma | 3 |
| | | | Squamous cell carcinoma | 1 |
| | | | Tuberculosis | 1 |

**Fig-3:** *Photomicrograph of non-Hodgkin's lymphoma of tonsil showing diffuse infiltration of tonsiller tissue with neoplastic lymphocytes having prominent nuclei (H and E X 330).*

**Fig-4:** *Photomicrograph of squamous cell carcinoma of tonsil showing infiltration of tonsiller tissue with malignant epithelial cells having prominent nuclei and frequent mitosis. (H and E X 330).*

**Discussion:**

Chronic tonsillitis is the commonest indication for tonsillectomy[4] although this operation is also done in some of the cases of peritonsillar abscess[5], sleep apnoea syndrome,[6] and unilateral enlargement of tonsils with or without surface ulceration[3]. For exact diagnosis, it is important to do histopathology of tonsils after tonsillectomy.

In this study, 100 tonsillectomy specimens after histopathological examination revealed that in 94 cases the report was consistent with chronic tonsillitis (Fig -1) and in one which was clinically diagnosed as chronic non-specific tonsillitis, histopathological examination showed evidence of tuberculosis (Fig-2). Out of five unilaterally enlarged tonsils with or without surface ulceration, three had evidence of non-Hodgkin's lymphoma (Fig-3), one tubercular tonsillitis and one squamous cell carcinoma (Fig-4).

Since the patients in whom malignancy was reported did not turn up for follow up after they were referred for radiotherapy, the ultimate fate of those patients is not known.

In two cases of tubercular tonsillitis, after a couple of months of treatment by antitubercular drugs the ESR level came down to 25 mm and 20 mm in the first hour from pretreatment 100 mm and 80 mm in the first hour respectively.

In this series, it has been revealed that majority of the cases had been suffering from chronic non-specific tonsillitis. The incidence of tuberculosis and malignancy was quite significant. It is wiser to undertake histopathological examination of all specimen to avoid unnecessary risk. The incidence of pulmonary tuberculosis still is very high in Bangladesh but laryngeal and pharyngeal tuberculosis are relatively uncommon. Tubercular infection of tonsils and neck glands are usually caused by the bovine type while in pulmonary tuberculosis the human type is the usual causative agent. The source of the bovine tuberculosis in tonsils is mostly from infected cow's milk. The relatively low incidence of bovine tubercular infection is possibly due to less availability of cow's milk. The use of breast feeding will reduce this incidence to a still lower level.

In conclusion, it is suggested that the tonsils removed surgically should be examined histopathologically in all cases to avoid unnecessary risk like tuberculosis and malignancies especially in the countries where these diseases are common.

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REVIEW ARTICLE

J Bangladesh Coll Phys Surg 1995; 13: 60–72

# Thrombolysis in Myocardial Infarction—Current Concepts and Recommendations

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**Introduction:**

The early treatment of acute myocardial infarction (AMI) with intravenously administered thrombolytic agents represents an important advance in the management of AMI. A large body of data from more than 45 randomized controlled trials have convincingly demonstrated that thrombolytic therapy reduces short-term and long-term mortality after acute myocardial infarction[1]. The observation of Dewood et al that more than 85% of patiets with AMI have an occluded coronary artery within the first three hours[2] and the anatomical descriptions of atherosclerotic lesions in these patients by Davies and Thomas provided the foundation for the concept of acute thrombolysis at the site of a fissured or ruptured plaque and ushered the era of thrombolysis in AMI[3]. Since these seminal observations, several placebo-controlled randomized clinical trials have documented the beneficial effect of thrombolysis on early and late survival in AMI. Now the efficacy of thrombolysis on infarct size, left ventricular function, short term and long term survival has been clearly demonstrated[4]. Thrombolytic therapy has been demonstrated to recannalize occluded coronary arteries, reduce infarct size thereby limiting cardiac dysfunction and reduce mortality. Intravenous thrombolysis has been shown to establish reperfusion in 50 to 90 percent of patients with myocardial infarction and to reduce mortality by approximately 30 to 40 percent when compared with placebo[5].

Approximately 66% of heart attack victims at hospital entry have ST segment elevation, making it likely that the process is caused by an occlusive coronary clot. In patients with this finding, clot dissolving therapy in the form of intravenous streptokinase (SK), recombinant tissue-type plasminogen activator (rt-PA) or anisoylated plasminogen streptokinase activator complex (APSAC) can dissolve the clot and restore flow, interrupt the infarction, reduce myocardial necrosis and improve survival if therapy is delivered within six hours of the onset of the attack[6].

**Currently available thrombolytic agents:**

Three thrombolytic drugs, streptokinase (SK), recombinant tissue plasminogen activator (rt-PA), and anisoylated plasminogen streptokinase activator complex (APSAC), are commercially available and widely used in the treatment of AMI[7]. Urokinase is a very effective thrombolytic but not yet approved by FDA in the treatment of AMI. rt-PA, SK and APSAC, these three drugs differ in their clearance, fibrin selectivity, plasminogen binding and in the potential to induce allergic reaction. Streptokinase is a natural product of haemolytic streptococci. In human circulation, SK forms a complex with plasminogen; the complex subsequently can activate plasminogen to form plasmin in the plasma and on the surface of thrombi. Anisoylated plasminogen streptokinase activator complex,

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Received : May 17, 1995 Accepted : May 22, 1995

or anistreplase, is a preformed complex of SK and plasminogen which becomes spotaneously activated after intravenous administration. Once activated, it behaves identically to SK except that its half life is longer. Although easier to administer, there is no compelling medical reason to choose APSAC rather than SK in any clinical situation[5]. rt-PA is a naturally occuring enzyme produced by a number of tissues, including vascular endothelial cells. The rt-PA molecule has a binding site for fibrain, allowing it to attach to a formed thrombus preferentially and lyse it, without extensively activating plasminogen in the general circulation. When rt-PA is given at current clinical dosages, however, some systemic plasminogen activation does occur[8]. Urokinase is a true enzyme, derived initally from urine and subsequently from renal parenchymal cell culture. Urokinase is a serine protease that directly cleaves a specific peptide bond in plasminogen and converts it to its active form, plasmin[9].

**Table—I**

*Comparison of available thrombolytic drugs*

| Characteristic | SK | APSAC | rt-PA |
|---|---|---|---|
| Plasma clearance time (min) | 15-25 | 50-90 | 4-8 |
| Fibrin specificity | minimal | minimal | moderate |
| Plasminogen binding | indirect | indirect | direct |
| Potential allergic reaction | yes | yes | no |

Adapted from anderson HV, Willerson JT. N Eng J Med 1993; 329: 703-9.

**Results of current megatrials :**

*GISSI-1*

The first large study on thrombolytic therapy was conducted in Italy and is known by the acronym GISSI (Gruppo Italiano per lo Studio della streptochinasi nell' Infarto Miocardico). In this trial 11,712 patients presenting within 12 hours of the onset of acute infarction and free of contraindications to thrombolytic therapy were randomly assigned to treatment with one hour intrarvenous infusion of 1.5 million units SK or to conventional care with no SK[10,11]. The 21 day mortality rate in the SK group was 10.7% compared to 13.0% in the control group, a singnificant 18% reduction in mortality. The earlier the treatment was started, the more effective it was. In patients whose treatement started within three to six hours, SK resulted in a 17% reduction in mortality; in zero to three hour group, it reduced mortality by 23% and in those treated within one hour of symptoms by 47%.

*GISSI-2*

In the Gruppo Italiano Per La Studio Della Streptochinasi nell' Infarto Miocardico-2 (GISSI-2) 12,490 patients with suspected AMI of less than six hours duration were radomized to rt-PA (conventional three hours infusion) or SK, and to receive subcutaneous heparin 12,500 units subcutaneously every 12 hours after rt-PA and SK or no heparin[12]. The primary end point of GISSI-2 was 15-day all-cause mortality, severe left ventricular damage or both. The latter was defined as symptomatic or asymptomatic left ventricular systolic dysfunction (left ventricular ejection <35%). At 15 days there was no significant difference in death or left ventricular damage between patients treated with rt-PA and SK (9.0% vs 8.6%).

*ISIS-2*

The investigators participating in the second International Study of Infarct Survival (ISIS-2) have reported baseline and outcome data in 17,187 patients with suspected myocardial infarction who were recruited within 24 hours of the onset of chest pain[13]. These patients were randomized to intravenous SK (1.5 million units over 60 minutes), oral aspirin (160 mg/day for one month) to both or to neither in a double-blind

fashion by means of matching placebos. When the data were analyzed for mortality at five weeks after trial entry, the ISIS-2 investigators observed that the 8,592 patients assigned to streptokinase treatment experienced 9.1% vascular deaths compared to 11.8% in the 8,595 patients assigned to receive placebo, a 23% reduction in mortality (P<0.00001)

*ISIS-3*

In the International Study of Infarct Survival-3 (ISIS-3) 41,299 patients with suspected AMI were randomized to rt-PA (conventional three hour infusion), SK or APSAC and to heparin 12,500 units subcutaneously every 12 hours started four hours later or no heparin[14]. The primary end point was 35-day all-cause mortality. There was no difference in mortality among patients treated with rt-PA, SK and APSAC (10.3%, 10.6% and 10.5% respectively.)

*TIMI -Phase 1*

Three hundred and sixteen patients with AMI were randomly assigned to Thrombolysis In Myocardial Infarction phase-1 (TIMI phase–1) trial to rt-PA or SK. In this randomized, double blind, multicentre trial, intravenous rt- PA was found almost twice as effective as intravenous SK in opening occluded infarct-related coronary arteries[15].

*ASSET*

Investigators participating in the Anglo Scandinavian Study of Early Thrombolysis (ASSET) randomized 5,011 patients with suspected myocardial infarction within five hours of onset to either 100 mg of rt-PA over three hours or placebo[16]. Aspirin was not given. At one month, the total mortality rate in the rt-PA assigned group was 7.2% compared to 9.8% in those assigned to placebo, a 26% reduction in mortality (P=0.0011).

*The European Cooperative Group*

The Eruopean Cooperative Group reported a randomized double blind, controlled trial comparing rt–PA (100 mg given over three hours) with placebo within five hours of symptom onset [17]. The 14 day mortlaity rate was 2.8% in the group assigned to rt-PA and 5.75% in the placebo group, a 51% reduction in mortality.

*AIMS*

APSAC Intervention Mortality Study (AIMS) group in the United Kindom conducted a multicentre, double-blind, placebo-controlled evaluation of APSAC (30 units intravenously over five minutes) in patients below 70 years of age admitted within six hours of chest pain associated ST elevation[18]. The preliminary report on 1,004 patients revealed a 30 days mortlaity rate of 12.2% in the placebo group and 6.4% in patients assigned to APSAC. The overall mortality reduction was 47%. The estimated one year mortality rate was 19.4% and 10.8% in the placebo and APSAC groups respectively, a 44% reduction in mortality (P=0.0006).

*GUSTO*

Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) randomly assigned 41,021 patients to four different thrombolytic strategies[19]. The mortality rates in the four treatment groups were as follows: SK and subcutaneous heparin, 7.2%; SK and intravenous heparin7.4%; accelerated rt-PA and intravenous heparin, 6.3%; and the combination of both thrombolytic agents with intravenous heparin, 7.0%. This represented a 14% reduction in mortality for accelerated rt-PA compared to other strategies. The rates of haemorrhagic stroke were 0.49%, 0.54%, 0.72%, and 0.94% in the four groups respectively which represented a significant excess of haemorrhagic strokes for accelerted rt-PA and for the combination strategy.

**Dose and administration of thromboytics:**

The standard dose of SK is 1.5 million units infused over 30 to 60 minutes. Common

complications of SK include hypotension and allergic reactions. It is recommended that another thrombolytic agent should be used if a patient has received SK in the past. The dose of APSAC is 30 units given intrvenously over two to five minutes. APSAC has a similar spectrum and incidence of complications as SK. rt-PA may be administered in two ways, in conventional dose and in acelerated dose as proposed by GUSTO. The current recommendation is to give 100 mg intravenoulsy over three hours– a 10 mg bolus is followed by an infusion of 50 mg over the first hour and then 20 mg/h is administered for the next two hours[5]. In GUSTO, rt-PA was administered in accelerated or front–loaded regimen consisting of 90 mg over 90 minutes. Front–loaded rt-PA has not yet been approved by the FDA[7]. A standard regimen of urokinase would be one to 1.5 million units as an intravenous bolus followed by an infusion of one to 1.5 million units over one hour.

Although intracoronary thrombolysis results in a greater rate of reperfusion at 90 minute than intravenous thrombolysis given at the same time point, randomized trials have not shown a greater benefit with respect to mortality. Possible reasons for this discrepancy include delayed administration of thrombolytic agents with the intracoronary route and an inadequte correlation between the 90 minute patency rate and efficacy. In the typical clinical setting, the intravenous route is the best for thrombolytic agents[5].

**Selection of optimal thrombolytic— is it an important issue?**

The weight of data from the large randomized trials indicate that it is more important to decide whether to give thrombolytic agents than which agent to give. Although GUSTO suggests that accelerated rt-PA offers a small survival benefit over SK (an absolute difference of one life saved per 100 patients treated), SK is six to 20 fold less expensive. The cost effectiveness of routinely using rt-PA therefore remains an issue[5]. Moveover, there was no difference in mortality among patients treated with rt-PA, SK and APSAC in ISIS-3 trial.[13] GISSI-2 trial also failed to document superiority of rt-PA over SK[12]. GUSTO investigators presume that rt–PA may be superior to SK despite the excess risk of strokes with rt-PA[19]. The more rapid delivery of the agent and presumably faster opening rates of occulded arteries, may have also accounted for the improved efficacy of rt-PA in the GUSTO trial[19]. But accelerated rt-PA has not yet been approved by the FDA[7].

In routine use, rt-PA in conventional dose does not have definite advantage over SK. But in special circumstances the choice may vary. SK is associated with a lower risk of intracerebral bleeding and is thus the preferred thrombolytic drug for the elderly patients with AMI. Hypotension is a common complication of all thrombolytic agents. SK and APSAC, unlike rt-PA, may cause hypotension in as many as 10% of all treated patients[1]. Thrombolytic therapy, particularly rt-PA, may be considered in patients with AMI complicated by cardiogenic shock if immediate coronary angioplasty or surgical revascularization is not feasible. The use of thrombolytic drugs such as SK and APSAC, which may cause hypotension, should be avoided in patients with AMI complicated by cardiogenic shock[1].

**Adjunctive therapy after thrombolysis :**

Thrombolytic agents act mainly by promoting lysis of an occlusive intracoronary thrombus. Approximately 20 to 30 percent of patients fail to reperfuse following thrombolysis[21-23] and approximately 10 to 25 percent undergo reocclusion following successful thrombolysis [24,25]. Both SK and rt-PA, and presumably all plasiminogen activators, are associated with a curious paradoxical phenomenon of increased local thrombin generation, probably as a result of its elaboration from the dissolving clot. This leads to enhanced platelet aggregabiliy, since thrombin is a potent platelet activator, and

therefore to an increased potential for thrombosis. There may be lesser degrees of this prothrombotic state when agents such as SK or APSAC are used, since they lead to slightly more systemic fibrinogen depletion and higher levels of fibrin degradation products than does rt-PA[9]. When combined with thrombolytic agents, antiplatelet and antithrombin agents are directed at reducing this procoagulant activity in an effort to maintain infarct related artery patency.

The first demonstration of the clinical efficacy of aspirin in acute myocardial infarction either alone or combined with thrombolytic therapy came from the ISIS-2 trial[13]. Within this trial, in the group of patients randomly assigned to receive aspirin alone, there was a 23% reduction in mortality, whereas in the gorup randomly assigned to receive intravenous SK alone, there was a 25% reduction. The group that received both aspirin and SK had a 42% reduction in mortality as compared to the group that received neither agent, suggesting that the benefits of this combination were additive[13]. When rt-PA is the thrombolytic agent given, intravenous heparin is required to help maintain vessel patency and prevent reocclusion. With other available agents the need for intravenous heparin is less clear. In a meta-analysis of trials involving approximately 70,000 patients, intravenous heparin appears to reduce mortality when used with other thrombolytic agents as well.

Based on standard practice and the GUSTO data, it is recommended to use intravenously administered heparin when rt-PA is used for thrombolysis. It is important that heparin be started within 90 minutes of rt-PA, since rt-PA does not induce a systemic lytic state. Heparin should be started with a bolus of 5,000 units followed by 1000 U/h and should be adjusted to maintain an activated partial thromboplastin time (aPTT) of 1.5 to 2.0 times control. Heparin should be started three to four hours after administration of SK. It remains unproved whether intravenously administered heparin adds benefit over subcutaneously given heparin after administration of SK[14,19,26,27].

The treating physician should consider giving a combination of a thrombolytic agent, 160 to 325 mg of oral aspirin and intravenously heparin to maintain the activated aPTT at 1.5 to 2.0 times the control value for 24 to 72 hours. Aspirin should be given immediately, and the heparin infusion should begin during or at the completion of the thrombolytic infusion[9]. Idealy heparin should be given for three to four days, although if aspirin is used, heparin can be safely discontinued after 24 hours, especially in patients at increased risk for bleeding[27].

**Complications of thrombolytic therapy :**

Bleeding is a common complication following administration of thrombolytic agents. The mechanisms responsible for systemic haemorrhage include lysis of haemostatic plugs, systemic depletion of fibrinogen and other coagulation factors, and platelet dysfunction[28]. Intracranial haemorrhage is the most serious complication of thrombolytic therapy, since it has an average mortality of 63%[22]. Haemorrhagic stroke usually occurs in 0.5 to 1% of patients treated with thrombolytics[29,30]. In the GISSI-2 trial, rt-PA was associated with an excess of four haemorrhagic strokes per 1,000 treated patients, compared to SK[12]. The GUSTO trial provided a unique opportunity to compare intracerebral bleeding rates with front-loaded rt-PA and SK in combination with IV heparin in more than 40,000 patients with AMI. In that trial, front-loaded rt-PA combined with IV heparin caused slightly but significantly more haemorrhagic strokes than SK combined with sub-cutaneous or IV heparin (0.72% vs 0.54% and 0.49% respectively). In practical terms, for every 1,000 patients treated, there is an excess of two haemorrhagic strokes with

rt-PA compared to SK (GUSTO). In GUSTO trial 5.4 to 6.3% of the patients treated with thrombolytics develped serious peripheral bleeding[19]. Gastrointestinal haemorrhage of varying severity can be expected in 5% of patients and genitourinary bleeding in similar number[6].

Hypotension is a common complication of all thrombolytic agents and can result from bleeding, anaphylaxis or the production of bradykinin during plasmin generation[31]. Patients receiving SK have an average decrease in systolic blood pressure of 35 mm of Hg. In ISIS-3, twice as many patients experienced hypotension with SK and APSAC compared to rt-PA[14]. Allergic reactions occur in 4-6% of patients treated with SK or APSAC due to interaction of the drug with preformed streptococcal antibodies[13-19]. Anaphylaxis occurs in 0.1 to 0.7 % of patients[5]. Prophylactic treatment with steroids did not prevent severe reactions in ISIS-2 trial and is no longer recommended[13].

**Monitoring after thrombolytic therapy :**

Before administration of thrombolytic agent, a baseline neurological examination, including mental status should be performed and blood should be sent for grouping, haematocrit, platelet count, prothrombin time and aPTT[5]. A brief neurological examination should be done several hours after thrombolysis and then daily. Haematocrit, platelet count and specifically aPTT should be checked daily to look for bleeding and to adjust the dose of intravenously administered heparin[28]. In case of major bleeding, thrombolytic agent, aspirin and heparin should be stopped and blood transfusion, fresh frozen plasma transfusion or cryoprecipitate administration may be needed[28].

**ECG evidence of coronary reperfusion after thrombolysis:**

Approximately 20 to 30% of patients fail to reperfuse the infarct related artery in the first several hours after thrombolytic treatment [21,22,32]. No single marker, including ventricular arrhythmias or resolution of chest pain, had sufficient sensitivity and specificity in detecting reperfusion of occluded coronary artery after thrombolytic therapy[33]. Accelerated idioventricular rhythm is a marker of reperfusion but it's specificity and sentistivity is approximately 60 to 70%[33]. Early abrupt increase in serum CK activity measured at 15 minute intervals is also a sign of reperfusion but it is inferior to the ECG markers in detecting reperfusion[34]. Findings from a study of ECG prediction of coronary artery patency after thrombolytic therapy suggested that the amount of early resolution of ST segment elevation might be a useful prognosticator[35]. In contrast to other ST segment markers with a higher sensitivity for coronary perfusion, resolution of ST segment elevation more than 70% at three hour after the start of thrombolytic therapy was a major predictor of favourable outcome. ST segment resolution more than 70% indicates favourable outcome and possibly reperfusion after thrombolytic therapy. According to the study of Saran et al, less than 30% ST segment resolution appeared to be cutoff point for predicting a unfavourable outcome [34]. ST segment resolution more than 70% at three hour after thrombolytic therapy does not only indicate reperfusion but also indicate the development of small infarct. These patients have a low short and long term mortality rate [35]. The group with ST segment resolution less than 30% includes not only patients with persistent vessel occlusion but also those in whom lack of reperfusion is associated with the developemnt of large infarcts and accordingly, high short and long term mortality rates[34]. Except ST segment resolution, early T wave inversion, within 24 hours of administration of thrombolytic therapy suggests reperfusion in the occluded coronary, better perfusion grade and left ventricular function and a more benign in-hospital course[36].

**Thrombolysis in elderly patients—is it rational?**

Meta-analysis and subgroup analysis of the large trials show a signficant improvement in mrotality in patients of all ages treated with thrombolytics[14,26,37]. Elderly patients with AMI have a strikingly high mortality both during and following hospitalization. In the Worcester Heart Attack Study of 2,115 conseeutive patients hospitalized with confirmed AMI between 1975 and 1984, the hospital case fatality rate of AMI increased from 5% in patients younger than 55 years, to 7.9% in those 55 to 64 years, to 16.1% in those 65 to 74 years, and to 32.1% in patients 75 years of age and older[38]. Similarly, in the MITI (Myocardial Infarction and Intervention) registry of 3,256 consecutive patients hospitalised for AMI, hospital mortality increased strikingly with advancing age (2% in patients less than 55 years, 4.6% in those 55 to 64 years, 12.3% in those 65 to 74 years and 17.8% in patients more 75 years)[39]. In five randomized prospective controlled clinical trials thrombolysis decreased hospital mortality from 22.1 to 17.9% in about 7,000 elderly patients with AMI[13,16,18,40]. Compared to younger patients, the overall absolute percentage in mortality rate in the elderly was two folds greater[1]. So it appears that thrombolytic therapy has a greater impact on the mortality in elderly patients. Although ISIS-2 and GISSI-2 found an increased risk of stroke in elderly, there was no excess in patients receiving thromblytics. This was because a slight increase in haemorrhagic strokes (approximately 0.4%) in patietns receiving thrombolytics was balanced by a decrease in ischaemic strokes[41]. The ISIS-2 determined that patients 80 years old and more had 20% mortality when treated with the combination of SK and aspirin, compared to a 37% mortality with placebo[13]. In terms of absolute lives saved per 100 treated patients, the elderly benefitted much more than younger patients. Advanced age itself is therefore no longer a contraindication to thrombolysis[5].

**Combinations of thrombolytics—is it justified?**

Since no more than 85% of all patients treated with any single thrombolytic drug achieve successful coronary reperfusion, efforts at optimizing efficacy of thrombolytic therapy led to the evaluation of the efficacy of the combination of two thrombolytic drugs. Three larger randomized trials showed greater early patency rates, lower recurrent ischaemic events and lower in-hospital complications with the combination of rt-PA with either SK or urokinase when compared with either drug used alone. These trials also documented no excess bleeding complications from combination of thrombolytic agents[42-44]. But the sample sizes were too small in these studies. Recently GUSTO trial results have been published. In GUSTO trial, compared to front-loaded rt-PA alone, the combination of low dose SK and low dose rt-PA in more than 10,000 patients was associated with a higher 30-day mortality, a lower early (90 minute) coronary patency, but a similar late reocclusion rate[19]. Moreover, bleeding complications, including haemorrhagic strokes were more common in patients who received the combination of rt-PA and SK compared to rt-PA alone[19]. Thus, in the GUSTO trial, the ombination of low dose rt-PA and low dose SK was worse than rt-PA alone, insofar as it was associated with higher mortality, lower early patency, more haemorrhagic strokes and similar reocclusion rate. Based on available data and on the conclusion of GUSTO trial, it can be concluded that thrombolytic combination therapy should not be recommended in AMI. Further research is required in this field.

**Thrombolysis in special subsets of patients:**

The use of thrombolytic agent in AMI with cardiogenic shock is controversial. SK and APSAC unlike rt-PA, may cause hypotension in as many as 10% of all treated patients. Thrombolytic therapy, particularly rt-PA, may

**Table–II**

*Criteria for thrombolysis in acute myocardial infarction*

| |
|---|
| Chest pain consistent with acute myocardial infarction |
| Electrocardiographic changes |
| ST segment elevation > 0.1 mV in at least two contiguous leads |
| New or presumably new left bundle branch block |
| ST segment depression with prominent R wave in leads V2 and V3 if this is thought to indicate a posterior infarction (benefit is doubtful if it is thought to indicate unstable angina) |
| Time from onset of symptoms: |
| <6 hours : most beneficial |
| 6-12 hours : lesser but still important benefits |
| > 12 hours : diminishing benefits but possibly still useful for continuing chest pain or "stuttering" infarct |
| Age: |
| Physiological age is more important than chronological age |
| < 75 years : clear cut benefits<br>> 75 years : fewer clear cut benefits |

Adapted from anderson HV, Willerson JT. N Eng J Med 1993; 329: 703-9

**Table–III**

*Relationship between reduction in hospital mortality and timing of thrombolytic therapy*

| Time (hours) | SK % | Placebo % | Reduction in mortality% |
|---|---|---|---|
| <1 | 8.2 | 15.4 | 51 |
| 0-3 | 9.2 | 12 | 26 |
| 3-6 | 11.7 | 14.1 | 20 |
| 6-9 | 12.6 | 15 | 13 |
| 9-12 | 15.8 | 13.6 | -19 |

Adapted from the GISSI Trial. Lancet 1986; 1: 397-401

be considered in patients with AMI complicated by cardiogenic shock if immediate coronary angioplasty or surgical revascularization is not feasible[1]. At present, uncontrolled hypertension defined as systolic blood pressure above 180 mm of Hg, a diastolic blood pressure above 110 mm of Hg or both is considered a relative contraindication to all three commercially available thrombolytic drugs[1]. About a third of the patients with AMI present with an initially elevated blood pressure or a known history of hypertension. The large majority of these patients respond promptly to sublingual and intravenous nitrates, intravenous beta-blockers, analgesics and bed rest. In the absence of any documented evidence of increased risk in these patients, these patients should receive a thrombolytic drug after control of their initially elevated blood pressure. Thrombolytic therapy should be considered in patients with an initial blood pressure in excess of 180/110 mm of Hg after effective lowering of blood pressure[1]. Diabetes is not a contraindication for thrombolytic therapy. Proliferative retinopathy but no background retinopathy is a relative contraindication for thrombolytic therapy. In the TAMI trials, bleeding complications were similar in diabetic and non–diabetic patients[45]. Prolonged cardiopulmunary resuscitation (CPR) has been considered an absolute contraindication for the use of thrombolysis primarily because of the fear that rib and sternal fractures may predispose patients to severe intrathoracic bleeding when treated with a thrombolytic drug[46]. To assess the bleeding complicatios in patients undergoing brief CPR less than 10 minutes after receiving thrombolytic therapy, 708 consecutive patients from the TAMI trials were evaluated but there was no increase in bleeding complication[47]. Patients with AMI complicated by cardiac arrest requiring CPR less than 10 minutes should receive thrombolytic therapy, if they have no clinical evidence of cardiac tamponade prior to initiation of thrombolysis. Left bundle branch

**Table–IV**

*Contraindications of thrombolytic therapy*

Absolute :

1. Recent (< 2months) thrombolytic stroke
2. History of haemorrhagic stroke, intracranial tumour, arteriovenous malformations or arterial aneurysm (recent or remote)
3. Previous neurosurgery or recent (<1 month ) head truma
4. Prolonged (>10 min) CPR complicated by strenal and rib fractures
5. Persistent severe uncontrolled hypertension (>180/110 mm of Hg) despite pharmacological therapy
6. Active gastrointestinal bleeding or active bleeding from non-compressible vessels
7. Aortic dissection
8. Bleeding diathesis

Relative :

1. Remote (>2 months) thromboembolic stroke or TIA
2. Prolonged (>10 minutes ) CPR
3. Recent puncture of a noncompressible vessel
4. Proliferative diabetic retinopathy

*Adapted from Habib GB. Chest 1995; 107: 528-34*

block (LBBB) has been an exclusion criterion in most thrombolytic clinical trials primarily because it may mask the typical ECG changes of AMI such as standard segment elevation. In ISIS-2 trial 27.7% of mortality reduction was documented in this subgroup of patients with LBBB and AMI[13]. Patients presenting with AMI and LBBB are a high risk subgroup and should receive thrombolytic therapy.

One important question is that whether patients presenting with the clinical symptom of AMI and ST segment depression should receive thrombolytic therapy. In both GISSI and ISIS -2 trials, patients with suspected AMI and initial ST segment depression derived no benefit from thrombolytic therapy [10-13]. In TIMI—3B trial 683 patients with unstable angina or non-Q myocardial infarction with initial ST segment depression were randomized to rt–PA or placebo.But there was no benefit documented over the placebo[48]. At present thrombolytic therapy is not recommended in patients with unstable angina or non-Q wave infarction[1].

Inferior wall infarction is associated with a lower short and long term mortality compared to anterior AMI [12,13]. Previously it was believed that anterior infarction has the highest mortality rate and benefits most from thrombolytic therapy and the efficacy of such therapy is less clear in inferior myocardial infarction[6]. Patients with inferior infarction did not have a significant reduction in mortality rate in GISSI trial[6]. But this view has been changed in recent past. In a large sample of 12,014 patients with inferior infarction, mortality was significantly reduced by 22% by administration of thrombolytics[37]. Thus on the basis of meta-analysis it would appear that thrombolysis confers a survival benefit in patients with acute inferior wall infarction. So thrombolytic therapy should be used in all patients with inferior wall infarction in the absence of absolute contraindications to thrombolytic therapy, particularly in the presence of right venrticular infarction[1,49].

**Late thrombolysis—how far it is beneficial?**

The GISSI trial showed that improvement in survival after thrombosis was inversely related to the delay in treatment. Hospital mortality decreased 51% in patients treated within one hour, 26% in those treated within three hours and 20% within three to six hours, after symptom onset, with no further improvement in survival after six hours [12]. Two randomized trials, Late Assessment of Thrombolytic Efficacy (LATE) and the Estudio Multicentrico Estreptoquinasa Republicas de America del Sur (EMERAS) trial have been published in the recent past. Both of these trials have evaluated the efficacy and safety of late thrombolysis. In LATE trial 5,711 patients

with symptoms and electrocardiographical criteria consistent with AMI were randomized to intravenous rt-PA or matching placebo [50]. Among patients treated six to 12 hours after symptom onset 35-day mortality reduction was 27%, significantly lower in the rt-PA group when compared with the placebo group (8.7% and 11.9%, respectively). Mortality rates were 8.7% and 9.2% respectively for those treated at 12 to 24 hours. LATE investigators concluded that the time window for thrombolysis with rt-PA should be extended to at least 12 hours from symptom onset in patients with AMI. In the EMERAS trial, patients with suspected AMI presenting between seven hours and 24 hours after symptom onset were randomized to SK or placebo[51]. Overall hospital mortality was similar in patients treated with SK or placebo. Unlike with rt-PA in the LATE trial, no significant reduction in hospital mortality occured in the subgroup of patients treated seven and 12 hours after symptom onset. Thus it can be presumed that SK does not improve survival in patients with AMI treated after the first seven hours. LATE trial suggests that rt-PA may be preferred thrombolytic drug in patients presenting six to 12 hours after symptom onset[7]. The possible mechanisms of benefit of late thrombolysis included improvement in ventricular function, prevention of ventricular remodelling or both, and reduction of ventricular arrhythmias due to an improved electrical stability [52-56].

**Primary PTCA vs thrombolysis :**

Though thrombolytic therapy is a very effective mode of treatment of AMI, in 20% cases it fails to achieve arterial patency and there is an increased incidence of recurrent ischaemia. Because of these limitations, there has been increasing interest in the use of immediate (primary) Percutaneous Transluminal Coronary Angioplasty (PTCA) as an alternative to thrombolytic therapy in AMI. Primary angioplasty is defined as angioplasty being performed without prior thrombolysis with a view to achieve reperfusion and salvage myocardium[57]. Recent studies have shown successful recanalization of the infarct related artery in 92 to 98 percent of patients after primary PTCA was performed an average of one hour after presentation [59,60]. This result is moderately better than that seen with thrombolysis. The results of randomized trials favour the use of primary PTCA. The largest of these studies was the Primary Angioplasty in Myocardial Infarction(PAMI) trial which enrolled 395 patients with ST segment-elevation and upto 12 hours of chest pain duration [60]. PAMI concluded that immediate PTCA reduced the combined occurrence of non-fatal reinfarction or death during hospitalization and at six months, was associated with a lower rate of intracranial haemorrhage and resulted in similar left ventricular (LV) function. A more recent study comparing immediate PTCA with SK has confirmed superior results of primary PTCA in terms of better LV function and lower rates of death and recurrent infarction[61]. Cardiogenic shock is a specific subset of patients with AMI where primary angioplasty is very effective in reducing mortality. The major limitation of primary PTCA even in advanced countries is the availability of 24 hours cardiac catheterization laboratory, surgical backup and trained personnel. So it is unlikely that primary PTCA can be offered to many deserving patients[57].

Primary PTCA is superior to thrombolytic therapy in selected patients with AMI[62]. The impressive survival benefit suggests that myocardial infarction complicated by cardiogenic shock should be managed with PTCA, if possible[5]. However, thrombolytic therapy will continue to be the mainstay of treatment due to cost and facility constraints associated with primary angioplasty.

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## CASE REPORTS

# Peripheral Odontogenic Fibroma (WHO Type ): A Case Report and Review of Literature

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**Summary:**

**A case report on World Health Organization (WHO) type of giant peripheral odontogenic fibroma with its clinical features, radiological findings, histopathological appearance and surgical treatment of the mandible is presented. Only twelve cases of WHO type of odontogenic fibroma has been reported in the various literature. The controversial issues surrounding this neoplasm is due to small number of reported cases in the literature. Its clinical, radiological, morphological and histopathological features, and its treatment are discussed from sparse available literature.**

*( J Bangladesh Coll Phys Surg 1995; 13 : 73–77)*

## Introduction:

The WHO type of peripheral odontogenic fibroma (POF) is relatively rare benign extraosseous destructive odontogenic tumour of fibrous connective tissue. Only twelve cases of WHO type of odontogenic fibroma have been reported in the various literature and few of them were peripheral type[1-4]. It is originated from mesenchymal odontogenic tissue i.e. dental follicle, dental papilla and periodontal ligaments[5,6] The characteristic feature of the lesion is a high histomorphological variability while clinical, radiological and histological behaviour is not specific contributing difficulties in diagnosis[7]. Therefore, further persistent clinical and experimental evaluation is still necessary because of the paucity of reported cases, and histomorphological spectrum, clinical features and radiological feature have not yet been established. The paper presents a case report on WHO type of POF and a discussion on controversies about this neoplasm.

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## Case report :

A 30 years old female with a huge tumour in the right mandible was referred from Jamalpur local hospital to the Department of Oral and Maxillofacial Surgery, Dhaka Dental College and Hospital (DDCH).

On clinical examination, there was a large mass on the right side and anterior part of the left body of the mandible which expanded in all directions specially in buccal vestibular area and a submandibular blunt pillar like extension was seen upto the level of angle of Luis with a broad base crescentic submandibular margin and almost whole of the morphological margin of ramus and body of the mandible (Fig-I). The three dimentional size of the mass of tumour was 17cm x 12 cm x 8 cm. The tumour was firm in consistency with diffuse smooth surface. The skin overlying the lesion was normal and not fixed. The right lower third molar was extracted and the rest of the lower posterior segmental teeth were loose. There was slight impairment of sensation on the affected side. The previous history suggested that this tumour was noticed about one and a half years back. The systemic examination and routine analysis of blood, urine, stool and the chest radiographs were within normal limit and lymphnodes wore not palpable.

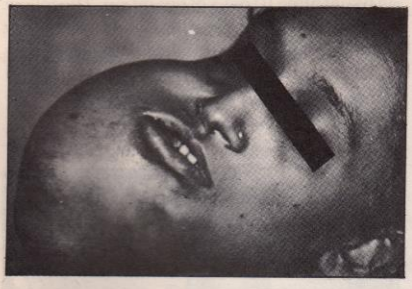

**Fig-1:** *Preoperative photograph of the patient with a huge swelling on the right side of the mandible*

The roentgenographic examination of mandible showed a huge translucency from the midmandible upto the half of the ramus indicating soft tissue tumour. The cortical plates in this area were totally absent. There was an area of bone or osteoid formation in radio-opaque fibre like lines indicating calcification and giving a 'sun ray' appearance similar to osteosarcoma. There was also huge expansion both palatally and lingually. The teeth in the involving area were almost in normal position without root resorption (Fig-2).

The tissue of the tumour with grey white cut surface was sent for histopathological examination. It revealed a highly cellular fibroma composed of interlacing fascicles of fibroblasts. The nuclei of the cells showed mild analplasia. However, mitotic figures have not been found. The diagnosis was made on the basis of histopathological report supplemented by radiological finding (Fig- 3a and 3b)

A decision was made for right hemimandibulectomy followed by reconstruction by simple metallic prosthesis. Under general anaesthesia, an incision was started from 2 cm left to the midline of the lower lip from vermilion border towards submental

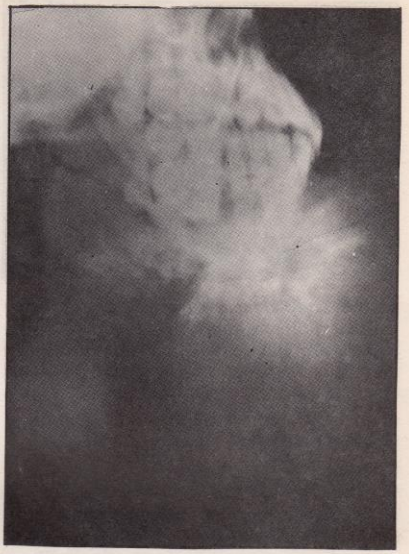

**Fig-2:** *Right lateral oblique radiograph of the mandible showing 'sun ray' like appearance*

**Fig-3a:** *The photomicroghaph illustrated highly cellular fibroma commposed of interlacing fascicles of fibroblasts without strands or islands of epithelial nests.*

**Fig-3b:** *The photomicroghaph illustrated highly cellular fibroma commposed of interlacing fascicles of fibroblasts without strands or islands of epithelial nests*

area. It was further extended backwards upto the right angle of the mandible following submandibular area. The mandible along with the tumoral mass as exposed, and its right half, anterior parts of left body of mandible along with temperomandibular joint was removed (Fig-4). A predesigned vitallium plate of mandibular shape was fixed to the remaining mandibular stump by screws. The muscles were attached to the metallic prosthesis and wound was closed in layers. During subsequent post-operative management the patient tolerated the procedure and results were satisfactory. The patient was discharged as usual after 10 days of operation. The follow up photograph was aesthetically satisfactory (Fig-5) and metallic prosthesis was in proper position as illustrated by radiographic photograph taken 40 days later.

**Fig-4:** *The photograph of resected mass of peripheral odontogenic fibroma weighing 3.5 pounds*

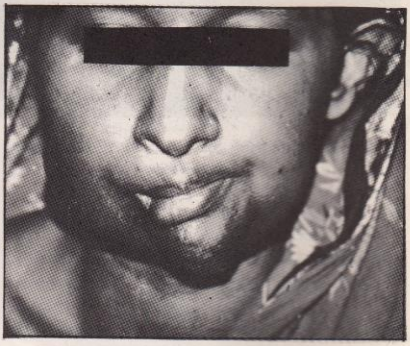

**Fig-5:** *The postoperative follow up photograph of the patient*

**Discussion :**

The POF is a nonaggressive, noncapsulated, gingival exophytic destructive and benign odontogenic tumour and WHO type of POF is the rarest among all the odontogenic fibromas[1].

The odontogenic fibroma originate from ectomesenchymal tissues: (1) dental follicle, (2) dental papilla and (3) periodontal ligament[5,6]. POF is also sometimes seen to originate from surface oral mucosa[8]. It is postulated that POF may be more closely related to fibrous epulis as both lesions show hyperplasia of basal layar of covering epithelium into double strands resembling odontogenic epithelium[9]. The odontogenic fibroma which is composed of mature fibroblastic tissue with rare nests and strands of odontogenic epithelium may be the mature end result of odontogenic myxoma[10,11].

It was found that most of the POF occur in male mandible whereas most of the central odontogenic fibroma (COF) occur in female mandible[8,9,10,12,13,14]. In the case described, the POF was located in the 30 years old female mandible. Devilliers et al in their clinicopathological study of 30 cases reported that the size of POF varied from 1-3 cm[8]. But in the case presented, the three dimensional measurement of the lesion was 17cm x 12 cm x 8 cm and weighed approximately 3.5 lbs (1.6 kg). In all probability the case may be the largest WHO type of POF presented in the literature so far. The odontogenic fibroma is firm in consistency, firmly attached to gingiva and their cut surface is predominantly white in colour[6,14]. Sometimes the tumour produces an expansile multilocular transluscency similar to that of ameloblastoma and the POF sometimes present cuffing calcification, and calcified tissue, if present, may resemble trabeculae of bone or osteoid or cementum like material or dentin or osteodentin, sometimes described as dysplastic dentin[14]. The characteristic features of this tumour is not yet established and there is still controversies surrounding this neoplasm.

In the case presented, the radiography showed a huge radiolucency from the midmandible upto the right half of the ramus indicating soft tissue tumour. The cortical plates in this area is totally absent. There was area of new bone or osteoid formation i.e. radio-opaque fibre like lines indicating calcification, similar to 'sun ray' appearance of osteosarcoma or chondrosarcoma[14]. The radiological finding and aggressive huge size of tumour may mislead the diagnosis. The teeth are in normal position without root resorption.

The odontogenic fibroma has been basically categorized into two types: the simple type of odontogenic fibroma similar to dental follicle and more complex (WHO) type of odontogenic fibroma consisting of variable amount of odontogenic epithelium in fibrous connective tissue with dentin or material resembling cementum[6,15]. There may be little difference, however, in terms of clinical or behavioral features between these subtypes[2,6]. The COF and POF are considered as similar entity histopathologically with exception of its sites, extraosseous and intraosseous[14]. According to the latest WHO definition, presence of odontogenic epithelium is not mandatory for the diagnosis of odontogenic fibroma[6,16].

The ten sections from five blocks and multiple sections from additional four new blocks of tissue were examined. The microscopic examination showed a highly cellular fibroma composed of interlacing fascicles of fibroblasts. The nuclei of the cells showed mild anaplasia and superficial areas of the tumour invaded by round cells. However, no mitotic figure have been encountered. Despite a dilligent search, no odontogenic nest could be found. The radiological findings when read with microscopy suggested the diagnosis of POF.

Thus, the case was diagnosed as the more complex WHO type of POF rather than simple type of POF based on histopathological report supplemented by grey white color of cut surface of tumour and bewilderig radiological 'sun ray' appearance indicating osteoid or calcification.

The conservative excision or enucleation of the odontogenic fibroma is the choice of treatment and there is least chance of recurrence as it is slow growing benign odontogenic tumour[6,7]. Even though the recurrence is rare, the odontogenic fibroma with more epithelial elements are more prone to recur[7]. Devillier et al[8] reported only one case recurring after fourteen months. Gardner[3] found one case to be reactive showing marked tendency to recur. Heimdal et al[17] presented a case of odontogenic fibroma recurring nine years after enucleation. It may be predicted that there is least chance of recurrence in the present case as the odontogenic epithelial element was totally absent[7].

In advanced stage and in recurrence, a radical resection should be done. Radical surgery such as hemimandibulectomy results in functional disability and facial deformity. In the case presented, right hemimandibuletomy was done and reconstructed with simple metallic prosthesis for the resected segment to restore facial contour and minimal functional ability. The metallic prosthesis showed satisfactory result maintaining aesthetic purpose and functional ability. The patient now looks more confident and not inhibited in the social gathering which was observed before the surgery. A secondary surgery with bone graft is under consideration if the patient remains healthy without recurrence at least for two years.

**Acknowledgement :**

We would like to express our sincere thanks to Prof. K M Nazrul Islam, Professor of Pathology (Retired), Institute of Post-Graduate Medicine and Research, Dhaka for his valuable comments on histopathological examination.

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Journal of Bangladesh College of Physicians and Surgeons
Vol. 13, No. 2, May 1995

# Ruptured Hepatic Adenoma: An Association with Oral Contraceptive

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**Summary :**

**A patient with history of prolong use of oral contraceptive presented with spontaneous rupture of hepatic adenoma. The association of hepatic adenoma with oral contraceptive is well known. Regular examination and ultrasonographic screening of liver in women taking oral contraceptive for more than five years might bring more cases to light.**

*(J Bangladesh Coll Phys Surg 1995; 13: 78–80)*

## Introduction:

The association of hepatic adenoma with prolonged use of oral contraceptive has long been established. Magnitude of the problem in our country is not known. Although oral contraceptives are widely promoted and used for several years, contraceptive associated hepatic adenomas are yet to be reported in our country.

## Case report :

Mrs. SH, a lady of 32 was admitted to Dhaka Medical College Hospital on 21.8.93 with sudden onset of severe abdominal pain of six hours duration, which started in the epigastrium and spreaded all over the abdomen. The pain was referred to the right shoulder. She also had a feeling of faintness and complained of gradual distension of the abdomen. She started her menstruations on the day before the onset of the pain. She was a known case of hypertension and diabetes mellitus.

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b. Saria Tasnim, Registrar, Maternity Unit, Dhaka Medical College Hospital
c. Md. Lutfor Rahman Khan, Assistant Registar, Surgery Unit, Dhaka Medical College and Hospital
d. Md. Mesbah-Ur-Rahman, Assistant Registar, Surgery Unit, Dhaka Medical College Hospital
e. Z. M. Chaudhury, Professor of Surgery, Dhaka Medical College and Hospital

**Correspondence to :** Md. Sohail Moosa, Registrar, Surgery Unit, Dhaka Medical College Hospital
Received : November 21, 1994 Accepted : May 8, 1995

The patient was married for 20 years. She had a regular menstrural cycle and gave birth to four healthy children normally. The youngest one was eight years old. She took contraceptive pills for a total period of 15 years and uninterruptedly for last eight years.

**Fig-1:** *Resected hepatic adenoma measuring 6 cm x 6.5 cm*

On examination, she was disoriented, severely anaemic, pulse was 130/min and blood pressure was 90/50 mm of Hg. Abdomen was tense, tender and distended. Rigidity and rebound tenderness were present. Shifting dullness was present and liver dullness was not obliterated.

On vaginal examination, the uterus was of normal size and retroverted. Fornices were full and tender. A slow trickle of blood through the cervix was noticed.

With the clinical suspicion of ruptured ectopic pregnancy, the patient was resuscitated and taken to the operation theatre.

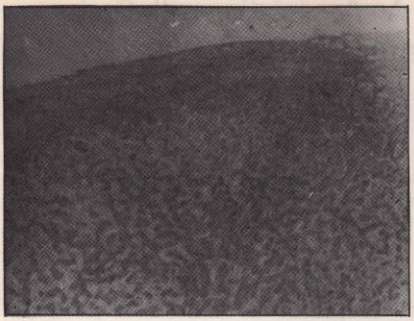

**Fig-2:** *Micrograph of hepatic adenoma, showing capsule*

**Fig-2:** *Micrograph of hepatic adenoma, no definite portal triad pattern*

Under general anaesthesia, colpopuncture was done and blood was aspirated. Laparotomy with lower right paramedian incision revealed haemoperitoneum but tubes and ovaries were found normal. Extending the incision upward, blood was found to be coming from the liver. There were multiple well circumscribed lesions in the liver, one of which was ruptured and was bleeding. By careful dissection the larger tumours were resected. Haemostasis was ensured and abdomen was closed in layers after placing two drains in place. Bilateral tubectomy was done. Post-operative recovery was uneventful except a minor degree of wound infection in the upper part of the wound. Histopathology showed hepatic adenoma.

Post-operative CT scan showed multiple remaining adenomas of various sizes occupying almost whole of the liver substance.

**Discussion :**

Benign tumours of the liver are rare and by the year 1944 only 67 cases of microscopically proven benign hepatomas had been recorded[1]. Most of them were probably regenerative nodules. This prevalence persisted since mid fifties, after which increasing number of benign hepatomas have been reported. Baum was probably the first to point out the association of benign hepatic tumours with oral contraceptives.[1] Subsequently, several reports came out indicating the association of benign liver tumour with oral contraceptives[2]. Certain particular contraceptives, especially oestrogen derivatives like mestranol containing compounds had been implicated but later on other synthetic oestrogens were also found to be associated with benign liver tumours[3]. Evaluation of possible role of the progesterone compounds have been made and they did not appear to be as important as synthetic oestrogens in producing liver alterations.

Further evidence of causal association of benign hepatic adenomas with oral contraceptives comes from the fact that there are records of spontaneous regression of benign hepatic tumours following withdrawal of oral contraceptives[4]. Usual clinical pesentations are mass in the right hypochondrium, pain, rupture with intraperitoneal haemorrhage and incidenal findings at laparotomy or during investigation of other diseases[5]. Spontaneous haemorrhage within the tumour or intraperitoneally following spontaneous rupture of the tumour usually occurs during menstruation.

The risk of development of benign hepatic tumour increases five fold after five years and 25 fold after nine years of oral contraceptive therapy.[3]

In our country, oral contraceptives are widely promoted and used but by far no case of benign hepatic adenoma associated with oral contraceptives has been reported and we are unaware of this danger of oral contraceptives. This is probably a warning and beginning of the appearances of more new cases.

Currently, it is recommended to palpate the liver routinely and to do liver function tests in women taking oral contraceptives for more than five years[2,3]. If the tumour is definitely known to be benign, simple withdrawal of the oral contraceptive and periodic ultrasonic examination is sufficient[6].

**Acknowledgement:**

We are grateful to our anaesthesiologist and surgical colleagues for their kind help. We wish to record our sincere thanks to the Director of the Hospital for allowing us to use the records of the patient. We are also grateful to Prof. Mahbubur Rahman for his kind help.

**References :**

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2. Emonsson HA, Henderson B, Benton B. Liver cell adenomas associated with use of oral contraceptives. N Eng J Med 1976; 294: 470-72.
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**Continuing Medical Education:**

A surgical seminar of free paper sessions was held in the Bangladesh College of Physicians and Surgeons Auditorium on 24-4-95 under the auspices of the Continuing Medical Education Programme of the Bangladesh College of Physicians and Surgeons. A good number of delegates (about 30) from Pakistan attended the seminar and read papers, on their return journey from Nepal after attending the conference of the SAARC country chapters of the International College of Surgeons. A large number of Bangladeshi doctors also participated and read papers. Lively discussion followed each session. Many participants renewed their old friendship, and new friendships were made.All delegates were entertained with tea and lunch. The detail programme was as follows:

Scientific session held on 24-4-95 at BCPS auditorium.

10.30.AM.

**Chairperson :** Prof. Baqai
Prof. C H Kabir

| | | |
|---|---|---|
| 1. | Prof. ANM Atai Rabbi | Personal experience of pancreatic surgery |
| 2. | Dr. Shafquat Hussain Khundker | Fasciocutaneous flap for lower leg reconstruction |
| 3. | Dr. Manzurul Haque | Laparoscopy experience |
| 4. | Dr. Humayun Kabir Chowdhury | Laparoscopic cholecystectomy in acute cholecystitis |
| 5. | Prof. M Alauddin | Head and neck surgery |
| 6. | Dr. Aminur Rashid | Role of DNA-ploidy patterns in oesophageal squamous cell carcinoma |
| 7. | Lt. Col. Haroon-ur-Rashid | Current activities on male sterilisation reversibility in Bangladesh |

11.00—12.30 PM

**Chairpersons:** Prof. Khalida Usmani
Prof. Mirza Mazharul Islam

| | | |
|---|---|---|
| 1. | Dr. Javed Rizvi | Medical education for future doctors |
| 2. | Dr. Majid Menon | Prevention of infection in surgical ward |
| 3. | Prof. Zaheda Baqai | IVF assisted reproduction |
| 4. | Prof. Faiz M Khan | Skin tumour |
| 5. | Prof. M Shamim | Use of sigmoid colon for vaginoplasty |
| 6. | General Azhar Ahmed | Malignancy in Pakistan |
| 7. | Dr. Md. Afzal Hossain | Intracranial space occupying lesion–a review of 500 cases. |

**Election of the Councillors and the Executive Committee :**

The election of 8 councillors of the college was held on 27-1-95.

**List of Councillors:**

Following is the 20 member list of the councillors

**Existing Councillors**

(for the session 1993-97)

1. Prof. A H M Ahsanullah
2. Prof. Md. Tahir
3. Prof. Md. Abdul Hadi
4. Prof. Tofayel Ahmed
5. Prof. Md. Nurul Islam
6. Prof. Md. Abdul Mobin Khan
7. Prof. Md. Harunur Rashid
8. Dr. Md. Ruhal Amin

**Newly eclected Councillors**

( for the session 1995-99)

9. Prof. AHM Towhidul Anowar Chowdhury
10. Prof. Golam Rasul
11. Prof. AKM Mahbubur Rahman
12. Prof. Mahmud Hasan
13. Prof. Rashid E Mahbub
14. Prof. Abdush Shakur
15. Dr. S A M Golam Kibria
16. Dr. Syed Atiqul Haq

**Existing Councillors nominated by the Government of People's Republic of Bangladesh (1993-97)**

17. Prof. M A Majed
18. Prof. Kazi Masihur Rahman
19. Prof. (Maj Genl. Retd) Anis Waiz
20. Prof. Matiur Rahman

**Executive Committee:**

The Election Commission of the Bangladesh College of Physicians and Surgeons has declared the members of new Executive Comittee for 2 years from March, 1995 as follows:

| | | |
|---|---|---|
| President | : | Prof. Md. Tahir |
| Senior Vice President | : | Prof. Md. Abdul Hadi |
| Vice President | : | Prof. AKM Mahbubur Rahman |
| Treasurer | : | Prof. Tofayel Ahmed |
| Members | : | Prof. Golam Rasul |
| | | Dr. Md. Ruhal Amin |

**Various Committees and Faculties of the Bangladesh College of Physicians and Surgeons:**

The Council members of Bangladesh College of Physicians and Surgeons has formed the following Committees and Faculties of the College for 2 years with effect from March, 1995.

**Examination Committee**

| | | |
|---|---|---|
| 1. | Prof. MD. Abdul Hadi | Chairman |
| 2. | Prof. MA Majed | Member |
| 3. | Prof. T A Chowdhury | Member |
| 4. | Prof. Nazmun Nahar | Member |
| 5. | Prof. Md. Nurul Islam | Member |
| 6. | Prof. M A Hai | Member |
| 7. | Prof Md. Humayun Kabir | Member |
| 8. | Prof. AKM Mahbubur Rahman | Member |
| 9. | Prof Md. Abdul Mobin Khan | Member |

**Reference Committee**

| | | |
|---|---|---|
| 1. | Prof. Md. Tahir | Chairman |
| 2. | Prof. AHM Ahsanullah | Member |
| 3. | Prof. Rashid E Mahbub | Member |
| 4. | Prof. Md. Harunur Rashid | Member |
| 5. | Prof. Latifa Shamsuddin | Member |
| 6. | Dr. Syed Atiqul Haque | Member |

**Finance committee**

| | | |
|---|---|---|
| 1. | Prof. AKM Mahbubur Rahman | Chairman |
| 2. | Prof. Tofayel Ahmed | Member |
| 3. | Prof. Md. Abdul Hadi Faquir | Member |
| 4. | Prof. Md. Moazzam Hossain | Member |
| 5. | Prof. Md. Hanif | Member |
| 6. | Dr. Zafar Ahmed Latif | Member |
| 7. | Dr. Syed Sirajul Karim | Member |

**Tender Committee**

| | | |
|---|---|---|
| 1. | Prof. AKM Anowarul Azim | Chairman |
| 2. | Prof. Tofayel Ahmed | Member |
| 3. | Dr. M Alimuzzaman | Member |
| 4. | Dr. Md. Israfil | Member |
| 5. | Dr. Md. Abdul Hannan | Member |
| 6. | Dr. Golam Muin Uddin | Member |
| 7. | Dr. T I M Abdullah Al Faruq | Member |

**Museum Committee**

| | | |
|---|---|---|
| 1. | Prof. A N M Atai Rabbi | Chairman |
| 2. | Prof. Syed Mokarram Ali | Member |
| 3. | Prof. F A Azim | Member |
| 4. | Dr. Kohinoor Begum | Member |
| 5. | Dr. Shahid Hossain | Member |
| 6. | Dr. A K M Khurshid Alam | Member |
| 7. | Dr. Md. Abdullah | Member |
| 8. | Dr. (Col.) Ali Akbar | Member |
| 9. | Dr. Afiqul Islam | Member |

**Library Committee**

| | | |
|---|---|---|
| 1. | Prof. Abdus Shakur | Chairman |
| 2. | Dr. Kaniz Mowla | Member |
| 3. | Dr. Md. Margub Hossain | Member |
| 4. | Dr. Selim Md. Jahangir | Member |
| 5. | Dr. Farhana Dewan | Member |
| 6. | Dr. Quamrul Hassan Tarafder | Member |
| 7. | Dr. Rezwana Quaderi | Member |
| 8. | Dr. Muhammad Ali | Member |
| 9. | Col. M. A. Moyeed Siddiqui | Member |
| 10. | Major A. M. Hossain Saad | Member |
| 11. | Dr. Parveen Shahida Akhter | Member |
| 12. | Major Harunur Rashid | Member |

**Journal Committee**

| | | |
|---|---|---|
| 1. | Maj. Genl. (Retd.) Anis Waiz | Chairman |
| 2. | Dr. S. Kamaluddin Ahmed | Editor-in-Chief |
| 3. | Prof. Nazimuddin Ahmed | Member |
| 4. | Prof. Md. Fazlul Haque | Member |
| 5. | Brig. C. Abdul Gaffar | Member |
| 6. | Prof. Md. Nazrul Islam | Member |
| 7. | Dr. S. Hussain Khundker | Member |
| 8. | Dr. Sameena Chowdhury | Member |
| 9. | Dr. Md. Afzal Hossain | Member |
| 10. | Dr. U. H. Shahera Khatun | Member |
| 11. | Dr. Chowdhury Ali Kawser | Member |
| 12. | Dr. A.K.M. Rafique Uddin | Member |
| 13. | Dr. Md. Abdus Salam | Member |
| 14. | Dr. Projesh Kumar Roy | Member |
| 15. | Dr. Nooruddin Ahmed | Member |
| 16. | Major Baredra Chakraborty | Member |
| 17. | Dr. Emran Bin Yunus | Member |

**Students Advisory Committee**

| | | |
|---|---|---|
| 1. | Prof. Md. Sadequzzaman | Chairman |
| 2. | Dr. A.K.M. Anisul Haque | Member |
| 3. | Dr. Hasan Md. Abdur Rouf | Member |
| 4. | Dr. Md. Wahiduzzaman | Member |
| 5. | Dr. Shamim Ahmed | Member |
| 6. | Dr. Ainun Afroza | Member |
| 7. | Dr. Md. Taiabur Rahman | Member |
| 8. | Dr. Narayan Chandra Saha | Member |

**Continuing Medical Education Committee**

| | | |
|---|---|---|
| 1. | Prof. Golam Rasul | Chairman |
| 2. | Prof. Anowara Begum | Member |
| 3. | Prof. Sultana Jahan | Member |
| 4. | Prof. Ferdous Ara J Janan | Member |
| 5. | Prof. N Akhtar Chowdhury | Member |
| 6. | Dr. Jahangir Kabir | Member |
| 7. | Dr. Abdul Kader Khan | Member |
| 8. | Dr. Md. Golam Rabbani | Member |
| 9. | Dr. Shahana Akhtar | Member |
| 10. | Lt. Col. Rabiul Hossain | Member |

**Fellows Welfare Committee**

| | | |
|---|---|---|
| 1. | Prof. Rashid-E-Mahbub | Chairman |
| 2. | Prof. AKMA Hakim Akan | Member |
| 3. | Dr. Shahid Karim | Member |
| 4. | Dr. F Mohammad Siddiqui | Member |
| 5. | Dr. APM Sohrabuzzaman | Member |
| 6. | Brig. M Jahangir Hossain | Member |
| 7. | Dr. Kanak Kanti Barua | Member |
| 8. | Dr. Rowhaan Ara Begum | Member |
| 9. | Dr. Md. Shahidullah | Member |
| 10. | Dr. Md. Rafiqul Alam | Member |
| 11. | Dr. Md. Lutfor Rahman | Member |
| 12. | Dr. Syed Mahbubul Alam | Member |
| 13. | Dr. Feroze Quader | Member |
| 14. | Dr. Md. Nurul Absar | Member |
| 15. | Dr. Khokan Kanti Das | Member |

**Faculty of Medicine**

| | | |
|---|---|---|
| 1. | National Prof. Nurul Islam | Chairman |
| 2. | National Prof. M R Khan | Member |
| 3. | Prof. SGM Chowdhury | Member |
| 4. | Prof. AKMN Chowdhury | Member |
| 5. | Maj. Genl. (Retd.) Anis Waiz | Member |
| 6. | Prof. Matiur Rahman | Member |
| 7. | Prof. M N Alam | Member |
| 8. | Prof. AKM Moslehuddin | Member |
| 9. | Prof. P Purkayastha | Member |
| 10. | Prof. MA Mannan Miah | Member |
| 11. | Prof. KMHS Sirajul Haque | Member |

**Faculty of Surgery**

| | | |
|---|---|---|
| 1. | Prof. Md. Nurul Amin | Chairman |
| 2. | Prof. S A Ashraf | Member |
| 3. | Prof. A S M Fazlul Karim | Member |
| 4. | Prof. S N Samad Chowdhury | Member |
| 5. | Prof. Md. Humayun Kabir | Member |
| 6. | Prof. M A Awal | Member |
| 7. | Prof. Md. Abdur Rashid | Member |
| 8. | Prof. Fazle Elahi Chowdhury | Member |
| 9. | Prof. M A Sadek | Member |
| 10. | Brig. Syed Ahsan Karim | Member |
| 11. | Brig M. Jahangir Hossain | Member |
| 12. | Col Md. Ali Akbar | Member |

**Faculty of Basic Medical Sciences**

| | | |
|---|---|---|
| 1. | Prof. Kazi Mashiur Rahman | Chairman |
| 2. | Prof. M A Hai | Member |
| 3. | Prof. M A Hai Fakir | Member |
| 4. | Prof. Syed Mokarram Ali | Member |
| 5. | Prof. S A R Chowdhury | Member |
| 6. | Prof. Md. Suhrab Ali | Member |
| 7. | Prof. M A Rashid | Member |
| 8. | Prof. M H Mullick | Member |
| 9. | Prof. A K M Nurul Anowar | Member |
| 10. | Prof. A B M Ahsanullah | Member |

**Faculty of Obstetrics & Gynaecology**

| | | |
|---|---|---|
| 1. | Prof. Abdul Bayes Bhuiyan | Chairman |
| 2. | Prof. Shahla Khatun | Member |
| 3. | Prof. Latifa Shahabuddin | Member |
| 4. | Prof. AKM Shamsuddin | Member |
| 5. | Prof. Sadiqa Tahera Khanam | Member |
| 6. | Prof. Anowara Begum | Member |
| 7. | Prof. Sultana Jahan | Member |
| 8. | Prof. Sultana Razia Begum | Member |
| 9. | Prof. Mahmuda Khatun | Member |
| 10. | Prof. Sayeba Akhter | Member |
| 11. | Dr. Sameena Chowdhury | Member |

The President and the Secretary of the College shall be the ex-officio members of all Committees.

**Examination News :**

Results of FCPS Part I, FCPS Part II and MCPS examinations held in January, 1995 are given below :

659 candidates appeared in FCPS Part I examination held in January, 1995 of which 69 candidates came out successful. Subjectwise results are as follows :

| Subject | Number appeared in theory examination | Number qualified for viva-voce | Number Passed |
|---|---|---|---|
| Medicine | 166 | 54 | 22 |
| Surgery | 180 | 67 | 21 |
| Paediatrics | 77 | 9 | 5 |
| Obs. & Gynae | 106 | 24 | 9 |
| Ophthalmology | 47 | 13 | 2 |
| Anaesthesiology | 22 | 1 | 1 |
| ENT Diseases | 21 | 3 | 2 |
| Psychiatry | 10 | 2 | 2 |
| Radiology | 8 | 0 | 0 |
| Radiotherapy | 4 | 0 | 0 |
| Physical Medicine | 8 | 6 | 3 |
| Haematology | 7 | 3 | 1 |
| Microbiology | 33 | 1 | 1 |
| Total | 659 | 183 | 69 |

93 candidates appeared in FCPS Part II examination in different subjects. List of candidates who satisfied the board of examiners is as follows :

| Roll No. | Name | Graduated from | Speciality |
|---|---|---|---|
| 1 | Dr. Md. Abdul Ahad Moral | Dhaka Medical College | Medicine |
| 5 | Dr. AKM Mosharraf Hossain | Dhaka Medical College | Medicine |
| 13 | Dr. Md. Mahbubur Rahman | Sir Salimullah Med. College | Medicine |
| 15 | Dr. Md. Sadiqul Islam | Sir Salimullah Med. College | Medicine |
| 16 | Dr. AKM Mujibur Rahman | Sir Salimullah Med. College | Medicine |
| 17 | Dr. Swapna Das | Sylhet Medical College | Medicine |
| 18 | Dr. Md. Atahar Ali | Rajshahi Medical College | Medicine |
| 21 | Dr. Md. Matiur Rahman | Sylhet Medical College | Medicine |
| 22 | Dr. (Major) Md. Julhash Uddin | Dhaka Medical College | Medicine |
| 28 | Dr. Md. Iqbal Faruque Khan | Dhaka Medical College | Surgery |
| 63 | Dr. Pranab Kumar Chowdhury | Chittagong Med. College | Paediatrics |
| 67 | Dr. Masuda Begum | Mymensingh Med. College | Obst. & Gynae |
| 68 | Dr. Most. Rebeca Khatoon | Rajshahi Medical College | Obst. & Gynae |
| 69 | Dr. Taufiqua Hussain | Sir Salimullah Med. College | Obst. & Gynae |
| 71. | Dr. Sufia Siddique | Dhaka Medical College | Ophthalmology |
| 73 | Dr. AHM Enayet Hussain | Sylhet Medical College | Ophthalmology |
| 75 | Dr. Md. Nazrul Islam | Sir Salimullah Med. College | Ophthalmology |

| Roll No. | Name | Graduated from | Spediality |
|---|---|---|---|
| 78 | Dr. Md. Jinnuraine Jaigirdar | Sylhet Medical College | Anaesthesiology |
| 83 | Dr. Md. Mazibar Rahman | Sir Salimullah Med. College | Anaesthesiology |
| 85 | Dr. Mohammad Nurul Amin | Chittagong Med. College | Anaesthesiology |
| 86 | Dr. Shyam Sundar Kundu | Rangpur Medical College | Radiology |
| 88 | Dr. Qamruzzaman Chowdhury | Sir Salimullah Med. College | Radiotherapy |
| 89 | Dr. Md. Mahbubur Rahman | Dhaka Medical College | Haematology |

262 candidates appeared in MCPS examinations in differnt subjects. List of candidates who satisfied the board of examiners is as follows :

| Roll No. | Name | Speciality |
|---|---|---|
| 14 | Dr. Muhammed Golam Noor | Medicine |
| 16 | Dr. Md. Abdul Mobin Talukder | Medicine |
| 25 | Dr. AKM Khurshidul Alam | Surgery |
| 31 | Dr. Pradip Kishore Mazumder | Paediatrics |
| 39 | Dr. Md. Abul Kalam Azad | Paediatrics |
| 40 | Dr. Gobinda Chandra Das | Paediatrics |
| 45 | Dr. Parveen Akhter | Paediatrics |
| 51 | Dr. Mamun Miah | Paediatrics |
| 55 | Dr. Parimal Kanti Nath | Paediatrics |
| 88 | Dr. Sultana Jahan | Obst. & Gynae |
| 99. | Dr. Mutah Ara Begum | Obst. & Gynae |
| 110 | Dr. Suraiya Sultana | Obst. & Gynae |
| 119 | Dr. Zebunnessa Parvin | Obst. & Gynae |
| 121 | Dr. Khodeza Tul Kobra | Obst. & Gynae |
| 135 | Dr. Nurun Nahar | Obst. & Gynae |
| 157 | Dr. Md. Helal Uddin | Anaesthesiology |
| 159 | Dr. Niaz Ahmed | Anaesthesiology |
| 182 | Dr. Benojir Ahmed | Clinical Pathology |
| 184 | Dr. Md. Obaidul Alam | Clinical Pathology |
| 186 | Dr. Syeda Afifa Huda | Clinical Pathology |
| 199 | Dr. ANM Nazmul Hossain | Dental Surgery |
| 207 | Dr. Md. Hasanuzzaman Bhuiyan | Forensic Medicine |
| 217 | Dr. Abu Muhammad Gulam Mustafa | Family Medicine |

**6th Convocation of the College :**

The 6th Convocation of the College was held on 26th January, 1995, at Bangladesh College of Physicians and Surgeons premises where Chowdhury Kamal Ibne Yusuf, Hon'ble Minister for Health and Family Welfare, Govt. of the People's Republic of Bangladesh distributed dipdlomas to the Honorary Fellows, Fellows without examination, Fellows and Members. The doctors who qualified in the FCPS and MCPS exsamination of the College from July, 1992 to January, 1995 were the participants of the Convocation. Total 19 Honorary Fellows from home and abroad, 6 Fellows without examination, 175 Fellows and 148 Members received their diploma certificates in the Convocation.