The placenta – a Cinderella story

Wright CA, MBBCh B(Wits), FCPath (SA), FRCPath (London), MMed (Anat Path) Wits, FIAC
Professor and Head of Division of Anatomical Pathology, University of Stellenbosch

Correspondence to: Prof CA Wright, e-mail:cawr@sun.ac.za

Abstract

Introduction

The placenta is rarely sent for histopathological examination, despite its availability after delivery and the valuable contribution it may make to understanding adverse pregnancy outcome.

This may be due to reluctance on the part of surgical pathologists to examine the placenta, due to a number of reasons that are applicable globally, amongst which are limited exposure to placentas during their training and the very different terminology applicable to the pathology of this organ.

Why should the placenta be examined by a pathologist?

Globally there are 4 million neonatal deaths and another 4 million stillbirths annually, and the overwhelming majority occurs in low- and middle-income countries. In South Africa there is limited data available through the Perinatal Problem Identification Programme (PPIP). The data from 2000-2002 showed the commonest primary obstetric cause of perinatal death to be unknown.

Contribution of placental pathology

Histopathological examination of the placenta may provide information that may not be determined clinically. There is poor correlation between maternal indicators of infection and placental findings, and many placental causes of fetal and perinatal death may be clinically silent.

Placental examination is vital to the determination and timing of intrauterine events that may result in adverse pregnancy outcome and in doing so may assist in the medico-legal assessment of cases. Cerebral Palsy (CP) was until fairly recently attributed to intrapartum hypoxia, with liability borne by the clinicians and delivery units. Studies where the placenta was submitted for histopathology have shown that in less than 10% of cases of CP was intrapartum hypoxia the possible cause of brain damage. It is now widely accepted that multiple early and recent insults act together to increase the risk of brain injury at birth, and many of these can be identified by histopathological examination of the placenta.

Conclusion

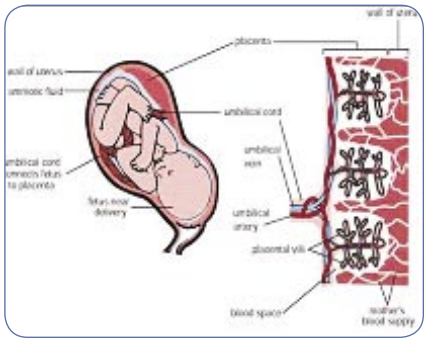
The contribution that the placenta may make to the understanding of the cause and timing of events resulting in adverse pregnancy outcome, as well as the management of the neonate, the mother and future pregnancies is being recognized by obstetricians, neonatologists, pathologists and administrators of health care institutions and medical insurance companies

SA Fam Pract 2007;49(7):4-8

Introduction

The placenta is the most under-examined, under-utilised and under-appreciated organ in the human body. The fetus is dependent on it for growth and survival. It provides oxygen and nourishment to the fetus by diffusion of soluble substances from the maternal blood in the intervillous space and the fetal blood in the fetal vessels within the villi. It also supplies an endocrine and excretory function. For 9 months it works day and night, devoting its entire life span to the fetus, and yet after delivery, with perhaps a cursory glance, it is relegated to the ashes.

Figure 1: The feto-placental unit [1]



Why is the placenta ignored?

Most surgical pathologists do not want to examine placentas. They have limited exposure to placental pathology during their training and find it hard to become accustomed to the very different terminology applicable to this organ's pathology. The interpretation of the pathological features is difficult as there is no one-to-one correlation between the pathology, the clinical presentation or the outcome. This is reflected in the poor intra- and inter-observer correlation obtained in the few studies which have been conducted in this area.[2,3] The outcome is that the placenta is globally acknowledged in general pathology as being "not examinable", which perpetuates this gap in the knowledge of general pathologists. The placenta is therefore usually relegated to specialist perinatal pathologists or pathologists with a special interest in placentas, but in countries such as the UK perinatal pathology has a low status.[4] An additional factor which makes pathologists reluctant to examine placentas is their sheer number. However, if good guidelines are established as to which placentas are submitted for pathological examination, pathologists would not feel overwhelmed.

Why should the placenta be examined by a pathologist?

Globally there are 4 million neonatal deaths annually. Approximately 99% of these occur in low- and middle-income countries. The highest rates are in sub-Saharan Africa, and 23% are estimated to be related to intrapartum events.[5]
In addition 4 million stillbirths occur annually and 26% of these are thought to occur during labour (intrapartum deaths).[6]

These figures are, however, estimates as only 3% of neonatal deaths and stillbirths occur in countries with verifiable data.

In South Africa, there are limited data available, and this shows that the contribution of intrapartum asphyxia to perinatal mortality varies from 10.8% in metropolitan areas to 26.4% in rural areas.[7]

In South Africa data are collected in many obstetric units in state hospitals in urban and rural areas, and amalgamated in the Perinatal Problem Identification Programme (PPIP) to provide information on the causes of perinatal death, as well as on contributing or avoidable factors. This not only quantifies the problem, but provides information which may highlight areas of substandard care and may guide health care policy.
The PPIP data analysed from 2000-2002 reflected that the commonest cause of primary obstetric death was recorded as UNKNOWN.[8]

Contribution of placental pathology

Examination of the placenta by a pathologist can provide valuable information which may not be determined clinically. There may be poor correlation between maternal indicators of infection and placental findings, and placental causes of fetal and perinatal death may be clinically silent, e.g. placental maturation defect and fetal thrombotic vasculopathy.[9] Clinical entities such as intrauterine growth retardation (IUGR) have a multifactorial aetiology related to fetal, maternal and placental pathology.
Through histopathological examination of the placenta the pathophysiology of an adverse pregnancy outcome may be explained, and this may contribute to the management of subsequent pregnancies, as many of the maternal and placental causes of this tragedy may recur. Identification of specific pathology in the placenta such as chorioamnionitis or villitis due to Cytomegalovirus infection may assist in the management of the neonate, both in the acute and longer term.

Placental examination is vital in the determination of timing of events that led to adverse pregnancy outcome and in doing so may assist in the medico-legal assessment of cases.

These contentions are validated by a few specific cases received in our laboratory.

CASE 1

A 24-year-old primigravida booked early and was followed through an uneventful pregnancy. At 37 weeks she reported absence of fetal movements for 1 day. On examination an intrauterine death was diagnosed, labour induced and she delivered a normal, fresh stillbirth baby. The placenta was noted to be pale.
Diagnosis: Sudden unexpected intrauterine death, cause unknown.
Placental pathology: Maturation defect.

Figure 2 a: Maturation defect

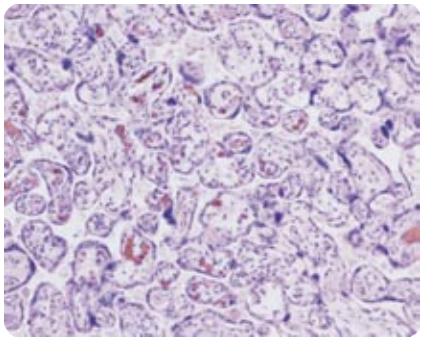
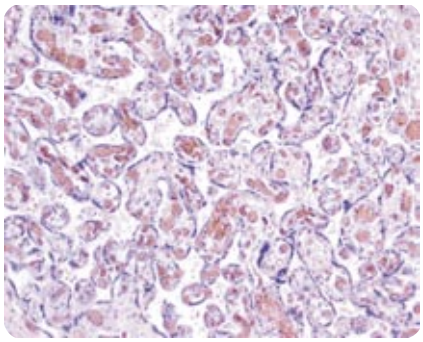


Figure 2 b: Normal-term placenta



Maturation defect / arrest

Approximately 3-4 / 1000 uneventful viable pregnancies will end in sudden in utero death. This accounts for 50% of all cases of perinatal mortality in developed countries. The commonest cause is placental maturation defect or maturation arrest. The incidence of this entity has been reported as 5.7% and is associated with fetal death in 2.3% cases.

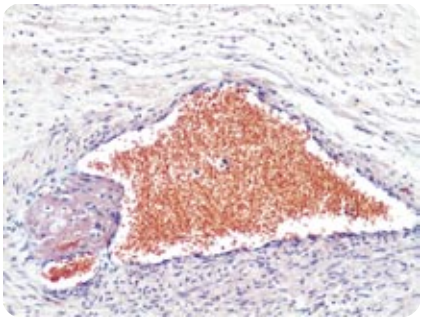
Of even greater significance to the clinician is that the recurrence risk is 5.4% or a 10-fold increase.[9,10]

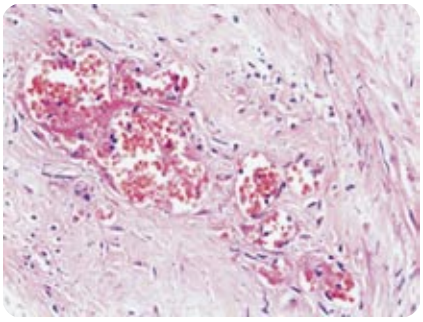
Histopathology shows markedly reduced vascularity of terminal villi with a paucity of vasculosyncytial membranes. This would result in poor transfer of oxygen to the baby and resultant hypoxia.

CASE 2

A 32-year-old female, with a history of a previous intrauterine death, booked late for antenatal care. At 36 weeks she noticed decreased fetal movements and on examination an intrauterine death was diagnosed.
She delivered a fresh stillbirth, and the baby was noted to show intrauterine growth retardation.
Diagnosis: Placental insufficiency.
Placental pathology: Fetal thrombotic vasculopathy.

Figure 3a and 3b: Organising thrombi in chorionic vessels





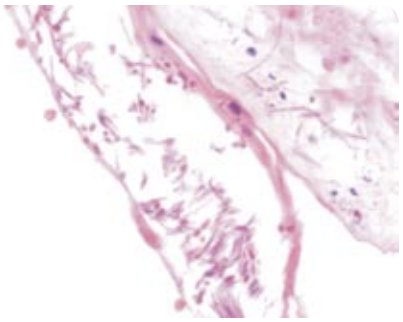
Fetal thrombotic vasculopathy

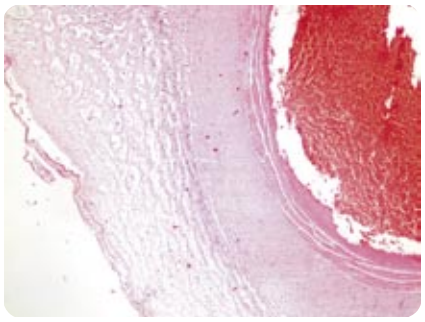
Demonstration of thrombi in the placental vessels is evidence that thrombi have occurred in the fetal circulation prior to delivery. This may result in pre- or perinatal death, neonatal encephalopathy and cerebral palsy. The pathogenesis may be due to emboli, thrombi elsewhere in the fetoplacental circulation or hypoxia secondary to extensive placental damage.[11,12]
Histopathology shows extensive avascular villi, because of thrombosis of fetal vessels, which may be seen as obliterated stem arteries, occlusive thrombi, recent or undergoing organisation and hemorrhagic endovasculitis.

CASE 3

A 22-year-old female presented in preterm labour. At delivery the placenta was noted to show 15% retro placental haemorrhage. The baby had poor Apgars at birth.
Diagnosis: Preterm labour because of abruptio placenta.
Placental pathology: Chorioamnionitis due to Candida infection.

Figure 4a and 4b: Funisitis (inflammation of the umbilical cord) due to Candida infection





Ascending infection – chorioamnionitis

Contrary to prior belief, this has been shown to be a cause of premature rupture of membranes and not a consequence and may be associated with abruptio placenta. Although the fetus may present with aspiration pneumonia and sepsis, damage may also result as a consequence of cytokine mediated vasoconstriction of the fetal vessels resulting in fetal asphyxia, leukomalacia and death. In addition, as the infection causes initiation of premature labour the fetus, though not infected, may be severely compromised as a result of the complications associated with prematurity.

The fetal vascular response – intensity and distribution – usually correlates with neonatal sepsis or neurologic impairment.

Litigation

In a survey of obstetricians conducted in 1985 and 1987 among members of the American College of Obstetricians and Gynecologists (ACOG) it was noted that 70% of obstetricians were sued at least once and 20% of all these lawsuits were related to brain-damaged infants. In a later survey of the ACOG in 1992, the number of obstetricians sued at least once had risen to 79%, with 33% of lawsuits related to brain-damaged infants and 13% to stillbirth/neonatal deaths.[13]
A 1985 NIH report stated that in the USA there were 850,000 mentally retarded children, 750,000 young people with cerebral palsy, and 10% of all school-age children were disabled. It was estimated that 42 million Americans have some form of neurologic or communicative disorder.[13]

This has spawned a global childbirth litigation industry. The problem is not confined to the USA – in 2001 the British NHS faced a 4.2 billion dollar medical negligence bill.[14]

Cerebral Palsy

Cerebral palsy (CP) was until fairly recently attributed to intrapartum hypoxia, and the obstetricians and delivery units bore the brunt of the anger and disappointment of the parents. The prevalence of CP remains constant at 1.5 to 2.5/1000 deliveries (1970-2000), unchanged despite significant improvement in fetal monitoring and neonatal intensive-care practice.[14] There has been a minimal reduction in term Hypoxic Ischaemic (HI) injury, but this has been offset by the increasing number of very-low-birthweight survivors as a consequence of this increased monitoring and sophisticated care.[15] Caesarean section rates have also increased by a factor of 10 as a result of this increase in fetal monitoring. The irony is that studies have shown that most children with CP showed no evidence of "fetal distress" prior to delivery.

Neonatal encephalopathy

Neonatal encephalopathy (NE) occurs in 3.8/1000 term births but Hypoxic-Ischaemic Encephalopathy[16] in 1.9/1000 births. This indicated the pathway from intrapartum HI injury to CP must progress through neonatal encephalopathy.[17]

There are four essential criteria to define whether an intrapartum event was sufficient to cause CP and all other identifiable etiologies must be excluded.
The Western Australia case-control

study into CP showed that 69% of children with CP had only antepartum risk factors, 25% had ante- and intrapartum risk factors, 2% had no recognised risk factors and only 4% of children with CP had intrapartum risk factors only.[18]
Blair and Stanley[19] showed subsequently that in only 8% of children with spastic CP was intrapartum hypoxia the possible cause of brain damage.

It is widely accepted now that multiple early and recent insults act together to increase the risk of brain injury at birth, i.e. perinatal asphyxia may be a CONSEQUENCE of rather than a CAUSE of neurological injury.[20]

In 2000 Redline investigated placental lesions associated with CP and NI at term in 40 infants with NI vs. 176 meconium-stained infants at low risk for NI.[21, 22] He documented the presence or absence of 5 lesions occurring within days of labour and delivery:

1. Meconium-associated vascular necrosis of the umbilical cord;
2. Severe fetal chorioamnionitis;
3. Chorionic vessel thrombi;
4. Increased nucleated red blood cells in the fetal vessels;
5. Retro placental haemorrhage (chronic).

He also documented 4 lesions known to have onset long before labour and delivery:

1. Diffuse chronic villitis;
2. Extensive avascular villi;
3. Diffuse chorionic haemosiderosis;
4. Perivillous fibrin.

In this study the risk of NI increased as a function of the number of lesions present (OR, 10.1: 95% CI, 5.1-20) as well as the temporal distribution of lesions (OR, 94.2; 95% CI, 11.9-747), showing that previous insults decrease the threshold for more recent events to cause severe injury to the fetus.

CASE 4

A 21-year-old primigravida was referred to Tygerberg with mid-pelvic arrest and meconium-stained liquor. In theatre delivery was attempted under spinal anaesthesia. The mother developed bradycardia, resuscitation was started and an emergency caesarian section performed.

The baby was delivered with signs of neonatal encephalopathy.
Diagnosis: Intrapartum hypoxia
Placental pathology: Meconium-associated vascular necrosis of the umbilical vessels.

Figure 5a: Meconium in amnion and meconium laden macrophages in chorion

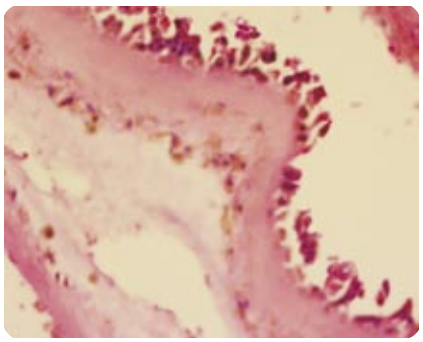


Figure 5b: Destruction of media of umbilical vessel

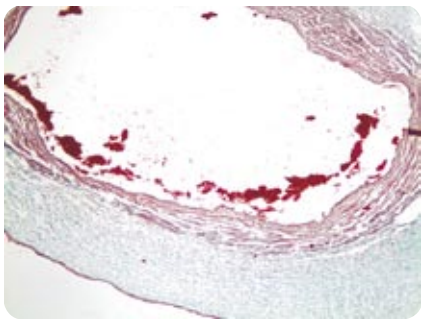
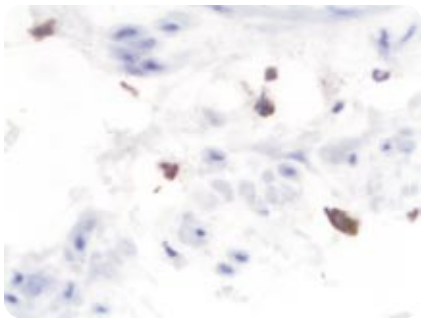


Figure 5c: Macrophages labelled with CD 68 in umbilical vessels



Meconium

Meconium may normally be passed by term fetuses during labour. If occurring in preterm fetuses or if present prior to labour, it may be considered a possible indication of fetal distress. Histopathology may estimate the duration of meconium passage. Macrophages containing meconium are present at the chorionic surface within 2-3 hrs and deep in membranes at 6-12 hrs.
Meconium in the amniotic fluid may cause vasoconstriction of umbilical blood vessels and hypoperfusion of the fetus if exposure is prolonged. Macrophages and necrotic arterial media in the umbilical cord indicate exposure 48 hrs prior to delivery, and this meconium-associated vascular necrosis of the umbilical cord shows significant correlation with severe neonatal encephalopathy and cerebral palsy.[21]

Placental pathology in Tygerberg hospital

Placentas from the obstetric unit are submitted for histopathology according to defined criteria which were established by obstetricians, neonatologists and pathologists and represent about 15% of all deliveries. In a recent audit conducted on placentas submitted to the pathology laboratory, the contribution of placental pathology was highlighted.[23]

Maternal hypertensive disorders are common in this population and may result in maternal under-perfusion of the placenta, resulting in a placenta unable to support the needs of the fetus. In this study, however, 36% of patients with no clinical evidence of hypertension showed features of uteroplacental insufficiency, reflecting the multifactorial aetiopathogenesis of this pathological entity.

There was reasonable correlation between clinically suspected chorioamnionitis and histopathological confirmation of inflammation, but the severity of the maternal and/or fetal presentation did not always correlate with the placental grade of inflammation. This can partly be explained by the virulence of the organisms responsible. Of concern is the number of placentas showing acute chorioamnionitis which was clinically silent.

In cases associated with adverse pregnancy outcome, for which the cause was clinically unknown, a histopathological diagnoses was possible in the majority of cases. Acute chorioamnionitis and uteroplacental insufficiency accounted for the majority of these diagnoses and were sometimes co-existent. Although some of these patients were unbooked, many were receiving antenatal care, but these entities were clinically silent.

A very high percentage of placentas from fetuses presenting with fetal distress severe enough to warrant delivery showed histopathological features of uteroplacental insufficiency. The placental function had been compromised to the degree that it could no longer support the needs of the growing fetus and unless the fetus is delivered either spontaneously or electively, death will be the outcome.

The placentas submitted in cases of suspected intrapartum hypoxia or death, represent a very important group of placentas. In all of these the clinical diagnosis was thought to be intrapartum

hypoxia or death. However, intrauterine infection was present in 70% of these placentas, confirming the fetus entered labour in an already compromised state. Without the pathology of the placenta, the medico-legal liability in more than 90% of these cases may well have been be placed at the door of the obstetrician and delivery unit.

Conclusion

At last, after decades of being ignored, the placenta has come of age. Her beauty, and the valuable contribution she can make to understanding adverse pregnancy outcome is being acknowledged by pathologists, obstetricians, neonatologists and administrators of health care institutions and medical insurance companies. Cinderella is going to the ball!

Fig 6: Cinderella is going to the ball

Acknowledgements

With thanks to Stellenbosch University for permission to reproduce this inaugural speech and to Mattie van der Merwe and her team for editorial assistance.
Ethics approval for the study was obtained from the Committee for Human Research of the Faculty of Health Sciences.

This article is based on the inaugural lecture of Professor Wright delivered at the Health Science Faculty of the University of Stellenbosch, *cawr@sun.ac.za.*

References

1. Byer CO, Shainberg LW, Galliano G. Dimensions of Human Sexuality. New York: McGraw-Hill 1999.
2. Naeye R, Travers H. CAP Conference XIX: Report of the working group on the role of the pathologist in malpractice litigation involving the placenta. Archives of Pathology and Laboratory Medicine. 1991;115:717-9.
3. Badawi N, Kurinczuk JJ, Keogh JM, Chambers HM, Stanley FJ. Why is the placenta being ignored? Aust N Z Obstet Gynaecol. 2000;40(3):343-6.
4. Fetal and neonatal pathology. Report of a joint working party. London: Royal College of Obstetricians and Gynaecologists; 2001.
5. Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: When? Where? Why? Lancet. 2005;356(9462):891-900.
6. Lawn JE, Shibuya K, Stein C. No cry at birth: global estimates of intrapartum stillbirths and intrapartum-related neonatal deaths. Bulletin of the World Health Organisation. 2005;83(6):409-17.
7. Buchmann EJ, Pattinson RC, Nyathikazi N. Intrapartum-related birth asphyxia in South Africa – lessons from the first national perinatal care survey. South African Medical Journal. 2002;92(11): 879-901.
8. Pattinson RC. Why babies die- a perinatal care survey of South Africa. South African Medical Journal. 2003;93(6): 445-50.
9. Stallmach T. Fetal and perinatal death-specific and unknown causes. ***Paediatric Pathology Society Update Course***. Western Cape, South Africa 2004.
10. Stallmach T. The clinical relevance of examination of the placenta: Rescue by birth: defective placental maturation and late fetal mortality. The XXIV th International Congress of the IAP; 2002; Amsterdam, The Netherlands; 2002.
11. Kraus FT, Acheen V. Fetal thrombotic vasculopathy in the placenta: cerebral thrombi and infarcts, coagulopathies, and cerebral palsy. Human Pathology. 1999;30:759-69.
12. McDonald D, Kelehan P, McMenahim J, Gordon W, Madden D, Tobbia I, et al. Placental Fetal Thrombotic Vasculopathy is associated with neonatal encephalopathy. Human Pathology. 2004;35:875-80.
13. Roberts DK. A Guest Editorial: Medicolegal aspects of placental examination. Ostet Gynecol Surv. 1993;48(12):777-8.
14. Hankins G, Speer M. Defining the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy. Obsetrics and Gynecology. 2003;102: 628-36.
15. Kraus FT. Perinatal Pathology, the placenta and litigation. Human Pathology. 2003;6:517-21.
16. Pithie AD, Chicksen B. Fine-needle extrathoracic lymph-node aspiration in HIV-associated sputum-negative tuberculosis. Lancet. 1992;340(8834-8835): 1504-5.
17. Hankins G, Erickson K, Zinburg S, Shulkin J. Neonatal encephalopathy and cerebral palsy: A knowledge survey of fellows of the American College of Obstetricians and Gynecologists. Obsetrics and Gynecology. 2003;101:1-7.
18. Badawi N, Kurinczuk JJ, Keogh JM, Alessandri LM, O'Sullivan F, Burton PR, et al. Intrapartum risk factors for newborn encephalopathy: the Western Australian case control study. British Medical Journal. 1998;317(7172):1554-8.
19. Blair E, Stanley FJ. Intrapartum asphyxia: a rare cause of cerebral palsy. Journal of Pediatrics. 1988;12:515-9.
20. Cox P. Perinatal brain injury. ***Paediatric Pathology Society Update Course***. Western Cape, South Africa 2004.
21. Redline R, O'Riordan MA. Placental lesions associated with cerebral palsy and NI following term birth. Archives of Pathol Lab Med. 2000;124:1785-91.
22. Redline R, Wilson-Costello D, Borawski E, Fanaroff A, Hack M. The relationship between placental and other perinatal risk factors for neurologic impairment in very low birth weight children. Pediatr Res. 2000;47(6):721-6.
23. Munbodh R, Hall D, Steyn W, Wright CA. Pathology examination of placentas in a high risk population group: Comparison of the clinical and histopathological diagnoses. ***Congress of the International Academy of Pathology, SA Division***. Durban, South Africa 2006.