CHEMOTHERAPEUTIC TREATMENT OF RETINOBLASTOMA

THESIS

SUBMITTED IN PARTIAL FULFILMENT FOR

MASTER DEGREE

IN

OPTHALMOLOGY

BY

NOREEN KAZMY FAHMY

M.B.B.Ch.

UNDER SUPERVISION OF

PROFESSOR Dr. ANWAR EL MASSRI

PROF. OF OPHTHALMOLOGY

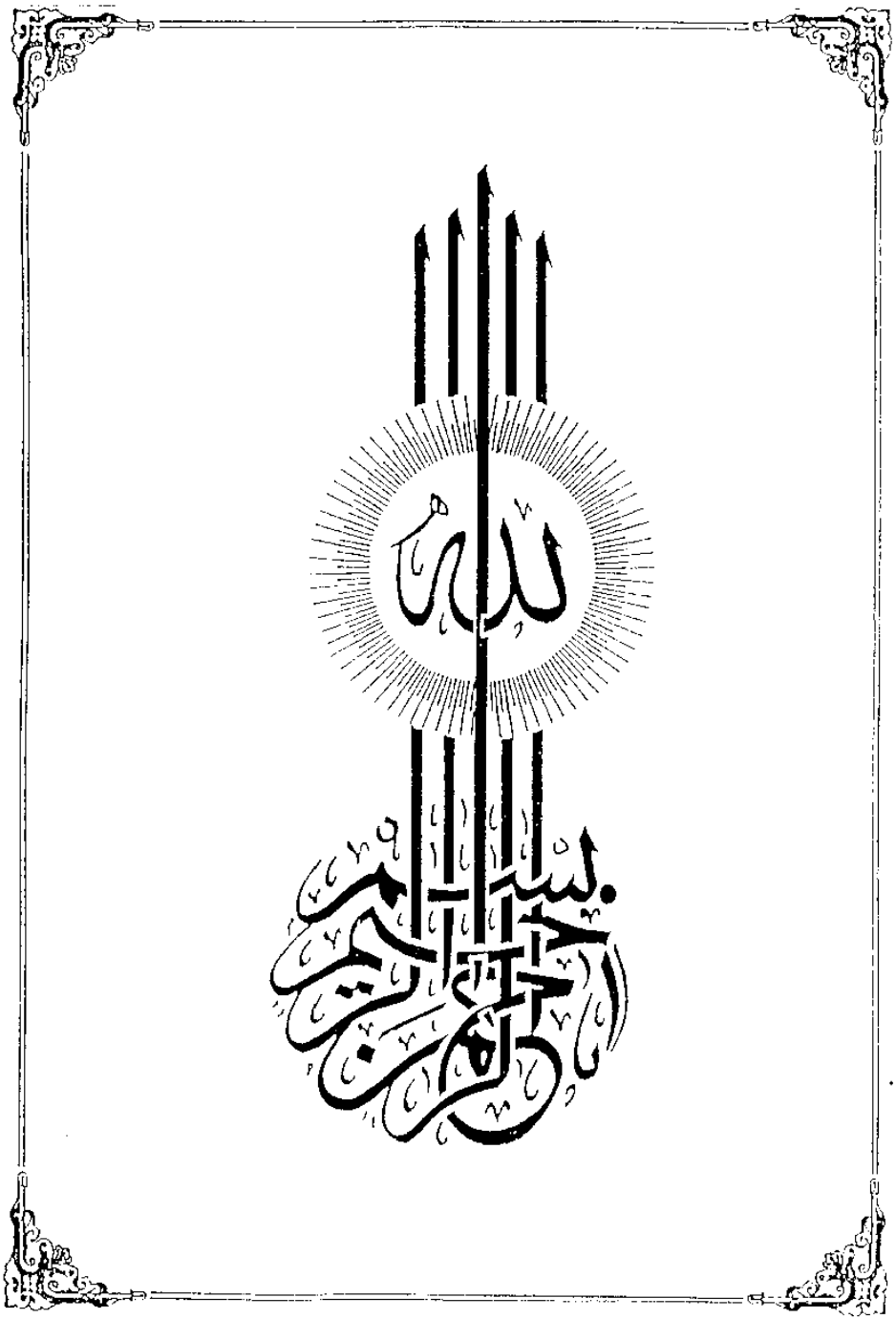
FACULTY OF MEDICINE

AIN SHAMS UNIVERSITY

1982

ACKNOWLEDGEMENT

It is a pleasure to express my ever lasting gratitude to Prof. Dr. Anwar El Massri Prof. of Ophthalmology in Ain Shams University for his kind supervision and precious advise. I wish also to express may deep gratitude to all Professors and Members of the Staff in the Ophthalmic Department in Ain Shams University.



CONTENTS

0-0-0-0-0-0-0

LITERATURES REVIEW OF SOME CLINICO-PATHOLOGICAL ASPECTS OF RETINOBLASTOMA

Retinoblastoma is the most common intra-ocular tumour of childhood and it is second only to malignant melanoma of the uvea among all intraocular tumours (Hogem & Zimmerman 1962).

History :

* The first patient with retinoblastoma was apparently observed in 1597 (Dunphy, 1964).

* Hayes, a London Surgeon, appears to have described the first case of retinoblastoma in 1765, including the pecular fundal reflex noted early in the disease and optic nerve involvement.

* Wardrop of Edinburgh in 1809 established retinoblastoma as an intety, gave a good clinical description of 35 cases and was the first to advocate early enucleation as a life saving measure. (Reese A.B. 1976).

* With the invention of von Helmholtz's ophthalmometer in 1851, it became possible to observe

the tumour within the eye (Graefe 1901).

* Virchaw in 1864 correctly identified retinoblastoma as a neoplasm which arose from the glial cell of the retina (Virchow, 1864).

* Flexner (1891), Wintersteiner (1963) and others believed the tumour to be of neuroepithelial origin the generally held view at present (Tso, MOM et al 1969).

* The present term "retinbolastoma" was coined by Verhoeff to reflect the fact that the tumour is derived and resembles cells of undifferentiated retina (Verhoeff and Jackson, 1926).

Incidence :

Falls and Neel have estimated its frequency as 1 for each 20.288 live births.

Another various incidence figures have been reported for different countries, 1 case of retinoblastoma in 14,000 births in Holland, 1:32,000 in England, 1: 27,000 in N. Ireland.

(Barry G., Mullaney J, 1971).

The recent series tend to show an increasing incidence of this tumour in part due to the lower mortality rate and partly due to improvements in methods of invistigations and diagnosis.

Age and Sex :

Ratinoblastomar is the tumour which occur in children. It might arise at very early ages (weeks or months) or sometimes may occur as late as 9 to 10 years, (El Massri A. 1978).

Reese A.B. reported that the average age at time of diagnosis in his series was 18 months. (Reese A.B. 1976).

One case have been reported in patient of 52 years old. (Makly T.A. 1963).

There is no significant sex or race distribution.

Bilaterality :

According to the literatures the bilateral cases was about 25 - 30%.

Reese A.B reported that the bilateral cases at his clinic was 80%.

Lennox E.L., Dorper G.J. and Sanders reported in their study of 268 cases that the bilateral cases was 41%. In bilateral cases the ratinoblastoma originates from separate sites in the two eyes.

It is extremely rare for the disease to extend from one eye to the other via the optic chiasma (de Buen S. 1960).

Histopathology :

A ratinoblastoma is composed of undifferentiated anaplastic cells that are uniformly small, round or polygonal and have a scanty or almost invisible cytoplasm that stain poorly.

Their relative large nuclei, rich in chromatin and stain deeply with hematoxylin.

For practical purposes there are only two types of retinoblastoma:

By far the most common is composed of highly undifferentiated retinoblast, the other composed partially of somewhat more differentiated cells characterized by rosette formation, it is often called neuroepithelioma.

When the retinoblastoma arise from the external nuclear layer it tends to grow in the subretinal space and pushes the retina inward.
It is frequently referred to clinically as exophytum type.

If arising from inner layers, the tumour mass extends early into the vitreaus cavity and is frequently refered to clinically as endophytum type.
It is impossible in most instances to determine from which retinal layer the tumour originated because the tumour extends from one layer to another by direct invasion. (Reese A.B. 1976).

Mutliple Foci :

A common and important feature of the tumour is its multiple origin. Eightly - four percent of retinoblastoma patient have multiple tumours sometimes five or more, in the affected retina. These multiple foci are independent, not disseminated from a primary focus or from the other eye.
They should not be confused with tumour implants or intraretinal metastasis (Reese A.B, 1976).

Rosettes, Fleurettes and Pseudorosettes :

The neuroepithelimatous type of ratinoblastoma that show photorecept or differentiation into rossetes and fleurettes seems more resistant to radiation than anaplastic retinoblastoma, a finding that supports the general principle that the radiosensitivity of cells varies inversely with their degree of differentiations (Ts'oMOM, et al 1970).

Fleurettes can be seen by light and electron microscopy.

Pseudorosottes also shown such arrangement as perivascular growth particularly arround small vascular channel or a small group of tumour cells that degenerate and leave a clear space containing cellular depris surrounded by a ring of variable cells.

Implantation Growths :

Since retinoblastoma have a little stroma the cells tends to disseminates throughout the eye. Implantation growths may be found at any sites where the nutrition is adequate. The most common sites is the choraidal surfaces the surface of

the retina and the posterior surface of the cornea at the region of the angle.

An implantation growth of retinoblastoma transferred from a doner eye containing retinoblastoma to the eye of a 54 years old woman during a successful cornea transplant operation has been described (Hata B. 1929).

Extension of the Tumour :

A. Extension into the Optic Nerve :

Ratinoblastoma has a great tendency to invade the optic disc and nerve.

The tumour rarely extends more than a few millimeters beyond the lamina criluosa. If the extension is as much as 10 m.m., it gains access to the subarachenoid space at the site where the central vessels leave the nerve and spread rapidly to the chiasmaand brain (Reese A.B. 1948).

b. Extension into the charoid :

In about 25% of cases the tumour invade the charoid, usually when far advanced.

It reachsthe choroid by means of implantation growths along the choroidal surface or around the margin of the opic nerve where the lamina vitrea terminates.

C. Extension into the Orbit :

Orbital extensions are responsible for orbital recurrence and should be suspected in advanced cases especially when secondary glaucoma is present. It is well to consider that once the tumour reaches the choroid it may extend through the emissaria as well as directly through the thin border tissue separating the choroid from the nerve.(Reese A.B. 1976).

Spontaneous Regression :

Spontaneous regression in retinoblastoma have been well documented in the literatures.
These have been discovered not uncommonly in asymptomatic older children and adults with family members affected with retinoblastoma and in adults with phthisis bulbi (Stewart, et al 1956).

The pathogenesis of this process has not been well characterized, but may depend on such factors as a progressively inadequate tumour vascular supply or more likely, host immune mechanisms leading to tumour necrosis.
On ophthalmoscopic examination, the spontaneously

arrested lesions appear to be identical with the arrested processes we have observed in patient treated with irradiation and chemotherapy.

Genetics of Retinoblastoma :

Retinoblastoma occurs in two forms :

a- Sporadically (96 per cent cases).

b- In families.

The majority of cases are sparaadic and most frequently unilateral. These cases are thought to result from somatic mutation resulting during a disturbed embryogenesis of the retina. This type is not transmitted.

All bilateral cases and small number of unilateral arise as a germinal mutation and are transmitted as an irregular dominal trait with incomplete penetrance.

Reported family trees gives very strong evidence of this form of transmission. (Carlson E.A. et al 1979).

Second Primary Tumours :

Bilaterally affected patients, treated successifully for their retinoblastoma, have a 10% risk of developing a second primary tumour before they reach

reproductive maturity. (Kitchin F.D. and Ellsmarth R.M. 1979).

The second tumour is often an osteosarcoma and even occurs in individuals who have not received chemotherapy or who not had radiation to the site of the new tumour.

Such second primary tumours are rarely encounted in unilateral cases.(Carlson E.A. et al 1979).

Diagnosis of Retinboalstomas :

(1) Presenting signs or symptoms :

1- Leukocaria (white pupillary or cat's eye reflex).

2- Esotropia or exotropia.

3- Red painful eye with or without glaucoma.

4- Poor vision.

5- Exophthalmos, may be a late manifestation.

(2) Ophthalmoscopic Examination :

Ophthalmoscopic examination of the child must be done under general anaesthesia with dilatation of the pupil. Ofdiagnostic importance is the characteristic pale pink of the tumour in which newly formed blood vessels extend over the surface into its substance.

Disseminated tumour seeds may be present in the vitreous.

The more advanced tumours may be accompanied by implantation growths recognizable as white foci over the iris, in the angle of the anterior chamber, along the dependent portion of the posterior surface of the cornea appearing as a hypopion, on the surface of the retina and in the vibreous.

(3) Examination of Subretinal and Anterior Chamber Fluids :

Subretinal fluid has been withdrawn for diagnostic purposes in difficult cases.

The disadvantage of this method is the risk of tumour seeding. It has been suggested that the detection of catecholamines in the urine of retinoblastoma patient may be of diagnostic value. (Brown D.H.: 1966).

It has been shown that L.D.H. (lactic acid dehydrogenase) can be measured simply and that its ratio in aqueous humar provides and index to intraocular necrosis and perhaps tumour metabolism. Elevated ratios has been reported in retinoblastoma. (Porter R, Skillen A.W. 1972).