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THE REGISTRAR: MS PRECIOUS MATSOSO
MEDICINES CONTROL COUNCIL
2nd Floor, Hallmark Building
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Pretoria

Dear Ms Matsoso

MCC Review of its Special Registration of Nevirapine for Perinatal Administration, and its Recent Recommendation that Nevirapine be Administered Together with AZT in Perinatal Applications

In this memorandum we will be drawing Council's attention to human and animal medical research literature, some of it very recent and some still in press, nearly all omitted from consideration in the World Health Organisation's draft *Antiretroviral drugs and the prevention of mother-to-child transmission of HIV infection in resource-constrained settings: Recommendations for use: 2004 Revision* guidelines (hereinafter referred to as 'the WHO Recommendations'), which has conclusively found and unequivocally predicts that:

(a) ***AZT and AZT+3TC treatment of pregnant women in South Africa will kill, mentally or neurologically cripple, and\or otherwise seriously physically harm a number of their babies;***

(b) ***Most of these babies will sustain 'moderate to severe' mitochondrial damage from in utero and postpartum exposure to these drugs;***

(c) ***Unlike the case of thalidomide babies, the drug damage caused to babies during gestation and post-partum will not be evident at or soon after birth, and so the toxic cause will therefore be masked, because the harm that AZT and 3TC causes to foetal and neonatal mitochondria only becomes symptomatically evident in children many months after exposure – and, in the case of mostly poor black women and babies in South Africa, long after they have left hospital and have returned traceless to their communities;***

(d) ***Where the damage caused by AZT and 3TC is less obvious than death, complete or partial paralysis, complete or partial spasticity, blindness, repeated convulsions or mental retardation, it may result in subtler neurological damage giving rise to lifelong neurobehavioural deficits that may easily be mis-attributed to a range of harmful infant challenges, from the 'very unfavourable psychological and social environments' attending poverty, through 'prematurity', to other serious childhood diseases;***

(e) ***Apart from brain and other neurological damage, pre-, peri- and postpartum exposure to AZT and AZT+3TC will also result in some cases to permanent bone marrow destruction, with potentially fatal consequences, and to cardiac muscle and other muscle and tissue damage of varying severity, that may be fatal;***

(f) ***The combination AZT+ 3TC+nevirapine regimen recommended in the WHO Recommendations for administration to pregnant women will cause life-threatening and in some cases fatal diseases in some of them.***

We will further substantiate our charge that the WHO Recommendations recommending the administration of AZT+3TC+nevirapine to prevent mother to child transmission of HIV ('pMTCT'):

(a) wholly inadequately canvassed the substantial corpus of published human and animal nucleoside analogue (AZT and 3TC) foetal toxicity data published to date of issue (7 January 2004), and disregarded critically important studies;

(b) trivialised their significance where it mentioned them at all; and,

(c) grossly misrepresented the crucial significance of the final report of the French Paediatric HIV Infection Study Group (citation 44 of the WHO Recommendations, and hereinafter referred to as 'the Barret study', after lead author Béatrice Barret).

In this memorandum we will also draw Council's attention to the very latest studies on the transplacental mitochondrial toxicity of AZT and 3TC for primate, human and rodent foetuses – reported in January, April and June 2004 respectively – all subsequent to the issue of the WHO Recommendations, and all of which Council evidently missed, and consequently failed to take into account, when issuing its new recommendation that in addition to nevirapine HIV-positive pregnant women in South Africa should also be encouraged to take AZT.

It will become obvious to Council on reading the new data pointed out in this memorandum that the WHO Recommendations on which it relied in recommending

the use of AZT, 3TC and nevirapine during pregnancy have been superannuated, and are now dangerously out of date.

To keep this memorandum within manageable proportions, we have not focussed on d4T, a drug proposed by WHO Recommendations as an alternative to AZT in the AZT+3TC+nevirapine regimen. The literature on d4T is less extensive than on AZT, but like AZT d4T is a nucleoside analogue and has essentially the same severe toxicities – predictably since nucleoside analogue compounds are widely used in cancer chemotherapy to intentionally poison off human cells. We might mention, however, that the WHO Recommendations's sunny estimation of d4T as a drug good for pregnant women is not shared by the manufacturer itself:

On 2 February 2001 the *New York Times* reported an urgent alert issued by the European Medicines Evaluation Agency [EMEA] after

> seven cases of lactic acidosis – three of them fatal – had been reported worldwide in pregnant women taking the two drugs in combination [d4T (stavudine), sold by Bristol Myers-Squibb as Zerit; and ddI (didanosine), sold by BMS as Videx]. … Echoing last month's warning by the US Food and Drug Administration, the EMEA pointed out that lactic acidosis is a known side effect of the class of HIV drugs called nucleoside reverse transcriptase inhibitors (NRTIs). The use of this class of drugs is not recommended during pregnancy unless the potential benefit clearly outweighs the potential risks.

Although the drugs' labels already included strong warnings that lactic acidosis could occur in any patient, the US FDA warned in a special advisory that 'new evidence showed pregnant women have a greater chance of developing the condition' (*per* Reuters report). Bristol-Myers Squibb added this warning to its labelling, and chased the change with a letter sent to fifty thousand AIDS doctors, warning them of the danger.

Reference in the WHO Recommendations to 'reports of a small number of serious adverse effects possibly associated with exposure to ART [antiretroviral therapy] in the form of mitochondrial dysfunction (43-45), but an increased rate of serious clinical manifestations has not been confirmed by other studies (46-48)' creates the falsely misleading impression that:

> (a) the evidence concerning the potentially crippling effect of in utero exposure to AZT or AZT+3TC is doubtful and at best tenuous;
>
> (b) only three studies suggest 'a possible association' between 'serious adverse effects' of exposure to AZT or AZT+3TC in the womb; and,
>
> (c) subsequent studies disconfirmed tentative earlier ones.

Before we canvass the dire implications of the findings and conclusions reported in the Barret study, which the WHO Recommendations cursorily mentioned, misrepresented and effectively disregarded, it might assist if we recapitulate:

In September 1999 the French Paediatric HIV Infection Study Group published an alert in *Lancet* (citation 43 of the WHO Recommendations, and hereinafter referred to

as ‘the Blanche alert’, after lead author Stéphane Blanche) in which, as the AIDS doctors summarised it in their report of the follow-up and confirmatory Barret study, they ‘described eight cases of children presenting principally neurological symptoms compatible with persistent mitochondrial dysfunction. The symptoms and biochemical abnormalities were identified several months after the exposure to antiretroviral drugs.’

But the damage wasn’t merely identified several months after the drug exposure: it only became manifest at that time among children who had hitherto appeared normal. That is, there was a time lag of many months between the drug damage and its manifestation in serious symptoms, in some cases ultimately fatal.

The ‘neurological symptoms’ – which the AIDS doctors might less delicately and more frankly have called massive brain and nerve damage – took the form of extensive cortical necrosis, cortical blindness, epilepsy and spastic quadriplegia in five children. Three further children were described as ‘symptom-free’ but had ‘severe biological or neurological abnormalities’– portending serious health problems and misery in later life. The AIDS doctors also described findings of severely impaired energy metabolism and corresponding muscle and other cell damage, manifesting in heart muscle injury and muscle weakness generally.

The AIDS doctors accordingly concluded in their alert: ‘Our findings support the hypothesis of a link between mitochondrial dysfunction [in infants] and the perinatal administration of prophylactic nucleoside analogues.’ That is, the appearance of the permanently crippling, and in some cases fatal, mitochondrial disease observed in several children led the AIDS doctors to postulate the discomforting misgiving that the AZT or AZT+3TC that they had used on the pregnant women in their study, and on most of the children for a few weeks after their births, might be the cause of it.

In a commentary on the Blanche alert in the May-June 2001 issue of the French journal *Therapie* (56(3):261-6), entitled (in translation), **Antiretroviral agents and pregnancy: mitochondrial dysfunction and nucleoside analogs**, Loubeyre-Unique et al. highlighted that the brain-damaging effects of AZT or AZT+3TC will not always be as grotesquely conspicuous as those reported in the Blanche alert, and may take subtler ‘neurobehavioral’ forms:

> An alert was published during 1999 by the French Perinatal Cohort: eight cases of mitochondrial dysfunction were reported among 1754 infants exposed to nucleoside analogues in utero and during the neonatal period. These eight infants were not infected by HIV. Mitochondrial toxicity of nucleoside analogues is clearly described in adult HIV patients receiving NRTI [nucleoside analogue reverse transcriptase inhibitors]. Zidovudine [AZT] (the only and the first NRTI studied) induced mitochondrial DNA dysfunction in animals (monkeys) and neurobehavourial effects in mice at a dose similar to the human dose.

Indeed so: numerous research papers have reported ‘neurobehavioural’ anomalies in rodents following experimental pre-natal AZT exposure, none of which the WHO Recommendations saw fit to mention in their approbation of AZT and similar chemicals for ingestion by pregnant women in developing countries like ours. And as

we will show, the damaging effect of AZT and 3TC on foetal mitochondrial DNA has been shown in several studies not only in primates, but also in humans.

In 1997 Petyko et al. reported **Learning disturbances in offsprings of zidovudine (AZT) treated rats** in *Neurobiology* (5(1):83-5); in 1998 Applewhite-Black et al. noted **Neurobehavioral and pregnancy effects of prenatal zidovudine exposure in Sprague-Dawley rats: preliminary findings** in *Neurotoxicology and Teratology* (20(3):251-8); in 1999 Rondinini et al., of the Laboratorio di Fisiopatologia di Organo e di Sistema, Istituto Superiore di Sanita, Rome, Italy, described the **Long-term effects of prenatal 3'-azido-3'-deoxythymidine (AZT) exposure on intermale aggressive behaviour of mice** in *Psychopharmacology* (145(3):317-23); in 2000 the same core group of Italian researchers, now led by Venerosi, found **Prolonged perinatal exposure to AZT affects aggressive behaviour of adult CD-1 mice**, reported in *Psychopharmacology* (150(4):404-11); in 2001, in *Teratology* (63(1):26-37), the group, led as before, reported related findings following **Prenatal exposure to anti-HIV drugs: neurobehavioral effects of zidovudine (AZT) + lamivudine (3TC) treatment in mice**; a second paper in 2001 by the group, led by Ricceri, published in *Psychopharmacology*, reported **Prenatal AZT or 3TC and mouse development of locomotor activity and hot-plate responding upon administration of the GABA(A) receptor agonist muscimol**; in 2002 the group, led by Venerosi again, discussed **Animal models of anti-HIV drugs exposure during pregnancy: effects on neurobehavioral development** in the light of the Blanche alert in *Progressive Neuropsychopharmacology and Biological Psychiatry* (26(4):747-61) – mentioning the French report of 'severe yet few human cases of cardiomyopathy [heart muscle damage] and neurological disease likely associated with mitochondrial dysfunction in uninfected infants of seropositive mothers perinatally exposed to AZT'; in the same year, 2002, Melnick et al. made positive findings in their investigation of **The effects of perinatal AZT exposure on the acoustic startle response in adult rats**, reported in *Neurotoxicology and Teratology* (24(6):773-81); and the most recent study in this subject, by Levin et al., published this year in the January-February issue of *Neurotoxicology and Teratololology* (26(1):65-71), returned a **Neurobehavioral assessment of mice after developmental AZT exposure**, in which the researchers recorded their observations of 'subtle neurobehavioral impairments in mice after prenatal AZT exposure at clinically relevant doses'.

Hart et al. propose a mechanism by which AZT mitochondrial toxicity causes neurological damage in their paper, **Acetyl-l-carnitine: a pathogenesis based treatment for HIV-associated antiretroviral toxic neuropathy**, still in press for publication in *AIDS* 2004, 18:1549–1560, but published online by Pubmed on 23 July 2004: 'Nucleoside analogue reverse transcriptase inhibitors (NRTI) disrupt neuronal mitochondrial DNA synthesis, impairing energy metabolism and resulting in a distal symmetrical polyneuropathy (DSP), an antiretroviral toxic neuropathy (ATN) that causes significant morbidity..' This results from AZT's potent activity as an oxidizing agent, as pointed out in Papadopulos-Eleopulos's et al. paper we sent up both in hard-copy and on CD, **A Critical Analysis of the Pharmacology of AZT and its Use in AIDS**, published as a special supplement to the prestigious academic medical journal *Current Medical Research and Opinion* in mid-1999 (archived at www.theperthgroup.com)

For those members of Council who might have forgotten their biology lessons, and so do not immediately appreciate the significance of mitochondrial damage, it bears emphasizing for the safety of generations of our country's children, black and poor particularly, that mitochondria are intracellular organelles that generate the energy necessary for a wide range of vital cellular processes. When oxidized by a 'mitochondrial toxin' such as AZT (as the drug was described by Lamperth et al. in **Abnormal skeletal and cardiac muscle mitochondria induced by zidovudine (AZT) in human muscle in vitro and in an animal model**, published in *Laboratory Investigations*, 1991 Dec;65(6):742-51), mitochondria are unable to produce this essential energy, and several secondary toxic effects follow, including mitochondrial DNA depletion and mutation.

It's relevant to mention here that of all such 'mitochondrial toxin[s]', AZT is the most poisonous: in 1997, in the *Journal of Neurological Science* Benbrick et al. reported a comparative study of the **Cellular and mitochondrial toxicity of zidovudine (AZT), didanosine (ddI) and zalcitabine (ddC) on cultured human muscle cells** (149(1):19-25). Although they found that 'AZT, ddI and ddC all exert cytotoxic [cell-poisoning] effects on human muscle cells and induce functional alterations of mitochondria..AZT seemed to be the most potent inhibitor of cell proliferation'.

It follows that it would be the most potent inhibitor of foetal cell growth too: in May 1994 Toltzis et al. reported the **Comparative embryonic cytotoxicity of antiretroviral nucleosides** in the Journal *of Infectious Diseases* (169(5):1100-2). The cellular toxicity of ddI, ddC, and d4T, all AIDS drugs in the same chemical class, was compared with that of AZT, which the lead author and other researchers had already found to be 'cytotoxic to early murine embryos both in vivo and in vitro' three years earlier (see citation 38 of the WHO Recommendations). The experiment established that the 'cytotoxicity of all three drugs was significantly less than with zidovudine at equivalent concentration', which is to say that AZT was found best at killing foetal tissue.

Since the term 'mitochondrial toxicity' might have a dry and uninteresting ring to those members of Council who've never heard of it before, appended to this memorandum is an excerpt from the Blanche study, describing the earliest-detected eight children worst-affected in the drug experiment on them. It graphically details what we're talking about. (Reading it requires a strong stomach or a hard heart.)

Although the WHO Recommendations claim, 'Short-term..tolerance of the ARV prophylactic regimens has been demonstrated', it's legion among doctors in South Africa that for most of them even a few days of AZT treatment following hypodermic needle pricks is unbearable, due to the extremely unpleasant subjective experience of the drug's toxicity. Yet the WHO Recommendations suggest that pregnant women should take it for six months of their pregnancies – even right throughout them:

> For pregnant women it may be desirable to initiate ARV treatment after the first trimester of pregnancy, that is after the period of major organ development in the fetus, although for pregnant women who require treatment or who are severely ill, the benefit of early therapy [during the first semester] would likely outweigh any potential fetal risks and therapy should be initiated in such cases.

Notwithstanding GlaxoSmithKline's childish pretensions in its marketing motto, 'Our global quest is to improve the quality of human life by enabling people to do more, feel better and live longer', rather than making a killing in the business sense, irrespective of the human cost, the toxic ill-effects of AZT and similar drugs are unendurable for most people – as was found in an investigation to quantify this problem by Fellay et al., written up as the **Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study** published on 20 October 2001 in *Lancet* (358(9290):1322-7).

The researchers reported 'a high prevalence of toxic effects' in a cohort of 1160 patients on AZT and related drugs, more than two thirds of whom suffered side effects severe enough to affect treatment adherence – in other words prevent them from continuing to take the drugs as prescribed. Forty-seven per cent reported clinical problems like vomiting, diarrhoea, nausea, abnormal fat growth, mood swings, insomnia and fatigue. Blood tests revealed 'potentially serious' abnormalities among twenty-seven per cent. The researchers classed a 'significant proportion' of these adverse events as 'serious or severe'. Kidney dysfunction and severe fatigue that were 'probably or definitely' due to the drugs led to some patients winding up in hospital.

And just by the way: rather than 'enabling people..to live longer', AZT helps them to live shorter – as Andrew Phillips at the Royal Free Hospital School of Medicine in London and George Smith at the University of Bristol reminded their medical colleagues in a letter to the *New England Journal of Medicine* on 27 March 1997: 'Extended follow-up of patients in one [AZT] trial, the [well-conducted, large-scale, double-blind] Concorde study [which found AZT to be useless as an AIDS drug], has shown a significantly increased risk of death among the patients treated early.' Needless to say, you don't see this mentioned in GlaxoSmithKline's package insert.

As might be expected, pregnant women find the drugs as hard to take as Fellay et al. found people generally do. In 1998 in *AIDS* (12:F241-247) Lorenzi et al. reported **Antiretroviral therapies in pregnancy: maternal fetal and neonatal effects:** '..29 out of 37 women and..14 out of 30 babies [suffered] one or more adverse events.' Reuters Health synopsized the trouble:

> Following combination antiretroviral therapy administered during pregnancy, most HIV-positive mothers and about half of their children developed one or more adverse events. Of thirty babies, 'the most common adverse event was prematurity (ten infants), followed by anemia (eight infants). The investigators also noted 2 cases of cutaneous angioma [blood vessel malformation presenting as spotty tumours], 2 cases of cryptorchidism [testicles retained within the abdominal cavity], and 1 case of transient hepatitis. Two infants ..developed..intracerebral hemorrhage [bleeding on the brain]' and one 'extrahepatic biliary atresia [potentially fatal constriction of bile duct].

In contradistinction to the WHO Recommendations's allegation that AZT is readily tolerated by pregnant women, the Blanche study cited three contrary investigations – published in *J Acquir Defic Syndr Hum Retrovir* 1995;9:401-07; *Lancet* 1994;344: 207-09 (the latter paper appositely entitled **Zidovudine for mother, fetus and child: hope or poison?**) and *Drug Saf* 1995;12:274-82 – in support of its note that 'Tolerance of this treatment has been a concern.' Actually, a bit more than a concern:

in *Teratology*. 2000 Aug;62(2):93-9, Patterson et al. pointed out that 'many pregnant women are unable to tolerate AZT because of toxicity'. So who's not telling the truth?

When AZT and similar drugs make pregnant women in the developing world desperately sick, just as all the literature and the skull and crossbones on Sigma Chemical Co.'s label predicts, the WHO Recommendations advise that they be forced to stay the course:

> Adherence to ARV drugs for prevention of MTCT or treatment is of critical importance, and should be promoted from the time ARV is started, and reinforced throughout prophylaxis and/or treatment, ideally at the family and community level. Guidance should include discussion with women about the known potential adverse effects of the ARV regimen they have been prescribed and importance of adherence, so they can anticipate and know how to manage minor and/or transient side effects and do not inappropriately stop therapy. After starting ARV treatment or prophylaxis, women should be seen frequently to reinforce the need for adherence to the regimen and to assess and manage any side effects of the drug. … When ARVs are used as prophylaxis to prevent MTCT, side effects such as ARV-associated nausea, which may compound the pregnancy-associated sickness, or fears that ARV drugs might harm the foetus, should not be considered to be a contra-indication or a reason for stopping ARV treatment.

Four years after the publication of the Blanche alert, the Barret study, which followed up a 'large..cohort' of '2644 of 4392 children..exposed to antiretrovirals' conclusively 'confirmed..a preliminary report' (the Blanche alert) that, as opposed to the unexposed, 'Children exposed to nucleoside analogues during the perinatal period are at risk of a neurological syndrome associated with persistent mitochondrial dysfunction ... a risk about 30 times higher than that in the general population.'

The WHO Recommendations, however, gave these very serious and conclusive findings just a passing mention, dishonestly representing their purport in doing so: 'There have been reports of a small number of serious adverse effects possibly associated with exposure to ART in the form of mitochondrial dysfunction (43-45)'. (The Barret study is citation 44, the Blanche alert 43, and another definitive study by Poirer et al., discussed below, is 45.)

Reading the WHO Recommendations, ignorant of the data reported in these three studies, one would think that the safety of AZT during and after pregnancy was a sure thing: 'The safety of ARV's used for a limited period of time in pregnancy for the purpose of prevention of peri-partum MTCT has been demonstrated. … The potential short-term toxicity in exposed infants, if any, is expected to be very small.'

Perhaps WHO Recommendations's author needs glasses, because as the Blanche alert reported, far from being 'short-term', the effect of foetal and neonatal exposure to AZT and 3TC is 'persistent mitochondrial dysfunction..months or years after the end of antiretroviral treatment', sometimes causing brain damage that shows up in Magnetic Resonance Imaging (MRI) scans, and other serious tissue damage, fatal in some cases.

As for the WHO Recommendations's allegation that the incidence of these ill-effects was 'very small', it is apparent from the Barret study that its '30 times higher than that in the general population' assessment of the risk of serious mitochondrial damage and consequent brain, neurological, muscle and organ tissue injury – high enough as it is – was actually conservatively computed; and we submit that the risk of serious harm that Council threatens South African children, mostly black, mostly poor, by advocating their exposure to AZT or AZT+3TC before and after birth is very much higher indeed. In fact the AIDS doctors admitted as much: 'The true incidence [of the risk] could be higher because additional children in the cohort have similar symptomology, and several arguments strongly suggest a mitochondrial origin for these cases.'

The number of children reported injured in the Barret study was parsimoniously arrived at in a process employing 'restrictive criteria', in which the majority of suspected cases of '196 children presenting with at least one major sign or two minor signs [of] mitochondrial dysfunction' of the 2644 drug-exposed were eliminated, leaving a remainder of just twenty-nine cases of mitochondrial dysfunction that the AIDS doctors considered 'established'.

Ninety-one children, including eleven who died, were thrown off the roll of 'possible' injury cases, notwithstanding their exhibition of 'at least one major sign or two minor signs on two different occasions as defined in the screening procedure', for the reason that the AIDS doctors identified 'another cause that could account for the symptoms and/or resulted in no suspicion of mitochondrial dysfunction for 91 children'. (The defective logic of these people leaps off the page. But then they're AIDS doctors.)

It's noteworthy that 'This group of 91 cases included 11 children who died during the study period.' Nobody thought of exhuming their remains for autopsies to determine what killed them, more especially in view of the fact that AZT poisoning frequently leaves pathologists with clear biochemical clues.

In the case of '61 children, the symptoms identified in the database, which were confirmed by the investigator, disappeared spontaneously: various investigations during the symptomatic period were not conclusive.' Because they were not 'conclusive', they were eliminated – not monitored for the possible reappearance of their symptoms, or other ones. Without explanation, the AIDS doctors figured: 'Complementary investigation after clearance of the symptoms was not considered justified.' Just like that.

One would have thought that in a properly conducted investigation, no effort and no expense would have been spared in conducting the most thorough examination of every drug-exposed child possible, employing every diagnostic tool, assay, psychometric and psychomotor test available to medicine and to toxic neurophysiology and toxic neuropsychology. But the children weren't deemed worth it – probably because, as appears from the Blanche alert, most of them were black. (As are most victims of foetal AZT poisoning in the US and European inner-cities.)

Since 'For 15 children, complementary evaluation was not possible (child lost to follow-up, parental refusal)', there is no way of knowing how many of them were hurt or killed. For eight more, 'results from complementary investigations are not yet fully available and conclusions not yet possible'. What we do know is that those eight

children would have exhibited ‘at least one major, or two minor signs’ of ‘“possible” mitochondrial dysfunction’ to warrant the ‘complementary investigations’.

As they excluded the children exhibiting ‘at least one major, or two minor signs’ of ‘“possible” mitochondrial dysfunction’ the AIDS doctors admitted: ‘The diagnosis of mitochondrial disease in children is sometimes considered to be very difficult and even arbitrary. … Only cases of “established” mitochondrial dysfunction are presented here.’ Their use of inverted commas around “possible and “established” were used to indicate the arbitrariness of the body count, and that only the most severely injured were included in the tally. This implies that many more could have been.

That the AIDS doctors weren’t at all sure about the extent of the harm they had caused, and that they may have missed many injured children, was suggested in their report:

> In some children, the symptoms [of ‘toxic-induced mitochondrial dysfunction’] are very strongly expressed. In others, the symptoms are mild and only a specific and adapted program of complementary examinations can diagnose or suggest the existence of mitochondrial toxicity. … The symptoms in the children in our study were not specific, and may therefore not have been identified as toxic effects of treatment.

The AIDS doctors also employed a surprisingly crude and imprecise method for gathering information about the harm that they had caused the children by supervising their exposure to AZT or AZT+3TC before and after they were born: ‘The attending clinician was allowed to decide the extent of these investigations: consequently the investigations performed varied with the severity of the symptoms and the clinician’s evaluation of the pertinence of the mitochondrial hypothesis.’ In other words, things depended on how clever or stupid the particular doctor was.

How many drug injury cases on the less-severe end of the spectrum were missed and therefore unaccounted for, because of this ridiculous procedure, is anyone’s guess. Presumably the ‘attending physician’ had also administered or prescribed the toxic medicine, and, if so, would naturally have been less than astute to expose as many of his medical disasters to the world as possible.

The most extreme forms of injury to the chemically-crippled children were noted in the Barret study as ‘motor abnormality’ (typically involving muscular impairment such as trouble walking, talking and hand-control), ‘repeated seizures’ (i.e. epilepsy), ‘major cognitive delay’ (i.e. mental retardation), ‘tetraplegia’ (total limb paralysis), ‘hemiplegia’ (left or right side paralysis) ‘retardation of language acquisition’ (evidencing brain damage), ‘cardiomyopathy’ (damaged heart muscle, predicting early death), ‘nystagmus’ (uncontrollable rapid movement of the eyes, evidencing brain damage) and ‘severe malaise’ (non-specific persistent ill-health and weakness, consistent with toxic chemical poisoning).

In the case of twelve children in the Barret study, cerebral MRI scans revealed brain tissue atrophy (wasting), necrosis (tissue death) and other serious abnormalities. It is noteworthy, however, that in arriving at this figure, the AIDS doctors applied a remarkably restrictive protocol for interpreting MRI brain scans of children who

appeared to have sustained brain damage through pre-, peri- and postnatal AZT and AZT+3TC exposure:

> All the cerebral MRI data underwent two independent expert analyses. In cases of divergent interpretations, the "least severe" interpretation was used for the final analysis of the results: an MRI that was judged to be normal by one party and to be abnormal by the other was considered to be normal, regardless of the number and severity of the abnormalities observed. If the MRI findings were considered to be abnormal by both parties, only the abnormalities observed by both were included in the analysis.

Obviously, had the AIDS doctors designed a more sensitive protocol for a higher vigilance and detection level, many more cases of visible drug-damage to brain tissue would have been recorded.

Even so, it's important to keep in mind that it's trite in neurology that even profound, clinically apparent neurological damage or deterioration, whatever the cause, is not necessarily manifest in any observable brain tissue anomaly. Advanced Alzheimer's disease, for example, as discussed in the modern standard reference, the *Oxford Textbook of Medicine*, is a case in point.

As they reported the iatrogenic horror that they had wreaked on the babies upon whom they had earlier been experimenting with their poisonous chemicals, one can only wonder how much greater the scale of the harm that would have been ascertained and reported had an independent panel of scientists been convened to audit the scale of the disaster. The conservative reporting bias corrupting the integrity of the Barret study findings, as bad as they were, was inevitable, given that the self-same group of AIDS doctors who had caused the carnage with its reckless medical experiments was in charge of ascertaining its extent and human cost.

The Barret study confirming the transplacental mitochondrial toxicity of AZT for human foetuses and neonates was preceded by another one by the same group of AIDS doctors, this time led by Laurent Mandelbrot, published in the *Journal of the American Medical Association* on 25 April 2001 (285(16)2083-93): **Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1** (citation 26 of the WHO Recommendations).

Yet again, of babies born to 445 AZT+3TC treated mothers enrolled in the study, 151 children suffered 'moderate to severe hematologic adverse events' resulting from their exposure to the drugs, including such 'frequent serious adverse events' as 'neutropenia and anemia, requiring blood transfusion in nine children and premature treatment discontinuation in nineteen. Two uninfected children died at age 1 year from neurologic complications related to mitochondrial dysfunction.' The AIDS doctors concluded that

> Lamivudine-zidovudine may be effective in preventing maternal-infant HIV transmission. However, severe adverse effects..occurred. Thus, the role of this combination therapy in this setting is as yet unclear, and further research involving a variety of strategies is needed to definitively ascertain its utility for preventing maternal-infant HIV transmission.

That is another way of saying that however excited they were by their scintillating laboratory test results, the AIDS doctors' enthusiasm was chilled by the deaths of the children they had killed with their drugs, or poisoned – some so severely that they needed blood transfusions (an inevitably fatal procedure in many cases). These disagreeable real-world outcomes understandably made the AIDS doctors reticent about recommending to others the drug combo they had just tried on their pregnant patients and their babies.

But the doctors hired by the WHO, in pressing the administration of AZT mixed with 3TC and nevirapine on poor women and their babies in third world countries, had no such qualms:

> ZDV [AZT], 3TC and NVP are the drugs of first choice to be used to prevent peripartum MTCT. … All three drugs can be taken twice daily and infant formulations are available. To further simply the treatment, ZDV and 3TC are available in a co-formulation, thus reducing the number of pills to be taken. … Where available a highly potent ARV prophylactic regimen for these women would be the triple cocktail of ZDV+3TC+NVP from 32 weeks of gestation through delivery and for three days post-partum.

We pause to mention here that a few days after the draft WHO Recommendations were published on 7 January 2004, insouciantly selling the above-mentioned drugs to pregnant women in the developing world to be taken during most of their pregnancies, nevirapine manufacturer Boehringer Ingelheim issued a special safety alert in the US concerning the use of its drug in pregnancy. The English online news service AIDSmap captured it in a report on the 30th:

> Boehringer Ingelheim, the manufacturer of the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine (*Viramune*) has issued important new safety information in a letter to doctors in the US about the drug's potentially fatal liver toxicities. Safety information contained in packets of the drug will now caution that women with CD4 cell counts above 250 cells/mm^3, including pregnant women, who are taking nevirapine for chronic HIV infection, have a twelve-fold greater risk of serious liver side-effects, and that these have sometimes been fatal. Liver events present the greatest risk of fatality if they occur in the first six weeks of nevirapine treatment, and are often associated with a rash. However, the risk continues after this time and Boehringer Ingelheim is cautioning doctors to closely monitor patients for the first 18 weeks of nevirapine therapy. Even when nevirapine treatment is discontinued, the manufacturer is warning that in some instances hepatic injury has continued to progress. Boehringer Ingelheim also uses its letter to remind healthcare providers that any patient taking nevirapine can experience hepatic toxicities. Because of this some doctors recommend that nevirapine-treated individuals should be monitored more often than once a month. In particular, it is recommended by some experts that liver function be monitored before nevirapine treatment is started, at the time of nevirapine dose escalation and two weeks later.

In other words, a higher CD4 cell count – read by AIDS doctors (but not by informed immunologists) like the fall of a diviner's bones and shells as an optimistic indication of how healthy you are – predisposes you to dying of liver failure if you take

nevirapine. This phosphorescent wisdom has been adopted by AIDS doctors as their latest new doctrine.

Although the WHO Recommendations punted nevirapine together with AZT and 3TC as a 'first-line' treatment combination to be administered during pregnancy and to babies after their births, American AIDS doctors were jolted a few months later into having different ideas. A paper about fatal and other serious **Maternal Toxicity With Continuous Nevirapine in Pregnancy: Results From PACTG 1022** by Hitti et al. had bitter pills to report on 1 July 2004 in the *Journal of Acquired Immune Deficiency Syndromes* (36(3):772-776).

The AIDS doctors had teed off with the 'OBJECTIVE: To compare the safety of nelfinavir and nevirapine-based antiretroviral treatment in HIV-1-infected pregnant women', giving seventeen of thirty-eight pregnant women 'nevirapine with zidovudine plus lamivudine', and the rest the latter two drugs with nelfinavir in place of nevirapine. Within two to twenty-six weeks of treatment, drug toxicity caused five women in the AZT+3TC+nevirapine group – twenty-nine per cent of them – to abandon the drugs. But it was too late for an ailing African-American woman (who had been admitted perfectly healthy into the study) after her baby was cut from her: '1 subject developed fulminant hepatic failure and died, and another developed Stevens-Johnson syndrome.'

With these disappointments, the study was smartly aborted. But instead of fingering the drugs on the strength of all that had been published about their toxicities, underscored by the CDC's ban, on the advice of the FDA, of even short-term nevirapine prophylaxis for doctors and nurses suffering needlestick injuries, the AIDS doctors brilliantly blamed the fatality and life-threatening adverse effect on the alleged unique allergic predisposition to nevirapine toxicity mentioned above: 'Continuous nevirapine may be associated with increased toxicity among HIV-1-infected pregnant women with CD4 cell counts greater than 250 cells/microL, as has been observed in non-pregnant women.'

A month after publication of the Barret study, AIDS doctors from the same study group, this time led by Le Chenadec, reported further unpleasant findings under the title, **Perinatal antiretroviral treatment and hematopoiesis in HIV-uninfected infants** (*AIDS*. 2003 Sep 26;17(14):2053-61): In utero AZT exposure may lead to 'persistent inhibition of hematopoietic stem cells [causing a] significant and durable effect on hematopoiesis up to the age of 18 months'. And as might have been expected, the authors found: 'Combinations of antiretroviral treatments were associated with larger decreases [of hematopoietic stem cells] than monotherapy up to 15 months of age.'

Expressed in lay terms, the French AIDS doctors found that AZT and 3TC poisons off babies' bone marrow – old hat to Sigma Chemical Co., whose AZT label has always told us: 'TOXIC Toxic to inhalation, in contact with skin and if swallowed. Target organ(s) Blood Bone marrow. … Wear suitable protective clothing'.

This ought not to have hit the AIDS doctors as any big surprise in any event: the potent stem-cell and general haematological toxicity of AZT reported everywhere in the medical and scientific press is surely too notorious to need labouring in this memorandum, but for any members of Council ignorant of it, or who could use a

refresher in this subject, some of the published research on this score is summed up (as at 15 November 2000) in paragraphs 10 to 13 of *Debating AZT: Mbeki and the AIDS drug controversy* (appended hereto as an excerpt for easy reference), and in David Crowe's collection of citations annexed to our second letter.

That antiretroviral drugs reach and can destroy foetal bone marrow was already known to doctors (who read their journals) by 1998: in the May issue of *Pediatric Infectious Diseases Journal* (17(5):435-436), Watson et al. had reported **Profound anemia in a newborn infant of a mother receiving antiretroviral therapy**. The HIV-negative baby, born to a positive mother who had been treated with a cocktail of AZT, 3TC and a protease inhibitor, was found to be suffering 'high output congestive heart failure secondary to profound anemia'. The paediatricians excluded 'infection, nutritional deficiencies, congenital leukemia and congenital red blood cell aplasia in the child' and naturally considered the 'cause of the life-threatening anemia in our infant..to be in utero erythroid marrow suppression by one or more of the antiretroviral agents administered to the mother'.

The WHO Recommendations mentioned Le Chenadec's et al. findings about persistent anaemia in children exposed to AZT or AZT+3TC in utero and after birth (citation 37bis), but cavalierly dismissed them with the comment that their 'clinical significance' is 'unknown'. In reality, it is elementary in paediatric medicine that persistent anaemia in an infant is a very serious condition indeed. It means, practically, that no matter how much he breathes, the child is unable to get enough oxygen, becomes breathless after any exertion, is constantly tired, and has poor resistance to infections. He's chronically very pale and unwell.

And far from being of 'unknown clinical significance', in May 1999 Mocroft et al. reported their finding in *AIDS* 3(8):943-50 that **Anaemia is an independent predictive marker for clinical prognosis in HIV-infected patients from across Europe**), confirming that 'low haemoglobin levels were found to be 'a strong independent prognostic marker for death'. Which is to say that the 'clinical significance' of persistent anaemia is that it's 'a strong independent prognostic marker' for dying young. (No prizes for guessing that Mocroft et al. also 'found that 78.2% of the patients with mild or severe anaemia at baseline had received zidovudine'.)

What the WHO Recommendations scandalously neglected to mention is that the Barret study specifically addressed the likely reasons why 'other studies' (in the words of the WHO), which preceded their report, had not found the 'serious clinical manifestations' (ibid) of nucleoside analogue foetal toxicity that they had. Barret and colleagues explained the reason:

> In a preliminary report we described eight cases of children presenting principally neurological symptoms compatible with persistent mitochondrial dysfunction …The symptoms and biochemical abnormalities were identified several months after the exposure to antiretroviral drugs. Subsequently, a review of five different US cohorts failed to identify mortality specifically linked to mitochondrial disorder, but it is important to note that the review did not address possible symptomatology in living HIV-uninfected children. … Children born to HIV-infected mothers, even when they themselves are not infected, may show symptoms of various types. These symptoms are often

> associated with easily identifiable causes, but in some cases are not readily explained. Investigators of the French paediatric study have for some years been interested in a series of symptoms, mostly neurological, of children born to HIV-infected women. The neurological symptoms include cognitive delay, behavioural disorders, motor abnormalities and convulsions. Demonstration of drug toxicity during pregnancy is not easy when the suspected event is rare and the symptoms non-specific.

Contrary to the deceptive suggestion in the WHO Recommendations that there is any lingering uncertainty about the issue, there is no question at all that exposing babies to AZT in utero will cause them some degree of permanent mitochondrial damage, from sub-clinical to fatal; and there is a wealth of research data, including some very recent papers, establishing this:

Two months before the publication of the Barret study, Poirer et al., all staff scientists at the US National Cancer Institute (hereinafter referred to as 'the NCI group'), published a study reported in the June 2003 issue of the *Journal of Acquired Immune Deficiency Syndromes* (33(2):175-83 – citation 45 of the WHO Recommendations): **Long-Term Mitochondrial Toxicity in HIV-Uninfected Infants Born to HIV-Infected Mothers**, in which they stated their findings concerning drug-caused mitochondrial DNA damage categorically and unequivocally: 'AZT exposure causes a persistent depletion of mtDNA [mitochondrial DNA]' among babies exposed to AZT in the womb.

Interviewed about these findings by Reuters Health on 8 July 2003, Miriam Poirer remarked: 'We were stunned. We thought there might be some subtle changes, but we did not expect anything so striking.' She also mentioned that in her group's preceding primate studies, in which monkey foetuses had been exposed to human-equivalent doses of AZT+3TC, 'we found major morphological damage in mitochondria of umbilical cords, and depletion of mitochondrial DNA in the brain, the heart, and the skeleton'.

The primate studies to which Poirer was referring were all published in 2000, and all returned findings with the gravest negative implications for the continued use of nucleoside analogue drugs during human pregnancy. The WHO Recommendations, however, completely ignored them.

In May 2000, led by Gerschenson, the NCI group noted findings starkly conveyed in the title of their paper **Fetal mitochondrial heart and skeletal muscle damage in Erythrocebus patas monkeys exposed in utero to 3'-azido-3'-deoxythymidine**, published in *AIDS Research and Human Retroviruses* (16(7):635-44). Human-equivalent doses of AZT were given to pregnant monkeys during the second half of their gestational terms. Their babies were killed at birth, after which their 'cardiac and skeletal muscle' tissues were structurally examined by electron microscopy and with oxidative phosphorylation enzyme assays. It was found that

> At the human-equivalent dose of AZT (6 mg of AZT/kg bw), there was an approximately 85% decrease in the specific activity of NADH dehydrogenase (complex I) and three- to sixfold increases in specific activities of succinate dehydrogenase (complex II) and cytochrome-c oxidase (complex IV).

The NCI group reported that ‘a dose-dependent depletion of mitochondrial DNA levels was observed in both tissues’, and concluded: ‘The data demonstrate that transplacental AZT exposure causes cardiac and skeletal muscle mitochondrial myopathy in the patas monkey fetus’.

The heart damage and partial and complete human paralysis in children exposed to AZT and AZT+3TC in utero, observed and described in both the Blanche alert and the Barret study, is consistent with the NCI group’s ‘cardiac and muscle mitochondrial myopathy’ finding in their primate study, and indeed with the vast mass of AZT-induced human and animal mitochondrial myopathy research data, both clinical and biological, reported in the medical and scientific press – briefly overviewed (as at 15 November 2000) in *Debating AZT: Mbeki and the AIDS drug controversy* and in Crowe’s collected AZT citations.

In June 2000, led by Ewings, the NCI group reported its research into the transplacental mitochondrial toxicity of AZT for foetal monkey brains, and again announced appalling findings in the title to their paper, **Genotoxic and functional consequences of transplacental zidovudine exposure in fetal monkey brain mitochondria,** published in the *Journal of Acquired Immune Deficiency Syndromes* (24(2):100-5). Performing the same EM and enzyme assay investigations as before, this time of neonatal brain tissue, the NCI group found that ‘in fetal patas monkeys given a human equivalent daily dose of AZT during the last half of pregnancy, mitochondria in the fetal cerebrum appear to sustain moderate damage’.

Since the cerebrum controls and coordinates all voluntary activity in the body and governs the lower parts of the nervous system, these findings explain the crippling physical manifestations of brain damage among babies and children reported and described in the Blanche alert and in the Barret study.

In November 2000 two of the NCI group, Gerschenson and Poirer, published a further primate study of the mitochondrial toxicity of AZT for monkey foetuses, exposed to human-equivalent doses of the drug during the second halves of their mothers’ pregnancies, in the *Annals of the New York Academy of Sciences* (918:269-81) – again bluntly entitled **Fetal patas monkeys sustain mitochondrial toxicity as a result of in utero zidovudine exposure**. ‘The fetal tissues examined include heart and skeletal muscle, which have high energy requirements, and placenta, which is less dependent on mitochondrial integrity.’ Their study ‘demonstrate[d] that mitochondrial toxicity, evidenced by depletion in mtDNA and OXPHOS enzyme abnormalities, is manifested similarly in heart, skeletal muscle, and placenta of AZT-exposed monkey fetuses’.

In January this year, in *AIDS* (20(1):91-100), the NCI group, led by Gerschenson, reported their investigation of the foetal mitochondrial toxicity of AZT when combined with 3TC, in a paper entitled **Mitochondrial toxicity in fetal Erythrocebus patas monkeys exposed transplacentally to zidovudine plus lamivudine**. Electron microscopy examination of ‘drug-exposed fetal cardiac and skeletal muscle cells showed mitochondrial membrane compromise, mitochondrial proliferation, and damaged sarcomeres, while mitochondria in brain cerebrum and cerebellum were morphologically normal’. The drugs were found to have resulted in massive mitochondrial DNA depletion –

> (>50%) in heart, skeletal muscle, cerebellum, and cerebrum from drug-exposed fetuses compared to unexposed controls. Overall, the data indicate that significant mitochondrial damage was observed at birth in monkey fetuses exposed in utero to AZT plus 3TC in a human-equivalent dosing protocol.

These research findings were published in the same month as the WHO Recommendations, and like those of the NCI group's preceding findings, their baleful implications were not considered in them.

That children exposed to even a so-called 'short course' of AZT in utero and after birth are liable to suffer serious permanent harm is predictable from the massive corpus of published literature on the mitochondrial toxicity of AZT resulting from adult and paediatric ingestion – a toxicity with multiple pathways, both short- and long-term, as investigated and discussed by Massini et al. in **Zidovudine-induced experimental myopathy: dual mechanism of mitochondrial damage,** published in July 1999 in the *Journal of Neurological Science* (166(2):131-40).

Exacerbating the danger of foetal toxicity is the fact that following maternal ingestion, nucleoside analogues have been found in numerous human and animal studies to readily cross the placenta, accumulating in foetal blood and foetal tissues to concentrations equal to or much higher than maternal levels:

Hankins et al., in a study of the **Transplacental transfer of zidovudine in the near-term pregnant baboon** reported in the *American Journal of Obstetrics and Gynecology* in September 1990 (163(3):728-32), found 'higher fetal concentrations of the medication and its metabolite' 5'-glucuronide azidothymidine than in maternal blood.

In a **Preliminary study on the transport of AZT (Retrovir-zidovudine) through the placenta** (translated from French) reported in the same year in the *Journal of Gynecology Obstetrics and Biological Reproduction* 1990;19(2):177-80, Gillet et al. described a human study on six pregnant volunteers about to undergo elective abortions. All agreed to take AZT before the procedure. Following their abortions, levels of the drug found in their aborted foetuses were measured. The study found that 'The concentrations of the drug in the liquor and in the fetal blood were higher or equalled those found in the maternal blood.'

Pons et al. reported alike the following year, 1991, in the *European Journal of Obstetrics, Gynecology and Reproductive Biology* (40(3):229-31) in their paper, **Placental passage of azathiothymidine (AZT) during the second trimester of pregnancy: study by direct fetal blood sampling under ultrasound**:

> AZT-therapy during pregnancy is actually contraindicated. Two HIV-positive pregnant women, who were due to have an induced abortion in the second trimester of pregnancy, were treated with AZT. Blood samples from mothers and fetuses and amniotic fluid samples were taken simultaneously. AZT crossed the placental barrier in the two patients. AZT and GAZT concentrations from the two fetuses were close to those obtained in the two women and in six non-pregnant volunteers.

As the Barret study summed up what is now well established: ‘Transplacental passage of nucleoside analogues such as zidovudine or lamivudine is high and fetuses and newborns exposed, sometimes for several months, to the drugs must therefore also be exposed to their effects.’ Indeed so: numerous studies have confirmed high levels of AZT in foetal tissues after maternal treatment with the drug, but it would seem futile to recite them all here in view of the latest lunatic fad among AIDS doctors. The old medical concern, expressed in 1991 by Pons et al., cited above, that especially vulnerable unborn (and newborn) babies should not be exposed to harmful chemicals with transplacental permeability has gone out of fashion in the age of American AIDS medicine, with many AIDS doctors now urging unblinkingly that AZT be administered directly to newborn babies for the first few weeks of their lives.

Actually, babies do well to go on AZT for a good solid six weeks after birth, enthuse American AIDS doctors in the **Recommendations of the US Public Health service task force on the use of zidovudine to reduce perinatal transmission of human immunodeficiency virus**. *MMWR Morb Mortal Wkly Rep* 1994;43 (RR-11):1-20.

The WHO Recommendations similarly vaunt an ‘antepartum + intrapartum + postpartum ZDV+3TC regimen’ as proven most ‘effective’, citing studies claiming pMTCT benefits of ‘Long (4 weeks)’ and ‘(6 weeks)’ and ‘Short (1week)..Post-partum infant’ treatment with AZT or AZT+3TC, but finally settle, whimsically and without any cited authority, on the prescription of ‘ZDV+3TC for three days after delivery’.

Why AIDS doctors should still be pressing AZT on newborn babies, when it has officially been found too poisonous for older children is one of the many dazzling wonders of the AIDS epoch. In a study in the US, designed by Dr Janet Englwood, and sponsored by both the National Institute of Allergies and Infectious Diseases and the National Institute of Child Health and Human Development, 839 HIV-positive children were divided into three groups and treated with AZT, ddI and a combination of both. The ‘AZT alone’ wing of the study had to be called off abruptly in February 1995 due to the ‘more rapid rates of..bleeding and biochemical abnormalities’ exhibited by the children in this group.

On 14 February 1995 the *New York Times* reported Englwood’s et al. findings without mincing words: *AIDS drug AZT fails completely*:

> In a major surprise, the drug AZT – now the standard treatment for children infected by the AIDS virus – proved so ineffective in halting disease progression that federal officials have called off part of a large study involving it. AZT, or zidovudine, also had unexpectedly high rates of adverse side effects in children, like bleeding and biochemical abnormalities, officials said Monday. … Children receiving AZT alone had more rapid rates of disease progression, AIDS-related infections, impaired neurological development and death. The findings clearly caught health officials by surprise. AZT is widely considered the drug of choice in treating HIV-infected children and adults.

Another clinical trial involving the closely similar drug, d4T, **A phase I/II evaluation of Stavudine (d4T) in children with human immunodeficiency virus infection**, ended just as dismally – as Kline et al. reported the following year in *Pediatrics* (96:247-252):

> Thirty-five of thirty-seven subjects [children] experienced serious clinical adverse events, including infection (33 subjects), lymphadenopathy [damage to lymph nodes] (19 subjects), hepatosplenomegaly [abnormal swelling of liver and speen] (15 subjects), chills and fever (12 subjects), and development of an AIDS-defining condition (4 subjects). …Clinical adverse events of lesser severity that were reported by more than 20% of subjects included rhinitis [inflamed nasal passages] (76%), cough (70%), diarrhea (68%), rash (62%), nausea and vomiting (51%), abdominal pain (43%), anorexia [appetite suppression] (41%), respiratory disorder (38%), headache (35%), pharyngitis [inflammation of throat] (32%), pruritis [general itching] (30%), pain (22%), peripheral neurologic symptoms [loss of sensation and/or pain in hands and feet] (22%), and nervousness (22%).

Notwithstanding these findings, GlaxoSmithKline and Bristol Myers-Squibb continue to indicate AZT and d4T for kids in their package inserts, without a word about these clinical trial disasters.

The speed with which AZT reaches the foetus after maternal ingestion has been reported in many studies: Little et al. began investigating this in rodent models, and published their findings concerning the **Pharmacokinetics of azidothymidine during late pregnancy in Long-Evans rats** in September 1989 in the *American Journal of Obstetrics and Gynecolology* (161(3):732-4):

> The drug crosses the placenta to reach concentrations in the placenta and fetus that are comparable to 75% and 58%, respectively, of those in the maternal serum by 2 hours after administration. By 4 to 6 hours after administration azidothymidine concentrations in the placenta and fetal liver significantly exceed maternal concentrations.

Boal et al., reporting **Pharmacokinetic and toxicity studies of AZT (zidovudine) following perfusion of human term placenta for 14 hours** in *Toxicology and Applied Pharmacology* in March 1997 (143(1):13-21) found ‘AZT readily crossed the placenta into the fetal compartment reaching equilibrium with maternal levels within 60-90 min after addition of each administration of AZT’.

The following month, reporting their study of **Transplacental pharmacokinetics and fetal distribution of azidothymidine, its glucuronide, and phosphorylated metabolites in late-term rhesus macaques after maternal infusion** in April 1997 in *Drug Metabolism and Disposition* (25(4):453-9), Patterson et al. noted that ‘AZT-monophosphate was detected in almost all fetal tissues examined’.

The NCI group, led by Olivero et al., investigated **3’-azido-3’-deoxythymidine [AZT] transplacental perfusion kinetics and DNA incorporation in normal human placentas in similar terms perfused with AZT** and reported these findings in July 1999 in *Mutation Research* (428(1-2):41-7). Concerned because ‘transplacental exposure studies demonstrated that AZT is a moderate to strong transplacental carcinogen in mice [and] the consequences of transplacental AZT exposure to the [human] fetus remain unknown’, the NCI group investigated ‘the extent and kinetics of AZT transfer across the human placenta’. They reported their findings with the following warning: ‘Since AZT crosses the human placenta and becomes rapidly incorporated [within 2 hours of AZT perfusion] into DNA of

placental tissue in a dose-dependent fashion, [this suggests] that even short exposures to this drug might induce [human] fetal genotoxicity.'

We should mention that we respectfully disagree with the NCI group's finding that AZT is incorporated into foetal DNA; and that whatever the drug's danger to human foetuses, we don't consider the danger of incorporation into foetal DNA to be one of them. So as not to burden this memorandum with a technical discussion of the inappropriate assay that we contend was employed by the NCI group in arriving at their erroneous conclusion here, let alone the basic AZT triphosphorylation problem (which AIDS doctors haven't ever heard about), we will provide the reasons for our dissension from the NCI group on this aspect separately, if requested. We point out, though, that it is generally accepted in medicine that AZT is incorporated into human foetal DNA after maternal ingestion/infusion (e.g. as stated in the Blanche alert); and we mention that the NCI group have published two further papers making this claim in relation both to apes and humans: **Incorporation of 3'-azido-3'-deoxythymidine (AZT) into fetal DNA and fetal tissue distribution of drug after infusion of pregnant late-term rhesus macaques with a human-equivalent AZT dose.** *J Acquir Immune Defic Syndr*. 1999 Dec 15;22(5):477-83; and **Incorporation of zidovudine into cord blood DNA of infants and peripheral blood DNA of their HIV-1-positive mothers.** *Ann N Y Acad Sci*. 2000 Nov;918:262-8.

Although the worst cases of AZT-induced mitochondrial disease in children exposed to the drug in the womb have proved fatal, or have resulted in conspicuously obvious permanent brain damage, or other serious injury – described in the Blanche alert as 'symptom-free..severe biological or neurological abnormalities' – the absence of a narrow, distinct set of symptoms of mitochondrial poisoning makes it difficult to identify and diagnose – all the more so in a developing country like ours without a widely available first world medical infrastructure to monitor the time-bombing mess.

In **A comparison of genetic mitochondrial disease and nucleoside analogue toxicity. Does fetal nucleoside toxicity underlie reports of mitochondrial disease in infants born to women treated for HIV infection?** in *Annals of the New York Academy of Sciences* in November 2000 (918:247-61) Haas et al. made the same point:

> Recent reports of mitochondrial disease in infants whose mothers were treated in pregnancy with nucleoside analogues are of concern. Chronic nucleoside analogue treatment of adults has long been known to cause mitochondrial DNA depletion with the risk of multisystem disease. Combination nucleoside analogue treatment regimens [e.g. AZT+3TC] may have the greatest risk of toxicity.

In other words, mitochondrial poisoning in utero can result in a wide array of disease conditions among children. Again the point was made in the report of the Barret study, noting that the 'clinical expression..of the mitochondrial toxicity of nucleoside analogues..is highly variable, from peripheral neuropathy to severe lactic acidosis'.

As Le Chenadec et al. were also to discover in 2003 (their study discussed above), Haas's et al. observation that the combination of nucleoside analogues such as AZT together with 3TC during pregnancy 'may have the greatest risk of toxicity' has been repeatedly confirmed:

The NCI group, led by Olivero, reporting the **Transplacental genotoxicity of combined antiretroviral nucleoside analogue therapy in Erythrocebus patas monkeys** in *Journal of Acquired Immune Deficiency Syndromes* on 1 April 2002 (29(4):323-9), found exactly that – noting that 'the total DNA damage sustained by [monkey] fetuses exposed to both drugs [AZT and 3TC] was at least double that observed in fetuses exposed to ZDV [AZT] alone'.

Walker et al. found similarly, reporting in *AIDS* (16:2165-2173) in the same year, with the title of their paper pointing up their finding of **Increased long-term mitochondrial toxicity in combinations of nucleoside analogue reverse transcriptase inhibitors.**

Naturally the authors of the WHO Recommendations didn't think fit to mention any of this when recommending that pregnant women in the developing world, and their unborn and newly born babies, be given AZT and 3TC mixed.

It is crucially important to appreciate that the frequency and severity of mitochondrial damage caused to children exposed to AZT in utero is not always immediately clinically obvious, even when it is severe, and that it may be initially clinically asymptomatic, as the Blanche alert noted – where the crippling, sometimes fatal, effects of AZT and AZT+3TC exposure in utero only became manifest among children several months after exposure.

Recent research on the subject of mitochondrial toxicity of nucleoside analogue drugs for human foetuses by the NCI group, led by Divi, which the scientists described as a 'pilot study', was published a few months ago in April 2004 in *AIDS* (18(7):1013-21) – subsequent to the publication of the WHO Recommendations – under the title, **Mitochondrial damage and DNA depletion in cord blood and umbilical cord from infants exposed in utero to Combivir** (i.e.AZT and 3TC). The NCI group found that a

> cohort of HIV-1-uninfected Combivir-exposed infants with no clinical symptoms showed morphological and molecular evidence of mitochondrial damage. … In umbilical cords from six of nine infants born to HIV-1-infected mothers taking Combivir moderate to severe mitochondrial morphological damage was observed.., while none of seven unexposed infants showed similar damage.

Having regard to all the data on the mitochondrial toxicity of AZT published to date, along with findings made about the rapid transport of AZT across the placenta and its accumulation in foetal blood to equivalent or higher than maternal levels, there is no reason to doubt that the findings of Divi's et al. pilot investigation – that two thirds of babies exposed to nucleoside analogue drugs in utero will suffer 'moderate to severe' mitochondrial damage – will in time be confirmed by a future large scale study.

The most recent research on transplacental nucleoside analogue foetal mitochondrial toxicity, conducted by Bishop et al., was reported online on 30 June 2004 by Pubmed, in advance of print publication in *Toxicological Science,* under the title **Mitochondrial Damage Revealed by Morphometric and Semiquantitative Analysis of Mouse Pup Cardiomyocytes Following in Utero and Postnatal Exposure to Zidovudine and Lamivudine**:

> That myopathy and cardiomyopathy, related to mitochondrial damage, develop in some adults chronically treated with ZDV has long been known; recently, reports have suggested that similar adverse effects may occur in some infants exposed perinatally. Using a mouse model of human neonatal exposure, we treated pregnant CD-1 mice twice daily with doses of 75 mg/kg ZDV plus 37.5 mg/kg lamivudine throughout gestation and lactation; pups were exposed by direct gavage beginning postnatal day (PND) 4 and sacrificed on PND 28. Hearts were removed rapidly, and ventricles were processed for electron microscopy. Morphometric and semiquantitative morphological analyses were performed on 3 micrographs from each of 3 blocks from each of 3 females and 3 males from the control and treated groups. Treated mice showed significant increases in the mean area and decreases in the mean number of cardiomyocytic mitochondria compared to controls. We observed clusters of damaged mitochondria more frequently in treated animals than in controls; damage included fragmentation and loss of cristae. These results, demonstrating alterations in cardiomyocytic mitochondria of mice exposed in utero and postnatally, may model cardiac damage reported in human infants similarly exposed to ZDV.

Even before it was licensed by the FDA as an AIDS drug in 1987, AZT had been found to be carcinogenic by FDA toxicologist Harvey Chernov in a review of numerous studies entitled *Review & Evaluation of Pharmacology & Toxicology Data* that he sent up in December 1986 for consideration by the licensing panel. Since local GlaxoSmithKline medical director Peter Moore is on record candidly warning much the same – 'Long-term use of AZT ['for more than six months'] does contain risks, including cancer' (*Mail & Guardian*, 1 December 1999) – we won't lumber this memorandum with all the published studies.

But as far back as 1997, the NCI group, particularly concerned about the potentially carcinogenic consequences of exposing human foetuses to AZT, conducted animal investigations into this, and found positively, as indicated in the title of their paper published in November that year in the *Journal of the National Cancer Institute* (89(21):1602-8), **Transplacental effects of 3'-azido-2',3'-dideoxythymidine (AZT): tumorigenicity in mice and genotoxicity in mice and monkeys.**

Pregnant mice and monkeys were given AZT in the second halves of their gestational terms. By one year of age, the mice exposed to AZT in utero 'exhibited statistically significant, dose-dependent increases in tumor incidence and tumor multiplicity in the lungs, liver, and female reproductive organs'. 'AZT,' the NCI group accordingly noted, 'is genotoxic in fetal mice and monkeys and is a moderately strong transplacental carcinogen in mice examined at 1 year of age.' They advised accordingly: 'Careful long-term follow-up of AZT-exposed children would seem to be appropriate.'

Having established that 'AZT is unequivocally a transplacental genotoxin and carcinogen [and] given transplacentally to mice, benzopyrene [a known carcinogen employed in research laboratories to induce cancers] produced lung and liver tumour multiplicities similar to those observed [with AZT]', the NCI group recorded their concern that 'the current practice of treating HIV-positive women and their infants with high doses of AZT could increase cancer risk in the drug-exposed children when they reach young adulthood or middle age'.

Only GlaxoSmithKline's lawyers took note: on 4 March 1998, to hedge the company against damages actions arising from the development of cancers in people exposed to AZT before they were born, the 'PRECAUTIONS: Information for Patients: Carcinogenesis, Mutagenesis, Impairment of Fertility' section of AZT's 'PRODUCT INFORMATION' was amplified; to the sentence, 'The long-term consequences of in utero and infant exposure to Retrovir [AZT] are unknown', was added the phrase, 'including the possible risk of cancer'.

The subsequent appearance of cancers in children exposed to AZT in utero, just as the NCI group's animal studies predicted, hasn't caused any alarm among AIDS doctors who promote the drug as a perinatal anti-HIV prophylactic – due, it appears, to a typical medical mindset problem, particularly among those whose professional reputations are deeply invested in this asinine treatment. In a private note to the writer, praising the 'good comprehensive review of the literature you performed' in *Debating AZT: Mbeki and the AIDS drug controversy*, Ofelia Olivero of the NCI group remarked upon this phenomenon: 'During my research I noticed a lot of resistance from many different people to believe our data. In general there is resistance to the "bad news".'

This 'resistance to the "bad news"' is well illustrated in the case of Ellen Cooper, one of the US FDA panellists who approved the licensing of AZT as an AIDS drug in February 1987 (see the fraud spilled in *Licensing AZT* in the appendices to *'Just say yes Mr President': Mbeki and AIDS*) and Principal Investigator of the Women and Infants Transmission Study (ACTG076, sponsored, like the original licensing trial, by the drug's manufacturer) on the basis of which AZT, previously strenuously contraindicated in pregnancy by numerous authorities, is today used in pregnancy – a study meticulously analysed and completely debunked by Papadopulos-Eleopulos et al. in their exhaustive, 130 000-word *Mother to child transmission of HIV and its prevention with AZT and nevirapine* monograph, which we sent you in hard-copy last month. (If you've lost it it's archived online at www.theperthgroup.com.)

Cooper was quoted in the September/October 1998 issue of *Mothering* magazine: 'We don't know what the long-term effects of AZT use during pregnancy might be, but so far we have seen virtually no adverse effects in the short term. ... Not one single tumor. Not one. ... I mean [the children] have cancers, lymphomas, and other problems like that..but there's no reason to link those cancers to AZT.'

But given Olivero's findings that AZT has exhibited transplacental carcinogenicity in animal models, and Pluda's et al. discovery of the **Development of non-Hodgkin lymphoma in a cohort of patients with severe human immunodeficiency virus (HIV) infection on long-term antiretroviral therapy**, published in *Annals of Internal Medicine*, in August 1990 (113(4):276-82) – just under half of them within three years, an incidence of the disease about fifty times higher than normal – there would seem to be every reason in common sense to 'link those cancers to AZT'.

Whether in decades to come, the 'unequivocally' established 'transplacental genotoxi[city] and carcinogen[icity]' of AZT in animal models likewise manifests among human adults exposed to AZT in their mother's wombs, like thousands of DES victims in the first world today, remains to be seen.

The transplacental carcinogenicity of DES had been well-established in many animal studies, all ignored by medical experts and doctors lauding the drug. To quote Nora Cody speaking in July 1999 at the National DES Research Conference in Bethesda in the US: '30 years ago today DES was still being prescribed to pregnant women in this country and, indeed, around the world. By 1969 scientists had studied this scientific substance for over three decades. Over and over, they had found cancer in laboratory animals.'

For those girls lucky enough not to be born with deformed, virilised genitals, only when they reached adulthood did the harm the drug had caused become apparent in the form of ordinarily rare carcinomas in their vaginas and cervixes (among other problems).

It's significant in this regard that the murine studies of the NCI group led by Olivero, reported in 1997 (discussed above), found that mice exposed to AZT in utero 'exhibited statistically significant, dose-dependent increases in tumor incidence and tumor multiplicity in the lungs, liver, and female reproductive organs'.

The NCI group, led by Diwan, published further findings of **Multiorgan transplacental and neonatal carcinogenicity of 3'-azido-3'-deoxythymidine in mice** in *Toxicology and Applied Pharmacology* in November 1999 (161(1):82-99). Following up on their 1997 study of one-year-old mice exposed in utero to AZT,

> Findings for all remaining offspring up to 2 years old are reported here. AZT effects were most prominent in female offspring, with a significant threefold increase in lung tumors, a reduction in lymphoblastic and follicle center cell lymphomas, and a significant increase in histiocytic sarcomas (0 in controls, 3% after low-dose AZT, and 8% after high-dose AZT, p = 0.022). Dose-dependent incidences of mammary gland, ovarian, and seminal vesicle tumors were low but significant: 0/106 controls, 3/105 low-dose, and 8/105 high-dose mice presented one of these neoplasms (p = 0.0025). Incidences of females showing any clearly AZT-related neoplasm, in lung, liver, ovary, or mammary gland or histiocytic sarcoma, in the second year, were 12/32 after the low dose and 14/27 after the high dose vs 3/23 controls (p = 0.0045). Also, the sensitivity of neonatal mice was assessed by administration of 25, 50, 100, or 200 mg/kg AZT on postnatal days 1 through 8. The effects at 2 years were similar to those seen after transplacental exposure, with significant increases in lung, liver, and mammary tumors in females. The results confirm that AZT is a moderately effective perinatal carcinogen in mice, targeting several tissue types.

Another study by the NCI group, led by Bialkowska, **Oxidative DNA damage in fetal tissues after transplacental exposure to 3'-azido-3'-deoxythymidine (AZT)**, was published the following year in the May 2000 issue of *Carcinogenesis* (21(5):1059-62). Noting that 'AZT has been found to be a perinatal carcinogen in mice' the NCI researchers investigated possible mechanisms for this in further studies with pregnant mice and monkeys. In the case of mice they found that exposing mice foetuses to AZT ('the transplacental carcinogenesis regimen'!) led to

> Significant increases in 8-oxo-2'-deoxyguano-sine (8-oxo-dG)..in the livers, a target tissue for transplacental carcinogenesis, and in the kidneys. … Tissues

> were also obtained from fetal patas monkeys (Erythrocebus patas), whose mothers had received 10 mg AZT/day during the last half of gestation. Although limited numbers of samples were available, possible increases in 8-oxo-dG were noted, relative to controls, for placenta and for fetal lung and brain (P = 0.055 for treatment-related increases in these tissues). These results suggest that an increase in reactive oxygen species could contribute to the mechanism of transplacental carcinogenesis by AZT in mice, and that this may also occur in primates.

Presuming that Council is even aware of the AZT transplacental carcinogenicity data canvassed in this memorandum, which we doubt, it's hard to imagine that its members will be happy to take a wait-and-see position in regard to whether South African babies, born to mostly poor and black mothers, develop cancers in childhood and adulthood, thanks to the AZT they have just recommended their mothers ingest while carrying them. Surely not any black members.

The administration of AZT to pregnant women and their newborn babies is justified, one reads over and over like a stuck gramophone, on the basis that it saves babies' lives. As Blanche et al. were blanching over their sinking suspicion confessed in their 'Early report' in *Lancet* in 1999 that they had crippled and in some cases killed children in the most terrible way with their strong drugs, they defended themselves saying, 'Prophylaxis of mother-to-child transmission of HIV-1 infection has saved thousands of children from death.'

But in a paper that was otherwise thoroughly referenced, there was no reference put up to support this show-stopping claim. That's because there isn't one to cite. Just as there isn't one for leading American AIDS expert Lynne Mofenson's foundational claim in September 2000 in the *New England Journal of Medicine* (343(11):803-805) in an editorial, **Perinatal Exposure to Zidovudine – Benefits and Risks**: 'Mother-to-child transmission of the human immunodeficiency virus (HIV) causes a chronic and ultimately fatal pediatric infection..' There's no reference supporting that either – but the French AIDS doctors who published the Blanche alert and Barret study bought it anyway, citing the Mofenson editorial in their AZT+3TC paper discussed above (Mandelbrot et al. in *JAMA* 285(16)2083-93.)

There is no good evidence that children privileged enough to get AZT while in their mothers' wombs, and immediately after birth for a while, do better and go on to live happier, healthier lives than children sadly deprived of it. On the contrary, when AIDS doctors are finished playing in their laboratories with all their little tests, and return to the real world in which their AZT-burned infant patients have to make their way, and they look at how the drug-treated babies have turned out, as against untreated children, they consistently find that AZT-exposed babies are very much worse off. Which is to be expected by anybody with even a fleeting familiarity with the toxic pharmacology of the drug.

That exposure to AZT in the womb and after birth leads to a higher death and serious disease rate among drug-exposed babies than untreated ones has been apparent for several years, but in the contemporary AIDS craze this has simply been disregarded:

1. In **Rapid disease progression in HIV-1 perinatally infected children born to mothers receiving zidovudine monotherapy during pregnancy**, reported in May 1999 in *AIDS*, (13:927-33) de Martino et al. reported that

> Comparison of HIV-1-infected children whose mothers were treated with ZDV with children whose mothers were not treated showed that the former [AZT treated] group had a higher probability of developing severe disease (57.3%..versus 37.2%)..or severe immune suppression (53.9%..versus 37.5%..) and a lower survival [rate] (72.2%..versus 81.0%..)'.

2. In June 2000, De Souza et al. published consistent findings in *Journal of Acquired Immune Deficiency Syndromes* (1;24(2):154-61) concerning the **Effect of prenatal zidovudine on disease progression in perinatally HIV-1-infected infants.** Their objective was to

> determine the influence of prenatal zidovudine (ZDV) prophylaxis on the course of HIV-1 infection in children by comparing the clinical outcome of infants born to HIV-1-seropositive mothers who did versus those who did not receive ZDV during pregnancy. … The main outcome measure was rapid disease progression (RPD) in the infant, defined as occurrence of a category C disease or AIDS-related death before 18 months of age. … Among infected infants, the RPD rate was 29.4% in the no ZDV group compared with 70.6% in the ZDV group … The rate of RPD was five to six times higher among infants born to treated compared with untreated mothers..

3. In July 2000, in the *Journal of Infectious Diseases* (182(1):104-11), Kuhn et al. reported likewise in their study of 325 HIV-positive children born between 1986 and 1997 until death or diagnosis with AIDS, under the title, **Disease progression and early viral dynamics in human immunodeficiency virus-infected children exposed to zidovudine during prenatal and perinatal periods**. Their findings were summarised in a report by Reuters Health:

> Among infected children who did not receive ART before AIDS diagnosis, 44% developed AIDS or died before age 12 months when they were exposed to prenatal or perinatal zidovudine. However, among HIV-infected infants not exposed to zidovudine prophylaxis, rate of death or progression to AIDS was only 24% … Zidovudine exposure before birth or perinatally appears to accelerate disease progression in HIV-infected infants.

4. In **Timing of perinatal human immunodeficiency virus type 1 infection and rate of neurodevelopment**, reported in *Pediatric Infectious Diseases Journal* in September 2000 (19(9):862-71) Smith et al. reported late-presenting evidence of neurological and brain damage caused by exposure to AZT in utero and after birth. As the Blanche alert had noted a year previously – subsequently confirmed by the Barret study in mid-2003 – the stultifying drug injury to the brain took time to become symptomatically evident, and, in the study in point, only became apparent when the children were specially tested for cognitive function and performance:

> Infants with early positive HIV-1 cultures demonstrated a notable decrement in neurodevelopmental functioning within the first 30 months of life. They achieved motor developmental scores that were increasingly and significantly

> discrepant both from the average and from scores achieved by late HIV-1-positive children over the course of the study period. Those children with early HIV-1-positive cultures also demonstrated a trend toward a similar decline in mental functioning over time ... The mothers of infants with early [HIV] positive cultures were more likely to receive ZDV [AZT] treatment during pregnancy, and their infants were more likely to receive ZDV treatment prophylactically during the first 6 weeks of life.

5. Concerning the WHO Recommendations's advocacy of a return to long-course AZT for pregnant African women, rather than the short-course treatment that has become the fashion among AIDS doctors in recent years, the data entered in Table 3 in **A trial of shortened zidovudine regimens to prevent mother-to- child transmission of human immunodeficiency virus type 1** by Lallemant et al., published in the *New England Journal of Medicine* on 5 October 2000 (343(14):982-91), reaffirmed the harm this causes children: a 7% congenital abnormality rate following long-course exposure versus 1% after short-course exposure; likewise a 7% neutropenia and leukopenia rate versus 2%; infections or other 'HIV-related' events were 43% versus 33%; and neonatal or other obstetrical events occurred in 22% versus 14% of cases. Mothers on long course AZT treatment had a higher rate of stillbirth (8% vs. 4%), severe anaemia (7% vs 4%), infection or other HIV events (20% vs 17%), and events related to pregnancy or delivery (24% vs 17%) than mothers who received the short course. Which is not to say that short-course foetal exposure to AZT is safe:

6. In support of the suggestion that AZT may safely be taken in pregnancy – 'There have been reports of a small number of serious adverse effects possibly associated with exposure to ART [antiretroviral therapy] in the form of mitochondrial dysfunction (43-45), but an increased rate of serious clinical manifestations has not been confirmed by other studies (46-48)' – the WHO Guidelines cite a study (citation 47) by Chotpitayasunondh et al., including staffers of the US CDC, **Safety of late in utero exposure to zidovudine in infants born to human immunodeficiency virus-infected mothers: Bangkok**, published in *Pediatrics* in January 2001 (107:E5). The happy title notwithstanding, the researchers reported a five times higher febrile convulsion rate and an 11% higher incidence of serious disease among the short-course AZT-exposed babies as compared with the unexposed. (This the AIDS doctors dismissed as 'a slightly higher risk for disease progression among ZDV-exposed, HIV-infected children during the 18-month follow-up period, although this difference was not statistically significant.') And as for the dishonest suggestion in the WHO Guidelines that this study was at variance with others that reported mitochondrial dysfunction among AZT-exposed babies – in the sense of disconfirming them – Chotpitayasunondh et al. specifically conceded that

> our sample size was chosen to determine the efficacy of short-course ZDV and to identify adverse events that occur with high frequency; it was not large enough to detect an increased rate of adverse events that occur rarely. Also, the number of infected children is too small and follow-up too short to draw conclusions about disease progression related to ZDV exposure. Second, our review of clinical conditions potentially associated with mitochondrial dysfunction was retrospective and could not evaluate the incidence of subtle clinical findings or laboratory abnormalities that might suggest mitochondrial

> dysfunction. Third, as in other studies to date, our follow-up period of 18 months is too short to enable us to evaluate the incidence of conditions, such as cancer, that may take many years to develop.

7. But the striking 'incidence of conditions, such as' infant death following the treatment of babies and children with AZT and a similar drug, ddI, was revealed by Chotpitayasunondh himself in an interview he gave Karen Emmons for her article in the *San Francisco Examiner* on 31 May 1999:

> Of the children who were born HIV-positive in Bangkok in the past four years and received the combination drug treatment, Chotpitayasunondh said that one-fourth died in their first year, about 33 percent by their second year, 40 percent by age 3, and then the mortality tapered off.

To repeat: forty per cent of the AZT-treated babies were dead before their third birthday. But to the wide-eyed American reporter, this was evidence that **Thailand wins a round in fight against HIV**, as she called her piece, rather than 'An iatrogenic disaster in Thailand'.

8. The conclusion that this appalling death rate was the result of AZT (and ddI) poisoning is supported by a similar fatality tally among AZT-exposed children reported by Lipshultz et al. in *Circulation* on 26 September 2000 in their paper **Cardiac Dysfunction and Mortality in HIV-Infected Children** (102(13):1542-8): 'Other factors associated with lower cumulative survival included..a history of zidovudine therapy.' Table 1 in the published report reflected that 37.5% of children given AZT died, as against 22.8% of the untreated children – which is to say that treatment with AZT almost doubled their death rate.

Yet even as they reported these brute facts, many of the AIDS doctors who conducted these studies were telling us what great stuff AZT is, and that its use in pregnancy should unquestionably be continued. They weren't put out by their own data showing that AZT-exposed infants get sick and die at a much higher rate than unexposed ones. That AZT causes AIDS one might say. As Heresi et al. did, more or less, in September 1997 in their report in *Clinical Infectious Diseases* (25(3):739-40), describing **Pneumocystis carinii pneumonia in infants who were exposed to human immunodeficiency virus but were not infected: an exception to the AIDS surveillance case definition**: 'We present two cases of severe PCP [pneumocystis carinii pneumonia, a classic and original AIDS-defining disease] in infants who were perinatally exposed to HIV [and AZT] but who were uninfected with HIV.' An unremarkable turn for the worse in the babies' health, really, since as the *The Physician's Desk Reference* revealingly notes, 'It was often difficult [in AZT clinical trials] to distinguish adverse events possibly associated with administration of Retrovir from underlying signs of HIV disease or intercurrent illnesses.'

And likewise, in company with De Martino, de Souza, Kuhn and fellow AIDS doctors, having just confirmed that indeed, as they had feared, AZT and 3TC cripples and in some cases kills children exposed to it before and after birth, the French AIDS doctors in the Barret study tried slapping down any worries by asserting emotively, again without authority in the shape of any controlled study, 'It is clear that the number of children worldwide who suffer because that have not received

antiretroviral treatments is inestimably larger than the number of children who suffer due to the toxicity of these treatments.'

It was the same spiel in the Blanche alert: 'We are aware that the suggestion that antiretroviral drugs are toxic raises delicate issues.' Which the doctors tried stilling by immediately laying their earnest claim on us that 'Prophylaxis of mother-to-child transmission of HIV-1 infection has saved thousands of children from death.' Except that, when clinical outcomes are considered – and not meaningless, unvalidated, non-specific blood tests (about as scientific as an apartheid Race Classification Board inspector's pencil test) – the 'children who suffer' turn out to be the beneficiaries of American medicine.

The sort of canards professed by the French AIDS doctors in excusing the atrocities they had perpetrated are known in a religious context as articles of faith; and, in the high purpose that the doctors proclaim in their healing mission against the sex-virus (especially prevalent among blacks, such AIDS doctors say), they are used to justify the violence they deploy against women and children, well knowing that it will injure many of them, as we see. Implying, though, that strong measures are called for. That a firm approach is needed with these people.

Indeed, against what US Secretary of State Colin Powell described to Larry King on 11 July 2003 as a 'weapon of mass destruction', formally declared 'a threat to US national security' by former US President Bill Clinton on 29 April 2000 (bringing the NSC and the CIA with all its internationally-situated spooks and goons into the game), 'aggressive, effective action' is what's needed – so insisted former US ambassador Cameron Hume at Rhodes University on 21 October 2002.

The Barret study confirms and predicts with absolute, incontestable certainty that children exposed to AZT before birth will be injured, and in some cases killed. We wonder whether Council joins in the view expressed by the Americans, and by those white AIDS doctors in France, that the killing and maiming of mostly black, mostly poor children by 'aggressive, effective action' in the holy war on AIDS is acceptable collateral damage. Because we think it's criminal and we think it's obscene.

Especially since, as you will have read by now, the vacancy of the entire pMTCT project (just like the 'weapons of mass destruction' ruse for the Americans' other neo-colonial business further north) was revealed as Papadopulos-Eleopulos et al. demolished it brick by brick in their *Mother to child transmission of HIV and its prevention with AZT and nevirapine* monograph. Did you understand it?

To be honest, we think that any member of Council who, after having read that jolly big paper, still subscribes to any of this MTCT mythology – this new American idea that mothers, mostly black, mostly poor, can kill their babies by bearing them, giving birth to them and by breastfeeding them, and that they do well from transplacental exposure to carcinogenic, mutagenic cell-poisons – really needs new batteries.

Way back in 1991 Hayakawa et al. made an alarm call, **Massive Conversion Of Guanosine To 8-Hydroxy-Guanosine In Mouse Liver Mitochondrial DNA By Administration Of Azidothymidine** in *Biochemical and Biophysical Research Communications* (176, 87-93), warning, in the light of their findings, that 'it is urgently necessary to develop a remedy substituting this toxic substance, AZT'.

In their monumental 25 000-word examination and explosion of GlaxoSmithKline's core claims in biochemistry for AZT as a medicine, **A Critical Analysis of the Pharmacology of AZT and its Use in AIDS**, Papadopulos-Eleopulos et al. took the same view:

> A critical analysis of the presently available data which claim that AZT has anti-HIV effects shows there is neither theoretical nor experimental evidence which proves that AZT, used either alone or in combination with other drugs, has any such effect. The recommendation that AZT, either alone or in combination, is administered to HIV seropositive or AIDS patients warrants urgent revision.

Particularly because, as they point out, 'the scientific literature..elucidate[s] a number of biochemical mechanisms which predicate the likelihood of widespread, serious toxicity from use of this drug'.

The French AIDS doctors conducting the Barret study grudgingly conceded that it's high time that AZT in maternity hospitals – like bloodletting, arsenic and mercury as earlier standards of medical care – should be ditched: 'Many antiretroviral molecules of different therapeutic classes are now available and it is very plausible that certain molecules or combinations of molecules be better tolerated than others by the fetus and newborn.' Better tolerated.

It's just a pity that stuck in their virus/chemo rut the AIDS doctors didn't ponder any wider alternatives to these deadly poisonous compounds, such as nutritional support for mothers fallen ill, in the form of nutrient-rich diets supplemented by micronutrients and antioxidants. Both Pubmed and the Cochrane Database lists dozens of directly relevant studies, published in the world's leading medical journals, reporting not only the clinical benefits of micronutritional therapy for pregnant women, but also encouraging results in testing procedures that AIDS doctors think indicate MTCT.

Apart from being non-patentable, and therefore inexpensive, micronutrient preparations have the added advantage of being completely safe for both mother and child. You surely saw the Harvard School of Public Health's big study, published last month in the *New England Journal of Medicine* (351;1), **A Randomized Trial of Multivitamin Supplements and HIV Disease Progression and Mortality**, by Fawzi et al., which turned in splendid results for everybody. What's more it was a randomized, placebo-controlled, double-blind clinical trial, the way it was supposed to be. Which you can't say for any AIDS drug trial, ever.

The WHO Guidelines, it should be noted, spring directly from the germ-chemotherapy paradigm of AIDS promoted by the pharmaceutical cartel, and by all those busy bees in the research industry and in academia that it supports, flying them around and lavishing grants upon them, and who in turn faithfully serve it; and they take no account of available alternatives to the aggressive use of highly toxic chemicals on developing world mothers and their unborn and newborn babies.

And more's the pity that the French AIDS doctors didn't share Hayakawa, Papadopulos-Eleopulos and their colleagues' sense of urgency as they surveyed the wasteland after waging their noble battle in maternity wards in what the WHO

Recommendations calls the 'fight' against 'the HIV/AIDS epidemic' – a 'fight' joined by a sprinkling of loyal natives such as William Makgoba (to whom we'll return) and Kgosi Letlape, who heads the South African Medical Association, against an epidemic strangely invisible to most other Africans, other than in the drearily familiar form of diseases of poverty, which have afflicted them ever since they lost their lands. But which big-time local AIDS expert Professor Jerry Coovadia attributes, as all non-African AIDS doctors do, to the 'unbridled sexuality' of 'newly independent people' – by which he means the unique, fantastic promiscuity of the servants.

Admittedly it would have taken a lot of courage for the French AIDS doctors reporting the Barret study to have publicly repudiated their deadly medicines; and as they demonstrated, none of them were man enough for it. The question is: is Council? Alexander Pope once gave the problem an encouraging spin, however: 'A man should never be ashamed to admit that he has been in the wrong, which is but saying, in other words, that he is wiser today than he was yesterday.' Generations of affected South Africans, mostly black, mostly poor, will be looking back and asking: how could this have been allowed to happen? Wasn't there anyone there to protect us?

After the lessons supposed to have been learned in the precedent thalidomide disaster, well they might wonder. But a brief review of that tragedy in the 3rd edition of the *Oxford Illustrated Companion to Medicine* explains things in terms of the characteristic constipation of the medical mind:

> It was then widely believed that the human placenta was impervious to poisons except in such doses as killed the mother. Yet there was already widespread evidence that this was untrue and that fetuses could be deformed by external influences, including poisoning and therapeutic drugs..but most of it had been ignored because this suited the contemporary mind-set or *Denkstil.* … Why did the medical profession ignore the extensive existing evidence that teratogenic substances (causing developmental abnormalities in the fetus) could cross the placenta? It is useful to look at the question as part of a mind-set or a shared view of reality that controls, organizes, and limits perception and understanding. We all tend to ignore what does not fit the theories and beliefs with which we live.

As disaster-porn, the brain damage and other crippling harm that AZT causes during pregnancy and after birth does not make such salaciously spectacular copy for the newspapers as that caused by thalidomide – whipping up public interest and sympathy, and therefore good for circulation and profits – but for the victims, their parents, their siblings and others close to them, the consequences, kicking in several months after drug-exposure, are just as horrible, just as tragic. Every minute, every hour, every day, for a lifetime.

We do understand that it is very embarrassing for doctors, pompous experts especially (and goodness, our country has enough of them), to admit that they have been mistaken – doubly so when their medicaments, ladled down with the best intentions, to gratifying public acclaim, turn out to have been harmful and sometimes deadly; but the history of Western medicine is one of grand errors, usually lasting centuries and sometimes millennia, and scarcely credible afterwards.

We trust that in the light of the data presented in this memorandum, however, Council will act robustly, and not faff around in the manner of Supreme Court of Appeal Judge Edwin Cameron, who, when confronted with the AZT toxicity data for unborn babies set before him by President Mbeki in mid-March 2000, in a fifteen-page reply to the former's appeal for the provision of this elixir to pregnant women, told reporters that his 'heart sank' as he read it 'with a sense of fear and dismay' – not because the data appalled him as it had the President when he read an early draft of *Debating AZT: Questions of safety and utility*, causing him to change his mind radically about the drug, but because, it appears, he winced at owning to what a fool he had made of himself in publicly advocating the drug.

We must confess, to be frank, that, although he likes publicly to declaim that 'I have no doubt that I have natural intellectual gifts', we find little evidence of them in his prosecution of his pet cause. Despite being presented with the case against the use of AZT in pregnancy thrice in 2000 – by President Mbeki, African historian Professor Charles Geshekter of UC California at Chico, and this writer – he has failed to weigh it, much less apologise to President Mbeki for aspersing him repeatedly from local and foreign podia on account of his well-founded concern over this drug – perhaps in the sort of terms in which the English novelist John le Carré framed a complimentary review of *Debating AZT: Mbeki and the AIDS drug controversy*:

> I agree with (the alas late) Donald Woods: [AZT] needs much more serious debate than Big Pharma and the usual club of fringe beneficiaries are permitting. There is simply too big a case to answer, and it's not being answered. Having said that, I suppose I look a bit of a fool because I'm one of the numberless well-intentioned people who have been championing cheapo antiretrovirals for the Third World's afflicted etc.

We hope that unlike his lordship, Council will react rather more responsibly, and will move quickly to revoke its latest recommendations, however awkward this might be. After which, some resignations might be in order, if, in this country, ordinary principles apply to failure in public office – evidenced by Council's disgraceful ignorance of the published literature in its field.

Council really wouldn't be acting out of turn in grasping the nettle and doing the right thing by making this radical move. After all, the Americans are allowed to fundamentally change their minds about AIDS treatment every five minutes. As with AZT for AIDS cases in extremis only (what the FDA licensed it for). Then for people told they're HIV-positive – when their cell counts are down, even if they're feeling just fine. As with warning against exposing foetuses to AZT. Then urging it as a good thing. As with the 'hit early, hit hard' approach in the mid-nineties – you gobble bracing doses of AZT and other drugs the moment you light up the test. Since AZT turned out to be no good alone. Then the big official U-turn in early 2001, recommending that it's better to leave the virus alone for as long as possible, before going on the poisonous drugs, so that the patient can live longer. These are the experts, kids.

Although we are still to receive any formal acknowledgement from Council of any of our correspondence, we have learned that individual members have been telephoning Dr Tshabalala-Msimang, telling her that they were 'amazed' by the 'detailed research' in our preceding letters, and that they had been 'unaware' of it. It is obvious that

Council has been equally unaware of most, if not all, of the research findings reported in this memorandum. But it certainly knows of them now.

We also know from a confidential disclosure made by one of Council's members that it is running scared of being sued by the TAC – a not unjustified apprehension, to be fair, in view of the resolution the TAC passed in August 2002 to sue if Council disturbs its victory over the government in the courts, and the fact that the South African judiciary, in its loftiest reaches, holds the TAC in such high esteem. Why it even enjoined the government to hold hands with it in the battle against AIDS. Because gee we must all fight this together.

But the question we think everyone needs to start asking is: for how much longer are our new democracy, our people and Council going to be held hostage to the pharmaceutical cartel by a neurotic, clinically depressed, scientifically illiterate, American-financed drug industry pimp, posing as a human rights crusader against our liberation movement – appropriately qualified for his controlled, loyal opposition role in the drug business (hence the active assistance of the US Consulate General in Cape Town in getting him funding) with the experience he derived from his work as male prostitute, and a Standard Six. (It should be conceded, though, that the Treatment Action Campaign's foreign millions are generously shared: unemployed black people from the peri-urban ghettos called out to dance on demand for the cameras get a free summer tee-shirt and R100 ('for transport and refreshments').)

As far as deregistering nevirapine for perinatal use is concerned – what we started out asking about, and now long overdue – we don't think you need lose much sleep over the prospect of being over-ruled and reversed if attacked in the courts by this dreadful person, in the light of a new paper in the pipe, **Low efficacy of nevirapine (HIVNET012) in preventing perinatal HIV-1 transmission in a real-life situation**, by Quaghebeur et al, still in press for publication in *AIDS* 2004 Sep 3;18:1854-1856 but posted online by Pubmed already.

The researchers found that when 'in a real-life situation in Kenya' they tried the HIVNET 012 regimen (a hit of nevirapine each for mother and child), it was an unmitigated flop: 'The perinatal HIV-1 transmission rate at 14 weeks was 18.1%, similar to the 21.7% before the intervention. These data call for further evaluation of the simple nevirapine regimen in field conditions, and underline the need for alternative strategies.' Game over, so to say.

The authors lamented that 'despite the lack of validated efficacy data outside research settings' doctors everywhere went dilly for this ludicrous medical gimmick – just as our clever judges did in prescribing nevirapine for heaving women and their newborn babies in South Africa, one of whom found the good they were all doing so terribly moving that he burst into tears afterwards. (Told in *The trouble with nevirapine* on the CD we sent you, but also archived at www.tig.org.za.)

And as for retracting your recommendations over AZT use in pregnancy, and then doing whatever it takes, either by way of deregistration, or the issue of a special urgent alert like the FDA and EMEA do from time to time, to ensure pregnant women and babies don't come anywhere near this poison, we can't see that in litigation launched by the TAC a judge with any brains will interfere with your moves after he's seen the dope contained in this memorandum.

In conclusion might we raise what could seem a rather tangential point? Actually it goes right to the heart of things.

In 1794, writing from a prison cell in Paris for speaking too plainly, the English radical Thomas Paine persisted irrepressibly in *The Age of Reason*:

> As the object of the Church, as is the case in all national establishments of Churches, was the power and the revenue, and terror the means it used, it is consistent to suppose that the most miraculous and wonderful things they had collected stood the best chance of being voted. … The resurrection and ascension, supposing them to have taken place, admitted of public and ocular demonstration, like that of the ascension of a balloon, or the sun at noonday, to all Jerusalem at least. A thing which everybody is required to believe requires that the proof and evidence of it should be equal to all, and universal. … Instead of this a small number of persons, not more than eight or nine, are introduced as proxies for the whole world, to say they saw it, and all the rest of the world are called upon to believe it.

So taking Tom Paine's cue, if it isn't too impertinent of us to ask: could we also be shown this virus, about which such a fuss is made, on which so much public money is spent, and high-mindedly fighting which, to the great benefit of the pharmaceutical business, so many South African children, mostly black, mostly poor, are in jeopardy of being really messed up, even killed?

At the second meeting of the International AIDS Advisory Panel in Johannesburg in July 2000, this writer was personally witness to a solemn pact clinched, on behalf of the believers, by Professor Barry Shoub, Director of the National Institute for Communicable Diseases, and Professor William Makgoba, then Director of the MRC, and now VC of the University of KwaZulu-Natal.

With his very own eyes this writer saw them pledging to conduct an experiment in which they'd have a go at isolating this terrifying virus in the standard, accepted manner (no short-cuts) from the blood of a person declared infected because his blood had lit up one of these antibody tests used to tell hundreds of South Africans daily, to their great dismay, that they've got the virus in them. But we're all still waiting, because as the gents concerned have shown, they're not good for their promises; and like bankrupt hucksters they just duck and dive and make all sorts of excuses whenever reminded.

Could Council maybe give them a friendly call, and ask them what's holding up the show? It could explain, very properly, that it needs to know, because the continued registration of a whole lot of extremely poisonous big-ticket drugs is on the line. And could you let us know whether it's because they quietly fret that if the experiment is carried out as agreed they could just come up empty-handed?

It's a simple request we pose; and if indeed no virus is found – just a few biologically ambiguous traces – it could save the public purse an awful lot of waste, money that could then be much better spent, and spare many people, big and small, but mostly black, mostly poor, unnecessary poisoning and unnecessary suffering. But then again, we reckon that this might be the very impediment, for if no virus is found, and regular folk discover that they've all been taken for one hell of a ride, it will be the end of the

money for the experts, and guys like Messrs Shoub and Makgoba might have to exchange their white vestments for blue overalls and go out looking for new jobs on the railways. With everyone laughing.

We do appreciate that our wonder about 'HIV' sounds rather off-the-wall. Just as it would have been to question the experts a couple of centuries ago with their doctorates in divinity, devilry and demonology, who were telling us that the Devil was corrupting the realm, and that he did so by way of obsession (possession) or by affording ungodly people with maleficent, preternatural powers; whose learned tomes on the subject filled library shelves at the University of Cambridge; and whose evidence in court got the accused (invariably from the working classes) hanged and burned in their umpteen thousands – in England, right up to 1736. (Lynching of accused witches continued in rural parts for well over a century.)

They claimed to know the certain tests: the hidden mole in the armpit, black cats, failure to sink when swum in ponds – dropped in to see, with left thumb tied to right big toe and vice versa – even introspective loneliness among the old, and insufferable insolence among the young. Since hey they were the experts. And some professional witchfinders, like the renowned Mathew Hopkins Esquire, whose evidence saw many people off, went about making a real good living out of it. As luminaries in the AIDS oligarchy do today.

But as you might have understood after reading that all-important Appendix XI to *Mother to child transmission of HIV and its prevention with AZT and nevirapine*, namely, *A critical examination of the evidence for the existence of HIV*, our request is maybe not so foolish after all. (If you found the detail and all those two hundred odd references a taxing read, there's a simplified version in press for imminent publication in the journal *Medical Hypotheses.* Email us for a preview if you can't wait.

This is our final friendly request for a formal response from you on the pressing issues we have raised in our correspondence to date. We know you are listening. And you know everyone's watching. We appreciate that you are sweating in fear of being attacked by the TAC. After all, they do have fans in high places – noisy some of them too, hectoring like a fishwife all the time. We don't mean to rush you unreasonably. We know that many of the matters raised in this letter will be new: nobody has critiqued the Barret study before, for instance, or lined up all the very latest foetal toxicity studies to demonstrate just how truly crazy it is to give AZT and 3TC and nevirapine to pregnant women and their babies.

Unless, maybe, with South Africa leading the world as its most important and influential new democracy in what our President has rightly called the African Century, thereby threatening the balance of power set by the good ol' boys, and with anywhere between a quarter and a half of all black women said (by AIDS doctors) to be infected with HIV, there's some sort of long-term geo-political agenda in play. With AZT lobbed into the country to really take care of things.

We'd like an indication please: how long does Council anticipate it needs to consider all this stuff and make up its mind? We expect an answer to this question in ten working days from date of delivery of this memorandum, calculated from the hour. This business isn't something we can all dilly-dally over any longer, who'll disagree?

Yours faithfully

ADV ANTHONY BRINK
CONVENOR AND NATIONAL CHAIRMAN
TREATMENT INFORMATION GROUP

Cc: The South African Government, all Provincial Health MECs, media and other interested parties.

Annexure A

Eight drug-injured children, two fatally, described by Blanche et al. in **Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues**, *Lancet* 1999 Sep 25;354(9184):1084-9.

At age 4·5 months, the first patient presented with visual impairment. Cerebral nuclear magnetic resonance imaging showed initially (at age 5·0 months) demyelinating lesions of the brainstem that became more severe and secondarily associated (at 11·0 months) with sustentorial lesions. From age 4·5 months to 11·0 months, the growth was abnormal and associated with vomiting. There were no important hepatic, pancreatic muscle enzyme, or haematological abnormalities, but blood and cerebrospinal fluid lactate concentrations were high (2·5 mmol/L [normal <1·5 mmol/L] and 4·5 mmol/L [<2·0 mmol/L], respectively). The child died aged 13 months because of respiratory and cardiac-rhythm disorders. The symptoms were compatible with Leigh's syndrome and mitochondrial investigations were done at age 12 months.

The second patient, from age 4 months until death at 11 months, had refractory epilepsy and deterioration of cognitive and psychomotor abilities. Cerebral imaging showed diffuse demyelinating lesions associated with massive cortical necrosis (figure). There were no substantial biological abnormalities for liver, pancreas, muscle, or haematological markers. The blood lactate concentration was high (2·5 mmol/L) but cerebrospinal fluid lactate was normal. Several disorders were excluded because of normal results from the following diagnostic procedures: organic-acid chromatography (urine), aminoacid chromatography (serum, urine, cerebrospinal fluid), serum cholesterol, triglycerides, vitamins A and E, pyruvate dehydrogenase activity in lymphocytes, fatty-acid oxidation and biotinidase activities (lymphocytes), very long-chain fatty acids (serum), lysosomal enzymes (galactosidase, galactosylceramidase, arylsulfatase A, mannosidase, GM1 and GM ganglioside), copper and ceruloplasmin (serum), and oligosaccharide excretion (urine). These symptoms were consistent with ALPERS syndrome, and led to mitochondrial investigations between ages 5 months and 7 months.

At age 8 months, during a febrile episode, patient three had a seizure and was thought to be hypotonic. At age 15 months, the child showed symptoms of hypokinetic hypertrophic cardiomyopathy. Blood hepatic and pancreatic enzyme concentrations were normal but the child had neutropenia neutrophils 0·931 09/L [normal > 1·531 09/L), high concentrations of muscle creatine phosphokinase in blood (350 IU/L [<250 IU/L]), and persistently high blood lactate concentrations (4mmol/L), although

cerebrospinal lactate was normal. Endomyocardiac biopsy showed intracytoplasmic vacuolisation in myocytes, but without inflammation. The cardiomyopathy progressively improved and symptoms of peripheral myopathy were seen at age 2·5 years. At age 4·0 years, the child's cardiac function was normal, but moderate muscular deficit persisted; lactate and muscle creatine phosphokinase concentrations in blood remained high. Electroretinography showed macular and peripheral abnormalities. Cerebral nuclear magnetic resonance imaging was normal.

In the fourth patient, early development was normal. Between ages 14 months and 27 months, the child had four episodes of febrile seizures. Neurological assessment at age 27 months showed mild spastic diplegia. Haematological and biochemical findings, including lactate concentrations in blood and cerebrospinal fluid, were normal. Cerebral nuclear magnetic resonance imaging showed moderate hypersignal of the white matter in T2-weighted images, with no evidence of necrosis (figure).

From age 7 months until 15 months, patient five had repeated seizures. Cognitive development and neurological assessments between episodes were normal until age 15 months. The child developed status epilepticus for 4 h, which led to severe neurological dysfunction with cortical blindness and spastic tetraparesis. Biological tests at 15 months showed only high blood hepatic enzyme concentrations (aspartate and alanine aminotransferases 200 IU/L [<40 IU/L]), which progressively returned to normal. Blood and cerebrospinal fluid lactate concentrations were measured only at the time of mitochondrial assessment and were not retrospectively available. Nuclear magnetic resonance imaging at age 16 months showed large necrotic lesions of the white matter and cortical grey matter. At age 3·5 years the child had severe sequelae and microcephaly.

Patient six was symptom-free until age 14 months, but persistent biochemical abnormalities were seen on standard follow-up of the epidemiological survey (which included lactate assays). The child had had high concentrations of blood lactate (4 mmol/L), hepatic aspartate aminotransferase (50 IU/L), and pancreatic lipase (200 IU/L [<150 IU/L]) since birth that persisted until age 14 months. Cerebrospinal fluid lactate was normal. These biological abnormalities led to specific mitochondrial investigation, including cerebral nuclear magnetic resonance imaging that showed delayed myelinisation, which is difficult to interpret at that age.

Patient seven was symptom-free until age 4 months, at which time he became hypotonic with apnoea. The child regained normal breathing and consciousness after resuscitation, with no apparent sequelae. There were no biological abnormalities during routine biological follow-up, but blood lactate concentrations (routinely assayed in this institution) were continuously high (>4 mmol/L) from the first test at 4 weeks to 7 months. Cerebral nuclear magnetic resonance imaging was normal. Near-miss syndromes and lactataemia justified mitochondrial investigations.

The eighth child was symptom-free. Persistent hepatic and pancreatic abnormalities (alanine aminotransferase 80 IU/L and lipase 180 IU/L) were seen from birth in the routine prospective biological follow-up. Blood lactate concentrations that were systematically added to the normal screening in the institution were normal, as were cerebrospinal fluid concentrations. At age 20 months, biological abnormalities persisted unchanged; a specific mitochondrial investigation was therefore done,

including electroretinography, which was abnormal, and cerebral nuclear magnetic resonance imaging that showed abnormalities of the periventricular white matter.

No child was infected with HIV-1, and all were HIV-1 seronegative at age 15 months, or at death before this age for patients one and two. For all children, repeated tests for HIV-1 by PCR and by culture were negative.

Annexure B

Debating AZT: Mbeki and the AIDS drug controversy

Anthony Brink

Paragraphs 10-13

[10] In his answer to my essay, Martin admits that AZT destroys bone marrow, but then hedges: HIV "may" be the real culprit. This is a tired old tale rehashed. Mercury and arsenic salts - doctors' favourites for ages - poisoned the patient, whose death was then blamed on unbalanced humours or germs. That AZT destroys bone marrow is frankly declared by its manufacturer. So let's not fudge. In 1987 in *Annals of Internal Medicine*, Gill *et al* reported *Azidothymidine Associated with Bone Marrow Failure in the Acquired Immunodeficiency Syndrome (AIDS)*: "Four patients with [AIDS], and a history of Pneumocystis carinii pneumonia developed severe pancytopenia [marked decrease in all types of blood cells] …12 to 17 weeks after the initiation of azidothymidine therapy … Partial bone marrow recovery was documented within 4 to 5 weeks in three patients, but no marrow recovery has yet occurred in one patient during the more than 6 months since AZT treatment was discontinued." In the same year in the *New England Journal of Medicine* Richman *et al* reported *The Toxicity of Azidothymidine (AZT) in the Treatment of Patients with AIDS and AIDS-Related Complex*: "Anemia…developed in 24% of AZT recipients and 4% of placebo recipients ($P<0.001$). 21% of AZT recipients and 4% of placebo recipients required multiple red-cell transfusions ($P<0.001$). Neutropenia (<500 cells per cubic millimeter) occurred in 16% of AZT recipients, as compared with 2% of placebo recipients ($P<0.001$)." The next year, Walker *et al* followed up in *Annals of Internal Medicine* reporting *Anemia and erythropoiesis in patients with the acquired immunodeficiency syndrome (AIDS) and Kaposi sarcoma treated with zidovudine*: "In the current study, transfusion-dependent anemia occurred in 6 of 15 patients with AIDS and Kaposi sarcoma who were receiving zidovudine therapy. All 6 affected patients required their first blood transfusion between 3 and 9 weeks after starting zidvoudine therapy, and each required 4 to 14 units of packed erythrocytes to maintain a hemoglobin level above 100 g/L over a 12-week study." Consistent with this, Costello reported in the same year, in the *Journal of Clinical Pathology* that, "Blood transfusion is often necessary in patients with AIDS, especially in those receiving AZT, a drug which produces severe anaemia in a proportion of recipients. Forty nine (36%) of 138 patients treated with AZT required blood transfusion at least once." For AIDS doctors slow to the point, Harrison's *Principles of Internal Medicine* spells it out: "[AZT], used for treating [HIV], often causes severe megaloblastic anemia…caused by impaired DNA synthesis." Even in the modern age where AZT dosing levels are now hugely reduced, in 1998, in the *New England Journal of*

Medicine, Hymes *et al* investigated and reported *The Effect of Azidothymidine on HIV-related Thrombocytopenia*, and found again: "The hematocrit [red blood cell count] decreased in the same patients...with three of eight patients requiring red-cell transfusion by the fourth week of treatment." So did Mocroft *et al* in their paper in *AIDS* in 1999: *Anaemia is an independent predictive marker for clinical prognosis of HIV-infected patients from across Europe*: "We found that 78.2% of the [HIV-infected] patients with mild or severe anaemia at baseline had received zidovudine".

[11] In their 1988 paper in the *British Journal of Haematology*, entitled, *3'-Azido-3'-deoxythymidine inhibits proliferation in vitro of human haematopoietic progenitor cells*, Dainiak *et al* reported their investigation of "the mechanism by which cytopenias develop [*i.e.* cell depletion, which is]…a serious, dose limiting toxicity of AZT therapy…" Observing that "Anaemia [during AZT therapy] appears to be due to bone marrow suppression [and] nearly one half of patients treated with AZT for [HIV]-associated disease develop transfusion-dependent anaemia due to bone marrow depression", they concluded from their study that "AZT is a potent inhibitor of haematopoiesis *in vitro*, and that erythroid progenitors are particularly sensitive to its action. These results may explain the marrow hypoplasia that occurs during AZT administration *in vivo*."

[12] AZT reaches and can destroy foetal bone marrow too. In the May 1998 issue of the *Pediatric Infectious Diseases Journal*, Watson *et al* at the University of Rochester Medical Center in New York reported the case of an HIV-negative baby born to a positive mother who had been treated with a HAART cocktail of AZT, 3TC and a protease inhibitor, suffering "high output congestive heart failure secondary to profound anemia." The paediatricians excluded "infection, nutritional deficiencies, congenital leukemia and congenital red blood cell aplasia in the child" and considered the "cause of the life-threatening anemia in our infant…to be in utero erythroid marrow suppression by one or more of the antiretroviral agents administered to the mother."

[13] Martin alleges that "toxicity in most cases is reversible." This optimistic jive was flatly contradicted by Mir and Costello just a year after AZT was approved. They reported their concern in the *Lancet* in 1988 that "bone marrow changes in patients on zidovudine seem not to be readily reversed when the drug is withdrawn. These findings have serious implications for the use of zidovudine in HIV positive but symptom-free individuals."