INQUIRY UNDER THE FATAL ACCIDENTS AND SUDDEN DEATHS INQUIRY (SCOTLAND) ACT 1976 INTO THE DEATH OF EMMA AGNES FRAME

UNDER THE FATAL ACCIDENTS AND SUDDEN DEATHS INQUIRY (SCOTLAND) ACT 1976

INTO THE DEATH OF

EMMA AGNES FRAME (DATE OF BIRTH: 30 April 1996)

Held at LANARK and HAMILTON on: 20,21,22,23,28,29 and 30 September, 1,4,5,6,7,8,11,12,13,15 October and 1 November 2004

Hamilton: 24 May 2005

The Sheriff, having considered all the evidence adduced,

DETERMINES:

In terms of section 6(1)(a) of the Fatal Accidents and Sudden Deaths Inquiry (Scotland) Act 1976 that Emma Agnes Frame, born 30 April 1996, died at 04.35 hours on 24 November 2001 within Wishaw General Hospital;

In terms of section 6(1)(b) of the Act that the cause of her death was adrenal insufficiency due to inhaled steroid therapy prescribed for chronic asthma;

In terms of section 6(1)(c) of the Act that there were reasonable precautions whereby Emma Frame's death might have been avoided, namely:

- the active intervention of the consultant respiratory paediatrician at the Royal Hospital for Sick Children at Yorkhill, Glasgow in the management of the care and treatment of Emma Frame by giving strong advice to her general practitioner regarding the reduction in his prescription of high dose fluticasone propionate and by arranging regular review at Yorkhill to monitor the success of dosage reduction and possible side-effects until this was achieved, and
- the issue to Emma Frame's parents by her general practitioner or pharmacist of a steroid card, when it became clear that she was likely to be prescribed high doses of inhaled corticosteroids for a prolonged period of time, in order to alert health care practitioners to the fact that she was being prescribed high doses of these drugs so that appropriate action could be taken in relation to any treatment which she had to receive;

In terms of section 6(1)(e) of the Act other facts which are relevant to the circumstances of Emma Frame's death are:

- that the emphasis placed by the manufacturer of fluticasone propionate upon its safety in the promotion and marketing of the drug contributed to the

complacency by many within the medical profession about its safety which in turn contributed to the practice of prescribing high doses of the drug;

- that while the drugs regulatory agency, at the relevant time the Medicines Control Agency, carried out an appropriate and timeous review of all inhaled and nasal corticosteroids and in 1998 issued a bulletin in order to set out the advice of the Committee on Safety of Medicines based thereon, the terms of the bulletin were not sufficiently robust and did not sufficiently reflect concern about the practice of prescribing high doses of inhaled corticosteroids, proportionate to the potential risks in so doing;
- that the British Guidelines on Asthma Management 1995 Review and Position Statement issued to medical practitioners in 1997 lacked clarity in relation to the maximum recommended dosage of fluticasone propionate for children under 5 years and that this contributed to the decision by Emma Frame's GP to prescribe high doses of fluticasone propionate for her;
- that events following Emma Frame's death have highlighted a need for a review of the practice and procedures whereby, in the case of a death which has been reported to him, the procurator fiscal ascertains the wishes of next of kin in connection with a request from appropriate medical authorities for the retention of organs after a post-mortem for the purposes of further detailed examination;
- that the circumstances of Emma Frame's death have highlighted a need for a review of the procedure in the Royal Hospital for Sick Children at Yorkhill, Glasgow, when outpatient appointments are requested, in order to ensure that referrals are acknowledged to referring practitioners, with notification of the date offered for a first appointment or the likely time-scale within which an appointment will be offered;
- that the appropriate authorities should consider conducting a review of the practice of general practitioners and hospital specialists when prescribing inhaled corticosteroids, with a view to assessing whether it is appropriate to issue comprehensive guidelines in relation to issues concerning prescribing, specialist referral, informing patients about possible side-effects and monitoring to detect side-effects and in relation to ancillary matters such as the issue of steroid cards;
- that the cause of Emma Frame's death should be registered as specified in section 6(1)(b) and her death certificate amended accordingly.

SHERIFF

Emma's death

Emma Agnes Frame died on 24 November 2001 at Wishaw General Hospital. She was five years old.

Emma was born on 30 April 1996, the younger child of Stewart and Karen Frame.

When she was 7 weeks old Emma was taken to her GP, Dr Frank Shapiro, with a cough. Thereafter she had recurring respiratory symptoms. She was diagnosed by Dr Shapiro as possibly asthmatic. When she was about 19 months old, Dr Shapiro treated Emma's respiratory symptoms with budesonide, an inhaled corticosteroid drug, and a short course of the oral steroid, Prednisolene. About 7 weeks later, her prescription was changed to 1,500 micrograms per day of another inhaled

corticosteroid drug, fluticasone propionate (hereinafter referred to as fluticasone). Thereafter, apart from a further period of approximately 6 weeks when she was again prescribed budesonide, Emma remained on a prescription for fluticasone of between 500 micrograms and 2,000 micrograms throughout her life.

Dr Shapiro referred Emma to the Royal Hospital for Sick Children at Yorkhill, Glasgow (Yorkhill) for specialist advice about her respiratory symptoms and his treatment of them. Emma was seen by Dr Dominic Cochran at Yorkhill on four occasions during her life.

On occasion Emma had a very bad cough, to the extent that she would vomit. On one occasion she was admitted to hospital with possible dehydration due to vomiting. She also sometimes had problems with her ears. Otherwise, Emma was generally a healthy child who led a normal life and took part in normal childhood activities. .

On 23 November 2001, Emma woke up complaining of a sore stomach. She was vomiting and appeared to be generally unwell. Later in the day, she became extremely lethargic and an emergency appointment was arranged at her GP's surgery where arrangements were made for her to be admitted to Wishaw General Hospital.

By around 7 pm when Emma arrived at hospital she had deteriorated further. On arrival in the ward, she had a convulsive fit. On examination she was noted to have large, red tonsils. Blood tests showed no obvious abnormalities

At approximately 10 pm, Emma's respiratory rate, breathing, blood pressure, heart rate, peripheral perfusion and cardiac function were all normal, she was a little dehydrated and her score on the Glasgow Coma Scale was 14 out of a possible 15. She was given fluids intravenously and treated with antibiotics. Dr Catherine Lees, consultant paediatrician in charge of Emma's care, thought that Emma may have meningitis.

Emma's condition continued to deteriorate and she had a further convulsion. Paediatric intensive care support was requested from the Royal Hospital for Sick Children in Glasgow (Yorkhill), where arrangements were made for the paediatric unit at the Royal Hospital for Sick Children in Edinburgh to attend at Wishaw General Hospital. Around 1:10 am, Emma had a respiratory arrest. She was intubated and seemed to stabilise. Treatment was administered to control convulsions. The paediatric intensive care unit team from the Royal Hospital for Sick Children in Edinburgh, arrived at 3:20 am. Emma continued to deteriorate. Her blood pressure was difficult to control. A variety of drugs and other methods of stabilisation were tried.

Emma did not respond to any treatment. The medical staff informed Emma's parents that nothing further could be done for her. The breathing tube was removed and at 4:35am Emma was pronounced dead.

A post-mortem examination of Emma was carried out on 28 November 2001 by Dr Howatson at Yorkhill. A preliminary report was sent to the procurator fiscal to advise

that the cause of death was not established at that time and a full range of additional investigations were arranged with a view to making a more precise diagnosis. A report was sent to the procurator fiscal to this effect.

Calum Frame, Emma's brother had also been diagnosed as asthmatic by Dr Shapiro and had been on a prescription of high dose corticosteroid inhalants to treat the symptoms. About one month after Emma's death, on 21 December 2001, Calum, then aged seven, complained of a sore stomach and was very sick. Because of what had happened to Emma, Mr and Mrs Frame took him immediately to the Strathaven Medical Centre from where he was referred to Wishaw General Hospital.

At Wishaw General Hospital, tests were carried out on Calum and two doctors from Yorkhill attended and examined him but the cause of his illness was not established.

Calum was transferred to Yorkhill where he was given a CT scan which showed that his brain was swelling. He was transferred to the intensive care unit. He remained there for three days, was ventilated and sedated and the swelling in his brain reduced. On 29 December 2001 he returned home where he made a full recovery.

After Calum's discharge from Yorkhill, a member of staff at the hospital noticed that the results of the blood tests taken when Calum was in hospital showed that he had a lower level of cortisol than would have been expected. It was arranged that Calum be recalled for synacthen tests to check this.

Dr Howatson prepared a second report for the procurator fiscal on 8 February 2002 in which he detailed the results of the additional investigations, stated that Emma's death appeared to have been the result of natural causes, as yet undetermined and concluded that death certification should remain unchanged as "Ia Not Ascertained". Dr Howatson noted in this report that Emma's brother had been admitted to Yorkhill Hospital intensive care unit "in a state of acute onset unconsciousness with a symptom complex almost identical to that of his sister sometime after her death". He went on to say that: "Investigations of adrenal function are not yet complete and I am unaware of any other specific information."

In March 2002, Calum was recalled to Yorkhill hospital for synacthen tests to be carried out. The results of these tests showed that Calum had severe adrenal suppression. On 19 March 2002 Dr Malcolm Donaldson examined Calum at the endocrine clinic at Yorkhill. Dr Donaldson concluded from the results of the synacthen tests, the fact that Calum had been on high dose fluticasone and that his sister had died and that she had been on high dose fluticasone, that both Calum's illness and Emma's death were related to acute adrenal insufficiency.

On 5 April 2002, Dr Howatson wrote to the procurator fiscal about Calum's illness and the diagnosis of adrenal insufficiency probably secondary to drug treatment which he was receiving for asthma. He said that Emma had been receiving similar therapy and in the light of that and the small adrenal glands which he had identified at the post-mortem examination, and which he had thought to be stress-related, he was of the view that Emma's death "would now appear to be the result of a similar aetiology, i.e. adrenal insufficiency and suppression due to inhaled steroid treatment for asthma."

The fatal accident inquiry

In terms of section 1(1)(b) of the Fatal Accidents and Sudden Deaths Inquiry (Scotland) Act 1976, it appeared to the Lord Advocate that it was expedient in the public interest that an inquiry be held into the circumstances of Emma Frame's death.

At the inquiry the procurator fiscal was represented by Mr Houston. Mrs Dougall, advocate, instructed by Drummond and Miller, WS and Mr Pugh, solicitor, appeared on behalf of Calum Frame, representing Emma's family. Mr Holmes, solicitor, appeared on behalf of the Medical Defence Union in Scotland, representing the interests of Emma's general practitioner, Dr Shapiro. Mrs Robertson, solicitor, appeared on behalf of NHS Lanarkshire and NHS Greater Glasgow, representing the interests of the relevant consultants at Wishaw General Hospital and the Royal Hospital for Sick Children at Yorkhill, Glasgow. Mr Lindsay, advocate, appeared for the Advocate General's office, representing the Medicines and Healthcare Products Regulatory Agency. Mrs Abernethy, solicitor, and Miss Hill, solicitor, appeared on behalf of GlaxoSmithKline, the current manufacturers of the drug, fluticasone.

The inquiry lasted approximately four weeks. The following witnesses gave evidence:

Mr Stewart Frame, Emma's father

Dr Catherine Lees, consultant paediatrician at Wishaw General Hospital, Wishaw

Dr Frank Shapiro, GP, Strathaven Health Centre, Strathaven

Dr Alan Howatson, consultant paediatric and perinatal pathologist, Royal Hospital

for Sick Children,Yorkhill, Glasgow

Dr Dominic Cochran, consultant respiratory paediatrician at Royal Hospital for

Sick Children,Yorkhill, Glasgow and Southern General Hospital, Glasgow

Dr James Paton, consultant paediatrician at Royal Hospital for Sick Children,

Yorkhill, Glasgow

Mr John Milne, lead pharmacist in cancer services, Lanarkshire Acute Hospitals,

NH Trust

Dr Geoffrey Todd, consultant chest physician, Antrim Area Hospital, Northern

Ireland

Dr Jeremy Rafe Suvarna, senior medical assessor in the Pharmacovigilance Risk

Assessment Unit, Medicines and Healthcare Products Regulatory Agency, London

Dr David Leather, director of primary care, GlaxoSmithKline, UK Ltd

Professor Peter Helms, Professor of Child Health at the University of Aberdeen and

Honorary Consultant Paediatrician at the Royal Children's Hospital, Aberdeen

Dr Peter William Thornton, GP, Carnoustie, Angus

Dr Malcolm Donaldson, senior lecturer in child health at the Department of Child

Health, Royal Hospital for Sick Children, Yorkhill, Glasgow

Many of these witnesses are experts in their own specialised field of medicine. The evidence was not only lengthy but often complex and technical.

Many issues were raised regarding facts and circumstances which may, to a greater or lesser degree, have contributed or been relevant to Emma's death.

At the conclusion of the hearing of evidence parties' representatives addressed me on a substantial number of issues of relevance to the determination in this case.

SUMMARY OF EVIDENCE

In order to facilitate a full understanding of the matters raised in relation to Emma's death I have set out the evidence before the inquiry, which has been accepted by me, regarding the facts and issues which I consider to be of relevance and the background information which has substantially informed my determination in this matter.

Details of the care and management of Emma by her general practitioner

Dr Frank Shapiro qualified as a doctor in 1976 and has practised as a general practitioner for most of the time since then. He is currently one of the partners in the Strathaven Medical Centre.

The other doctors in the practice refer asthma cases which are difficult to manage to Dr Shapiro. He cares for approximately 90% of the child asthma patients and 50/60% of the adult asthmatics within the practice. The practice has an asthma nurse.

Dr Shapiro has had a particular interest in the diagnosis and management of asthma for 25 years dating from a period of GP training in a paediatric unit and a period working as a locum in a paediatric unit.

Dr Shapiro himself decides upon the management and the treatment of asthma patients whenever possible but he refers these patients to a consultant when he requires reassurance regarding his management of particularly difficult cases. He

refers child patients in this category to Dr James Paton who is a consultant respiratory paediatrician at Yorkhill.

Dr Shapiro's first contact with Emma Frame was on 17 June 1996 when Emma was 7 weeks old. He noted that she was "chesty already" and had a marked cough and that there was a strong family history of atopic disease.

Dr Shapiro saw Emma again on 8 November when he noted that she had "chestiness".

Dr Shapiro's next consultation with Emma in relation to respiratory problems was on 8 May 1997, when he took a history of Emma's respiratory symptoms since birth, noted that she was sometimes chesty with colds and prescribed a non-steroid combined lung opener, Combivent.

The next relevant consultation was on 10 October 1997, when Dr Shapiro noted that Emma had had a cough for 10/14 days and was chesty with every cold. He prescribed a non-steroid lung stabiliser, Sodium Cromoglycate and requested a review in three weeks.

On 28 October 1997, Dr Shapiro noted that Emma was better and should be continued for six months on the Sodium Cromoglycate inhaler.

On 5 November 1997 Dr Shapiro had a consultation with Emma when he noted that she was feverish but that her chest was normal. He suspected that she may have a virus and that cold and smoke from a fireworks display was triggering asthma. He prescribed steroids for Emma for the first time, namely budesonide (brand name Pulmicort), an inhaled corticosteroid, via an aerochamber at a daily dose of 800 micrograms and also prescribed the lung opener Salbutamol, to be taken if she was symptomatic. He asked to see Emma again in 48 hours.

On 7 November 1997 Dr Shapiro noted that Emma was breathless and using accessory muscles of respiration. He prescribed a short course of Prednisolone, an oral steroid.

On 12 November 1997, at the end of the oral steroid course, Emma's condition was reviewed and she was noted to be "not much better but coping". A chest x-ray was arranged, which proved to be normal, and a further review was arranged.

On 26 November 1997 Emma was noted to have had a cough for 24 hours but to be otherwise well. As she was still symptomatic she was put back on Combivent. A treatment plan was devised whereby if Emma was still coughing in one week then either the dose of budesonide should be doubled or her inhaled corticosteroid prescription should be changed to fluticasone.

On 4 December 1997 Emma was noted to be less chesty but with still "the odd cough" and Dr Shapiro put the treatment plan on hold.

On 22 December 1997, Emma was seen by Dr Shapiro's partner, Dr Hassall who prescribed antibiotics.

On 29 December 1997 Dr Shapiro noted that Emma had been prescribed an antibiotic by his partner. Dr Shapiro did not consider that the use of antibiotics was appropriate in the management of asthma. As Emma was coughing and wheezing Dr Shapiro reverted to his treatment plan of 26 November and prescribed the inhaled cortisosteroid, fluticasone (brand name Flixotide) for Emma for the first time. The dose prescribed was 1,500 micrograms daily. A review was arranged for three weeks time.

On 20 January 1998, Dr Shapiro saw Emma again and noted that she was better but not symptom free. He decided that it was now necessary to refer Emma for specialist assessment.

On 21 January 1998 a referral letter was sent by Dr Shapiro to Dr Paton at Yorkhill Hospital in which Dr Shapiro stated *inter alia* that Emma's "symptoms are reduced on a dose of 1,500 micrograms of Flixotide a day via an aerochamber but she still easily becomes chesty. I think in view of her age and the doses we are using it would be worthwhile you seeing her for reassurance. As always, I am trying to use the lowest dose of steroid that keeps the child free [of symptoms]. I wonder if it might be useful sometimes to send you photocopies of my notes as since you only see the child once it is often difficult with this snapshot to assess the level of problem. I therefore have taken the liberty this time of sending a photocopy of the A4 pink sheets".

At each of his next two consultations with Emma, on 19 March and 13 May 1998, Dr Shapiro noted that Emma was "well" and reduced the total daily dosage of fluticasone to 1,000 micrograms and 750 micrograms respectively, with a two month review requested on each occasion.

On 2 June 1998 Emma was noted to be "not thriving". She was not gaining weight at the rate Dr Shapiro would have expected and she looked unwell. Upon examination, Dr Shapiro noted that Emma had enlarged glands, which suggested infection. He therefore arranged haematology investigations to check iron and blood sugar levels. The results were normal.

On 29 September 1998, Emma was reviewed and was noted to be well. The therapy was again reduced to a total of 500 micrograms daily. A further review was requested for the beginning of December.

On 1 December 1998 Dr Shapiro saw Emma and noted that she had been symptomatic for 2 or 3 weeks with a marked cough. Accordingly, Dr Shapiro increased the fluticasone prescription to 1,000 micrograms daily and prescribed Galpseud, a decongestant. An early review was arranged for four weeks. Dr Shapiro noted a plan to add Serevent, a long acting lung opener and decrease the steroid again at review if possible.

On 17 December 1998, Dr Shapiro saw Emma and noted that she was "miserable". She had been taking 1,000 micrograms of fluticasone daily for two weeks but despite that was coughing so severely that she was vomiting at the end of the cough. Her chest was clear. Dr Shapiro commenced a "rescue" course of the oral steroid, Prednisolone, which he hoped would produce a response within 24 hours. He

increased Emma's dose of fluticasone to 2,000 micrograms per day and also prescribed Serevent. He asked to see Emma again the following week.

On 22 December 1998, Dr Shapiro reviewed Emma and noted that she was 75% better but was still symptomatic. He set out a plan to continue the therapy for four weeks, when he would review the situation with a view to decreasing the fluticasone prescription.

On 11 January 1999, Dr Shapiro noted that Emma was still symptomatic but that he would need to decrease the steroid. He prescribed 60 milligrams 12 hourly of Slophylline, an anti-inflammatory drug, with a view to reducing Emma's symptoms and reducing the steroid dose. He noted a further treatment plan to reintroduce sodium cromoglycate if that did not work.

On 20 January 1999, Dr Shapiro noted that Emma was "chesty until she vomits". Nevertheless he decreased the fluticasone dose to 1,500 micrograms daily. He also prescribed sodium cromoglycate. He also noted a treatment plan to the effect that he needed to use less steroid again. He arranged to see Emma in four weeks. Dr Shapiro also noted that his referral of Emma to Yorkhill the previous year had not resulted in contact with the hospital. He wrote again to the hospital requesting an urgent appointment.

On 6 February 1999, Dr Shapiro saw Emma and noted "little new medically, bit grumpy, afebrile, chest is clear". He did not change the therapy.

On 29 March 1999, Dr Shapiro saw Emma for review. By that time, Dr Cochran at Yorkhill had seen Emma and had written to Dr Shapiro. Dr Shapiro reduced the fluticasone dose to 1,000 micro-grams daily. He also followed Dr Cochran's recommendation and stopped the sodium cromoglycate prescription and changed Emma over from an aerochamber to a volumatic inhaler device.

On 23 June 1999 Dr Shapiro saw Emma for review. Prior to that, she had been seen by Dr Cochran at Yorkhill again but the letter sent by Dr Cochran after that consultation had not yet arrived at Dr Shapiro's surgery. Dr Shapiro decreased the fluticasone prescription to 750 micrograms daily with a view to reviewing this at Christmas when he intended to reduce it further to 500 micrograms daily if Emma was well.

On 7 October 1999, Dr Shapiro saw Emma and noted that she had become increasingly symptomatic over a month but had had seven good months out of eight. Dr Shapiro increased the dose of fluticasone to 2,000 micrograms daily, with a review in 17 or 18 days, at which time if she was symptom free, the dose should be reduced to 1,500 micro-grams daily for two or three weeks then reduced further again to 1,000 micro-grams daily over the winter.

On 28 October 1999 Emma was seen by a locum and the fluticasone was reduced to 1,500 micrograms daily, in accordance with Dr Shapiro's plan.

On 3 December 1999, Dr Shapiro noted that Emma had fever and was shaky, her drinking had increased and that she was otherwise alert and well. Due to the

reference to increased drinking, Dr Shapiro arranged a test of Emma's urine to check that she was not diabetic. The results were negative. Dr Shapiro continued Emma's prescription for Montelukast which had been prescribed by Dr Cochran on 11 November 1999. Dr Shapiro noted a plan to see Emma in January with a view to decreasing the steroid dose.

On 2 February 2000, Dr Shapiro saw Emma, who had an upper respiratory tract infection. He noted that she had had two days of cough in the last two months. He noted that they should wait 2 weeks and then decrease the steroid to 1,000 micrograms daily.

Dr Shapiro did not see Emma until 26 June 2000 when he noted that she had been well for two months. He reduced the Flixotide to 750 micrograms daily. He noted that there were problems with volumatic spacer. He arranged to review Emma in 12 weeks.

However, he subsequently saw Emma again (date not noted) when he found that she had deteriorated on this dose and he increased the dosage to 2,000 micrograms per day, provided that if she was symptom free within two weeks, the dosage should be reduced to 1,500 micrograms daily. He arranged to see her in five weeks.

On 17 August 2000, the Flixotide was reduced to 1,500 micrograms.

On 30 August, it was noted that she had become symptomatic on this dosage. Dr Shapiro did not increase the steroid dose but he provided two types of dry powder breath activated inhalers, in the hope that this would improve the delivery of the steroid to the lungs, thereby allowing a decrease in the steroid dose.

On 14 September 2000, Dr Shapiro saw Emma using the inhaler devices and noted that she seemed to be able to use a turbohaler. He therefore changed her steroid prescription to budesonide as Flixotide is not available with a turbohaler device. He prescribed 1,600 micrograms daily.

On 10 October 2000, Dr Shapiro noted that Emma was doing well and was symptom free. He reduced the budesonide dose to 800 micrograms daily. He arranged to see her in two weeks, with a plan to convert to 500 micrograms Seretide, which is a combination of the lung opener, Salmeterol, and fluticasone, administered by accuhaler.

On 26 October 2000, Dr Shapiro noted that Emma had become symptomatic on the decreased steroid dose and that her mother had increased the budesonide to 1,600 micrograms daily. Dr Shapiro changed Emma to a prescription of Seretide which provided a dose of 1,000 micrograms of fluticasone daily. He requested a two week review.

On 8 November 2000, at review, Dr Shapiro noted that Emma was well and decided not to change her therapy at that stage.

Dr Shapiro saw Emma on 16 February 2001. She was well. Dr Shapiro reduced Emma's Seretide accuhaler therapy to 500 micrograms of fluticasone daily. He requested a review in 12 weeks.

Emma returned on 26 April 2001, having not tolerated the decrease in steroid, which had been increased by her parents to the original Seretide accuhaler dose of 1,000 micrograms daily of fluticasone. Dr Shapiro also prescribed a nasal steroid, as treatment for Emma's catarrh. He requested a review in two months.

In May 2001 Emma was referred by one of Dr Shapiro's partners to an ear, nose and throat specialist.

Dr Shapiro next saw Emma on 20 November 2001 when she presented with a bulging right eardrum. He prescribed the decongestent, Galpseud and doubled her nasal steroid prescription. He requested a review in four weeks.

On 23 November 2001, Emma was seen by Dr Shapiro's partner, Dr Campbell and was admitted acutely to Wishaw General Hospital where she died in the early hours of the following morning.

Details of the care and management of Emma at Yorkhill

On 20 January 1998, Emma was referred by Dr Shapiro to Dr Paton at Yorkhill Hospital. This referral did not result in Emma being seen at Yorkhill. (This matter will be dealt with at another part of this determination.)

On 25 February 1999, following upon a further referral by Dr Shapiro, Emma was seen at Yorkhill by Dr Cochran.

Dr Cochran is a consultant in paediatric respiratory medicine and in paediatric neonatal medicine at Yorkhill and at the Southern General Hospital in Glasgow.

Dr Cochran noted, mainly from the history given by Dr Shapiro and by Emma's parents, that Emma had quite significant persistent chest symptoms which were consistent with a diagnosis of asthma despite quite intensive asthma therapy.

He arranged a chest x-ray and a sweat test for Emma to exclude the possibility of other chest conditions and cystic fibrosis. The results of these tests were normal.

Dr Cochran recommended that delivery of the fluticasone and salmeterol which was being prescribed for Emma by Dr Shapiro be changed from an aerochamber to a large volume spacer, as that there was some evidence that a larger volume spacer gave better delivery of treatment into the lungs, thereby getting the best benefit from the treatment which was already been given.

At that time, Emma was being prescribed 1,500 micrograms of fluticasone daily by Dr Shapiro. In the letter which he sent to Dr Shapiro after his first consultation with Emma, Dr Cochran's comment in relation to this level of medication was that "given there has been such a poor response to intensive treatment it would seem reasonable to reduce Emma's current treatment to minimise unnecessary

medication. In particular I note her dose of fluticasone is high and at this dose there is the potential for significant systemic absorptions. A high dose of Flixotide would be worthwhile if it was producing improved control but this does not seem to be the case". His letter also stated "consider reduction in dose of fluticasone".

On 3 June 1999 Emma had a further appointment with Dr Cochran to review her progress. During the three month review period, Emma's asthma symptoms had been less severe and her dosage of fluticasone had been reduced by Dr Shapiro.

Dr Cochran found that Emma's height and weight had increased appropriately, indicating a normal growth velocity.

A further appointment was arranged at the request of Emma's parents.

On 9 November 1999, Dr Cochran had a further consultation with Emma. Her symptoms had deteriorated and she was again receiving 1,500 micrograms of fluticasone daily. She had a very severe cough, which sometimes resulted in vomiting. Dr Cochran advised that if the symptoms lasted more than a few days, the only additional treatment likely to help was a short course of the oral steroid, Prednisolone. He also recommended Montelukast for a trial period.

On 9 November 2000, Dr Cochran saw Emma again. He noted in his follow-up letter to Dr Shapiro that "Emma has quite a heavy load of chronic asthma symptoms which fluctuate from month to month. I note that you have successfully managed to reduce the dose of fluticasone without any evidence of deterioration in Emma's asthma control".

At that time, Emma's treatment was 1,000 micrograms of fluticasone and 100 micrograms of salmeterol daily, both drugs given as a combined Seretide preparation. She was also being prescribed 5 micrograms of Montelukast and 120 micrograms of Slophyllin daily.

At that time, Dr Cochran did not recommend any change in Emma's treatment but noted "as previously, I would comment that she is receiving a relatively high dose of inhaled steroids. Although this is certainly acceptable if it leads to better symptom control, I also feel we should try to reduce the dose whenever possible since there is no benefit from her being on very high doses of steroid if they do not produce superior symptom control to lower doses".

Dr Cochran also noted that Emma was using a dry power accuhaler device and said that he "would have a low threshold for returning to a large volume spacer if her asthma deteriorated particularly since large volume spacers minimise systemic absorption of high dose inhaler steroids when compared to dry power devices".

Dr Cochran arranged to see Emma in one year's time, at the request of her parents. Emma did not attend her appointment on 8 November 2001 and shortly afterwards Dr Cochran heard about her death on 24 November 2001.

Details of the care of Emma at Wishaw General Hospital

Dr Catherine Lees is a consultant paediatrician at Wishaw General Hospital. She has 13 years experience in paediatrics. She was the consultant paediatrician on call at the time of Emma's acute admission to Wishaw General Hospital. She gave evidence regarding Emma's care from the time of her admission.

Emma was admitted to Wishaw General Hospital around 7.30pm on 23rd November 2001, with a history of vomiting all day and coughing. She was noted to have large, red tonsils on which there were exudates, which is evidence of infection. As she arrived in the ward, Emma had a generalised convulsion.

Blood tests were taken from which the following was ascertained:

sodium level was a little low, a fairly common pattern when a patient has been vomiting;

blood sugar was normal;

potassium level was low/normal;

white-cell blood count was high at 20.73, with a high neutrophil count of 17.14, suggestive of bacterial infection

When Emma was examined by Dr Lees at approximately 10 pm, she was noted to be pale and quite unwell. Her respiratory rate and breathing, blood pressure and heart rate, peripheral perfusion and cardiac function were all normal. She was a little, but not severely, dehydrated. Mrs Frame felt that Emma was not recognising. Her score on the Glasgow Coma Scale was 14 out of a possible 15. Dr Lees assessed that Emma had infection, perhaps meningitis. However, there was no restriction of her neck movement.

She had been receiving continuous intravenous fluids from the time of her arrival at hospital. She had also been given antibiotics. Dr Lees changed that prescription to broad spectrum antibiotics, to cover the possibility of more serious nervous system infection.

Over the next two hours, Emma became worse and her mother felt that she was becoming more confused and agitated.

Around midnight, she had a further convulsion, predominantly affecting the left side of the body, which led Dr Lees to suspect meningitis or encephalitis. Emma's condition was such that a lumbar puncture test to check for meningitis could not be carried out and therefore that could not be excluded as a diagnosis.

Dr Lees then focused on controlling Emma's airways. She contacted the intensive care unit at Yorkhill Hospital to arrange for paediatric intensive care support. Yorkhill Hospital was unable to provide this but arranged that the paediatric unit at the Royal Hospital for Sick Children in Edinburgh would attend.

In the meantime, arrangements were made to have Emma intubated so that breathing support could be given.

During that time, around 12:40 am, following upon discussion with the consultant at the paediatric intensive care unit at Edinburgh, 11 mg of the steroid dexamethasone was administered to Emma as part of the standard treatment when brain swelling is suspected.

While Emma was being prepared for intubation, around 1:10 am, she had a respiratory arrest. After intubation she seemed to stabilise and her blood pressure and heart rate were fairly normal. Further advice was sought from the consultant at the paediatric intensive care unit at Edinburgh, who suggested maintenance treatment with the drug phenytoin to control the convulsions.

The team from the paediatric intensive care unit at the Royal Hospital for Sick Children in Edinburgh, consisting of a doctor and a nurse, arrived from Edinburgh Royal hospital for sick children at 3:20 am. Emma continued to deteriorate. Her blood pressure was difficult to control. A variety of drugs and other methods of stabilisation were tried. It was not possible to transfer Emma to Edinburgh until she had been stabilised. There was further consultation with the consultant on call from the intensive care unit at the Royal Hospital for Sick Children in Edinburgh. Emma did not respond to any treatment. The breathing tube was removed and at 4:35 am Emma was pronounced dead.

Emma showed none of the indications of a typical adrenal suppression presentation, namely hypoglycaemia, high potassium levels and low blood pressure.

During 13 years of working in paediatrics, Dr Lees had never seen a child with an acute presentation of adrenal insufficiency.

Post-mortem and diagnosis of cause of Emma's death

Dr Alan Howatson is a consultant pathologist, specialising in paediatric and perinatal pathology. He is based at the Royal Hospital for Sick Children at Yorkhill in Glasgow.

On 28 November 2001 Dr Howatson carried out a post-mortem examination of Emma. The opinion in his preliminary report, dictated on 30 November 2001, was that death appeared to have been the result of natural causes, as yet undetermined and in the first instance cause of death was certified as "not ascertained (pending results of further investigations)".

In this preliminary report, Dr Howatson commented *inter alia* that: "Two organ systems reveal pathology. Within the lungs there is marked pulmonary oedema with associated pleural effusion. At this stage there is no convincing evidence of a primary lung infection (ie pneumonia) but this will be further assessed on histological examination. The pulmonary oedema and associated effusions could be the result of the brain pathology and also of the need to provide fluid support to maintain cardiac output. The second and more significant pathology lies within the brain. There is very severe brain swelling in the absence of any focal abnormality or sign of trauma. It is possible that the cause of the presentation and subsequent demise lies with the pathology affecting the brain."

He also stated that: "The adrenal glands (right 1.5 g, left 1.6 g) appear unremarkable both externally and on sectioning. The adrenal glands are not unduly haemorrhagic."

In the preliminary report Dr Howatson said that: "In circumstances such as this it would be essential for the brain to be submitted to a detailed neuropathology examination which takes several weeks. Unfortunately authorisation and consent for this procedure was not granted by the procurator fiscal and the examination which has been performed represents an incomplete study which may not permit a definitive diagnosis to be made in this important case."

Dr Howatson detailed a full range of additional investigations which were under way in an effort to ascertain a more precise diagnosis and said that the results of these investigations would take several weeks and would be transmitted to the procurator fiscal in a second and full report.

Dr Howatson prepared a second report, which was dictated on 8 February 2002. In that report it was again stated that death appeared to have been results of natural causes, as yet undetermined and that death certification should remain unchanged as "Ia Not Ascertained". The results of the histology, bacteriology, virology, biochemistry, toxicology and neuropathology investigations were detailed.

The findings set out in the preliminary report in respect of the adrenal glands were repeated. It was noted that when Emma was admitted to Wishaw Hospital, biochemical analysis revealed a low blood sodium level, which was attributed to sodium loss as a result of recurrent vomiting. The other blood tests revealed nothing out of the ordinary.

Dr Howatson stated in this second report that the ancillary investigations had contributed little to any greater understanding of the cause of Emma's death. The biochemical investigations had not identified any obvious deficiency of adrenal gland function or any obvious metabolic abnormality which could explain Emma's death.

Dr Howatson noted in this report that Emma's brother had been admitted to Yorkhill Hospital intensive care unit some time after Emma's death "in a state of acute onset unconsciousness with a symptom complex almost identical to that of his sister sometime after her death". He went on to say that: "Investigations of adrenal function are not yet complete and I am unaware of any other specific information."

In this second report, Dr Howatson repeated his concern that limitations had been imposed on the examination due to the procurator fiscal not granting authorisation for a full neuropathology examination.

On 5 April 2002, Dr Howatson sent to the procurator fiscal at Hamilton a letter in which he referred to Calum's admission to Yorkhill with "an identical symptom complex" and said that it had "been identified that Calum has suffered from adrenal insufficiency probably secondary to drug treatment which he was receiving for asthma."

Dr Howatson said in his letter that "Emma was also receiving similar therapy and in the light of that the small adrenal glands which I identified at the post-mortem

examination, and which I thought were stress-related because her biochemical derangement was not unduly severe, would now appear to be the result of a similar aetiology, i.e. adrenal insufficiency and suppression due to inhaled steroid treatment for asthma."

In the light of this, Dr Howatson recommended an alteration in the notification of death to the Registrar General from the original certification: Ia Not Ascertained, to: Ia Adrenal insufficiency, Ib Inhaled steroid therapy, Ic Chronic asthma.

Action taken at Yorkhill after diagnosis of adrenal suppression in Calum

Following upon Calum's diagnosis of adrenal suppression, meetings were held at Yorkhill with the hospital medical director and it was agreed that all children and adolescents who had at some point attended Yorkhill and who were receiving inhaled fluticasone in doses of 500 micrograms or more would be recalled for synacthen testing.

The respiratory and endocrine teams at Yorkhill carried out this undertaking. 426 children were identified as receiving fluticasone from January 2000 onwards. 140 of these children were receiving fluticasone within licence and it was assumed that they had never been outwith licence. The patients who did not attend for testing in response to two written requests to do so had letters sent to them to warn them that they should assume that they had adrenal impairment until proved otherwise and that they should make emergency provisions. 214 children were tested with low dose synacthen testing.

By the time the children were tested, 78 of these 214 children were receiving fluticasone within licensed doses. 34 of these 78 children had impaired adrenal function, with cortisol peaks of between 250 and 499 nanomols per litre, 44 had normal readings. None of these children had severe impairment of adrenal function.

Of the 214 children tested 136 children were on fluticasone of 500 micrograms or more at the time of testing. 6 of these children had severely impaired adrenal function, with cortisol peaks of less than 250, 51 had impaired adrenal function, including a child who was symptomatic, and 79 had normal readings.

The children who were taking doses of fluticasone above 500 micrograms daily were evaluated for the potential to reduce the dose. Only in those patients in whom it was as clear as it possibly could be that their symptoms were intolerable on lower doses was the need for high dose accepted. Those patients who remained on a higher dose were kept under regular review at Yorkhill.

Of all the children tested 3%, that is 6 children, had cortisol peak levels indicating severe impairment of cortisol production. All of these children were on a dose of 1,000 micrograms or greater. One of these six children was Calum. The other five children with severe impairment were asymptomatic at the time of diagnosis.

A further 40 % of the children showed cortisol levels which were impaired but not severely impaired with readings of between 250 and 500 nanomals. All of these children were asymptomatic except one child who remains under the care of Dr

Donaldson at Yorkhill as he has not yet shown a normal response to synacthen testing, although he is no longer taking steroids regularly. None of the children had obvious cushingoid features.

Asthma

Asthma is a very common illness and in its more severe form, it is a disease that still has significant mortality.

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A definition of asthma is recurrent episodes of coughing and/or wheezing in the absence of any specific explanation. There is no single feature or test. Diagnosis is reached by building a list of a number of features until there is sufficient in the doctor's judgement to justify diagnosis.

The underlying mechanism of asthma is intermittent or variable constriction of the air passages and inflammation or irritability of the lining of the air passages.

Asthma is a condition which is predominantly treated in general practice. All general practitioners have to have skills in treating asthma. Advice and treatment on a week to week basis will come from the general practitioner. The hospital specialist integrates specialist advice and management with the treatment and frequent appointments that the patient has with the general practitioner.

Asthma in children

In the 2001 Asthma Audit compiled by the National Asthma Campaign (now known as Asthma UK) it was estimated that about one in nine children in Scotland were receiving treatment for asthma. Acute asthma is the most common single cause for admission to children's hospitals. Approximately 1% of children with asthma are seen at specialist centres.

There is a separate body of information on aspects of asthma which are specific to children as opposed to adults, such as the child's use of an inhaler and growth and development issues.

Treatment of asthma with inhaled corticosteroids

Asthma is treated by trying to firstly, dilate the bronchi and, secondly, relieve the inflammation or irritability. Inhaled corticosteroid therapy is designed to do the latter.

Corticosteroids are analogues of the body's own natural steroid hormones. They have an anti-inflammatory action and are used to treat inflammatory conditions.

Inhaled corticosteroids were developed in the early 1970s. They are used to treat asthma and other respiratory complaints in both adults and children. They are administered through an inhaler device. The drug goes to the lining of the respiratory tract and is absorbed into the cells that line the respiratory tract where it binds with the steroid receptors inside the cells. Airways inflammation is one of the key features

of asthma. The anti-inflammatory action of the inhaled corticosteroids reduces inflammation in the cells lining the lungs. Reduction of inflammation of the airways reduces the likelihood of the airways becoming narrowed by asthma or other respiratory diseases.

One would expect to wait a minimum of two to four days before seeing an improvement in asthma symptoms treated with inhaled corticosteroids. Often, two to four weeks pass before any benefit is apparent. There is evidence that there is further long term improvement over months of treatment.

Step up and step down practices of prescribing inhaled corticosteroids

With the step up practice of prescribing, the patient is started at a low dose of medication and, if the patient remains symptomatic, the dose of medication is increased in stages with a view to reaching the lowest possible dose at which the patient is symptom-free. The perceived disadvantage of this system of prescribing is that the patient remains symptomatic for the period of time during which the appropriate dose is being identified. This may also potentially result in the patient losing confidence in the treatment.

In around the mid-1990s, a step down practice of prescribing began to be advocated. With the step down practice of prescribing, the patient is started at a much higher dose of medication with a view to rapidly obtaining full control of symptoms then quickly reviewing the patient with a view to reducing the therapy in stages to the lowest possible level at which the symptoms remain controlled.

Hypothalamus/pituitary/adrenal axis

There are three tiers to the adrenal axis, namely the hypothalamus, which is the gland at the base of the brain, the pituitary glands, which lie just below the hypothalamus and the adrenal glands themselves.

The hypothalamus receives messages from the higher centres and elements such as fear, excitement, illness and fever are recognised by the hypothalamus, which stimulates the pituitary glands, which in turn secrete the hormone called ACTH. This hormone then stimulates the cortisol production in the adrenal glands.

The adrenal glands are situated adjacent to the kidneys. One of the functions of the adrenal glands is to produce the steroid cortisol to assist the body in coping with what might be putting it under stress, such as infection or trauma.

Adrenal suppression/adrenal insufficiency/adrenal excess

Adrenal suppression may occur if, as a result of steroids being given (exogenous steroids), the body does not require to produce its own (endogenous) steroids in order to maintain the necessary level of hormones and, as a result, the body's ability to produce its own steroids diminishes.

If the body is unable to produce appropriate amounts of cortisol, this results in adrenal insufficiency. Insufficiency may occur when cortisol levels are not high

enough for the body's needs under normal circumstances or it may occur when there is a sufficient level of cortisol to deal with normal conditions but an inability to produce sufficient cortisol to respond to stress situations.

Adrenal insufficiency may be due to genetic abnormality. It may also occur as a result of adrenal suppression due to the introduction of exogenous steroids. It may also occur due to the sudden cessation of exogenous steroids. For example, a patient who is using exogenous steroids such as inhaled corticosteroids and has adrenal suppression, may become unwell with vomiting and diarrhoea and stop using the inhaler. As the inhaler is not being used, the supply of exogenous steroids stops. At the same time, due to the stress of the illness, additional steroids are necessary. In these circumstances, adrenal insufficiency may result.

Adrenal excess can occur when the body produces too much endogenous steroids for internal reasons, for example a tumour of the adrenal glands, or it can be due to the fact that exogenous steroids have been introduced into the body. An excessive amount of cortisol can lead to features of Cushing's syndrome, which includes weight gain, increased body hair and, in children, poor growth. These features, which come about as the result of excess steroid may therefore be present both in a person whose body produces too much steroid and in a person who has been given too much exogenous steroid, as a result of which the body's endogenous steroid production is suppressed.

The more steroids are absorbed into the system the more likely is suppression of the body's own steroid production. Topical steroids, which are applied directly to the affected area, such as the skin, nose or lining of the lungs are less likely to cause side-effects than oral steroids which distribute a much larger dose of steroid to the whole body.

Synacthen test

Synacthen is short for synthetic ACTH. ACTH is the hormone produced by the pituitary glands which stimulates the adrenal glands to produce cortisol.

In a low dose synacthen test the patient is given a low dose of synthetic ACTH in order to ascertain the extent to which the adrenal glands can produce cortisol with a hormone stimulus at a natural level.

In a standard dose synacthen test the dose of hormone administered is closer to that which would be produced by the body when it is under great stress.

Off-licence prescribing of drugs

Doctors are not restricted to prescribing drugs within the dosages for which they have a licence.

Doctors may also prescribe for children drugs which are not licensed for use with children or may prescribe drugs for children who are outwith the licensed age range for that drug.

It is common for drugs to be prescribed off-licence in paediatric medicine, considerably more than in adult medicine. This is a cause for concern for paediatricians but is accepted by them as unavoidable.

Clinical need is the reason for off-licence prescribing. The clinician takes responsibility for prescribing medication off-licence for the benefit of the patient, taking the risks and benefits into consideration.

Drugs Regulation

The Medicines and Healthcare Products Regulatory Agency (MHRA) is the Government Agency responsible for *inter alia* approving the initial licensing of medication and, once a drug is licensed, monitoring and supervising its use. Its predecessor was the Medicines Control Agency (MCA).

The Committee on Safety of Medicines (CSM) is a Committee comprising medical specialists who advise the Government on the safety of medicines.

When new medicines are authorised, they are given a black triangle designation and the drug companies are requested to place a black triangle on the Summary of Product Characteristics (SPCs) and all promotional material, next to the name of the product, usually for two years but sometimes longer.

The yellow card scheme is a system whereby health care professionals report suspected drug reactions on a yellow card to the MHRA.

In respect of new medicines, recognised by the inverted black triangle, medical practitioners are asked to report suspected reactions, however minor, which could conceivably be attributed to the medicine, even if the reaction is well recognised or if the practitioner is unsure of the causal relationship.

In respect of established medicines, medical practitioners are asked to report serious suspected reactions, including those which are fatal, life threatening, disabling, incapacitating or which result in prolonged hospitalisation, even if the reaction is well recognised. There is no need to report minor reactions for established medicines.

The companies which market licensed medicines are required to submit safety update reports six monthly after the grant of the initial licence for the first two years, then every year for five years, then five yearly after that. The information for these safety reports comes from reports of adverse drug reactions, studies which the drugs companies have conducted and any relevant published literature.

The pharmacovigilance unit of the MHRA also examines the medical literature for details of any new clinical trials or epidemiological studies.

If a potential safety issue is identified from assessment and prioritisation of the information obtained, an assessment report is compiled by MHRA, based on all relevant data sources and this, together with recommendations and a draft of regulatory action is submitted to the CSM for consideration. After deliberation the CSM gives advice to the MHRA as licensing authority.

If the CSM is of the view that a safety issue does require to be addressed, a range of actions might be taken, including an update of the SPC and the patient information leaflet (PIL) relating to the drug, adding an adverse drug reaction to the list contained in the SPC, adding a warning containing more detail of precautions which clinicians should take, adding a contraindication for the drug or, when the risk/benefit balance is no longer positive, the licence may be varied or may be completely revoked.

When there are matters which the MHRA wishes to bring to the attention of health care professionals, this may be done in various ways including the following:

- publication in 'Current Problems in Pharmacovigilance' (CPIP), the bulletin published jointly by MHRA and CSM, which is sent free of charge to every doctor and pharmacist in the UK and generally published once or twice each year.
- a faxed letter signed by the chairman of the CSM and sent to doctors and pharmacists, where the issue is considered to be sufficiently urgent.
- a letter from company marketing the product sent to an appropriate distribution of health care professionals.
- press releases and the use of the media, in order to get instant information to the public as well as to health care professionals.
- additional articles etc written for publications other than CPIP.
- information bulletined on the MHRA website

Monitoring of drug safety by the manufacturer of fluticasone

GlaxoSmithKline was represented at the inquiry as the manufacturer of the drug, fluticasone. Fluticasone was originally manufactured by Glaxo Wellcome. Subsequently, Glaxo Wellcome and Smith Kline Beecham amalgamated and the new company, which now manufactures fluticasone, is GlaxoSmithKline. The drugs company which owns the drug, fluticasone, will be referred to throughout the remainder of this determination as Glaxo, it being understood that this refers to whichever of Glaxo Wellcome or GlaxoSmithKline is the relevant company name for the appropriate time frame.

Glaxo monitors the safety of drugs through its pharmacovigilance department. That department performs a safety review every six months for the first two years after a drug has been licensed, then every year for the next two years, then every five years thereafter.

During safety reviews, the literature is searched for reports of side-effects. Case reports on side-effects or adverse events which have been submitted to the company are examined and professional expert opinions may be sought. The information obtained is submitted to the MHRA for review.

In addition, publications and reports which have a potential link to one of Glaxo's medicines are investigated.

Sources of information about drugs

When a drug is licensed, the licensing agency also issues a Summary of Product Characteristics (SPC), which summarises *inter alia* the diseases which the drug is suitable to treat, the licensed dose ranges, the presentations in which the drug is available and warnings about potential side-effects.

The SPC is contained within:

- the Datasheet Compendium of the Association of the British Pharmaceutical Industry, which is a collection of the datasheets provided by almost all of the drug companies who have licensed products in the UK. This used to be sent to all general practitioners but is now forwarded on request. It is also available online.

Information from the SPC is incorporated within:

- the Monthly Index of Medical Supplies (MIMS), which is distributed monthly and free of charge to all doctors in the UK. This is a very short prescribing guide which contains a summary of products, their indications, their major contraindications and their potential side-effects;
- the British National Formulary (BNF), which is published 6 monthly by the British Medical Association (BMA) and the Royal Pharmaceutical Society of Great Britain and is distributed free of charge to healthcare professionals, including doctors. This contains prescribing advice about all drugs that are licensed and available for prescribing, including information regarding licensed doses and side-effects, guidelines for treatment, precautions, warnings and safety information. It is regarded as the standard guide used by doctors in the NHS.
- the product information leaflet (PIL) which is contained in every pack of medication and contains information useful to the patient or the patient's carer regarding the use of the medication, the importance of taking the drug regularly and usually information about potential warnings of when to seek extra medical advice. This document is also agreed and approved by the MHRA.
- the product monograph which is usually produced by the drugs manufacturer around the time of the launch of a new medicine. It contains a range of basic scientific information and background information about the drug and contains references to clinical studies relating to the efficacy and safety of the drug.

Fluticasone

Fluticasone is an inhaled corticosteroid. It is used to treat asthma. It was produced by Glaxo Wellcome, the predecessor of GlaxoSmithKline. The brand name of the drug is Flixotide.

The other two inhaled corticosteroids are beclomethasone and budesonide. Beclomethasone is also manufactured by Glaxo.

Fluticasone has been marketed worldwide over the last ten years.

Fluticasone is considered to be more, perhaps twice as, potent as the other inhaled corticosteroids. The reasons for this which were given to the inquiry include its having a higher receptor affinity, that is, a greater attraction to the steroid receptor,

and having a more rapid and prolonged lung residency, being very fat-soluble and therefore well absorbed and thereby staying on the receptor for a longer period of time.

Licensing of fluticasone

Before the licence for fluticasone was granted, Glaxo submitted a regulatory dossier to the MCA, containing information about the drug.

Flixotide, the brand name for fluticasone was licensed by the MCA in 1993 for use with adults and with children between 4 and 16 years, with 200 micrograms specified as the maximum daily dose for children.

Flixotide was available initially in two inhaler devices, namely: a metered dose inhaler, which is an aerosol device available in 25, 50, 125 and 500 microgram strengths, the latter two licensed only for use in adults; and a dry powder device known as a disk inhaler which releases the drug from a blister of powder, in 50, 100, 250 and 500 microgram strengths, the latter two doses licensed only for use in adults.

In 1995, the Accuhaler was introduced. This is another dry powder device, licensed for use in 50, 100, 250 and 500 microgram strengths, the latter two licensed for use only in adults.

The earliest SPC for fluticasone which was made available to the inquiry was the 1995 SPC for the Flixotide Accuhaler. Included in this SPC was the following information:

Under the heading "*Posology and Method of Administration*" and subheading "*Children aged four years and over*", the dosage was stated to be 50 to 100 micrograms twice daily. It was specified that 'the starting dose should be appropriate for the severity of the disease. The dose should be adjusted until control is achieved or reduced to the minimum effective dose according to individual response.' and it was further stated that 'Flixotide Accuhaler 250 micrograms and Flixotide Accuhaler 500 micrograms are not suitable for use in children'.

Under the heading "*Special Warnings and Precautions for Use*" it was stated that 'Adrenal function and adrenal reserve usually remain within the normal range on inhaled fluticasone propionate. However, some systemic effects may occur in a small proportion of adult patients after prolonged treatment at the maximum recommended daily dose. Patients transferred from other inhaled steroids or oral steroids remain at risk of impaired adrenal reserve for a considerable time after transferring to inhaled fluticasone propionate.'

'Patients in a medical or surgical emergency, who in the past have required high doses of other inhaled steroids and/or intermittent treatment with oral steroids, remain at risk of impaired adrenal reserve for a considerable time after transferring to inhaled fluticasone propionate..... The possibility of residual impaired adrenal response should always be borne in mind in emergency and elective situations likely to produce stress and appropriate corticosteroid treatment must be considered.'

'In children taking recommended doses of inhaled fluticasone propionate adrenal function and adrenal reserve usually remain within the normal range. Very rarely biochemical changes suggestive of systemic effects have been reported. The clinical relevance of these changes has not been substantiated and, in particular, no stunting of growth in children has been observed. The possible effects of previous or intermittent treatment with oral steroids should not be discounted. The benefits of inhaled fluticasone propionate should minimise the need for oral steroids.....'

In 1996 the drug manufacturer applied to increase the licensed dose of fluticasone for children but the application was refused by the MCA.

In 2000 a further application was made and in 2001 the MCA licensed an increase in the maximum daily dose of fluticasone for children between 4 and 16 years to 400 micrograms and a new SPC was issued in which these doses were specified.

Promotion of fluticasone

Product monograph

At the time of the launch of Flixotide the product monograph, which contained 68 references to studies or data on file, was issued by the manufacturers. This included the following information:

Under the heading "*Systemic side-effects*" was stated *inter alia:*

'Mean plasma cortisol concentrations remained within the normal range for adults and children demonstrating that, even at high doses (2,000 micrograms), fluticasone propionate is well tolerated with regard to systemic effects, When fluticasone propionate was compared with beclomethasone dipropionate, the mean serum cortisol concentrations did not decrease in any study following fluticasone propionate but was found to fall in one study during beclomethasone dipropionate 1,000 micrograms twice-daily treatment. In the substantial majority of patients, even at daily doses of fluticasone propionate of 2,000 micrograms, no adverse effect on adrenal function or reserve has been shown'.

Advertising material

This included leaflets with teddy bears, teddy bears standing beside measuring rules and slogans such as :

"Designed For Control With Safety In Mind",

"Putting A Smile On The Face Of Asthma",

"An inhaled steroid to grow up with"

"A good friend in childhood asthma "

"For children, Flixotide"

and text such as:

"Formulated with safety in mind, Flixotide combines high topical anti-inflammatory activity with negligible oral systemic availability. Flixotide is effective where it is needed in the lungs with minimal potential for steroid side-effects from the swallowed portion."

Monitoring the safety of corticosteroids, including fluticasone

The MCA assessed that some yellow card reports and also some reports in the medical literature, including Dr Todd's 1996 report in the Lancet, of suspected adrenal suppression and adrenal insufficiency, raised a safety issue which required to be addressed. Many of these reports related to very high, off-licence doses of steroids. Accordingly, in 1997 the MCA conducted a review of all the possible systemic side effects of all inhaled and nasal steroids. The review was submitted to the CSM at the beginning of 1998 and thereafter the CSM gave advice on this issue.

Representatives of Glaxo and the MCA met to discuss the MCA review in April 1998. It was agreed that changes would be made to the SPC and the PIL for fluticasone, in accordance with the advice of the CSM.

The May 1998 Current Problems in Pharmacovigilance bulletin focused on corticosteroids and recorded the advice and recommendations of the CSM following upon the MCA review.

In the bulletin, under the heading *"Withdrawal of Systemic Corticosteroids",* was *inter alia* the following:

'Topical administration of corticosteroids (e.g. inhaled) may allow disease control to be maintained while systemic corticosteroids are being withdrawn. There is evidence that inhaled corticosteroids are absorbed and that they have some systemic activity including suppression of the HPA-axis. Although this activity is less than systemically administered corticosteroids, the precise long term effects are unknown.'

Under the heading *"The Safety of Inhaled and Nasal Corticosteroids"* is the following:

'Many patients, both adults and children, are now prescribed inhaled and nasal corticosteroids for the prophylactic treatment of asthma and rhinitis respectively. By delivering the drugs directly to the airways, these products maximise the beneficial therapeutic effects of corticosteroids whilst minimising the adverse systemic effects. Following a review of the available evidence, we have concluded that clinically important systemic adverse effects can occur at licensed doses of these products. The risks of these effects occurring are increased following long, high dose therapy, although susceptibility to these effects varies between individuals. The risks with intranasal corticosteroids are generally lower than with inhaled steroids as the doses used in clinical practice are lower. Five main areas of concern were identified: adrenal suppression, osteoporosis or changes in bone mineral density, growth retardation in children, cataracts and glaucoma. Following our assessment of these areas the following conclusions have been reached:

The dose should be titrated to the lowest dose at which effective control of asthma or rhinitis is maintained.

Potency of corticosteroids varies between individual drug substances. Greater potency does not however necessarily equate with greater efficacy. All inhaled corticosteroids have the potential to cause systemic side effects, the frequency and severity of which will be dependent upon the dose and duration of treatment.

Systemic effects of inhaled and nasal corticosteroids may occur, particularly at high doses prescribed for prolonged periods. Possible systemic effects with inhaled corticosteroids include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. In children receiving nasal corticosteroids at licensed doses growth retardation has been reported.

It is recommended that the height of children receiving prolonged treatment with inhaled or nasal corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled or nasal cortisosteroid, if possible, to the lowest dose at which effective control of asthma or rhinitis is maintained. In addition, consideration should also be given to referring the patient to a paediatric specialist.

Prolonged treatment with high doses of inhaled corticosteroids, or higher than recommended doses of nasal corticosteroids may result in clinically significant adrenal suppression. Additional systemic cortisosteroid cover should be considered during periods of stress and elective surgery.

It is important to emphasis that inhaled and nasal corticosteroids provide proven, effective control of asthma and rhinitis respectively and may, in some patients, remove the necessity for oral cortisosteroid therapy. The recognition that systemic effects may occur and that the lowest effective dose should be used, does not alter the favourable risk-benefit profile of these medicines.'

In July 1998, the wording of SPC for the Flixotide Accuhaler was changed, to read as follows:

Under the heading 'Special Warnings and Precautions for Use' was stated:

'Systemic effects of inhaled corticosteroids may occur particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is important therefore that dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroid, if possible to the lowest dose at which effective control of asthma is maintained. In addition,

consideration should be given to referring the patient to a paediatric respiratory specialist.

Prolonged treatment with high doses of inhaled corticosteroids, particularly higher than recommended doses, may result in clinically significant adrenal suppression.

Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.'

This wording was inserted in the BNF and MIMS within nine months of the change to the SPC. This wording was also contained in the datasheet published in the Data Sheet compendium for Fluticasone for 1999/2000.

The PIL was also changed for the Flixotide Accuhaler to read as follows:

"The usual starting dose is one blister of Flixotide Accuhaler, 50 micrograms twice a day. This can be increased to one blister of Flixotide Accuhaler, 100 micrograms twice a day. This medicine is not recommended for children below four years of age."

It was also stated that: "it is very important that you keep to your doctor's instructions as to how many blisters to inhale and how often to use your Flixotide Accuhaler. Do not use more often than you are told to".

There was reference to side-effects which included the following: "In very rare instances, treatment with Flixotide Accuhaler may affect the normal production of steroids in the body. This is more likely to happen if high doses are being used over a long period of time. One of the rare effects is that children and adolescents may grow more slowly than others. Children and adolescents who are receiving treatment over a long period of time will have their height checked regularly by their doctor. Other effects are thinning of the bones and certain eye disorders known as cataracts and glaucoma. Your doctor will help prevent this by prescribing the lowest dose of steroid at which your asthma is well controlled."

In 1999, on the advice of the CSM that this information be made available to interested prescribers or scientists, the review which the MCA had carried out relating to the potential for inhaled and nasal corticosteroids to cause systemic adverse effects was published in a journal called Pharmacology and Therapeutics, Volume 83.

At the section of the review headed 'Hypothalmic-pituitary-adrenal-axis suppression in children' was stated *inter alia* the following:

'Discussion- From the evidence reviewed in the previous sections it is possible that HPA axis suppression may occur at currently licensed doses in children. However, the literature is far from consistent, with a number of well-designed studies showing no effect at licensed doses. However, children with severe chronic asthma are increasingly being prescribed high doses of inhaled corticosteroids to control their symptoms as an alternative to oral corticosteroids and possibly in the belief that this is a safe alternative with few system effects. At these high doses there is convincing

evidence that significant adrenal suppression, with clinically relevant sequelae, occurs.

In children with early onset of asthma, and hence, early use of inhaled corticosteroids, systemic side effects are of particular concern. Alveolar development is probably complete by 18 months of age, after which, lung and body growth occurs in a highly proportional fashion. Paediatric dosage recommendations, however, often apply to children 4-16 years of age, and, therefore, there will be a greater potential for systemic activity in very young children, in whom blood volume is smaller. Assessment of the dose in terms of micrograms per squared meter per day, as opposed to absolute dose, may, therefore, provide a more valid comparison amongst young children of different ages and weights. As such, Prifits et al (1990) reported that although only one child in their study population was taking greater than 800 micrograms per day of inhaled beclamethasone, 13 were taking greater than 460 micrograms per square metre per day, which is considered the upper limit of the conventional adult dose. It is particularly important, therefore, that in children, the dose is titrated to the lowest possible dose at which effective control of symptoms is maintained.

Subsequently, the MCA carried out a review of the safety of fluticasone, in particular the balance of its risks and benefits in adult doses, particularly in the range of 1,000 to 2,000 micrograms a day. The review was prompted because of evidence of some degree of adrenal suppression at high licensed doses of fluticasone, which is licensed for adults at up to 2,000 micrograms daily. Following upon the review, an article entitled 'Reminder: Fluticasone propionate (Flixotide): use of high doses (greater than 500 micrograms twice daily)' was published by the MCA and CSM in the August 2001 bulletin of Current Problems in Pharmacovigilance.

The article stated *inter alia* the following:

'Different inhaled corticosteroids have different potencies. The dose required for disease control with fluticasone propionate may be lower than that required with some other inhaled corticosteroids.

New advice:

To minimise the risk of systemic adverse effects at very high doses of fluticasone propionate, the following important new advice for prescribers will be included in the product information of all fluticasone propionate inhaler products.

This advice is specific to fluticasone propionate, doses of which are higher in potency terms than equivalent doses of any other licensed inhaled corticosteroid.

.....For patients with mild asthma an appropriate starting dose is 100 micrograms fluticasone propionate twice daily. In moderate and more severe asthma, starting doses may need to be between 250 to 500 micrograms fluticasone propionate twice daily.

....Due to the risk of systemic effects, doses above 500 micrograms twice daily should be prescribed only for patients with severe asthma where additional clinical

benefit is expected and is demonstrated by either an improvement in pulmonary function and/or in symptom control, or by the ability to reduce oral corticosteroid therapy. Such doses should be initiated by a specialist in the management of asthma (such as a consultant physician or a general practitioner with appropriate experience).'

In 2001, after application by the drugs manufacturer, the licensed dose of fluticasone for children between 4 and 16 was increased by the MCA and the SPC was amended. The wording of the SPC for the Flixotide Accuhaler gave information regarding the new licensed dose for 'Children aged 4 years and over' namely 50 to 200 micrograms twice daily and the information contained under 'Special Warnings and Precautions for Use' remained the same as in the 1998 SPC.

Action taken in relation to fluticasone after Emma's death

On 22nd March 2002 one of Glaxo's representatives became aware of the death of a child and that the drug fluticasone might be involved. A second representative obtained a medically substantiated report around 22nd April 2002 confirming that a child had died while taking fluticasone.

Glaxo submitted a safety report to the MCA on 25th April 2002, in accordance with the requirement that a serious unexpected adverse event be submitted to the regulatory authority within 14 days.

In April 2002, the MCA was advised through the yellow card scheme of the fatal and very serious cases of adrenal suppression involving Emma and Calum Frame respectively. Around the same time, the MCA was also informed of a publication of a survey (referenced Zahra S et al Arch Dis Child 2002; 86 Suppl 1:A39) of endocrinologists and paediatricians on the extent to which adrenal suppression and adrenal insufficiency had been noted in patients receiving inhaled corticosteroids. These gave rise to concern that there may have been previous undetected or unreported cases of adrenal suppression and, in particular, a possible concern over the use of high doses of fluticasone. After an initial investigation it was decided that a full review should be carried out.

On 27 April 2002 a Glaxo medical adviser met with Dr Paton, consultant paediatrician at Yorkhill to obtain full details of the death of Emma Frame and the case of Calum Frame.

In May 2002 Glaxo wrote to the MCA suggesting that Glaxo write to all doctors in the UK to remind them of the licensed dose of Flixotide and to give appropriate advice about its use.

The representatives of the MCA and of Glaxo met in August 2002 at which the MCA asked Glaxo to provide specific information about the use of fluticasone in practice in asthma in the UK. A risk management plan was prepared, which included the distribution by Glaxo of a letter of advice and guidance to all healthcare professionals in the UK, in relation to the issue of adrenal suppression in children associated with inhaled corticosteroids, and a programme of meetings across the UK to reinforce the BTS guidelines with GPs and secondary care physicians.

An assessment report was compiled by the MCA and presented to the CSM in around September 2002. The CSM gave its advice regarding amendments to the product information for fluticasone and the advice of the CSM was summarised in the October 2002 Current Problems in Pharmacovigilance bulletin, which included the following information in an article entitled 'Inhaled corticosteroids and adrenal suppression in children':

'Adrenal suppression is a well-established adverse reaction of all inhaled corticosteroids. There have been rare reports of adrenal suppression leading to adrenal crisis. Symptoms and signs associated with adrenal suppression and crisis may be under-recognised, particularly in children receiving higher than licensed doses of inhaled corticosteroids. .....

Adrenal suppression is a dose related class effect of all inhaled corticosteroids. Adrenal crisis has been observed more frequently following the use of fluticasone, possibly because higher than licensed doses of fluticasone are prescribed more widely in children than other inhaled corticosteroids. All inhaled corticosteroids are associated with an increased risk of adrenal crisis when used at higher than licensed doses but prescribers are reminded that fluticasone should normally be used at half the dose of beclomethasone.. or budesonide because of its greater potency.

Although case reports have highlighted children taking fluticasone at higher than recommended doses, (typically greater than or equal to 1,000 micrograms/day of fluticasone) prescribers are reminded that these are dose related class effects and are strongly advised that the paediatric licensed dosages of all inhaled corticosteroids should not be exceeded.

Prescribers are reminded that:

...it is important to review therapy regularly and titrate down to the lowest dose at which effective control of asthma is mintained

....if a doctor considers that a child's asthma is not controlled on the maximum licensed dose of their inhaled corticosteroid, despite the addition of other therapies, the child should be referred to a specialist in the management of paediatric asthma.'

[The maximum licensed doses of inhaled corticosterids in children were then set out]

The letter to the healthcare professionals, which had been agreed by the MCA and GlaxoSmith Kline was sent out by Glaxo to healthcare practitioners on 20th November 2002 and was in the following terms:

'Dear Healthcare Professional

Re: Inhaled Corticosteroids and adrenal suppression in children - Current Problems in Pharmacovigilance Article

We would like to draw your attention to the recent article in the Current Problems in Pharmacovigilance. This article, which we have enclosed for your reference,

discusses the issue of adrenal suppression and adrenal crisis in children following the use of higher than licensed doses of inhaled corticosteroids.

As a company we would like to highlight the following points for medicines:

the maximum licensed dosage of fluticasone propionate and beclomethasone dipropionate (CFC containing) for children in the UK is 400 mcg/day.

GlaxcoSmithKline does not endorse the use of any of its medicines at doses in

excess of those stated in the Summary of Product Characteristics.

It is important to review therapy regularly and titrate down to the lowest dose of inhaled corticosteroid at which effective control of asthma is maintained.

If a doctor considers that a child's asthma is not controlled on the maximum licensed dose of their inhaled corticosteroid, despite the addition of other therapies, the child should be referred to a specialist in the management of paediatric asthma.

All inhaled corticosteroids may cause side-effects, even at licensed doses. However, when these drugs (beclomethasone dipropionate, budesonide and fluticasone propionate) are used at doses greater than those that are licensed, the risk of side-effects is increased.

The risk of adrenal suppression and crisis in children is associated with the use of higher than licensed doses of inhaled corticosteroids.

Situations that produce metabolic stress (e.g. infection, trauma, major surgery or a sudden withdrawal of inhaled corticosteroid therapy) may precipitate adrenal crisis. The symptoms of adrenal suppression and crisis are initially non-specific such as anorexia, abdominal pain, weight lost, tiredness, headache, nausea, vomiting but can progress to include decreased level of consciousness, hypoglycaemia and seizures. Any child receiving high dose inhaled corticosteroid therapy in whom adrenal suppression and crisis is suspected should be referred for urgent medical assessment in hospital.

Prescribers should be aware that fluticasone propionate is as effective as other inhaled steroids, at half the mcg daily dose. For example, a 100 micrograms of fluticasone propionate is approximately equivalent to 200 micrograms dose of beclomethasone dipropionate (CFC containing) or budesonide.

The above guidance will be reinforced in the forthcoming BTS/SIGN asthma guidelines, which will also clearly differentiate between adults and children in terms of dosage requirements for inhaled corticosteroids.'

A telephone number was given for any questions regarding the use of fluticasone propionate in paediatric patients.

The product information for fluticasone was amended and the SPC for the Flixotide Accuhaler include the following information under the heading 'Special Warnings and Precautions for Use' :

'Prolonged treatment with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Children aged less than 16 years taking higher than licensed doses of fluticasone (typically equal to or greater than 1,000 micrograms/day) may be at particular risk..... '

Full references and brief summary of articles, reports and other publications referred to at the inquiry and in the determination

(N.B. Many publications were cited and quoted from in the inquiry. Detailed below are only those referred to in the determination)

(1) Issues in Chest Medicine, a publication highlighting topics arising during a two-day meeting of UK chest physicians on 28-30 January 1994

Under the heading "Fluticasone propionate: pre-clinical pharmacology" is included the following:

FP has low oral bioavailability and is effectively metabolised in the liver to an inactive metabolite. If FP does enter the circulation, either from the intestine or from the lungs, it is rapidly metabolised during the first passage through the liver and thus becomes inactive. Further, as the other inhaled corticosteroids, about 80 percent of the dose is swallowed, but very little FP is absorbed from the intestine into the bloodstream. These properties mean that the potential for systemic effects is minimised. FP has also been shown to have a high specificity for the glucocorticoid receptor.

(2) Professor George Russell, Editorial in Thorax 1994;49:1185-1188 - Inhaled corticosteroid therapy in children: an assessment of the potential for side effects

Professor George Russell, now retired, was a consultant paediatrician at Aberdeen Children's Hospital. He was at respiratory specialist with a research record in asthma and other conditions and expertise in different aspects of asthma, including its treatment.

In the introductory section of this article, Professor Russell wrote:

"In the United Kingdom both beclomethasone and budesonide are licensed for administration to children in doses of up to 400 micrograms daily and numerous studies testify to the apparent safety of such doses.... However, childhood asthma is by no means always controlled by conventional doses of inhaled corticosteroid therapy and higher doses may have to be used especially in younger children with recurrent wheeze and in children with otherwise intractable asthma."

In the section headed "Adrenal Suppression", Professor Russell wrote:

"Any papers on adrenal function in children receiving inhaled corticosteroid therapy were reassuring, reporting either no adrenal suppression or adrenal suppression only on high doses. Most recent studies have continued to offer reassurance although caution has been advised in the use of higher doses.... Adrenal stimulation tests are by no means physiological but Law et al measuring nocturnal cortisol secretion in asthmatic children receiving inhaled corticosteroid therapy reported reduced adrenal secretion, a delayed rise from the nocturnal nadir and low early morning cortisol levels.... Although these effects were more significant in higher doses, they occurred at all dosage levels, cortisol secretion being reduced on daily doses as low as 400 micrograms. Other authors have also found that relatively modest doses of inhaled corticosteroid therapy can cause adrenal suppression... There is therefore good evidence that inhaled corticosteroid therapy, even when given in normally recommended doses, can produce adrenal suppression. There is no firm evidence that any child has ever come to harm as a result of adrenal suppression induced by inhaled corticosteroid therapy.... In most stimulation studies it has been notable that basal cortisol is much more sensitive than stimulated cortisol to the effects of inhaled corticosteroid therapy. This suggests that an adequate adrenal reserve is maintained in most cases, a suggestion which has been confirmed in adults with acute severe asthma"

(3) Dr Todd et al, Article in Lancet 1996;348:27-29 - Growth and adrenal suppression in asthmatic children treated with high-dose fluticasone propionate

This article was published in the Lancet in July 1996 by Dr Geoffrey Todd and colleagues. Dr Todd gave evidence at the inquiry.

The article reported upon a study in which growth retardation was seen in six severely asthmatic children after the introduction of high-dose fluticasone propionate treatment and assessment of cortisol response was by one of three methods.

The interpretation of the results, as stated in the article, was that when high doses of fluticasone propionate are used, growth may be retarded and adrenal suppression may occur.

(4) Cade et al, Letter to The Lancet, published 21 September 1996;348:819

This letter was submitted by Alan Cade and colleagues at the Department of Paediatrics at Leeds General Infirmary in response to Dr Todd's article.

It criticises Dr Todd's study as 'anecdotal and failed to demonstrate in a scientific and controlled way the relation between growth, adrenal suppression and high dose inhaled steroids'. It hihglighted several perceived limitations to this study, including lack of data control or control patients and deficiencies in growth measurement.

(5) Lenney, Letter to The Lancet, published 21 September 1996;348:819-820

This letter was submitted by Warren Lenney of the Academic Department of Child Health at City General Hospital, Stoke-on Trent.

It criticised the methodologies and lack of statistical analysis in the Todd study.

(6) Paper entitled 'Adrenal Suppression With Inhaled Budesonide And Fluticisone Propionate Given By A Large Volume Spacer to Asthmatic Children', Thorax, September 1996, by Clark, Clark and Lipworth.

The results of this study were summarised as follows:

"The results of the study show that when given by large volume spacer to asthmatic children single inhaled doses of fluticisone propionate of 400 to 1250 micrograms produces suppression of urinary cortisol compared with a placebo whereas corresponding doses of budesonide do not".

The conclusion of the study included following:

"Our study provides clear evidence of adrenal suppression with single doses of inhaled fluticisone propionate given by spacer to asthmatic children. It is likely that with repeated dosing the differences between fluticisone and budesonide would be greater due to the longer plasma half-life and receptor binding affinity as well as enhanced systemic tissue retention for fluticisone than for budesonide. Further chronic dose ranging studies are now indicated to resolve this issue."

(7) Article entitled "Drug companies criticised for exaggeration", published in BMJ volume 318, dated 10 April 1999

This article reported that complaints against pharmaceutical companies for breaching the industry's voluntary advertising code of practice remained at high levels in 1998, according to a report from the Prescription Medicines Code of Practice Authority.

One of the examples referred to in the article was as follows: "A consultant chest physician took Glaxo to task for claiming that fluticasone (Flixotide) given at half the daily dose of budesonide was more effective than budesonide at improving morning peak flow. His complaint was upheld."

(8) Brutsche et al, the Lancet, 12 August 2000; Comparison of Pharmacokinetics and

Systemic Effects of Inhaled Fluticasone Propionate in Patients with Asthma and Healthy Volunteers: A Randomised Cross-over Study

This was a double blind, randomised, cross-over study in eleven patients with asthma and thirteen matched healthy controls, receiving 1,000 micrograms intravenous dose or 1,000 micrograms daily for seven days inhaled fluticasone propionate, with monitoring of plasma fluticasone propionate and cortisol concentrations.

Under the heading "Interpretation" was the following:

Systemic availability of fluticasone propionate is substantially less in patients with moderate to severe asthma than in healthy controls. Inhaled cortisosteroids that are absorbed through the lungs need to be assessed in patients who are receiving doses appropriate for decease severity, and not in normal volunteers.

(9) Paper entitled "Dose response relation of inhaled fluticisone propionate in adolescents and adults with asthma: meta-analysis", by Holt et al published in the British Medical Journal, on 4 August 2001

The conclusion in this paper is that:

In adolescent and adult patients with asthma most of the therapeutic benefit of inhaled fluticasone is achieved with a total daily dose of 100 to 250 micrograms and the maximum effect is achieved with a dose of around 500 micrograms a day. However, these findings were limited by the lack of data on individual patients and by the paucity of dose-response studies that included doses of greater than 500 micrograms per day.

A commentary was written on this paper by Andrew Herxheimer entitled "Dosage needs systematic and critical review". Included in this commentary were the following observations:

'With any new drug that has therapeutic activity an appropriate dosage regimen must be worked out from a clear understanding of the pharmacokinetics and the dose response relation. ...

Why did it take until now, from the first marketing of fluticasone in 1993, to discover that the maximum useful dosage from most cases is only about half of that hitherto recommended by guidelines and the manufacturer? ...

My guess is that the scientists at GlaxoWellcome (sponsor of the trials in the meta-analysis) and at the Medicines Control Agency and the clinicians and academics working on asthma had not appreciated the need for and value of systematic reviews and appropriate meta-analysis."

(10) Patel et al: Symptomatic adrenal insufficiency during inhaled corticosteroid treatment, Arch. Dis. Child. 2001; 85: 330-4, and commentary by Professor Russell

This article describes 8 children, 5 of whom had received fluticasone in doses of 500-1,000 micrograms daily (one of whom had received another inhaled steroid previously) and 3 of whom were on other inhaled steroids. 3 children had dosages of 500 micrograms fluticasone daily, 1 child had a dosage of 1,000 micrograms of fluticasone daily, 1 child had previously been prescribed 400 micrograms of budesonide daily and was then prescribed a dose of 500 micrograms of fluticasone daily, 2 children were receiving a licensed dose of 400 micrograms of budesonide daily and one was receiving a licensed dose of 600 micrograms of beclomethasone daily. Six of the children had impaired cortisol response levels in standard dose synacthen testing and 2 children did not have stimulation testing but did have low cortisol levels.

Professor George Russell's commentary states *inter alia*:

".....A common feature in reports from the mid-1980s onwards has been dose related adrenal suppression, a side-effect that has generally been regarded as benign, representing nothing more than a physiological response to exogenous

corticosteroid. Clinical symptoms of hypoadrenalism have not appeared to be a problem. It is therefore surprising that after more than a quarter of a century's relatively trouble free use of ICS, Patel *et al* should report no fewer than eight cases of clinically significant adrenal suppression in children on ICS therapy.

.... We can only guess the prevalence of clinically significant adrenal suppression in children on inhaled corticosteroids but clearly we can no longer claim that it is non-existent, nor can we be sure that the distribution of the individual corticosteroid molecules used by these children is anything other than a child's phenomenon. The authors are rightly cautious in refusing to comment but it can hardly pass unnoticed that only one of these 8 children was on beclomethasone whereas the others were on what is sometimes described as second or even the third generation inhaled corticosteroids. Beclomethasone was the first and is still the most widely used inhaled corticosteroid in the United Kingdom. In England in 1998, 8.43 million National Health Service prescriptions were filled for beclomethasone compared to only 1.88 million of budesonide and 1.54 million of fluticasone. We too are cautious in our interpretation of these proportions but await with interest further reports of inhaled corticosteroid related adrenal suppression. So what are the conclusions to be drawn from this report? In our current state of knowledge it would be quite wrong to suggest a major change in established practice. Inhaled corticosteroid treatment has been of immense value to literally millions of children and other anti-asthma therapies best regarded as steroid sparing rather than a true alternative to inhaled corticosteroids. Nevertheless, we should review our practice and pay more attention to existing recommendations on the importance of stepping down as well as stepping up inhaled corticosteroids and as everyone must be constantly vigilant to unforeseen side-effects in even the best established drugs. Whatever else we do, we must not panic and endanger the lives of the countless children whose respiratory and endocrine systems coexist happily on inhaled corticosteroids."

(11) National Asthma Campaign, Asthma Audit 2001; "Out In The Open, A True Picture Of Asthma In The United Kingdom Today": The Asthma Journal, Special Supplement, September 2001

This paper is a summary of information about asthma in the UK from an audit compiled in 2001 and produced by the National Asthma Campaign (now known as Asthma UK).

Under the heading 'Mortality' is stated *inter alia:*

'... around 1500 people still die from asthma each year in the UK.'

(12) Asthma Audit 2001 Summary: Scotland; Factsheet 40, Updated February 2003

This paper provides a summary of data relating to Scotland from the 2001 National asthma campaign audit .

Under the heading 'How many people in Scotland have asthma?' is stated *inter alia*:

'Statistics from the recent Scottish Health Survey indicate that there are 400,000 people receiving treatment for asthma: 1 in 15 adults and 1 in 9 children. We

estimate that 636,000 people in Scotland will be diagnosed with asthma at some point in their lives'.

Under the heading 'How many people die from asthma?' is stated *inter alia:*

'Over 1200 people died from asthma in Scotland between 1990 and 1999 of which 43 % were under the age of 65'.

(13) National Asthma Campaign, Asthma Audit 2002; "Starting As We Mean To Go On": An Audit Of Children's Asthma In The UK": The Asthma Journal, Special Supplement, May 2002

This document was produced by the National Asthma Campaign.

Under the heading 'Prevalence' is stated *inter alia:*

Respiratory disease is the most commonly reported long term illness in children accounting for over 40% of all long term illnesses' and

'Over 80 % of long-term respiratory illnesses (and nearly a third of all long-term illnesses) in childhood are due to doctor-diagnosed asthma'.

(14) Todd et al (also referred to as Zahra et al): Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom, Arch Dis Child 2002;87:457-461, and commentary by Professor Russell

This paper reports upon a UK survey of 3000 patients of whom 33 were identified as having acute adrenal insufficiency. Of those 33 patients, 30 were on fluticasone. 80% of the 33 patients were being prescribed within the dosages set out in the BTS guidelines. Under the heading 'Methods' is stated:

Questionnaires were sent to all consultant paediatricians and adult endocrinologists registered in the UK Medical Directory asking whether they had encountered asthmatic patients with acute adrenal crisis associated with ICS. Those responding positively completed a more detailed questionnaire. Diagnosis was confirmed by symptoms/signs with normal hypothalmic pituitary adrenal axis function test results.

Professor Russell wrote an editorial in which he referred to this study and in which he said *inter alia*:

'..... complacency was shattered with the publication of the three papers describing acute adrenal failure cited by Todd *et al*. These papers were multi-author and multi-centre and did not give the reader a feel for the frequency of this complication. This deficiency has now been remedied by Todd et al...who in addition to showing that this problem is alarmingly common have also implicated fluticasone propionate (FP) the least frequently prescribed form of ICT in the great majority of their cases ....

What are the implications for the practising clinician? The findings of this survey cannot be ignored but nor should they be used for an excuse for a further outbreak

of steroid phobia. Nevertheless, there are implications both for patients already on high dose FP and for those for whom this therapy is contemplated.'

(15) Cochrane Review: Inhaled fluticasone versus inhaled beclomethasone or inhaled budesonide for chronic asthma, published in: The Cochrane Library, Issue 3, 2004. Chichester, UK

The objective of this review was to compare the efficacy and safety of fluticasone to beclomethasone or budesonide in the treatment of chronic asthma.

The review carried out a meta-analysis of randomised trials in children and adults comparing fluticasone to either beclomethasone or budesonide in the treatment of chronic asthma in a dose ratio of 1:2, i.e. using fluticasone at half the microgram dose of budesonide or beclomethasone.

Fluticasone was found to produce a significantly greater improvement in lung function in all drug doses, age groups and delivery services although subgroup analysis suggested that the relative benefit of fluticasone may be greater in more severe patients treated with higher doses of inhaled corticosteroid. No difference between fluticasone and beclomethasone or budesonide were seen for trial withdrawals. A higher likelihood of pharyngitis was apparent when patients were treated with fluticasone at twice the dose of beclomethasone or budesonide.

FINDING IN TERMS OF SECTION 6(1)(a): WHERE AND WHEN EMMA'S DEATH TOOK PLACE

All parties were agreed that a finding should be made in terms of section 6(1)(a) that Emma died at 4.35 am on 24 November 2001 at Wishaw General Hospital, Wishaw.

Dr Catherine Lees, consultant paediatrician at Wishaw General Hospital, testified to this and her evidence was supported by Emma's hospital case notes. Emma's father, Mr Stuart Frame, also gave evidence regarding the place and time of Emma's death. He agreed with the procurator fiscal's proposition that the time of death was 4.45 am but I accepted the evidence of Dr Lees, who certified Emma's death, in relation to this detail.

FINDING IN TERMS OF SECTION 6(1)(b): THE CAUSE OR CAUSES OF EMMA'S DEATH

I was invited by the procurator fiscal and those representing the NHS, Glaxo and the MHRA to find that the cause of Emma's death was adrenal insufficiency due to inhaled steroid therapy prescribed for her chronic asthma, as concluded by Dr Howatson and set out in his letter to the procurator fiscal of 5 April 2002.

Mrs Dougal agreed that this finding should be made and submitted that an amendment to this effect should be made in Emma's death certificate, as this has not yet been done, despite Dr Howatson's recommendation in his letter of 5 April 2002.

Mr Holmes said that none of the skilled witnesses who gave evidence at the Inquiry took issue with the finding as to cause of death as set out by Dr Howatson in his

letter to the procurator fiscal of 5 April 2002 and he expected that the Inquiry's determination as to the cause of Emma's death would be to that effect. However, he submitted that such a finding should be subject to appropriate qualification to reflect the unique circumstances of Emma's death, her atypical presentation and the incomplete understanding of the mechanisms that led to her death. He referred to the fact that Dr Howatson had said in evidence that he had been able to undertake about 80 percent of his investigations, that only about 10 percent of the brain substance had been sampled and that it is recognised that limited examinations can miss encephalopathic or inflammatory changes elsewhere. He also referred to the fact that in his evidence Dr Howatson expressed the mistaken belief that Calum recovered without Acyclovir, the standard therapy for encephalitis.

I have given full consideration to the evidence relating to Mr Holmes's submission that the finding as to the cause of Emma's death should be subject to certain qualifications.

The evidence regarding the cause of Emma's death came principally from Dr Howatson and Dr Donaldson.

Dr Howatson confirmed that his conclusion regarding cause of death was based on the fact that Emma's presentation was consistent with that of her brother whose chemical results, clinical presentation and proven adrenal suppression led clinicians to conclude that he had been suffering from adrenal insufficiency due to inhaled steroid therapy. He agreed that, in reaching this conclusion, the results of his post-mortem examination of Emma were inconsistent with what he would normally expect to find in a case of adrenal suppression.

Dr Howatson and the colleagues whom he consulted were of the view that the results of Emma's blood tests carried out at Wishaw General Hospital were not diagnostic of adrenal insufficiency. Dr Howatson said that, at the time he prepared his second report, on 8th February 2002, while he may have had some suspicion that adrenal suppression was involved, he had no evidence of this. In fact, the evidence which he had was contrary to this conclusion.

Dr Howatson said that he had never heard of adrenal suppression with an encephalitic presentation before and understood that this was not referred to in the medical literature. Most children present with hypoglycaemia and a smaller number present with circulatory collapse. Accordingly, he concluded that either the adrenal suppression caused the brain swelling, not previously known to be associated with adrenal suppression, or that Emma suffered from adrenal suppression but that a different condition caused the brain swelling.

He said that he did not see any evidence of neurological infection. Although his examination of Emma's brain was limited, Dr Howatson said that if Emma had meningitis, which is more commonly bacterial than viral, he would have expected to see evidence of this, as you would see pus on the surface of the brain. He would also have expected to be able to culture bacteria. He said that encephalitis is more commonly viral. With that condition you would see a profusely swollen brain, as a reaction to the virus. As there was diffuse swelling of Emma's brain, he thought that she may have viral encephalitis. His preference had been to do further intracranial

examination to investigate the cause of the swelling. He was not authorised to do so and therefore considered that he had carried out only an 80 % examination of the brain.

Dr Howatson said that Emma probably had bacterial stress and that because her adrenal glands were suppressed, she succumbed. The nature of the stress suffered by Emma, resulting in her requiring to produce cortisol, was probably due to infective tonsillitis, as indicated also by a high white cell blood count. Dr Howatson took swabs and grew bacteria but could not find invasive infection other than in the lower lung. His view was that if Emma had not been adrenally suppressed she would still be alive as he did not think that the degree of any infection present was such that her body could not have coped with this naturally.

He said that he was 99% certain that inhaled steroids were the cause of the adrenal suppression. He could not see any other explanation although, while he had seen a child with adrenal suppression due to oral steroids, he had never seen a child with adrenal suppression due to inhaled steroids.

Dr Donaldson said that the fatal illness in Emma and near fatal illness in Calum Frame was cerebral oedema and hypomatremia, in his opinion due least in part to acute adrenal insufficiency secondary to inhaled fluticasone, probably precipitated by intercurrent illness and possibly compounded by discontinuation of the fluticasone during the acute illness.

Dr Donaldson said that Emma probably became ill when she did due to a group A streptococcus, tonsillitis. He said that group A streptococcus, which is the same organism that was cultured from Emma, was cultured from Calum's endotracheal secretions. Dr Donaldson said that one could only speculate that this may be the link between the admissions to hospital of the two children.

Dr Donaldson said that Calum was electively put on a ventilator as a pre-emptive step and he thought that that if Calum's illness had not been dealt with so promptly his life might not have been saved.

Dr Donaldson said that encephelopathy is a disease affecting the brain and that swelling of the brain, cerebral oedema, is one of the mechanisms which cause encephalopathy.

He said that Calum had cerebral oedema, this being apparent from a CT scan, and that Emma's symptoms of vision difficulty and impairment of consciousness suggests that she had cerebral oedema when she was admitted, although it may have been that she had cerebral oedema at post-mortem because of all the fluid she had been given.

Dr Donaldson said that it was possible that this cerebral oedema in the children was an effect of cortisol deficiency. He explained that cortisol is needed to enable the kidneys to secrete water load and in Calum's and Emma's case cortisol deficiency may have caused difficulty in the shifting of the fluid load, resulting in the cerebral oedema.

Dr Donaldson referred to one case report describing cerebral swelling in Addison's disease, which is a condition where the adrenal glands fail.

However, he said that the exact cause of the cerebral oedema in both siblings is debatable and "it is possible... that the siblings are very metabolically unusual and they responded in an atypical way to adrenal insufficiency". He also said that he wondered whether, if the children reported on in the reports by Patel and Todd and others had had CT scans as quickly as Calum, they might have been found to have cerebral oedema as well as hypoglycaemia.

He said that there was no question but that fluticasone caused the adrenal insufficiency and, in his mind, no question but that the adrenal insufficiency caused the fatal and near fatal illness. He said that the symptoms in both children were very, very similar with abdominal pain, vomiting and disorientation. He said that, given that both siblings were receiving high doses of fluticasone, well above the licensed dose of 400 micrograms daily for children, that Emma's adrenal glands were considerably smaller than normal and that adrenal function in Calum showed severe adrenal suppression, it was highly likely that the acute illness of encephalopathy was related at least in part to acute adrenal insufficiency.

I do not take issue with Mr Holmes' proposition that Emma's presentation was atypical. Her adrenal glands, although small, were not so small as to lead Dr Howatson to conclude that she was adrenally insufficient when he carried out the post-mortem examination. Indeed in evidence Dr Howatson said that, while the average weight of adrenal glands for a child of Emma's height is 7 g, he had seen glands as small as Emma's before and tests had established that they were normal. Emma did not show clear growth suppression, her blood chemistry was not so severely disordered as to be diagnostic of adrenal insufficiency, her blood pressure and pulse were not abnormal when she was admitted to Wishaw General hospital, there was no evidence of hypoglycaemia and only a modest reduction in sodium levels and there was a clinical presentation of encephalopathy.

However, I noted that Dr Howatson also said that he had never actually seen a child with adrenal suppression due to inhaled steroid therapy for asthma in 15 years of carrying out paediatric post-mortems although he had seen adrenal suppression with oral steroids, which was quite commonly understood. In spite of Emma's atypical presentation, Dr Howatson believed that adrenal suppression was responsible for Emma's death and he said that if she had not been adrenally suppressed she would still be alive. He further said that he was 99% definite that the inhaled steroid was the cause of the adrenal suppression.

I also accept Mr Holmes' submission that there is an incomplete understanding of the mechanisms that led to Emma's death.

Mr Holmes said that Dr Donaldson reached the view that adrenal insufficiency was implicated in Emma's death in the light of the findings relating to Calum but that he remained cautious in his conclusions as to the cause of Emma's death, concluding in his report that "it is highly likely that the acute illness, with encephalopathy was related, at least in part, to acute adrenal insufficiency."

When I asked Dr Donaldson about his use of the phrase "at least in part", in his report, he explained that a direct link between Emma's presentation of cerebral oedema and hyponatraemia and adrenal insufficiency is not widely recognised and that the exact mechanism of cerebral oedema found in Emma and Calum remains unclear. He said that Emma and Calum did not have the profoundly low blood sugars that have been reported in some case studies and that, although nothing has been found to show this, it was just possible that Calum and Emma were slightly different in the way they handled fluids within the cells. He said that it was just possible that there was some additional factor which was particularly relevant to Emma and Calum, which the medical professionals were not aware of and which he thought they would never find.

Nonetheless, when Dr Donaldson was questioned further on this point by Mrs Dougal, he said that he was "quite sure... that Emma would be alive... had she not been on Flixotide." He said that he was sure that this was "a very important factor in her death" and that he was "just sounding a note of caution that we completely assume this very atypical presentation was purely adrenal insufficiency."

Dr Donaldson went on to say that " it is possible that there was some, if you like, metabolic quirk in the siblings that we have been unable to discover." However, he said that nothing was found to show that there was any such "metabolic quirk" in Emma and Calum. Furthermore, no evidence was led by Mr Holmes or by any of the other parties to the inquiry to suggest that there may in fact have been any such "metabolic quirk".

I formed the view that Dr Donaldson was, quite properly, in his own words, simply "sounding a note of caution" about any assumption that such an atypical presentation arose "purely" from adrenal insufficiency. However, there was nothing in his evidence which led me to believe that adrenal insufficiency due to inhaled steroid therapy may not have been the cause of Emma's death. If there existed any other factor which contributed to Emma's death, its nature is unknown, even to Dr Donaldson who suggested the possibility.

Moreover, as I understood Dr Donaldson's evidence, the existence of any such factor does not alter the fact that the response of Emma and of her brother Calum, while it was atypical, was nevertheless a response to adrenal suppression, resulting in adrenal insufficiency. Dr Donaldson's opinion was that fluticasone caused the adrenal insufficiency and that the adrenal insufficiency caused the fatal illness.

Accordingly, notwithstanding that Emma's presentation was atypical, to the extent that it led to considerable initial difficulty in establishing the cause of death, and that the exact mechanisms that led to her death are not fully understood, I am satisfied on the evidence led at this inquiry that the cause of Emma's death is as set out by Dr Howatson in his letter of 5 April 2002.

In relation to the concern raised by Mr Holmes that, in the absence of authorisation for full neuropathology examination, only about 10 percent of the brain substance had been sampled, I noted that Dr Howatson did say that, while the specialist examination by a consultant neuropathologist of the samples submitted at the time of the post-mortem examination detected no pathology in the brain, there was a risk

that viral encephalopathy may have been missed because areas of the brain where lesions etc might have been may not have been examined.

However, Dr Howatson confirmed that there was no evidence, in the bacteriology or biology testing which was carried out, of neurological infection. He said that meningitis is usually bacterial and that he would have expected that any meningitis bacterial infection would have shown in the cultures from the brain fluids. He said that viral meningitis is very unusual. Viruses from the brain were not cultured due to the limited authorised examination of the brain. However, no viruses were found in the cerebral spinal fluid.

Dr Howatson said that he thought, at the time of the post-mortem examination, that Emma had viral encephalitis. However, I note that Dr Howatson said in evidence that the histology from numerous places in Emma's brain, although not as much as would normally be taken, did not show evidence of viral infection or viral reaction in any site. On the basis of all the other information which was finally available to him, Dr Howatson was satisfied with the diagnosis of adrenal insufficiency as the cause of Emma's death.

In relation to the matter of Dr Howatson mistakenly believing that Calum had not been administered Acyclovir, an anti-viral agent, it did not seem to me, on considering his evidence as a whole, that this was a significant factor in Dr Howatson's reaching his conclusion regarding the cause of Emma's death.

I am satisfied that the cause of Emma's death was adrenal insufficiency due to inhaled steroid therapy prescribed for chronic asthma and in the light of all the evidence before me at this inquiry, including the evidence of atypical presentation, Dr Donaldson's evidence of a possible 'metabolic quirk' and Dr Howatson's evidence regarding incomplete examination of the brain, I do not think it appropriate to record any qualification in respect of the finding as to the cause of Emma's death.

I noted that in his evidence Dr Howatson said that the Registrar General had received notification of the change of the cause of death from "unascertained" and that this had been registered. Mr Frame said that he was aware that a recommendation had been made that the the cause of death should be amended but said that the family had never actually had an amended death certificate. If in fact such a change has not yet been registered, as stated by Miss Dougal in her submissions, I recommend that this should now be done.

ISSUES ARISING IN TERMS OF SECTION 6 (1) (c), (d) and (e)

1. Prescribing of high dose fluticasone for Emma over a prolonged period

Introduction

I have determined that the cause of Emma's death was adrenal suppression due to inhaled corticosteroids prescribed for asthma.

Throughout most of her life, Emma was prescribed high, off-licence, doses of fluticasone, an inhaled corticosteroid which is said to have double the potency of the other two inhaled corticosteroids.

In the course of giving evidence, Dr Donaldson referred to the 2001 Patel et al paper (10) which described side effects from inhaled corticosteroids within licensed doses and he said that it was necessary 'to be aware of the slight risks within licence ...' and Dr Cochran said that '.....there have been a small number of cases when children have become ill with adrenal suppression on more conventional doses, doses... which there are very many, many thousands of children receiving'. It was also emphasised by several of the medical witnesses at the inquiry that taking any drug has the potential to cause side effects.

However, the relevant Current Problems in Pharmacovigilance bulletins referred to the potential risk of adrenal suppression with prolonged high dose inhaled corticosteroids, Dr Survana who spoke for the MHRA said that the majority of side effects are dose related and that it is known to every doctor that if you operate above the licensed dose you are much more likely to encounter those dose related side effects and, as I understand his evidence, Dr Donaldson associated Emma's death and Calum's illness with the fact that they were on high dose inhaled corticosteroids. All of the medical witnesses at the inquiry referred to the fact that Emma was prescribed "high dose" inhaled corticosteroids. I am satisfied, on consideration of all the evidence before me in this case, that the use of high dose fluticasone to treat Emma's symptoms over a prolonged period was the key factor in her death.

This inquiry must determine the reasonable precautions, if any, whereby Emma's death might have been avoided. I am of the view that Emma's death might have been avoided if she had not been prescribed high dose inhaled corticosteroids, mainly fluticasone, over the four year period leading up to her death. Both Dr Shapiro and Dr Cochran were in a position to influence and control Emma's inhaled corticosteroid prescription. I have therefore considered whether there were reasonable precautions which could or should have been taken by either or both of Dr Shapiro or Dr Cochran and which would have avoided Emma being on a prolonged high dose prescription of fluticasone.

1(a): General practitioner's prescription of high dose inhaled corticosteroids over a prolonged period

Sumissions

Mrs Dougall for the family said that the course of treatment Emma was prescribed was the precipitant for her death, with the particular factors of relevance to Emma's death being the selection of high dose inhaled corticosteroids as the method of managing her symptoms and the use of this treatment for a period of four years. Part of her submission on this point referred to the following aspects of Dr Shapiro's care and treatment of Emma:

- the selection of a high start dose of fluticasone by Dr Shapiro;

- Dr Shapiro's failure, as someone professing a specialist interest in asthma management, to familiarise himself with warnings about the potential risks of prolonged high dose inhaled steroid therapy;
- the failure by Dr Shapiro to seek specialist review of Emma for over a year after commencing high dose fluticasone;
- the failure of Dr Shapiro to act upon the warnings in the MCA "Current Issues in Pharmacovigilance" bulletins published in 1998 and 2001;
- the failure of Dr Shapiro to take into account the possible effects of the addition of other steroid medication to Emma's treatment regime.

Mr Houston for the Crown submitted that, looking at all the circumstances surrounding the death of Emma, Dr Shapiro could not be held responsible as he adhered to the British Guidelines on Asthma Management 1995 Review and Position Statement (hereinafter referred to as the BTS guidelines) which he claimed were ambiguous, as he was supported in his management of Emma by a specialist, Dr Cochran, and as he did attempt to step down the dosages prescribed for Emma.

Mr Lindsay on behalf of MHRA said that the advice given by the Agency in relation to off-licence prescribing is that the balance of risks and benefits and the overall safety, quality and efficacy of the medicine are positive and appropriate within the confines of the summary of product characteristics and the licence. Once a medical practitioner prescribes outside the confines of the licence the prescriber assumes full responsibility for his own actions.

Mrs Robertson for the NHS Greater Glasgow and NHS Lanarkshire said that there was perfectly valid evidence to support Dr Shapiro's practice of starting at a high dose with a view to stepping down. She was of the view that on the evidence before the inquiry, it was understandable that neither Dr Shapiro nor Dr Cochran should believe that adrenal suppression was a real risk. Mrs Robertson noted that Dr Shapiro was aiming to have Emma symptom free and said that it was broadly agreed that it was appropriate for clinicians to do so. She said that it was of crucial importance that Dr Shapiro did constantly strive to drive down the doses.

Mrs Abernethy for Glaxo emphasised that it was a matter of clinical judgement for doctors to decide the dose of any drug prescribed to a child. She said that, while the fact that it was claimed that the risk of Flixotide actually producing systemic side effects would be less than previously existing steroids would be a factor, there was no doubt that the reason that Dr Shapiro prescribed fluticasone to Emma was because he was "a disciple" of Dr Paton. However, she said that doctors were justifiably complacent about the bio-chemical evidence of adrenal suppression in the use of inhaled corticosteroids in their 25/30 years of use. Mrs Abernethy said that clinical evidence of adrenal insufficiency/suppression began to emerge in the mid 1990's because there had been a change of practice, partly brought on by the recommendations of the BTS Guidelines, which was also reflected in medical magazines, to use fluticasone and other inhaled corticosteroids in far higher doses than those at which they were designed to be used. Mrs Abernethy also said that prior to prescribing steroids for Emma, Dr Shapiro prescribed sodium cromoglycate by inhaler, which was in accordance with step 2 of chart 6 of the 1995 BTS guidelines. However, Emma was still symptomatic and Dr Shapiro said in evidence that he felt he needed to "take the next step in management".

Mr Holmes, representing the interests of Dr Shapiro, submitted that Dr Shapiro's management of Emma was reasonable when viewed in the context of contemporary knowledge of risks associated with inhaled corticosteroids and the prevailing medical practice. In support of that submission, he stated the following:

- along with what would appear to be the body of medical opinion at the time, Dr Shapiro understood the risk of adrenal suppression from inhaled steroids to be a theoretical one;
- at the relevant time, a body of medical opinion favoured starting with a high dose of inhaled corticosteroids to gain control of asthmatic symptoms then titrating the dose to as low a level as possible;
- the 1995 BTS Guidelines offered Dr Shapiro some level of reassurance as to his prescribing and had an effect on his management;
- Flixotide was offered as a development on the older inhaled corticosteroids given its lower bio-availability when swallowed;
- Dr Shapiro was reassured by feedback from Yorkhill Hospital and Dr Paton in particular in relation to certain patients referred by him who were prescribed 2,000 micrograms and, in one case 4,000 micrograms per day of Flixotide;
- Dr Shapiro was reassured by correspondence from Dr Cochran about Emma;
- Dr Shapiro heeded the advice from Yorkhill Hospital and at every opportunity sought to reduce the dosage that Emma was receiving;
- Dr Shapiro was by no means the only practitioner to be prescribing high dose Flixotide to paediatric patients at the relevant time.

Determination

Introduction

Dr Shapiro gave evidence at the inquiry and was questioned in detail about his care of Emma and the reasons for his choice of treatment.

Dr Peter Thornton gave evidence as an expert witness on general practitioner practice. He is a GP and has additional qualifications and experience including *inter alia* an honorary senior lectureship in general practice at the Faculty of Medicine at the University of Dundee, membership of the GP Clinical Advisory Panel of the Medical and Defence Union of Scotland, external professional assessor to the Health Service Commissioner for Scotland and performance assessor and professional linguistics examiner for the General Medical Council.

Asthma diagnosis and assessment of severity

Dr Donaldson said in evidence that, while it was perfectly reasonable to make a diagnosis of asthma in Calum and Emma at the time, one could speculate in retrospect that it is likely that neither Calum nor Emma had asthma. He based this point of view on the fact that Calum had come off medication so successfully but he said that it could be argued that Calum did have asthma and had simply outgrown it. He also said that the fact that the children suffered such severe side-effects suggested that they may possibly not have had asthma, the reason for this proposition being that it is thought that the more normal the lung the more prone is the patient to systemic absorption.

In her submission regarding the selection of a high starting dose of fluticasone, Mrs Dougall said that the starting dose of 1,500 micrograms a day was in excess of any published guideline for a child of Emma's age, even had that child been suffering from severe asthma, which was not the classification given to Emma by Dr Shapiro.

The issue of the severity of Emma's condition was explored to a limited extent throughout the inquiry. I have noted the following in connection with this matter: Dr Shapiro described Emma as a "moderate, perhaps moderate to severe but not severe" asthmatic as at 7 November 1997, when she had just been started on budesonide and had also been prescribed oral steroids; Dr Thornton said that the features of Emma's condition which were apparent from the medical records merited the classification of moderately severe asthma; Dr Todd said that it was difficult to assess the condition of a patient one has never seen but, based on the treatment she was given and the close attention given by Dr Shapiro, he classed Emma's asthma as at least moderately severe to severe and at worst as severe; Professor Helms said that Emma appeared to him to have moderate to severe intermittent asthma.

Mr Holmes said in his submissions that we could only speculate as to Emma's condition had she not received inhaled corticosteroids as prescribed by Dr Shapiro and that it was noticeable that throughout her asthma management, she did not require hospital admission. When this point was put to Professor Helms, he agreed that a reasonable interpretation of the fact that Emma had never had a hospital admission might be that the medication was achieving that effect rather than its being related to the underlying disease. He did point out nevertheless that Emma did not present with a severe episode requiring hospital admission before she was treated with inhaled corticosteroids so she had "not declared herself at that time as having very severe life threatening disease".

With this divergence in medical opinion and in the light of the possibility that the fluticasone therapy avoided an acute asthmatic episode for Emma, it does not seem to me to be possible to draw any conclusions regarding the diagnosis or the severity of Emma's condition when Dr Shapiro commenced the 1,500 micrograms fluticasone prescription. What is clear is that she was still symptomatic after therapy at the level of the step 3 non-steroid and the step 3 steroid therapy specified in chart 6 of the 1995 BTS guidelines.

Selection of high starting dose of inhaled corticosteroid therapy

The choice of the inhaled corticosteroid starting dose for Emma was made by Dr Shapiro. The first dosage he prescribed was 800 micrograms daily of budesonide. This was the maximum dosage provided for at step 3 of chart 6 of the BTS guidelines, at which recommended treatment with increased dose inhaled steroids is detailed.

Dr Shapiro described this as a "fairly high dose". He explained that he started at this high dose due to there being a change to 'step down' prescribing practice around that time. Dr Thornton confirmed in evidence that this change in prescribing practice was a relatively new idea in the late 1990's. He said that before then, people were very wary about steroids. They would start at low doses and, if control was not

achieved, they would step up the dosage in stages in order to find the lowest dose as which control was achieved. The 'step down' advice was to start with a high dosage in order to gain rapid control and ascertain how good the patient could be, then to step down from that dosage until reaching the minimum dosage at which the patient was kept as symptom free as possible. Dr Thornton said that this was an approach which was recognised in general practice at the relevant time and that it was a legitimate approach to take.

Accordingly, although high, it did not appear to me from the evidence that a starting dose of 800 micrograms of Pulmicort Budesonide was inappropriate, given Emma's poor response to the non-steroid therapy, the dosage specification contained in the BTS Guidelines and the "step down" prescribing practice which had been accepted by that time.

Selection of high starting dose of fluticasone

The issues raised by the initial dosage of Flixotide which was subsequently prescribed by Dr Shapiro are more open to enquiry.

Emma remained on the 800 micrograms budesonide prescription from 5 November 1997 until 29 December 1997. On the latter date, Emma was coughing and wheezing and Dr Shapiro changed her prescription to 1,500 micrograms fluticasone daily. He said that he changed to fluticasone because "we needed more potency, we needed more efficacy ...". He agreed in evidence that by this time, he had formed the view that fluticasone was perhaps the more effective drug. He said that it had done "very, very well in some very, very problematic patients".

Dr Shapiro said that his decision to prescribe a dosage of 1,500 micrograms was based, firstly on the fact that the dose needed to be higher than equivalent to the 800 micrograms daily dose of budesonide that Emma had been on as this had not been enough to stabilise her lung membranes and secondly on his having over two or three years received from Dr Paton at Yorkhill "continuous reassurance and feedback about other patients with ... moderate and severe disease, about what doses of fluticasone are appropriate".

However, when Dr Shapiro was questioned closely by Mrs Dougall about this choice of an initial dosage of fluticasone, he agreed with Mrs Dougall's proposition that by prescribing 1,500 micrograms daily he was in effect quadrupling the dose of steroids. This calculation was based on the premise, which as I understand it was accepted by all the relevant witnesses who gave evidence to the inquiry, that fluticasone has double the potency of budesonide and that accordingly equivalent potency is achieved at half the dosage. Dr Shapiro himself did not seem to have any doubt about this. He confirmed in evidence that he was aware that fluticasone was "a more potent, topically active steroid" and that "the more topical activity a drug has in terms of an inhaled drug ... the better results you would get. So that means when some falls on the lung tissue it works better microgram for microgram than another drug".

Influence of BTS Guidelines on selection of high dose fluticasone

Nevertheless, there was some imprecision in Dr Shapiro's evidence concerning the matter of equivalent doses and, on my understanding of his evidence, this arose from the content of chart 6 of the BTS Guidelines.

Step 4 of chart 6 specifies a dosage of "inhaled steroids (up to 2 mg/day)" and does not differentiate between fluticasone and the other inhaled corticosteroids.

The text of the BTS guidelines, the other steps in this chart and all the steps in the other relevant charts annexed to the guidelines differentiate between fluticasone and the other inhaled corticosteroids.

I am satisfied that Dr Shapiro was aware of the BTS Guidelines when he first prescribed inhaled corticosteroids for Emma. There was some confusion at one point in his evidence as to when he thought the guidelines were published but it is clear from his evidence in chief that he was aware that the guidelines were written in 1995 and published in February 1997 and that he received the publication some time after that, perhaps March 1997. He was asked if he was using that as a guide to the dosages that he was prescribing for Emma and he replied, "Yes, that without question had an effect on management".

When he was asked by Mrs Dougall whether the comparable dose of Flixotide at Step 4 of chart 6 would in fact be 1,000 micrograms a day, Dr Shapiro replied that "... firstly, it doesn't say that, even though it is an omission and secondly, looking at that step 4 in the light of what I was seeing done, it seemed exactly in line with what I was actually seeing happen".

Dr Shapiro was pressed by Mrs Dougall regarding his interpretation of the guidelines. In particular she asked him to confirm that the entirety of the guidelines, apart from step 4, makes it quite clear that fluticasone is prescribed at half the dose of budesonide. Dr Shapiro's response was that that was not something he "picked up on ... because the most prominent part of these guidelines was the stepwise plans". He went on to say that "step 4 was consistent with what I was seeing done regularly in my patients and I made the assumption that it was correct ...". Mrs Dougall asked him to confirm that this was not the correct assumption and he answered that he thought "there is an argument that says that it is not the correct assumption with the benefit of hindsight but it was not the only issue in terms of prescribing the drug."

When Dr Shapiro was asked if the omission at step 4 of chart 6 of the guidelines had caused him to fail to differentiate between fluticasone and budesonide when deciding upon the initial dose of fluticasone for Emma, his response was: "In itself probably not. I think if I had never seen anybody else using doses above 1,000 then it wouldn't have in itself been enough but the fact that I was getting a lot of feedback with doses up to 2,000 and even 4,000, I just kind of ... that was how I viewed it, that's fine, we have got 2 mg of steroid, that's OK because that is in the guidelines."

It therefore appears that, while Dr Shapiro did know about differences in potency between fluticasone and the other inhaled corticosteroids, the content of the BTS guidelines resulted in some lack of clarity on the part of Dr Shapiro as to the recommendations in the guidelines.

If Dr Shapiro had relied solely upon the BTS guidelines when he made his decision to prescribe for Emma an initial dose of fluticasone of 1,500 micrograms daily, it could certainly be considered that it would have been a reasonable precaution for him to have clarified whether the wording of step 4 of chart 6 was accurate, given the text of the guidelines and the differentiation between fluticasone and the other inhaled corticosteroids in the other steps and charts.

Influence of consultants at Yorkhill on selection of high dose fluticasone

However Dr Shapiro's evidence was that while the content of step 4 of chart 6 may have contributed to his being reassured about using as high an initial dose as 1,500 micrograms fluticasone, the primary factor in his decision to use such dosage was the fact that Yorkhill Hospital and, in particular, Dr Paton had recommended similar doses for other of his patients.

Dr Shapiro referred to this on several occasions as is indicated from the extracts from his evidence quoted above. He also said in evidence that he had "absolutely no experience or exposure to patients on more than 1,600 micrograms of Pulmicort [budesonide] whereas I had exposure and experience of patients by that time on or up to 2,000 micrograms of fluticasone." He said that Dr Paton used doses of fluticasone of 2,000 micrograms and had in one case suggested a dose of up to 4,000 micrograms. Dr Shapiro said that between 1995 and 2000/2001 he had referred between 12 and 17 significant asthmatics to Yorkhill, mainly to see Dr Paton "from whom there was feedback which commonly ran for each patient to about two or perhaps three letters of reassurance each year for each patient."

It was put to Dr Paton at the inquiry that Dr Shapiro had not started using high doses of fluticasone until he saw them being prescribed or recommended by paediatricians in Yorkhill and he was asked to comment on that. Dr Paton explained that there is a "sort of dialogue" between general practitioners and hospital consultants and that one of the ways consultants learned about drugs was seeing how general practitioners had used them and that undoubtedly one of the ways in which hospital consultants influenced care was by general practitioners seeing practices adopted by consultants and by applying them to other patients. He could not confirm Dr Shapiro's evidence regarding how he came to start using high doses, in terms of the timing, but he said that it was "quite possible".

I have no doubt from his evidence, which I accepted, that the principal influence upon Dr Shapiro when he prescribed 1,500 micrograms as an initial dose of fluticasone for Emma was the feedback regarding the drug and dosage which he had received from Yorkhill, and Dr Paton in particular, in relation to other patients. While the dosage referred to in the BTS Guidelines no doubt reinforced his confidence in prescribing such doses, it was very much an ancillary influence upon him and I am satisfied that it would not in itself have caused him to prescribe such a dose without enquiry into its accuracy.

Furthermore, it seems entirely reasonable that, as Dr Paton said, general practitioners should be influenced in their treatment of patients by noting the practices adopted by hospital consultants and applying them to other patients. In the case of Dr Shapiro, he saw that Dr Paton was prescribing high dose fluticasone and

he did so also. I also noted that Dr Donaldson pointed out that although the doses of fluticasone administered to the children were in excess of the recommended amount, the number of children recalled to Yorkhill for synacthen testing indicated that Dr Shapiro was by no means the only practitioner to be prescribing high doses of fluticasone to paediatric patients.

Conclusion regarding initial selection of high dose fluticasone

Dr Thornton said that he would not have started a child under the age of five on a dose greater than 500 microgrammes of fluticasone. He said that, if such prescribing had to be undertaken at all, it should only have been done under the supervision of a specialist with experience in the use of the drug in similar circumstances and at that dosage and an explanation of the unusual circumstances should have been given to the parents with a reasoned argument as to why it was in the patient's best interests. Dr Thornton and Professor Helms both said that 1,500 micrograms of fluticasone daily set a very high baseline from which subsequent management varied only a little up and a little down resulting in Emma being exposed to a very high cumulative dose of steroids.

No evidence was led at the inquiry as to how a practitioner would establish the level of severity of a patient's asthma prior to deciding the dosage at which any step of treatment in chart 6 should be initiated. This is clearly a matter for clinical judgement by medical practitioners.

In Emma's case, by the time she was prescribed 1,500 micrograms of fluticasone daily, she had failed to respond to step 3 non-steroid therapy and she had been prescribed the maximum amount of inhaled steroids specified at step 3 and was still symptomatic. The BTS guidelines (page S5) referred to "The importance of gaining control of asthma ... abolishing symptoms as soon as possible ...".

In all of these circumstances and taking account of the success which Dr Shapiro had noted in this treatment with "very, very problematic patients" and of the terms of the BTS guidelines but particularly given the specialist feedback from Yorkhill regarding the use of high dose fluticasone, I do not consider that Dr Shapiro's decision to prescribe an initial dose of 1,500 micrograms daily of fluticasone was an unreasonable one to make at the time in question.

Referral to a specialist

Mrs Dougall submitted that Dr Shapiro failed to seek specialist review for over a year after commencing high dose fluticasone, which resulted in Emma becoming established on high dose therapy at levels which were then difficult to reduce in a general practitioner's setting when review was taking place at 2-6 month intervals.

The proposition regarding the timing of the referral for specialist review is not accurate, as evidenced by the date of the referral letter. Neither is it the case that, during this period when an appointment was not made, the therapy was not being reduced within the GP setting.

It seems to me that the timing of Dr Shapiro's first referral of Emma to Yorkhill for specialist advice was entirely appropriate, as were his actings in January 1999 when Emma's condition had deteriorated and he once again became concerned about having to prescribe very high doses of fluticasone. At that time he noted that Emma had not yet been seen by a specialist and he took steps to secure an urgent appointment and tried to ascertain what had happened to his original referral by personally phoning the hospital.

As a result of this further referral, Emma was seen by Dr Cochran at Yorkhill on 25 February 1999. However I am satisfied from the evidence of Dr Shapiro and from the contents of Emma's medical notes that, even before she was seen by Dr Cochran, Dr Shapiro attempted to reduce the dose of inhaled corticosteroid which Emma was receiving. He did so throughout 1998 so that by the end of September 1998 the dose had been reduced to 500 micrograms daily. This was increased in December 1998 due to a deterioration in Emma's condition but even in January 1999, at the time of his second referral of Emma to Yorkhill, Dr Shapiro had reduced the dose again from 2,000 to 1,500 micrograms, despite the fact that Emma was 'chesty until she vomits'. Dr Shapiro said in evidence that he did so at that time as he was not happy with the dose and the plan noted was that if Emma was no worse at review in four weeks less steroid should be used. Dr Shapiro also usually arranged reviews for Emma at fairly short intervals. He confirmed that, in June 1999, after he had reduced Emma's dosage to 750 micrograms daily, he proposed a review 6 months later. However, he explained that he would not have been happy to further reduce the dose until it had been established that there was a significant period when Emma had remained stable and well, given her previous history. He said that he was concerned that if he reduced the steroid earlier, he may precipitate and increase her symptoms. In fact, on that occasion, he saw her 3 1/2 months later when she had again become symptomatic. Dr Thornton said that asthma is an episodic condition so it is difficult to say in a short space of time whether any improvement is the result of therapy or whether it is an improvement that would have occurred in any case. He confirmed that it was a matter of judgement as to how long one should persist with a dose of therapy once symptoms were under control and said that sometimes a month might not be too short but clearly doing well over three months is more evidence than doing well over one month or one week. Dr Cochran said that it would be unusual to change from one step to another in anything less than three or four months and six or 12 months or longer may be more typical, although he thought that Dr. Shapiro was using the high doses as short term rescue treatment in the way Dr Cochran would have usually used oral steroids.

Advice and reassurance given by consultant

There appears to be nothing in Dr Cochran's correspondence with Dr Shapiro to suggest that he was concerned about Dr Shapiro's management of Emma's asthma, despite the fact that Dr Shapiro had specifically raised his concern about "inordinate quantities of therapy". Certainly, Dr Cochran's written response to the referral was that Dr Shapiro should consider a reduction in fluticasone but this was already an issue for Dr Shapiro which he had been addressing for over a year.

It seems to be the case that, having taken the appropriate precaution of seeking specialist advice and guidance, Dr Shapiro received not only reassurance but, as Professor Helms expressed it, "tacit approval" for his management of Emma.

Dr Thornton said in his report, and confirmed in evidence, that "when Emma had been seen by Dr Cochran, Dr Shapiro received a letter approving of the then current therapy which included 1,500 micrograms of the fluticasone daily ... . The advice given by specialist paediatricians was also important in affirming to Dr Shapiro and his partners that the doses they were prescribing, although high, were justified." Dr Thornton also agreed that the fact that Dr Cochran was only seeing Emma on a yearly basis towards the end of his management of her would be reassurance to Dr Shapiro.

Dr Todd said that when a GP, who has to have expertise in all diseases and even has a 'social work' role to perform, refers a difficult clinical problem to a specialist, he expects help, support, input, guidance and activity regarding the management of the case. He said that he did not think it was sufficient just to pass the problem back to the GP.

Dr Shapiro followed Dr Cochran's advice by continuing to try to reduce the dosage of inhaled corticosteroid throughout the time he treated Emma. He also followed all the other advice and recommendations of Dr Cochran, such as stopping the sodium cromoglycate prescription, changing their delivery device from aerochamber to volumatic and prescribing Montelukast.

General practitioner's knowledge and understanding of risks associated with high dose inhaled corticosteroids

Mrs Dougall submitted that Dr Shapiro failed to familiarise himself with warnings about the potential risks of prolonged high dose inhaled steroid therapy. She also said that Dr Shapiro did not give any weight to the warnings published by the Medicines Control Agency in 1998 and 2001, despite his acknowledgement of the importance of the views expressed therein and his own use of high dose inhaled fluticasone.

It would certainly seem to be reasonable to expect that a prescribing physician should keep up to date with warnings about potential risks associated with the drugs prescribed and I have given particular consideration to this matter.

I noted that Mr Frame said in evidence that Dr Shapiro never at any time in his consultations with the family mentioned the possibility of adrenal suppression. He said that Dr Shapiro mentioned that growth retardation was a potential side effect and Dr Shapiro confirmed that this was probably the case. Dr Shapiro's explanation for this was that "there wasn't much else as far as I am aware we were actually concerned actually happened to patients therefore it would have been inappropriate to disturb someone with a risk which quantitatively I felt was minuscule." Dr Thornton said that the most significant side effects of inhaled corticosteroids which it would have been usual to describe to parents and, if appropriate children, was growth retardation and susceptibility to thrush infections of the mouth and throat.

Although Dr Thornton was critical of Dr Shapiro's actions in prescribing high dose steroid therapy for Emma, he did confirm in evidence that "branded medication is always dispensed with a full information leaflet and practitioners will encourage patients and parents to read this and raise specific concerns rather than swamping them with a long list of potential side effects within a consultation where other complex advice is also being imparted." He said that information should be given in a balanced way as over emphasis on the potential risk of treatment may inhibit its proper use. Dr Thornton said that patients often hesitate to accept prescriptions for steroids because they associate them with the anabolic steroids that athletes take and that if you reel off a long list of potential side effects or theoretical side effects the patients may take the prescription but never encash it or encash it but never take the medicine.

It therefore appears to me that Dr Shapiro acted appropriately and in accordance with Dr Thornton's description of best practice when he limited his warning about possible side effects to those which he understood at the time were matters which were of particular concern within the medical profession. I do not consider that this indicated a lack of awareness on his part about the potential risks.

Dr Shapiro said that he was concerned about the theoretical risk of several problems, mostly growth retardation and bone mineralisation osteoporosis, which he said were written about in medical journals. I have no reason to doubt his evidence in this respect. It also seems to me from consideration of all the evidence which was before the inquiry that the concerns which he had about the possible side effects of inhaled corticosteroids were those which were of particular concern within the medical profession generally at the relevant time.

Dr Shapiro said that he expressed concerns in virtually every letter to Yorkhill about high dose steroids. He also said in evidence that he referred Emma to a specialist in January 1998 because he thought "the dose ... was too high ... to be left solely in the hands of a general practitioner, even one with a special interest".

However, in addition to Dr Shapiro's evidence at the inquiry, his letter of referral of 21 January 1998 to Dr Paton at Yorkhill was available for consideration. In this letter, Dr Shapiro said that "her symptoms are reduced on a dose of 1,500 micrograms of fluticasone a day via an aerochamber but she still easily becomes chesty. I think in view of her age and the dosage we are using I feel it might be worth your while seeing her for reassurance. As always I am trying to use the lowest dose of steroid that keeps the child free." By the time Dr Shapiro wrote this letter, Emma had been on inhaled corticosteroids since 5 November 1997 and had been taking a very high dose of 1,500 micrograms fluticasone for three weeks, therapy which Dr Shapiro said was "at a level which I would not continue without worrying".

Dr Shapiro's evidence was that, throughout the time Emma was under his care he regularly reviewed her and reduced the dosage of inhaled corticosteroids whenever Emma became less symptomatic. He said that Emma "was seem extremely regularly, follow-up appointments were always requested and notes on her management clearly written with frequent references to future treatment plans."

He also said that the majority of his consultations with Emma involved reduction of inhaled steroids or referred to treatment plans to reduce steroids and that when he required to increase the dosage the plan was that this should be for short periods, with early review.

I am quite satisfied that Emma's medical records confirm this and that managing Emma's care in this way indicates Dr Shapiro's concern to drive down the dosage whenever possible.

General practitioner's knowledge and understanding of adrenal suppression as a risk associated with high dose inhaled corticosteroids

Dr Shapiro said that adrenal suppression was not something he had ever seen. He said that he never received any expression of concern from Yorkhill about there being a real risk of adrenal suppression in children on high doses of fluticasone. He said that in fact, to the contrary, all the reassurance he had received suggested that there was no reason why he should know about this as a potential danger of fluticasone in the doses which he was prescribing to Emma.

Similarly, he said that he had obtained no such information from any publication which he received or from any other source. He said that, while he did not recognise the May 1998 Current Problems in Pharmacovigilance bulletin (published by the Committee on Safety of Medicines and the Medicines Control Agency) when it was put before him at the inquiry, he did read the publication and he assumed that he would have read that issue. In any event he said that he had always had an awareness that adrenal suppression was a theoretical side-effect of inhaled corticosteroids but that nobody seemed to be concerned that it was a problem and therefore he did not think that the information contained in the 1998 bulletin was new. He said that the bulletin highlighted adrenal suppression as "an area of concern" but was not "a suggestion that it actually happened". He said that the 2001 bulletin included a warning about potential adrenal suppression with fluticasone but that it was "fairly general" and his interpretation was that "it said don't use any more than you need to, if you are using a lot make sure you have got either personal special interest or that the patient is under the care of a specialist." He also confirmed in cross-examination that the reminder contained in this bulletin referred to doses of Fluticasone over 1000 micrograms daily and that, at that point, Emma's prescription was for 1000 micrograms daily and that this dosage had not been exceeded since September 2000.

Dr Thornton said that he would expect general practitioners to read the Current Problems in Pharmacovigilance bulletin and that if it dealt with a medication which they prescribed frequently to pay close attention to what it contained. He said that a document like this would cause him to question reassurance about dosages of drugs which he had received from a hospital. His opinion was that Dr Shapiro should have given greater consideration to the warnings received from the MCA in 1998.

Dr Shapiro said that the recommendations in Current Problems in Pharmacovigilance were important but did not effect his prescribing pattern for inhaled steroids in view of the other reinforcement he had that this was appropriate prescribing. He agreed that a reasonable general practitioner would attached

considerable weight to such advice and guidance but said that everything a general practitioner receives has to be taken together with a huge amount of information received from a very large number of sources.

Having heard his evidence I have no doubt that Dr Shapiro was always aware that adrenal suppression was a theoretical risk with inhaled corticosteroids. Indeed, he gave evidence of some research into this area which he and his partner attempted to conduct in around 1990 by testing for cortisol levels in the urine of children in their practice who were being prescribed "reasonably high doses" of inhaled corticosteroids, mainly budesonide, as fluticasone was not being produced at that time. The results were inconclusive and the local biochemistry laboratory advised that the cost of the test was not justified as the test itself was not particularly reliable.

However, the distinction between theoretical and actual risk of adrenal suppression appears to be fundamental to the differences in opinion expressed on the subject by the medical witnesses at this inquiry.

I will go into this issue in greater detail when considering the position of Dr Cochran's care of Emma and the terms of the warnings issued by the Committee on Safety of Medicines and the Medicines Control Agency. At this stage, I have considered whether Dr Shapiro took reasonable precautions in the light of his knowledge of the risk of adrenal suppression with inhaled corticosteroids. I am satisfied from the evidence before me, including the terms of the May 1998 and August 2001 Current Problems in Pharmacovigilance bulletins, that his knowledge and understanding of this risk was reasonable for a general practitioner, even one with a special interest in the treatment of asthma, given the state of knowledge and understanding in the medical profession generally at the time when Emma was being treated with inhaled corticosteroid therapy and given particularly the advice and reassurance which he received from specialists in this area of medicine. Likewise when viewed in this context, the steps which he took, in particular regularly attempting to reduce the dosage prescribed for Emma and referring her at an early stage for specialist advice were the reasonable precautions which he might have been expected to take.

Prescribing of additional steroids

Dr Shapiro prescribed a nasal steroid spray for Emma in April 2001 and the dose was doubled on 20 November 2001. On 23 November 2001, Emma became acutely unwell and on 24 November 2001 she died.

Mrs Dougall submitted that, despite his use of high dose inhaled corticosteroid therapy, Dr Shapiro did not grasp the importance of the addition of other steroid medication to Emma's treatment regime. She said that he was of the view that the addition of nasal steroid preparations would have no effect as they were systematically inert. Mrs Dougall said that this was not correct.

Dr Shapiro said that the drug company claimed that the nasal steroid was systemically inert. He understood that it was said to be immeasurable in the systemic circulation. Dr Thornton said that general practitioners are concerned about giving additional steroid treatment to a patient who is already on steroids, whether they are nasal, inhaled or steroids applied to the skin. He said that a general practitioner

would suspect any steroid of being systemically absorbed. He believed that the nasal steroid in question does carry a warning about the possibility of systemic absorption. As to whether it was chemically inert when absorbed, he said that that was a matter for a pharmacologist or pharmacist.

Dr Paton was not asked directly about this matter but I noted that in another context he gave evidence that Dr Donaldson had published a paper on children from Yorkhill clinics who had asthma and rhinitis and were managed on doses of inhaled corticosteroids and also steroid nasal sprays. Dr Paton said that these children had significant growth delay and that Dr Donaldson had suggested that the combination of inhaled steroids plus potent nasal steroids was particularly significant for growth.

However, I do not consider that I have sufficient information before me to draw any conclusions as whether the addition of this medication contributed to the adrenal suppression that led to Emma's death or whether refraining from prescribing this was a reasonable precaution which Dr Shapiro might have taken whereby her death might have been avoided.

1(b): Consultants' influence in prescription of high dose inhaled corticosteroids over a prolonged period

Submissions

The procurator fiscal submitted that Dr Cochran should have adopted a much more positive role in Emma's case, which was one that was difficult to manage. He referred to the evidence of the two respiratory specialists, Dr Todd and Professor Helms, who said that they would not have prescribed the initial dose of 1,500 micrograms daily, would not have continued to prescribe such doses for almost four years and would have regularly reviewed Emma every two to three weeks and issued guidelines and advice to the general practitioner on the prescribed drugs and dosages.

Mrs Dougall for the family submitted that Dr Cochran failed to institute active management of Emma's case by regular review. She also said that Dr Cochran failed to properly acknowledge the potential risks of prolonged high dose inhaled cortisosteroid therapy when concerns were raised in 1996, and again by the MCA in 1998, and that he failed to adequately warn Dr Shapiro of these risks. She said that Dr Cochran failed to advise Dr Shapiro that the level of dose being prescribed for Emma was not a dose he would ever use. She also said that he failed to carry adrenal function testing on Emma. Mrs Dougall said that these failures on Dr Cochran's part led to the prolonged course of treatment of Emma with high dose inhaled cortisosteroid therapy, one of the factors which, if avoided, could have resulted in the avoidance of Emma's death.

Mr Holmes for Dr Shapiro referred to the influence upon Dr Shapiro of the recommendations made by Yorkhill Hospital, and Dr Paton in particular, in relation to prescribing high dose Flixotide for his patient group. He also said that from Dr Shapiro's first referral of Emma to Yorkhill he was concerned to draw attention to the high level of therapy prescribed for Emma and that the correspondence from Dr

Cochran to Dr Shapiro did not direct Dr Shapiro to reduce the dosages and could understandably be said to have reassured him.

Mr Lindsay for MHRA said that there was no merit in Dr Cochran's criticisms regarding the absence of footnotes in the May 1998 article in Current Problems in Pharmaco Vigilance, given that it is common for requests to be made by medical practitioners to the Post Licensing Division of MHRA for further information. He said that Dr Cochran could have done likewise.

Mrs Abernethy for Glaxo said that doctors were justifiably complacent about the biochemical evidence of adrenal suppression in the use of inhaled corticosteroids in their 25-30 years of use. She said that Dr Cochran's prescribing of fluticasone was based on his own researches and that he did not tend to prescribe fluticasone outwith the licensed dose. She also said that Dr Todd's Lancet paper was known to both Dr Paton and Dr Cochran, who had formed their own views upon and had responded appropriately to it. She said that fluticasone is a sound and effective drug used within licensed dose and that used outwith licensed dose it should be combined with appropriate monitoring.

Mrs Robertson for the NHS consultants said that any findings which are considered appropriate in the determination should be made under section 6(1)(e) and not under section 6(1)(c). She said that when Emma was seen at Yorkhill by Dr Cochran between 25 February 1999 and 9 November 2000, the reasonable state of knowledge amongst those in the medical profession who were involved in the treatment of children with asthma did not include an understanding that actual adrenal insufficiency leading to potential adrenal crisis could follow as a side effect from inhaled corticosteroids.

Mrs Robertson said that this was demonstrated by examination of the articles, guidelines, publications etc to which the inquiry had been referred, by the understanding of the medical witnesses that the possible side effect of adrenal suppression did not go beyond a benign biochemical manifestation and by the fact that none of the clinicians apart from Dr Todd had direct experience or knowledge of patients presenting in acute adrenal crisis.

Mrs Roberson pointed out that there are still no concrete data as to what level of inhaled corticosteroids will cause an adverse effect on the adrenal function of a patient and what level of impairment will actually result in clinically significant adrenal crisis causing potential harm. She said that clinicians today still have to deal with the issue of how to use inhaled corticosteroids, potentially still at high doses, safely.

Determination

Introduction

Dr Cochran gave evidence at the inquiry and was questioned in depth about the decisions which he took in respect of the management of Emma's care and treatment, the reasons for these decisions and about asthma management generally.

Dr Paton also gave evidence about aspects of his own practice as a consultant respiratory specialist at Yorkhill and about the treatment of asthma, including the use of inhaled corticosteroids.

Dr Todd gave his views on the prescribing of high dose inhaled corticosteroids and the use and marketing of fluticasone in particular and he also commented upon the decisions taken by Dr Cochran in Emma's case.

Professor Helms gave evidence about his own practice as a consultant respiratory specialist in Aberdeen and his opinion on the care given to Emma by Dr Cochran.

Dr Paton's influence upon Dr Shapiro's prescription of high dose inhaled corticosteroids for Emma

I have expressed my view that the key factor in Dr Shapiro's decision to prescribe such high doses of inhaled corticosteroids for Emma from the outset of her treatment was the advice and recommendations he had previously received in this respect from Yorkhill, mainly from Dr Paton. However, Dr Paton had no input into the management of Emma and had no direct influence upon her care and consequently was not in a position to take any precautions in relation to her.

Action taken by consultant and reassurance to GP after referral of Emma to Yorkhill

In contrast, from February 1999, when he first saw Emma, Dr Cochran was in a position to take whatever precautions he thought necessary in respect of Emma's treatment. When Dr Cochran first saw Emma her prescription of fluticasone was 1,500 micrograms daily and that had only recently been reduced from a dosage of 2,000 micrograms.

Dr Cochran said that the 1,500 micrograms per day which Emma was on was as high a dose as he had seen on a first referral from a general practitioner. He said that he considered that 500 micrograms daily of fluticasone was a high dose, that he had been prescribing fluticasone therapeutically from around 1995, usually in doses of 400-500 micrograms per day and he estimated that, over the course of around ten years, the number of children for whom he had prescribed 1,000 micrograms per day was in single figures. Moreover, Dr Cochran said that he was not aware of any research which showed that there was more benefit to be gained from doses of over 500 micrograms daily. Further, he considered that, as a general principle, one should always reduce the dose to the least possible amount.

Nevertheless, while at his first consultation with Emma in February 1999 Dr Cochran arranged for tests to be carried out to exclude diagnoses other than asthma and recommended a change in the delivery system for the drug, Dr Cochran did not give strong advice to Dr Shapiro to make changes to Emma's treatment with long term high dose corticosteroids.

Dr Cochran stated in his letter to Dr Shapiro that the dosage was high, which 'would be worthwhile if it was producing improved control but this does not seem to be the case' and that "at this dose there is the potential for significant systemic

absorptions". Dr Thornton commented on Dr Cochran's response to Dr Shapiro that 'sometimes the advice is much more specific than we find it here.' He said that he thought that if Dr Cochran had had well formulated views in his mind about Emma's future treatment, it would have been helpful to Dr Shapiro for Dr Cochran to have spelled them out more specifically than simply to say'consider reduction'.

When Dr Cochran was asked at the inquiry why he would be concerned about systemic absorption if he felt that the research papers were not raising any real concerns about actual problems arising from systemic absorption, he said that it was because of the broad principle that one would rather use doses at which there is little or no evidence of the drug in the rest of the body than use doses which were higher. He said that if one could choose one would choose to use lower doses and that what he was doing was giving encouragement to Dr Shapiro to try to move in that direction. He said that he wanted to highlight to the GP that 'we were in doses where the drug was absorbed and therefore it would be preferable if we could avoid those doses if possible'.

Dr Cochran said that, while he did highlight to Dr Shapiro that it would be preferable to reduce the dosage, he considered that he was not in a position to say that it was definitely possible to avoid these doses because like most hospital specialists he was not dealing with Emma's bad periods on a week to week basis the way the general practitioner is.

However, it was clear from his evidence and, indeed from both his first and his last letters to Dr Shapiro, some 20 months apart, that Dr Cochran was concerned by the fact that, despite such intensive treatment, there had been a poor response by Emma and that while a high dose would be worthwhile if it produced improved control, this did not seem to be the case as even these high doses were not controlling Emma's symptoms.

Moreover, even at the time of Dr Cochran's first consultation with Emma, she had already been on high doses of inhaled corticosteroids for a prolonged period of time. Therefore there were considerations in this case which went beyond leaving relatively straightforward day to day judgements, about varying dosage according to symptoms, in the hands of the general practitioner.

Dr Cochran said that he did make at least two comments, if not more, about the preferable course being to bring the dose down if at all possible and so it could not be said that he had made unreserved comment that the treatment was entirely satisfactory and that there were no issues to be dealt with. However, he agreed that he did not say anything that would lead Dr Shapiro to think that there was something fundamentally wrong with the treatment being given.

Misunderstanding by Dr Cochran of basis of GP's use of high dose inhaled corticosteroids

There also seemed to be some misunderstanding by Dr Cochran of the reasoning behind Dr Shapiro's use of very high doses of inhaled corticosteroids. Dr Cochran said that some doctors used a higher dose of inhaled steroids for a short time

instead of using oral steroids which were known to cause adrenal suppression. He said that

the BTS guidelines did not provide for this practice but simply dealt with the prescription of inhaled corticosteroids for continuous use over a long period of time. Looking at the way Dr Shapiro adjusted dosage up and down over short periods, Dr Cochran had assumed that Dr Shapiro was using short-term very high dose inhaled steroids to bring a difficult situation under control before reducing the dose. He did not think that Dr Shapiro's decision to use a dose of up to 2,000 micrograms was a misinterpretation by him of the guidelines although he subsequently ascertained that Dr Shapiro had indeed interpreted the dose of 2,000 micrograms on the chart as guidance.

It is not clear why Dr Cochran made this assumption about Dr Shapiro's use of high dose inhaled corticosteroids. Dr Shapiro himself had referred in his letter to his concern that Emma had been on "inordinate quantities" of therapy. Moreover, it appears to be the case from Emma's medical notes that when Dr Shapiro had been attempting to reduce the dosage, he had been doing so in a staged progression, 'stepping down' to the lowest level at which symptoms were controlled, as advised in the guidelines, and that his use of very high dosage did not appear to be simply a short-term "rescue" strategy.

Precautions which might have been taken by Dr Cochran

Professor Helms said in relation to Dr Cochran's first response to Dr Shapiro's referral of Emma, "... I would have expected something a little bit stronger than leaving it to Dr Shapiro and giving some warning about the systemic effects. I would be a bit more concerned."

Dr Todd said that the leading role in trying to solve the problem of severe asthma should be taken by the hospital specialist who should be the linchpin in the management. He was of the opinion that Dr Cochran's discharge of Emma to Dr Shapiro's care when she was on a 1,000 micrograms daily dose of inhaled corticosteroids could be criticised. He said that he believed that Dr Shapiro was concerned about Emma and he believed that most specialists would have taken a more active role in supervising the decrease in inhaled steroids which, he said, Dr Cochran had correctly identified as a problem. Dr Todd said that reducing high doses of inhaled or oral steroid was problematic for both the specialist and the GP and that it required a lot of specialist support. He said that when he has patients referred on high dose oral steroids, he reduces the dosage himself, reviewing the patient at 2 to 3 week intervals. His view was that Dr Cochran recognised that the dosage was too high and that he should have taken control of the situation.

Dr Cochran himself said that if he had known at the time what became known around the time of Emma's death relating to adrenal suppression, his advice to Dr Shapiro would have been completely different. He said that at the first sight of the dose Emma was receiving he would have provided strong advice that it should be reduced and that they should test for evidence of adrenal suppression and provide appropriate treatment for that if it was detected.

Dr Cochran said that there were three elements which changed his position regarding there being a link between high doses of inhaled corticosteroids and adrenal suppression, all of them occurring within the period of about six months around Emma's death.

The first was Calum's illness and its link with Emma's death. The second was the Patel report in 2001. The third was when cases of adrenal suppression were presented at a national meeting of the Royal College of Paediatrics and Child Health.

However, that was not his position at the time when he was treating Emma and Dr Cochran did not take a proactive role in reducing the amount of inhaled corticosteroids being prescribed for her. He was asked why he did not do so. As I understood his evidence, he had several explanations for this:

No evidence that a high dose would or could produce definite side effects as explanation for consultant not taking a pro-active role in Emma's care

As I understood his evidence, at the time when Emma was under his consultant care, Dr Cochran did not consider that there was clear evidence that a dose such as she was being prescribed would or could produce definite side effects. He said that, in 1999 when he first saw Emma, he was not aware of any link between high doses of inhaled corticosteroids and adrenal suppression. He said that this had been a subject of great importance since treatment with inhaled corticosteroids was introduced over 25 years previously. All doctors knew that steroids taken by mouth rather than inhaler could produce adrenal suppression. There had always been concern that the same side effect might result from a similar drug even though it was being given by different routes. He said that doctors had been looking for this side effect for more than 25 years.

Dr Cochran said that in the 1970s and 1980s, after the introduction of inhaled corticosteroids, the way to get children off oral steroids was to give high doses of inhaled steroids. As a result, adrenal suppression caused by inhaled steroids was being looked for and there were numerous research papers over 20 years or more measuring adrenal hormones in children taking inhaled steroids and showing reduced adrenal function. However, the adrenal suppression detected in these laboratory tests did not equate with illness from adrenal suppression. Accordingly, these results were not regarded as 'clinically significant'. They were regarded as 'a benign physiological response to treatment'. Dr Cochran said that the difficulty with all laboratory tests in medicine is that a measurement in the laboratory does not always equal a problem for the patient.

A definition given by Dr Cochran of clinically significant adrenal suppression was 'adrenal suppression that produced symptoms in the person affected'. He said that there were a number of different symptoms that could be very severe such as low blood pressure, loss of circulation, loss of consciousness through low blood sugar to more subtle symptoms such as reduced growth, lethargy and lack of energy.

Dr Cochran said that, as he worked with patients who tended to have more severe asthma and high levels of treatment, he regularly performed computer searches of research looking at this particular topic and, during the relevant period, he had never

been able to find a report of a single case of clinically significant adrenal suppression.

Dr Cochran was examined in detail regarding his response to various research papers, articles and MCA warnings on the subject of adrenal suppression. A summary of his position in relation to the principle publications referred to is as follows:

Professor George Russell's 1994 Editorial in Thorax- Inhaled corticosteroid therapy in children: an assessment of the potential for side effects (2)

Dr Cochran said that this editorial illustrated the need for some doctors in certain cases to move beyond what would have been considered conventional doses, that even at normally recommended doses there was some evidence that the effect of the inhaled steroid was detectable in the body and that the stimulation tests are probably a poor way of assessing the adrenal gland function. He also emphasised that Professor Russell was referring to laboratory tests for adrenal suppression when he referred to reports of 'adrenal suppression only on high doses'.

Dr Todd et al's 1996 Article in Lancet - Growth and adrenal suppression in asthmatic children treated with high-dose fluticasone propionate (3)

Dr Cochran was aware of this article when it was published. He considered that the data on growth suppression was unsatisfactory and did not meet basic standards of growth research and that the adrenal suppression results were in the same category as previous studies and did not correlate with adrenal suppression that might make you ill. Dr Cochran said that this article led to considerable discussion and correspondence, some of which he was referred to in evidence, within the medical profession. He said that there was nothing in Dr Todd's 1996 article that he, or the doctors who wrote to the Lancet in response, or other clinicians he spoke to, felt had changed practice.

Dr Todd was a witness at the inquiry which therefore had the benefit of seeking his response to the points made about his paper by Dr Cochran.

Dr Todd agreed that the patients in his study did not have clear cut symptoms of adrenal suppression but said that 'the degree of adrenal suppression described could not be described as anything other than clinically significant'. He said that the fact that the children were not showing symptoms did not mean that the adrenal suppression detected was not clinically significant. He also said that, in certain of the cases, an extremely poor adrenal response to stimulation tests was noted, which was not simply the adrenal suppression that had long been recognised with inhaled corticosteroids.

Dr Todd agreed that a series of 6 case studies does have limited application and obviously does not give a complete story but he also said that he understood that the most frequent reason for a drug being withdrawn is case reporting and that it rarely results from formalised studies. He said that a large number of second opinions were sought and his paper was well scrutinised before it was accepted for publication in the Lancet.

Clark, Clark and Lipworth's 1996 Paper in Thorax - Adrenal suppression with inhaled budesonide and fluticasone propionate given by large volume spacer to asthmatic children (6)

Dr Cochran said that this was one of a whole series of papers trying to evaluate the relative likelihood of one inhaled steroid to cause adrenal suppression over another. He said that for each piece of research which indicated that fluticasone had a more significant effect on adrenal suppression one could read later that year another study apparently showing the opposite. In addition, he said that, again, these tests were not physiological, they did not appear to relate to true adrenal function in real life and there was no evidence of any child or adult coming to harm as a result of adrenal suppression from this treatment. On the contrary, Dr Cochran said that it was commented on whether this type of research was necessarily helpful as if, after 25 years adrenal suppression was not being seen to be affecting children, despite many having been on very high doses, then it seemed a reasonable conclusion that these measurements did not have any relationship with real side-effects that would make a child ill. He said that there was constant examination of this question and that it was very hard to see how research like this would lead anyone to think that after that length of time anybody was going to become ill as a result of this treatment.

Section entitled "Safety of Inhaled and Nasal Corticosteroids" published in the May 1998 issue of the bulletin, Current Problems in Pharmacovigilance

Dr Cochran said that he discussed this article with colleagues because 'obviously one it concerned when advice from a national body seems to be contrary to one's own understanding of the evidence at the time'. He said that everyone he spoke to in the field agreed that there was no evidence to justify the statement relating to clinically important systemic effects occurring at licensed doses of inhaled corticosteroids, again due to there being no evidence of this occurring at the time that the bulletin was published. Accordingly, he considered that there was no reason for him to change his prescribing policy.

Holt et al's Paper in 2001 in the British Medical Journal - Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis (9)

Dr Cochran agreed with the writer of the commentary annexed to this article that if patients are taking doses that are too high for many years with unnecessary toxicity that is unacceptable and that there is a requirement to review doses and their efficacy.

Publications referenced as footnotes numbers 9-13 *in commentary by Professor George Russell to the 2001 Article by Patel et a l(10)*, *namely:*

9. Brown HM. Nocturnal adrenal suppression in children inhaling beclomethasone dipropionate. Lancet 1986;1:1269

10. Law et al. Nocturnal adrenal suppression in asthmatic children taking inhaled beclomethasone dipropionate. Lancet 1986;I:942-4

11. Bisgaard H et al. Adrenal function in children with bronchial asthma treated with beclamethasone dipropionate or budesonide. J Allergy Clin Immuninol 1988;81:1088-95

12. Pederson et al. Urine cortisol excretion in children with high doses of inhaled corticosteroids. Eur Respir J 1988;1:433-5

13. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy. Arch Intern Med 1999;159:941-55

Dr Cochran was aware of all these articles. Dr Cochran said that they did not present the whole picture given the distinction between adrenal suppression and clinically significant adrenal suppression. He said that this is why Professor Russell's commentary refers to dose related adrenal suppression as "a side effect that has generally been regarded as benign, representing nothing more than a physiological response to exogenous corticosteroid."

I have no hesitation in accepting Dr Cochran's evidence to the effect that he was satisfied that the research, reports and articles which had been published on the subject and which he had accessed at the time when Emma was under his specialist care, produced no evidence that patients taking inhaled corticosteroids showed symptoms of what he defined as clinically significant adrenal suppression. I am also satisfied that he came to this conclusion as a result of vigorous academic reasoning, based upon these publications and upon his own professional experience and understanding. I am also quite satisfied that, as would appear from the terms of Professor Russell's commentaries and other sources produced to the inquiry, he held this view in common with many in the medical profession.

I am quite satisfied from the evidence before me that the thinking within a significant section of the medical profession at the relevant time was that inhaled corticosteroids were not likely to produce the side effect of 'clinically significant' adrenal suppression, given the long history of apparently safe use and the interpretation of case reports and more formal studies in the light of the classification of suppressed adrenal function as not being *per se* clinically significant. However, it seems to me that it is going one step further to adopt Dr Cochran's position that he did not have the faintest idea that that this might be a side effect, which is my understanding of his evidence when he said that if he had 'had any faintest idea that this was a side effect that we might see then it is inconceivable that one would not have acted on it'**.**

While not producing external symptoms and thereby being classified as 'clinically significant', adrenal suppression had, in fact, been shown to occur to the extent that research had established that adrenal function might be impaired as a result of the use of inhaled corticosteroids, this being described by some commentators as a 'benign' effect.

As Dr Cochran said, when he was seeing Emma this was still an era of what appeared to be trouble-free use. However, the potential for adverse side-effects was not, so far as I was able to assess on the basis of the evidence before the inquiry, totally discounted.

I noted that the papers which were produced to the inquiry, and which referred to the fact that 'clinically significant' adrenal suppression had not been seen did not dismiss this as at least a potential side effect. For example, in his 1994 editorial in Thorax, when Professor Russell said that 'most recent studies have continued to offer reassurance' he went on to state 'although caution has been advised in the use of higher doses.' Further, when he stated in his conclusion that 'we must not allow this to lead to the undertreatment of a common, sometimes disabling and occasionally fatal disease' this was prefaced by the words 'although we cannot ignore the potential of this form of treatment to produce side-effects'. Further examples appeared in the responses, published in the September 1996 Lancet, to Dr Todd's article, such as a letter from Cade et al (4) which was largely critical of Dr Todd's study but which nevertheless began by stating that the work highlighted that 'inhaled steroids are not without side-effects' and served as a reminder that children should always be managed 'with the lowest possible efficacious dosage', and the letter submitted by Warren Lenney of City General Hospital, Stoke-on-Trent (5) which questioned the Todd study's methodology and analyses but began by agreeing with Dr Todd and his colleagues that it is important to monitor the safety aspects of inhaled corticosteroids as well as their efficacy.

It seems to me that Dr Cochran did not, in his management of Emma, exercise appropriately the caution advocated in these and other papers when he simply reminded Dr Shapiro that he should try to reduce dosage when possible, given that at a very young age, Emma was receiving particularly high doses of this treatment which were continuing over a very lengthy period of time. It also appears that he did to a certain extent, as expressed in Professor Russell's 1994 editorial, 'ignore the potential of this form of treatment to produce side effects', as he did not satisfy himself that Emma was indeed on the lowest possible efficacious dosage by personally overseeing a treatment plan to attempt to reduce the dosage and thereby decrease the possibility of such side-effects. Indeed he emphasised throughout his evidence his understanding of such side effects as being of a theoretical nature.

In this connection, I also noted Dr Cochran's response to Mrs Dougall's questions to him about the possibility that physical stress made adrenal suppression manifest, when he said that "it exposes it". Mrs Dougal then asked whether, if one had a low level of adrenal function but no symptoms, does one not have the potential for then having a clinically significant adrenal crisis, if one is subjected to stress. Dr Cochran's response was that that would certainly be true in certain cases but he did not think you could generalise.

Use of high doses by other clinicians as explanation for consultant not taking a pro-active role in Emma's care

Dr Cochran also gave as an explanation for not pro-actively seeking to reduce the dose prescribed to Emma the fact that he was aware that the use of higher doses of inhaled steroid was a practice that some clinicians used. However, as previously stated, this was not his own practice, he considered as a general principle that one should always reduce the dose to the least possible amount and he was not aware of any research which showed that there was more benefit to be gained from doses of over 500 micrograms daily. Given these views, it does not seem to me to be

consistent that Dr Cochran, whose specialist advice had been sought, should accept the use of long term, high dose inhaled corticosteroid treatment on this basis.

Avoidance of contradictory advice from GP and specialist as explanation for consultant not taking a pro-active role in Emma's care

A further explanation given by Dr Cochran was that he avoided changing prescriptions from those being prescribed by the general practitioner so that patients did not receive contradictory advice from the hospital doctor and the general practitioner. While it is understandable that a specialist would not wish to give advice which conflicted with that given by the general practitioner when it was felt that there was no particular reason for following one course rather the other, this was not the situation here, for the reasons set out in the previous paragraph. Moreover, Dr Shapiro was, quite clearly, as appears from his evidence and from his letters to Yorkhill, seeking advice and, indeed, did immediately follow all the advice which he was given in relation to other issues such as changing the device for the administration of therapy and adding a prescription for montelukast.

Consultant's confidence in GP's treatment of Emma as explanation for his not taking a pro-active role in her care

Dr Cochran said that he did not consider that Dr Shapiro's treatment of Emma was clearly dangerous or clearly unsatisfactory. He said that, if he had done so, he would have changed Emma's treatment. Dr Cochran was familiar with a number of patients referred by Dr Shapiro to the respiratory service at Yorkhill. He had formed the view that Dr Shapiro was very involved in asthma management and comfortable to take asthma treatment to a fairly advanced level compared with many other general practitioners.

Nevertheless, while it is understandable that, given the state of medical knowledge at the time, Dr Cochran should take the view that Dr Shapiro's treatment of Emma was not clearly dangerous, it is not clear to me why Dr Cochran should not have considered Dr Shapiro's treatment to be at least clearly unsatisfactory, given Dr Cochran's own views and stated practice in relation to the prescription of very high dose inhaled corticosteroids.

1(c): Summary of determination in relation to the prescribing of high dose fluticasone for Emma over a prolonged period

I accepted from the evidence before the inquiry that Dr Shapiro had a particular interest in the management and care of asthma patients and I am of the view that he was very proactive in the management of Emma's asthma. He tried other forms of treatment before resorting to inhaled corticosteroids. He used different kinds and combinations of medications and devices for administering these medications. He referred Emma to a specialist very soon after he first prescribed inhaled corticosteroids and as soon as he realised that the very high dose of inhaled corticosteroids which he had prescribed was not keeping her symptom-free. He reduced the dosage of inhaled corticosteroids prescribed whenever Emma became less symptomatic. He formulated management plans and discussed these with Emma's parents and he requested regular reviews of Emma. In all of these

circumstances and, particularly given the fact that, firstly, Dr Shapiro used high dose inhaled corticosteroids after specialist recommendation in other cases and, secondly, he sought specialist review of Emma's case, followed recommendations made and received 'tacit approval' for his care and treatment of Emma, I do not consider that there were further precautions which could reasonably have been expected of Dr Shapiro in respect of his prescription of the high doses of fluticasone for Emma.

Dr Shapiro did not take issue with the proposition put to him by Mr Lindsay that a doctor has to accept professional responsibility and accountability to his professional bodies when he prescribes outwith licence and I have given particular consideration to Dr Thornton's evidence that he would expect that a general practitioner who referred a patient to hospital for advice would follow that advice but not blindly, because the person who signs the prescription is the person who takes responsibility for that treatment.

Dr Thornton said that Dr Shapiro would have to have been satisfied that he was sufficiently confident that what he was doing was correct and appropriate.

In all of the circumstances of this case, I am of the view that Dr Shapiro did not follow the advice from Yorkhill blindly but had appropriate further reassurance from the terms of the BTS guidelines and, like Dr Paton and Dr Cochran and, as would appear from, for example, Professor Russell's 1994 commentary, like other respected members of the medical profession, his understanding was that adrenal suppression was a theoretical side effect that was not regarded as a real problem.

Dr Shapiro said that he thought that there were patients who had a level of problem where they really should be overseen by a consultant, no matter how good the GP is. He said that when he referred a patient to Yorkhill it was not a thing which he did lightly. He did it because he was really looking for some help, reassurance and advice.

Dr Cochran himself said that the role of the consultant respiratory paediatrician in relation to the management of patients referred to outpatient clinics by GPs is to establish that the diagnosis is correct, review the treatment that is already in progress, optimise that treatment, provide additional treatment and advice, provide information to families and answer queries raised by and provide information to the general practitioner.

Given the consensus in these two statements it seems to be a logical conclusion that the knowledge and expertise of and consequently the precautions which might reasonably be expected to be taken by a general practitioner do not necessarily equate in all respects with those of the paediatric respiratory specialist to whom a child is referred by the general practitioner.

I have come to the view from all the information which was before me, that it would have been a reasonable precaution for the consultant involved in Emma's care to have taken a more proactive role in reducing the dosage of fluticasone prescribed for her and that if such a precaution had been taken, Emma's death might have been avoided.

I must make it very clear that I was impressed by the calibre of Dr Cochran who struck me as a very knowledgeable and a dedicated physician. No doubt some specialists may have proceeded as Dr Cochran did. However, it was clear from the evidence of Professor Helms and Dr Todd that other specialists would have taken the necessary steps to ensure that every possible attempt was made to reduce Emma's dosage. It seems to me from all of the evidence which I heard that not only were there precautions which could have been taken by Dr Cochran in his consultant role but that it would have been reasonable to take such precautions in all of the circumstances of this particular case, with particular reference to Emma's age, the particularly high dosage prescribed and its very prolonged use.

Dr Donaldson said that Emma's death could and should have been prevented and that this was more of a reflection on the medical profession than on any individual practitioner.

Dr Donaldson said that he thought that the medical profession had been lulled into a false sense of security about inhaled steroids because they gave a much smaller dose of steroid than would be given orally. He said that despite reports dating from the 1980s that you could get side-effects from inhaled steroids, the medical profession considered that, while this may be reported, in real life it did not actually happen. He said that the medical profession had become complacent. He also said that he thought it was probably because fluticasone was very potent that the side-effects had become recognised. Dr Donaldson pointed out the fact that Yorkhill examined the cases of in excess of 400 children and actually tested 214 children because they were on off-licence levels of fluticasone, showing how prevalent that sort of prescribing was.

Having heard all of the evidence in this case, I agree with Dr Donaldson's assessment of the situation. Dr Cochran's care of Emma has to be viewed within this context. The complacency within the medical profession was based on what was described to the inquiry as 25 years of trouble-free use of inhaled corticosteroids. This resulted in higher doses of inhaled corticosteroids being used. In the case of prescriptions of fluticasone, for various possible reasons, some of which will be considered later in this determination, the dosages were higher still and high dosage use became more widespread.

I do not consider that such complacency within the medical profession was in itself entirely unreasonable, again for reasons which will be considered at a later stage in the determination. However, I do consider that, in this particular case, there were reasonable precautions which might have been taken to reduce the dosage prescribed for Emma.

No doubt Dr Cochran felt confident that Dr Shapiro was an experienced practitioner with the ability to give an advanced level of asthma care to Emma. However, Dr Cochran was a specialist and, as such, when he saw Emma he was fully up-to-date with the concerns being expressed about the potential side-effects from the use of high dose of inhaled corticosteroids. When he first saw Emma she was only two years and ten months old. She had already been taking inhaled corticosteroids for sixteen months, for the most part at a dosage which was regularly three and at one point four times greater than the maximum amount which he himself would

prescribe, despite the fact that he was involved in the treatment of asthma patients who were difficult to manage. He noted that this high dosage was not keeping Emma symptom free. He was aware of Dr Shapiro's own concerns about the "inordinate quantities" of therapy Emma was receiving and had himself never seen such a high dose on an initial referral. It therefore seems to me that it would have been reasonable for him in his consultant role to have given strong advice to reduce dosage significantly and to have involved himself, at least initially, in ensuring that a substantial reduction in dosage was effected so far as possible.

2. The issuing of a steroid card

Submissions

Mrs Dougall submitted that, in terms of sections 6(1)(c), one of the reasonable precautions whereby Emma's death might have been avoided was the issuing of a steroid card to Emma at the time of commencement of high dose inhaled steroid therapy.

Mrs Abernethy submitted that there should be a recommendation in terms of subsection 6(1)(e) for the use of steroid cards where any inhaled corticosteroid is used outwith licensed dose.

Mr Lindsay said that the advice contained with the British National Formulary is that patients receiving chronic oral steroids and high dose inhaled corticosteroids should be given a steroid card.

Determination

What is a steroid card?

Mr John Milne, who is a lead pharmacist employed by Lanarkshire Acute Hospitals NH Trust said that steroid cards are pro forma cards to which is added information specific to the patient regarding what steroid drug is being prescribed and which contains some do's and don'ts for the patient to follow. It is expected that the card will be shown to any health care professional whom the patient has to see so that appropriate action can be taken in relation to the treatment of the patient. The cards are obtained from an NHS central supplier. Mr Milne said that he had had problems in obtaining these cards from the central supplier as quite often they run out.

What guidelines exist in relation to the issuing of a steroid card?

Dr Suvarna, who gave evidence on behalf of the MHRA, said that the issue of steroid cards is the responsibility of the Department of Health but that the advice on issuing steroid cards is contained within the British National Formulary . He said that the advice there is that patients receiving chronic systemic corticosteroids and high dose inhaled corticosteroids should be given a steroid card. He read from the May 1998 bulletin of Current Problems in Pharmacovigilance, which was sent to all doctors and pharmacists, a section entitled 'Revised Steroid Treatment Card now available' in which it is stated that the Steroid Treatment Card has been revised by the Department of Health and that 'all patients prescribed systemic corticosteroids for

periods of more than three weeks should receive a Steroid Treatment Card at the outset of treatment' and that 'for patients on systemic corticosteroids for three weeks or less and patients prescibed topical, inhaled or nasal corticosteroids, a card may be issued at the discretion of the doctor or pharmacist'. It goes on to say that 'Pharmacists dispensing systemic corticosteroids should check that the patient has been given a Steroid Treatment Card and, if not, issue one if they consider it appropriate. They should inform the prescribing doctor that they have done so.'

It is important to note, as Dr Suvarna confirmed, that in connection with this matter, the word 'systemic' refers to oral steroids.

Practice in relation to the issue of a steroid card

Dr Shapiro was asked by Mrs Dougall if he had never considered that the Frame children should carry a warning with them about the fact that they were on high dose steroid inhalers. He said that around 1990 his practice had given consideration to the use of steroid cards for patients on high dose inhaled steroids as a precaution but that they were unable to obtain them from the chemist although they were freely given at one time. He said that it used to be the practice for patients on prolonged oral steroids to be given a steroid card, although he did not know whether it was automatic practice now.

Dr Thornton said that in the British National Formulary there is some reference to patients on long term steroid therapy being issued with a steroid card, but it was not made clear whose responsibility this was. He said that in relation to the issue of steroid cards to patients on inhaled steroids it was not made clear as to whether or not this was recommended. He thought that it was quite possible that doctors might issue steroid cards if prescribing high dose inhaled steroids, particularly now given all that has been heard about the systemic effects of inhaled steroids. Dr Thornton said that after listening to Dr Shapiro's evidence he spoke to his practice pharmacist to clarify her practice and ascertained that she issues a steroid card to any patient who is being dispensed oral steroids because she believes it is not very clear whose responsibility it is and it is better that two steroid cards be issued than none.

Dr Cochran said that there was no national regulation requiring the issue of a steroid card for patients who take either oral or inhaled corticosteroids. He said that the responsibility is to ensure that the family know about the risk and that should the patient become unexpectedly ill there would be some means of communicating to doctors the fact that they are having steroid treatment and a card is obviously one way of doing that but it is not the only way to do it.

When Dr Cochran was asked whether he was aware if steroid cards were issued in Yorkhill hospital when oral steroids are being prescribed long-term, he replied "They could be, yes.... Well to be honest, when I deal with that problem I usually provide patients with a letter that fulfils the function of the steroid card. I should also say that I have virtually no patients who are currently using long-term steroid treatment."

Dr Paton said that his understanding of the position was less good than it should be. He would expect that anyone on oral steroids should have a steroid card. He thought that in the past the respiratory service in Yorkhill had discussion with the pharmacist

about steroid cards but his recollection about this was hazy. He had not checked recently but had thought that 'if we prescribed high dose inhaled steroids you would get a card as well' but said that he had been speaking to some general practitioners recently and they said that that was not the case. He now understood that these cards were not routinely given out. He said that he was now not clear what the current situation is in hospital or in general practice.

Dr Todd said that in Antrim Hospital, patients on long term oral steroids should have a steroid card and that he did not prescribe high enough doses of inhaled steroids to justify a steroid card. He said that, in his opinion, even today the majority of asthmatics who are on higher doses of inhaled corticosteroids do not have a steroid card but he thought that this practice had been advocated by some people in the last 4 or 5 years.

Professor Helms said that individuals receiving inhaled steroids are not required or advised to carry steroid cards.

Dr Lees said that she understood that the steroid card was issued by the prescribing doctor. She said that she understood that a steroid card was issued to a person who was on oral steroid medication because oral steroids can make the body fail to respond to the added stress of infection or an episode of vomiting. When asked by Mr Lindsay why there was a difference in practice between oral and inhaled steroids in relation to the issuing of steroid cards, Dr Lees said that it had been thought that it was when steroids were given directly into the system that you would expect suppression effects to happen. She said that with the benefit of hindsight it was now known that this was not necessarily the case and that it was becoming evident that inhaled steroids can also have systemic effects and seemed to be able to cause suppression. She said that she had no experience of a child on inhaled steroids being expected to carry a steroid card. She was not aware whether there had now been any specific discussions about that matter.

Mr Milne said that a card should be issued to those taking high dose long term inhaled steroids and that that was the recommendation in the British National Formulary, both now and in the mid 1990s. He said that from 1997 when he started as dispensary manager at Hairmyers Hospital his dispensary staff were instructed to issue a steroid card, normally for doses of inhaled steroid over 800 micrograms. He said that this was a recommendation in the BNF, although he could not remember when the recommendation was made. He was not sure if pharmacists keep a record of issuing a steroid card. His view was that a steroid card should have been issued in Emma's case.

What steps might be taken if a patient in possession of a steroid card presents in an acute condition?

Dr Cochran said that you might get the correct diagnosis more quickly if you were dealing on an emergency basis with a patient who was in possession of a steroid card. He said that the symptoms of adrenal suppression can be rather vague and in many cases the doctor would not immediately recognise a case of adrenal suppression. When asked what action might be taken by a doctor, in these circumstances Dr Cochran said that you would give extra steroid by injection, give

fluids to support the circulation, measure the blood pressure, measure the blood sugar level and the blood salt level and if they are abnormal, take steps to correct them.

Dr Donaldson said that in the event of adrenal insufficiency, a high dosage of exogenous steroids may compensate for that but may be insufficient to provide the additional amount of steroid needed to cope with a stressful situation.

Dr Todd said that if Emma had had a steroid card the doctors treating her would have 'twigged on to what was going on earlier' and it is possible that they would have taken different action although he did not know if that would have resulted in a different outcome.

Professor Helms said that one of the first things a doctor would do when admitting for treatment a patient who, it was believed, may have adrenal suppression, would be to give a large dose of intravenous or intramuscular steroid to make sure there was a significant dose of steroid in the systemic circulation very rapidly.

What happened when Emma was admitted to Wishaw?

No steroid card to show that Emma was on prolonged and/or high dose inhaled corticosteroid therapy was produced to the medical staff at Wishaw General Hospital.

Emma showed none of the indications of a typical adrenal suppression presentation, namely hypoglycaemia, high potassium levels and low blood pressure.

While, around 12:40 am, quite a high dose of the steroid dexamethasone was administered to Emma, this was, as Dr Lees pointed out, administered quite late on, following upon discussion with the consultant at the paediatric intensive care unit at Edinburgh, as part of the standard treatment when brain swelling is suspected.

What additional steps might have been taken?

When Dr Cochran was asked if any of the steps, which he had described as likely to be taken in the case of a patient who presents in an acute condition and in possession of a steroid card, were not taken at Wishaw General Hospital when Emma was admitted, Dr Cochran said "I don't think she received any supplementary steroid treatment".

Dr Lees was asked whether, if Emma had been carrying a steroid card on admission to hospital, that would have affected her management of Emma in any way. Her response was: "I think it probably would. I think that would have made us conscious of the potential for the poor body response and we would have reacted to that by giving her steroids."

She said that if she had been shown a steroid card that would have affected her diagnosis in that she thought "it would have made us think is it possible that there was adrenal suppression" . When Dr Lees was asked whether she thought giving steroids may have made any difference in view of what she now knew about the

case and having discussed it with her colleagues her response was: "... I don't know. It may have done. I don't know enough about how advanced the cerebral oedema was to say whether that would have actually reversed the process."

Conclusion

All of the clinicians who gave evidence in relation to Emma's care at Wishaw General Hospital made it clear that everything possible was done for her, in the light of her presentation. I have no reason to doubt that this is indeed the case.

It is obviously not possible to say that Emma's death would have been avoided if she had been in possession of a steroid card and Dr Lees had administered exogenous steroids at an early stage as a precautionary measure.

However, Dr Lees' evidence was quite clear that, if Emma had been in possession of a steroid card, she would have been alerted to the possibility of adrenal suppression, despite the absence of other possible signs, and would have administered exogenous steroids at an early stage of her treatment at Wishaw General Hospital.

From the evidence before the inquiry it would appear that if Emma had been in possession of a steroid card when she was admitted to Wishaw General Hospital her death might have been avoided. There was no evidence before the inquiry of the precise terms of the BNF recommendation or of the precise date from which such a recommendation was made, but the inquiry had the evidence of Dr Suvarna that such a recommendation is set out there. Moreover, the May 1998 Current Problems in Pharmacovigilance bulletin was before the court and, while the advice contained there about the issuing of steroid cards in the case of inhaled steroids states simply that such a card may be issued at the discretion of the doctor or pharmacist, it seems to me that, given the dosage and period of time over which inhaled steroids were prescribed for Emma, it would have been a reasonable precaution to have issued such a card in this case.

Accordingly, I am satisfied that the issue of a steroid card was a reasonable precaution whereby Emma's death might have been avoided.

There seemed to be considerable uncertainty about and variation in the practice of issuing of steroid cards, certainly for patients prescribed high dose inhaled corticosteroids. It seems to me that this is too important an issue to be left to chance and the practice adopted by individual doctors and pharmacists. If practice varies, assumptions about patients will also vary. From the information before me at this inquiry, it would seem to me that it is quite reasonable to require that steroid cards be issued to all patients who receive high dose, long-term inhaled corticosteroids in addition to those who receive oral steroids. Several doctors spoke of the need to maintain patients' confidence in inhaled corticosteroids and of the suspicion patients have about these drugs. However, if the therapy is seen to be successful in treating asthma symptoms and if medical practitioners explain to their patients fully and appropriately the risk-benefit factors in relation to inhaled corticosteroids, it is difficult to see why the additional precautionary measure of issuing a steroid card, for presentation in the unlikely event of a medically stressful situation arising, will significantly increase the possibility of patients failing to comply with the treatment.

It does not seem to me that the appropriate forum for compiling detailed guidelines on the issue of steroid cards is a fatal accident inquiry. As Dr Cochran said, this is a matter for discussion and collaboration amongst medical personnel, with a view to deciding if there should be a baseline dose or timescale triggering the issue of a card and, if so, what these should be. Dr Cochran said that there have been a small number of cases of adrenal suppression occurring on more conventional doses which very many thousands of children receive and that, although the situation is perhaps a bit clearer regarding what to do about very high doses in terms of safety precautions, there is still considerable uncertainty about these occasional cases happening on lower doses. Difficult issues such as there will require to be addressed. However, what does appear to me to be clear is that such discussion and collaboration should now take place, at national level, to ensure that a practice is agreed, that information thereon is disseminated and that there is consistency in implementation.

3. Issues relevant to the background to the prescribing of inhaled corticosteroids, in particular fluticasone, at high doses

Introduction

During this inquiry, reference was made by medical witnesses to highly regarded articles, editorials or commentaries by Professor George Russell, formerly of Royal Aberdeen Children's Hospital, on the subject of inhaled corticosteroids and adrenal suppression.

One such commentary was appended to the 'Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom', published in 2002 in Archives of Diseases in Childhood (14). In his commentary, Professor Russell said *inter alia*:

'Clinically, ICT [inhaled corticosteroids] did not have an entirely clean bill of health. There was the occasional report of adverse systemic effects in patients on ICT ranging from oral candidiasis to overt cushingism and acute adrenal insufficiency both on and after discontinuing ICT. .....Despite these concerns and constant admonition to step the dose of ICT down as well as up to establish the minimum effective dose most clinicians have been complacent about the use of high dose ICT. This complacency was shattered with the publication of the three papers describing acute adrenal failure cited by Todd et al....who in addition to showing that this problem is alarmingly common have also implicated fluticasone propionate (FP), the least frequently prescribed form of ICT, in the great majority of their cases.....'

Dr Paton commented on Professor Russell's reference to complacency being shattered as follows:

'I think that is exactly right. You know we have become a little complacent and that had been underpinned in terms of ... I think not our carelessness but our failure to remember the evidence about the dose response relationship. Probably the evidence wasn't very well available for us and has become more available but in general I think we thought we were dealing with a safe drug and we had a long experience of using the drug so people were complacent, I think that is exactly right.'

It was apparent from the evidence at the inquiry that this complacency by the medical profession related to all the inhaled corticosteroids and not just to fluticasone. The question as to how this complacency came about arose at various points in the inquiry and it became apparent to me from the evidence that there were probably many contributory factors.

The factors which were raised at the inquiry in relation to complacency about prescribing high doses of fluticasone in particular were considered against a background of, firstly, a general acceptance that the class of drug known as inhaled corticosteroids was, as Dr Paton expressed it, 'a drug that has been used for a generation of asthma treatment' and which was being used, again in the words of Dr Paton, 'so commonly and which had, we thought, such a good safety record' and, secondly, an awareness in clinicians that inhaled corticosteroids did produce adrenal suppression to the extent that biochemical changes were noted in adrenal function but that this was a 'benign' effect which did not produce clinically significant sequelae.

Against that background, what seem to me to be certain key factors were examined at the inquiry in relation to the use of high doses of fluticasone, namely the claims made for and dissemination of information about fluticasone by the maunufacturer of the drug and the action taken by the regulatory agency in relation to sounding warnings about the use of high doses of inhaled corticosteroids. These issues will now be considered in terms of their potential relevance to section 6(1),(c), (d) and (e) of the Act.

3 (a) Claims made for and post-licensing dissemination of information about fluticasone by Glaxo

Submissions

Mr Houston submitted that claims by Glaxo, the manufacturers of Flixotide, as to the safety of the drug, were exaggerated and that Emma's death might have been avoided in terms of section 6(1)(c) had these claims not been made. He said that if it was not considered that a finding could be made in terms of section 6(1)(c), it should at least be made in terms of section 6(1)(e).

In support of his submission, Mr Houston referred to the product monograph for Flixotide in which there is only a brief reference to possible systemic effects and to several publications in which the drug manufacturers endeavoured to associate Flixotide with happiness and well-being. In particular, he referred to the following:

- a publication in which there are illustrations of teddy bears and a statement that the drug was "designed for control with safety in mind" and with the dosages disclosed in very small print;
- a publication with the face of a man smiling and under the heading "Flixotide", the words "putting a smile on the face of asthma" in bold print and with a reference to "minimal potential for steroid side-effects from the swallowed portion" in small print further below and again dosages in very small print;
- a publication showing a family of teddy bears with a measurement rule alongside, at the top of which in bold capitals there is the heading "an inhaled

steroid to grow up with" and at the bottom the statement "a good friend in childhood asthma".

Mr Houston said that these were produced in spite of the fact that it was recognised that there were possible risks of drug induced growth retardation.

Mrs Dougall submitted that a finding in this matter should be made in terms of section 6(1)(e) in relation to the marketing of fluticasone by Glaxo, which promoted its safety in children, and the methods of dissemination of information after licensing. She said that when Glaxo altered the data sheet for fluticasone in 1998 to highlight the potential for adrenal suppression they took no other steps to highlight this alteration such as by instructing drug representatives to point out such changes to prescribers. She said that the marketing of fluticasone promoted its safety in children, albeit in the age range 4-16, and that Glaxo were aware of the use of the drug in off-licence doses.

Mr Lindsay for MHRA said that there was no evidence that any of the doctors treating Emma or Calum Frame were influenced or misled by the advertising relating to fluticasone. He said that the advertisements accurately stated the licensed doses and age ranges. He also said that the advertisements were read in medical journals and publications by medical professionals and that while it might be considered that a lay person might be influenced by slogans and pictures of teddy bears, this would not influence medical practitioners.

Mrs Abernethy for Glaxo said that the drugs company did not promote the use of fluticasone outwith licensed doses. She said that the marketing strategy for Flixotide was to promote the use of the drug within licensed doses as a steroid that had been developed to have increased efficiency without risk of increased side effects and also to make clinicians aware that it had a licence for use in children as well as adults.

She said that Dr Shapiro said that he did not read adverts *per se* and that drugs companies were careful not to say things about using drugs outwith the data sheet recommendations. Mrs Abernethy said that Dr Shapiro had not been asked if papers and articles on fluticasone or small trials mentioned by drugs reps had influenced him in his prescribing. She said that, while Dr Shapiro had said that one of the big points being made about fluticasone in the first couple of years was that its risk of actually producing systemic side-effects would be less than previously existing steroids because its systemic absorption was less, there was no doubt that the reason he prescribed fluticasone for Emma was because he was a disciple of Dr Paton.

Mrs Abernethy said that Dr Cochran said that he would not rely on adverts, that the factors he took into account when considering the use of a new drug would be based upon research and knowledge about its mechanism of action and the doses others working in the same field were using.

She said that the data sheet played only a limited part in Dr Cochran's decision-making and that he was more influenced by papers not produced by the drugs company. She said that Dr Cochran had explained that drugs companies were not

interested in doing trials in the more difficult patients and that their goals were to get the drugs available for routine practice.

She said that Dr Cochran's prescribing of fluticasone was more based upon his own research, that he did not tend to prescribe fluticasone outwith licensed doses and that he was not influenced by the advertising and marketing of fluticasone by Glaxo.

Mrs Abernethy said that Glaxo did not mislead doctors at the launch of Flixotide. Its literature, advertising and meetings all reflected the state of knowledge at the time. She said that in 1993 a major concern in inhaled corticosteroids was their systemic bio-availability and that the distinguishing factor was the amount of drug absorbed from the gut, which in fluticasone is only 1 %.

Mrs Abernethy said that Glaxo monitor the safety of the drugs they promote, through periodic safety views and investigation of case reports, then report to the MHRA. She said that on the evidence before the inquiry, medical practice changed in the mid-1990s and inhaled corticosteroids were used in far higher doses than the doses at which they were designed to be used because fluticasone had a niche use in severe asthma and therefore the use of out of licence doses was disproportionately reported in Flixotide compared to other asthma therapies. She said that the 1995 SPC for fluticasone reflected the knowledge of Glaxo and the MCA at that time, that following a review by the MCA of nasal and inhaled corticosteroids, which had been triggered by a number of case reports of side-effects associated with high dose fluticasone and inhaled corticosteroid use, the SPC was revised in 1998 to include *inter alia* a warning that prolonged treatment with higher doses of inhaled corticosteroids may result in clinically significant adrenal suppression. She said that the patient information leaflet was also changed to include a warning about adhering to the doctor's instructions in relation to the use of the Flixotide Accuhaler and changes were made to the drug's data sheet for 1999/2000.

Mrs Abernethy submitted that Glaxo, as well as the MCA and doctors, responded appropriately to the Todd paper in the Lancet in 1996. She said that neither Dr Leather nor Dr Suvarna thought that a "Dear Healthcare Practitioner" letter was appropriate at that time, Dr Leather because he thought that it would have added nothing to the knowledge at the time and that it was probably felt that existing information and warnings were adequate and Dr Suvarna because the evidence was that this was a class effect, not restricted to one drug, and because it would have added nothing to the warning already published in Current Problems in Pharmacovigilance in 1998.

Determination

Introduction

Dr David Leather, Director of Primary Care Medical Affairs at Glaxo is a medical doctor and has a diploma in *inter alia* pharmaceutical medicine. He was formerly a GP and has worked for Glaxo since 1999. He gave evidence regarding the pharmacology and the marketing and promotion of fluticasone, and details of the way in which Glaxo monitors the safety in use of its drugs.

Dr Geoffrey Todd is a consultant chest physician at Antrim Area Hospital, Northern Ireland, with a particular interest in asthma. He told the inquiry that he had lectured for and received a research grant from Glaxo prior to 1996. Dr Todd was critical of the actings of Glaxo in its advertising and promotion of fluticasone.

Advertising literature

Dr Todd was referred to the advertising documents which Mr Houston referred to in his submissions. He confirmed that these were the kind of documents which he referred to when he spoke of Glaxo distributing reassuring advertising literature. He said that statements such as 'Designed for control with safety in mind', which appeared at the bottom of the page with teddy bears were aimed at being reassuring and were in fact misleading.

When Dr Shapiro was asked about the advertising literature for Flixotide, he said that he did not read adverts *per se* and thought that a lot of GPs would skip over the adverts which appear in publications such as the British Medical Journal. However, he also said that he thought that 'one of the big points that was being made about Flixotide in the first couple of years or so was that it was suggested that its risk of actually producing systemic side-effects would be less than previously existing steroids because its systemic absorption was less.' When he was asked by Mrs Dougall if it was promoted on the basis that you would have less chance of side-effects, Dr Shapiro replied, "absolutely".

Dr Cochran was also shown the advertising literature for Flixotide which Mr Houston referred to in submissions and he confirmed that it was the sort of literature he might have seen in relation to Flixotide.

Dr Thornton said that the first that general practitioners hear of new drugs is often through promotional material from the manufacturer. He said that the advertising material produced at the inquiry was very typical of the kind of material provided by the drugs company, both in terms of advertising in medical journals and in mail shots. He said that the manufacturer advertised Flixotide as particularly suitable for children using pictures of teddy bears although all the material made it clear that the drug was licensed only for children over the age of four years, detailed the recommended doses for children and stated that preparations of Flixotide in 125 micrograms and 250 micrograms doses were not suitable for use in children.

Dr Thornton said that when fluticasone came on the market, it was thought to have fewer systemic effects than the older drugs, beclomethasone and budesonide and that his knowledge of that came largely from the promotional material that was provided by the drugs company. Dr Thornton said that in the late 1990's it became known that inhaled steroids could carry a risk of systemic effects greater than had previously been thought. He said that 'the knowledge percolated gradually through to general practitioners via medical journals but advice remained conflicting. Whilst at times practitioners were advised to be aware of the risk of side effects of high dose prescribing, at others they were still encouraged to treat asthma effectively with initial high doses to gain adequate control of symptoms'.

Professor Helms said that he understood that fluticasone was engineered in many ways to be more active, more potent, and also to have less systemic effects when swallowed and he said that it was those aspects which were very heavily marketed. He said that he remembered very distinctly advertisements showing teddy bears and cuddly toys, with the recommended doses for children. He said that it was not recommended that anything other than the licensed dose be prescribed for children and it was made clear that the 50 microgram and 100 microgram inhalers were available for children but he said that 'it was very heavily marketed'.

Dr Leather said that the statement "with safety in mind" reflected the spirit in which fluticasone had been developed to be superior to beclomethasone. He said that he thought the marketing strategy was to promote Flixotide for adults and children and that the use of teddy bears was to draw doctors' attention to the fact that Flixotide is licensed for use with children. He confirmed that one of the adverts portrayed a measuring rule, explaining that at the time the adverts were prepared, the evidence suggested that there was minimal impact upon growth in children. He said that growth retardation was a particular challenge in relation to asthma in children and that poorly controlled asthma can itself cause growth retardation. However, he also confirmed that growth retardation in children is a potential side effect of Flixotide

Dr Leather agreed that slogans in the advertising literature such as "a good friend in childhood asthma" and "an inhaled steroid to grow up with" were reassuring statements. He also agreed that these statements were made against a background of the drugs company being aware of the risks attached to inhaled steroids.

He agreed that the prescribing information on the advertising leaflets was small but said that this was necessary as there is a requirement that such abbreviated prescribing information, which is quite a lengthy piece of text, should appear legibly on every piece of promotional material. He said that this type of print was standard in advertising throughout the industry and that a clinician would know that the licensed doses would be in small print but that the information is available in reference books such as the British National Formulary or Mims.

Product monograph

Dr Todd also referred to page 26 of the original product monograph for Flixotide where it was stated *inter alia* under the heading 'Systemic Side Effects' that 'In the substantial majority of patients, even at daily doses of fluticasone propionate of 2,000 micrograms, no adverse effect on adrenal function or reserve has been shown'. He said that this was the fundamental thrust of what doctors were being told by drug representatives and indeed by him when he was lecturing for Glaxo. He said that prior to 1996 doctors felt that they could prescribe high doses of this very potent new inhaled steroid with relative impunity and that fluticasone was marketed as the inhaled steroid of choice for severe asthmatics. Dr Todd agreed that this marketing occurred at the time of the launch of the drug and was based on studies available to the company at that time but he also said that, while changes were made to the Summary of Product Characteristics in 1998, there were 'no representatives knocking on doors telling doctors hang on a minute, things weren't just as rosy as we thought they would be at the beginning, you have to be careful here.'

Dr Todd was also critical about other aspects of the contents of the original product monograph for flixotide under the 'Systemic Side Effects' heading, namely the reference to 'mean plasma control concentrations' remaining 'within the normal range for adults and children demonstrating that even at high doses (2,000 micrograms), fluticasone propionate is well tolerated with regard to systemic effects'. He said that the least sensitive way to assess the effect of a drug on the adrenal gland is to measure the serum cortisol concentration and that 'mean' indicates an average and therefore reference to mean concentrations are not adequate as they do not give any information about the individual patient who may have developed significant adrenal suppression.

In relation to the product monograph for Flixotide, Dr Leather accepted that the wording of the section headed 'Systemic side effects' was a reason for criticism but he said that he did not think that this was misleading because the document was meant to be interpreted in its entirety and he referred to the first paragraph of the introduction where it is stated that: 'The currently available inhaled corticosteroids may cause systemic side effects such as adrenal suppression when used in high doses and so there is a need for potent inhaled steroids with a reduced potential for systemic activity'.

Dr Leather was asked about the information in the product monograph regarding pharmacokinetic analysis demonstrating a rapid plasma clearance of fluticasone propionate and the claim that no adverse effects on adrenal function or reserve was shown in the substantial majority of patients, even with daily doses of 2,000 micrograms of fluticasone. He said that the monograph is put together usually in conjunction with an expert panel who give indications of what data is of particular interest to clinicians and that these claims were referenced, so that the studies on which they were based would be available for scrutiny. He also said that the claims were made in respect of "the majority" and did not say "all".

He was also asked about Dr Todd's concern that the results referred to in the product monograph were mean and did not reflect individual responses. Dr Leather said that there were a number of reasons why the mean is used and that it is partly to help with statistical analysis and agreed that there was value in looking at individual responders and safety reporting was one of the good examples of that. However, he said that both mean results and individual reporting must be seen in context. He also said that a mean can have a wide range of results around it or a narrow range around it and that the mean is usually reflected in that way in studies.

Promotional meeting

Dr Todd said that claims about drugs generally are made not only in advertisements but at medical meetings and presentations, where doctors are 'exposed to promotion by all companies usually in very pleasant surroundings'. In relation to fluticasone in particular, he referred to a 2 day clinical update meeting in 1994, which was organised by the manufacturer and which he attended, to promote the drug.

Dr Leather was referred to the report of this meeting, entitled 'Issues in Chest Medicine'(1) and was asked for his observations on Dr Todd's comments that the drugs company failed to disclose at that meeting or in the report that the fraction of

the drug that went into the lung had 100% bioavailability. Dr Leather said that he thought that it was true to say that in 1993 it was a fact generally accepted by experts in pharmacology that 100% of the drug available at the lung was absorbed into the systemic circulation. He said that 'that was almost taken as a given at the time' and applied to all the inhaled corticosteroids. He said that, in fact, that had subsequently been shown to be inaccurate in that less inhaled corticosteroid is systemically available in asthma patients than in healthy study volunteers.

Claims regarding bio-availability of fluticasone

Dr Todd said that the claim made by the drugs manufacturer, that fluticasone had negligible oral bio-availability, was true but he said that this was misleading information as a doctor who does not have knowledge of pharmacology would have concluded that there was very little chance of side effects because of that. He said that, while most of the inhaled therapy goes down the gullet and into the stomach, and only a small portion goes into the lung, there is 100% bio-availability from the lung and that that is the most important part because it passes completely into the circulation. Dr Todd also claimed that these statements had not been retracted or corrected and that the claim for negligible oral bio-availability, which is only half the story, continues to feature prominently in advertising.

Dr Shapiro was asked by Mrs Dougall about his understanding of pharmacology, with particular reference to systemic absorption. He said he knew a bit more about this now. His understanding had been that 23% of beclametasone, 11% of budesonide and 3 or 4 % of fluticasone entered the systemic circulation, which is how you would expect that the side effects that you might get from steroids would be caused.

Dr Paton confirmed that one of the perceived benefits of fluticasone was that it had very limited oral bio-availability and that doctors thought that most of the toxicity was likely to arise from that fraction of the inhaled steroid which was swallowed and absorbed from the gastrointestinal tract. He said that it was understood that the fraction of the drug that was actually inhaled into the lungs was low, about 10% rising at best to perhaps 30%. It was not expected that lung absorption would result in significant systemic amounts of the drug getting into the body and being potentially available to casue side effects. It was expected that the amount of the drug that could ever be absorbed from the lungs would be tiny. Accordingly, the lack of oral bio-availability was thought to be a very important factor. Dr Paton said that he thought that at the time he would have seen that as an added safety feature of fluticasone. He said that what had become apparent to doctors was that this was quite wrong and that significant amounts of particularly potent inhaled steroids can be absorbed into the systemic circulation through absorption in the lung.

Professor Helms said that the claims for fluticasone were that it was virtually totally destroyed when swallowed so that there was no enteric uptake but that it was very potent biologically and that it 'built up in the tissues you were interested in....'

Dr Leather said that in 1993 the major concern of clinicians was the systemic bio-availability of inhaled corticosteroids, in other words the amount of drug that entered the circulation which had the potential to cause side-effects. In 1993 it was believed

that the distinguishing factor between the three inhaled corticosteroids was the amount of drug absorbed from the gut, through oral bio availability, being about 40% with beclomethasone, about 10% with budesonide and less than 1% with fluticasone. The fact that fluticasone had negligible oral bio-availability was the new factor. This this was seen to be the potential theoretical benefit of the medication and therefore the phrase "with safety in mind" was used. He said that when a patient uses an inhaled device only about 20-25 percent of the dose gets into the lung. The majority of the drug is swallowed. He said that the possibility of side effects from the inhaled portion of the drug was not mentioned in adverts because there was nothing new about this and a certain base level of knowledge has to be assumed in the reader, which the advert will supplement. He said that it was always a dilemma to decide how much information to put into an advert and thought that was why people would then go on to other information that is available to find out further scientific information.

Dr Leather also said that in 1993, it was believed that absorption from the lungs was similar with all the inhaled corticosteroids but that this has subsequently been proved to be incorrect. He referred to the Brutsche et al paper in the Lancet in 2000 (8) which concluded that people with moderate to severe asthma absorb much less fluticasone from the lung than healthy volunteers. He said that more sensitive and technical measures had shown the lung bio-availability of fluticasone is 10% of the total dose, the lowest of the three inhaled corticosteroids.

Dissemination of information about fluticasone other than by promotional material

Dr Leather said that Glaxo took reports of adverse events about their drugs very seriously. He said that Glaxo regarded the report on Dr Todd's case studies as a serious safety signal for the use of out of licence doses of inhaled corticosteroids. However, he said that many of the doses reported were 5 to 10 times the licensed dose and that this was quite an exceptional set of circumstances and was an unusual clinical situation. In relation to the Dr Todd's study, Dr Leather said that the children in the reports had been on high doses of other corticosteroids, some had been receiving oral steroids before being changed to fluticasone and that there was inadequate baseline data or monitoring of the children prior to the discovery of adrenal suppression.

Dr Leather said that he did not think that Glaxo brought to anyone's attention the fact that there was no distinction between the dosage specified for fluticasone and the other inhaled corticosteroids in the chart 6, step 4 of the BTS guidelines, because he thought that there would have been assumptions made that the clinicians involved would have known about the relative potencies. He said that the industry is encouraged to stay at arm's length from the process of drafting guidelines, to avoid potential conflict of interest.

Dr Leather said that Glaxo cannot disseminate information about studies relating to the use of the medicine outwith licensed doses.

He also confirmed that he did not think that Glaxo drugs representatives would have been instructed to highlight the change made to the SPC after the MCA review in 1998.

Complaint against Glaxo

Dr Todd referred to an article in the BMJ in 1999 entitled, 'Drugs Companies Criticised for Exaggeration' (7), in which reference was made *inter alia* to a complaint against GlaxoWellcome which had been upheld by the Prescription Medicines Code of Practice Authority for claiming that fluticasone given at half the daily dose of budesonide was more effective than budesonide at improving morning peak flow.

Dr Leather said that the Prescription Medicines Code of Practice Authority is a body which is part of the Association of the British Pharmaceutical Industry and is responsible for maintaining ethical standards in the promotion of medicines and that this article showed that self-regulation in the pharmaceutical industry really does work. Dr Leather that this was a good example of the state of knowledge at the time. He said that the complaint was upheld, presumably, as the balance of evidence at the time must have indicated that the claim was inaccurate but that the 2004 Cochrane review (15) had concluded that fluticasone did have this benefit over beclomethasone or budesonide and so the claim would probably be substantiated today.

Conclusion

It seems to me, from the evidence which was before the inquiry, that the main thrust of the advertising of Flixotide was to emphasise its safety, including when it was used with children.

The point was made by Dr Leather that, at the launch of any new drug, the drugs manufacturer places reliance upon the data available at that point in time but that with every medicine the data available will change, as knowledge increases due to experience gained from the use of the drug and the development of technology.

Clearly, that point is entirely fair and reasonable. At the launch of a new drug there is, inevitably, limited experience and, therefore, knowledge of the long-term effects of that drug. However, the prescribers of a drug can only base their prescribing practice upon the information which is provided to them. For that reason alone, it seems to me that it is incumbent upon the drugs manufacturer to be particularly careful to ensure that any claims made regarding a drug are substantially qualified to reflect the fact that the data currently available is limited.

The claims about the safety of fluticasone related in particular to its negligible oral systemic bio-availability, with minimal potential for steroid side effects. This was spoken to by several of the medical witnesses.

I noted that information regarding the bio-availability of fluticasone absorbed from the lungs did not appear in any part of the advertising or promotional material for fluticasone which was referred to at the inquiry.

When Dr Leather was asked about the question of bio-availability through the lung he said that the fact that there was 100% bio-availability at the lung was almost taken as a given in 1993. However, he said that this applied to experts in pharmacology and he referred later in his evidence to the fact that in his experience clinicians, quite rightly, do not usually have a detailed knowledge of pharmacokinetics and make the bulk of their decisions on clinical data.

In connection with this matter, I noted that Dr Paton said, '....I think I explained to you that very little of any inhaled medicine gets into the lung and I suppose it has also come as something of a surprise to us that you can get significant amounts of absorption of the medicine in a way that leads to systemic side effects through the route of the lung where particularly in children it is potentially such an inefficient delivery route'.

In the report entitled 'Issues in Chest Medicine' relating to the 2 day clinical update meeting in 1994, under the heading 'Fluticasone Propionate: Pre-clinical Pharmacology' it is stated *inter alia* that: 'If FP does enter the circulation, either from the intestine or from the lungs, it is rapidly metabolised during the first passage through the liver and thus becomes inactive.'

Dr Todd was asked whether the matter of potential side effects from absorption through the lung was discussed at this meeting, which he attended, and he replied, ' It never occurred to anybody. My impression was extremely favourable at this meeting and if I had not already done so at the time I certainly went home and changed a considerable number of my patients who were on high doses of other steroids over to fluticasone'.

It seems to me from the evidence on this subject which was heard at the inquiry, including that of the clinicians who spoke about their understanding of the safety claims made for fluticasone, that failure by Glaxo to qualify the claims regarding negligible oral bio-availability by referring to the fact that there continued to be absorption of significant amounts of the drug from the lungs, is likely to have made a considerable contribution to a positive view being taken by many members of the medical profession when making decisions about the use of this drug, particularly in high doses.

Dr Leather was questioned extensively about adverse case reports on drugs, in particular Dr Todd's published case studies concerning fluticasone. He said that 'it is a well-known and established fact that with all medicines....the vigilance of their safety after their launch is one of the ways the use of that medicine and its application will be formed in clinical practice'. He also said that individual case reports such as these were "absolutely vital in evaluating drug safety" but he appeared to qualify that when he said, "but what is very, very important when assessing the report of an adverse event is to put that event in the context of the use of the medication. Without knowing the context of the drug and how it was used, one can't make statements about relative risks of drugs compared to other medicines or one can't actually give a direct recommendation to guide physicians to use a drug more safely."

I did not understand Dr Leather's position to be that any difficulty about knowing the context of the drug and how it was used in Dr Todd's case studies meant that his report should be discounted. However, from his evidence, I understood Dr Leather's view to be that such shortcomings detracted from the significance of these reports to the extent that it was not possible for the drugs company to make 'statements' or 'recommendations' based upon them. This seems to me to be somewhat inconsistent with Dr Leather's comments regarding the company's emphasis upon safety vigilance and the effect of such vigilance upon clinical practice.

I also noted that Dr Leather did not appear to share what I understood to be the most significant concern of Dr Paton and Dr Cochran, namely that while there may have been evidence of biochemical adrenal suppression in the child patients, there was no evidence of clinically significant adrenal suppression. When Dr Leather spoke about the changes to the SPC for fluticasone in 1998, which had come about as a result of discussions with the MCA as part of their review, he said that he thought that review had been 'triggered by a number of case reports of side effects associated with high dose Fluticasone and inhaled corticosteroid use and may have been triggered by some reports published by Dr. Todd in the Lancet in 1996'. He was specifically asked about the words "clinically significant adrenal suppression" used in the SPC and was asked to confirm that this was not just referring to a theoretical situation. His response was "No, and it goes on to give warning about adrenal crisis". It would therefore appear that, certainly Dr Leather, who spoke at the inquiry for Glaxo, was of the view that the evidence which had been given to the MCA was indicative of clinically significant adrenal suppression and not just a 'benign' biochemical manifestation of this.

Further, Dr Leather described the dosages being used by Dr Todd and his colleagues as 'exceptional'. It seem to me that, if these doses were regarded as 'exceptional' the fact that such dosages were being prescribed in itself should have been a matter of immediate and serious concern for Glaxo, particularly as these doses were being used by a respiratory consultant whose paper on the subject had been accepted for publication in the Lancet and who had previously been employed by the company to lecture on their behalf. It seems to me that, in order to monitor the safety in use of a drug, a drugs company must ensure that it is fully informed as to the way in which the drug is currently being used in clinical practice. Accordingly, consideration of the actual use in practice of fluticasone should have been an essential part of the monitoring of its safety in use.

From the evidence before this inquiry alone, it is not clear why the use of these doses of fluticasone should have been regarded as 'exceptional'. The letters to the Lancet following upon the publication of Dr Todd's paper made no reference to these dosages being exceptional and the BTS guidelines provided for a maximum dosage of 2,000 micrograms (or, at the very least, 1,000 micrograms, if it is accepted that this is implied in respect of fluticasone), in the under 5 age group. Moreover, Dr Todd said that, at the time he prepared the report on his study, which was published in the Lancet in 1996, he and his colleagues also conducted two informal surveys to ascertain how widespread was the use of fluticasone at high doses: firstly, a survey of GPs in the Belfast area, which showed that one third of fluticasone prescriptions for children were for greater than the licensed dose and that 2% of all fluticasone prescriptions were for 1,000 micrograms or more daily; and, secondly, a telephone

survey of 21 paediatric hospital centres in the UK, in which 19 of the 21 centres identified fluticasone as the inhaled corticosteroid which they used if they were prescribing outside licensed doses. Clearly, information of this kind would have been accessible to Glaxo, even if only by means of conducting an informal survey such as that described by Dr Todd.

Certainly, by December 1997, Emma was being prescribed doses greater than or equal to five out of the six of the children reported upon by Dr Todd and his colleagues in their 1996 Lancet article.

It seems to me that, in order to have had an influence upon ensuring safety in clinical practice in regard to the prescribing of fluticasone, unless it was satisfied that the use of such exceptional doses was confined to Dr Todd and his colleagues, the drugs company ought to have taken steps to review a marketing strategy which was based upon safety claims and to remind practitioners of the potential risks of prescribing high doses, even of this drug.

Dr Leather said that Glaxo would never promote a drug outside its licensed use and emphasised that the claims regarding fluticasone's safety only applied to its use within licensed doses. He said that all the adverts related to the licensed doses. There was reference throughout this inquiry to the fact that the responsibility for off-licence prescribing rested with the prescriber and that this was a clinical decision which had to be made depending upon the circumstances of each individual case. However, it was also clear from the evidence led at the inquiry that it is fully accepted within the medical profession that off-licence prescribing is common practice, particularly in paediatrics. It seems to me that a drugs manufacturer does not carry out its promotional and marketing functions conscientiously and responsibly if it fails to take this reality into account. It also seems to me that, in the light of this fact, a drugs company must be particularly assiduous in ensuring that extreme caution is exercised when claims are made about the safety aspects of a drug.

Mr Lindsay for MHRA said that the advertisements were read in medical journals and publications by medical professionals and that while it might be considered that a lay person might be influenced by slogans and pictures of teddy bears, this would not influence medical practitioners. This begs the question as to why adverts would be placed by the manufacturers in the medical journals and publications, if they did not intend that such advertising would be a means of disseminating throughout the medical profession positive information about their product.

The doctors who were asked about this said that they did not make clinical decisions regarding the use of a drug on the basis of the contents of advertising material. I entirely accept this. However, it seems to me that it is unrealistic to discount such promotion as having no bearing whatsoever upon the use of the drugs which are being promoted.

The brief summary of the evidence of various doctors, which is set out at the beginning of this section, gives an indication of the impression that the promotional material for fluticasone had upon them. The following evidence given by Dr Shapiro highlights this point. Dr Shapiro said that he did not read advertisements *per se* and said that the drug companies would be appalled to know what happens to 99 per

cent of their advertising literature and that the advertising literature is 'not that useful'. On the other hand, when he was asked if the claims about fluticasone's safety would have been one of the things that persuaded him to prescribe it, replied "It would have. Unfortunately it would have been a factor. On paper it looked good."

Despite these comments, I agree with Mrs Abernethy's submission that the vital factor in Dr Shapiro's prescribing fluticasone for Emma was because he was a disciple of Dr Paton. Moreover, I formed the view from his evidence that Dr Paton based his prescribing practice, certainly not upon the advertising and promotion of any drug or group of drugs but rather upon years of experience in balancing risk and benefit in children who were very ill with asthma and in seeing the safety record and noting in practice the efficacy of inhaled corticosteroids generally.

I have no doubt that it is inconceivable that medical practitioners would rely simply upon the terms of manufacturers' advertisements when making such important decisions as those concerning their prescribing practice. However, from the evidence before the inquiry regarding the type of advertising literature which was produced to market Flixotide and the confirmation from the doctors who gave evidence about this, that they understood fluticasone to have been marketed as having less systemic effects, I am satisfied that the advertising and promotion of fluticasone was aimed at and did contribute towards establishing a feeling of confidence in the enhanced safety of this particular drug within a medical profession which had already become complacent about the safety of inhaled corticosteroids generally.

It is clearly not possible to quantify the extent to which this had a bearing upon the practices of Dr Shapiro, Dr Cochran or Dr Paton. From all of the evidence which was before me, I have come to the view that the decision to prescribe or to tacitly approve the prescription of high dose inhaled corticosteroid for Emma for a prolonged period came about, directly or indirectly, as a result of the consideration of many factors including study of clinical data and analysis of research and case studies by Dr Paton and Dr Cochran and certainly was not simply a consequence of the way in which the drug was marketed. I therefore do not consider that there is evidence before me which would lead me to conclude that Emma's death might have been avoided if the drug had not been marketed in the way it was. However, I am satisfied that the emphasis placed upon the safety of fluticasone in its promotion and marketing, including the advertising of the drug and the fact that no steps were taken by the company, through its representatives or otherwise, to bring to the attention of clinicians at least the changes to the SPC, which were based upon all the evidence available at that time, contributed to the complacency by many within the medical profession about its safety, which in turn contributed to high doses of this drug being prescribed and, accordingly, is a fact which is relevant to the circumstances of Emma's death.

3.(b) Warnings issued by the drugs regulatory agency in relation to the prescribing of inhaled corticosteroids, including fluticasone

Submissions

In his submissions Mr Lindsey said that no findings should be made in respect of the MHRA or its predecessor, the MCA, (hereinafter referred to as the agency) and that

there were no reasonable precautions which could have been taken by the agency, whereby the death of Emma might have been avoided and that there were no defects in the agency's system of working which contributed to her death.

He said that the warnings given at the time of the licensing of fluticasone regarding possible side effects were accurate and appropriate having regard to the state of knowledge at that time, that all precautions taken by the agency were appropriate and proportionate having regard to the state of knowledge at the time the precautions were taken and that it would have been disproportionate to highlight the risks associated with fluticasone as adrenal suppression is a class effect. He said that the advice given by the CSM evolved as more scientific information and medical knowledge became known about the potential side-effects of inhaled corticosteroids and of fluticasone in particular.

Mr Lindsey said that it is the function of the agency to regulate medicines, not to regulate the practice of medicine by individual doctors. He said that regulatory pharmacovigilance involves the detection and assessment of drug safety issues, in order to take action to reduce risks. When a safety concern is detected it is very important to ensure that all the relevant evidence is gathered and critically assessed before action is taken. He said that agency must take care not to precipitate regulatory action as a a result of individual publications or other "safety signals" as this could inappropriately undermine public and professional confidence in the value of important medicines.

Mrs Abernethey also said that the 1995 SPC for fluticasone reflected the knowledge of the Medicines Controls Agency and Glaxo at that time and that following a review by the MCA of nasal and inhaled corticosteroids, which had been triggered by a number of case reports of side-effects associated with inhaled corticosteroid use including high dose fluticasone, the SPC for fluticasone was revised in 1998 to include *inter alia* a warning that prolonged treatment with higher doses of inhaled corticosteroids may result in clinically significant adrenal suppression. She said that the patient information leaflet was also changed to include a warning about adhering to the doctor's instructions in relation to the use of the Flixotide Accuhaler and that changes were made to the company's data sheet for 1999/2000.

Mrs Abernethy submitted that the MCA also responded appropriately to the Todd paper in the Lancet in 1996.

Determination

Dr Jeremy Suvarna, senior medical assessor and team leader at the Pharmacovigilance Risk Assessment Unit at the MHRA gave evidence in relation to the work of the agency. He is a medical doctor and he also has a diploma in *inter alia* pharmaceutical medicine. Dr Suvarna joined the MCA in 2000 but he gave his views on the action taken by the agency prior to then, based on his understanding of the situation.

Dr Todd was critical of the actings of the agency in relation to the issuing of warnings about fluticasone. He said that doctors rely on the agency to keep them informed

and to take action to protect them from harming their patients. His view was that the agency needed to take more control of the situation.

Introduction

The action taken by the regulatory agency at the time of the MCA review of inhaled and nasal corticosteroids in 1997 was gone into in some detail at the inquiry and has been summarised earlier in this determination.

The advice and recommendations of the CSM, based upon the 1997 review undertaken by the MCA was published in the 1998 Current Problems in Pharmacovigilance bulletin. The review itself was published in the journal of Pharmacology and Therapeutics in 1999.

Dr Suvarna said that the Current Problems in Pharmacovigilance bulletin is intended to be a key safety message and is designed to be easily accessible and readable for GPs, hospital doctors and pharmacists so that they can very quickly take on board key safety messages. It is written in bulletin form, with bullet points, for this purpose. It is not considered helpful to include anything that is not key to the main new message that the MCA wants to get over. He said that he would expect medical practitioners to take on board the advice of the agency and apply it as they saw appropriate. He said that he would be surprised if practitioners had concerns about such advice and did not seek clarification but just ignored it.

The May 1998 Current Problems in Pharmacovigilance Bulletin was entitled: 'Focus on Corticosteroids'. The first section, extending to three pages, dealt with 'Withdrawal of systemic corticosteroids'. It was confirmed at the inquiry that 'systemic' here referred to 'oral' corticosteroids. The next section dealt with 'The safety of inhaled and nasal corticosteroids', which is the issue of particular relevance to this inquiry. It was contained in one page and appeared on the fourth page of the bulletin. The full text of this page is as follows:

'Many patients, both adults and children, are now prescribed inhaled and nasal corticosteroids for the prophylactic treatment of asthma and rhinitis respectively. By delivering the drugs directly to the airways, these products maximise the beneficial therapeutic effects of corticosteroids whilst minimising the adverse systemic effects.

Following a review of the available evidence, we have concluded that clinically important systemic adverse effects can occur at licensed doses of these products. The risks of these effects occurring are increased following prolonged, high dose therapy, although susceptibility to these effects varies between individuals. The risks with intranasal corticosteroids are generally lower than with inhaled steroids as the doses used in clinical practice are lower. Five main areas of concern were identified: adrenal suppression, osteoporosis or changes in bone mineral density, growth retardation in children, cataracts and glaucoma. Following our assessment of these areas, the following conclusions have been reached:

- The dose should be titrated to the lowest dose at which effective control of asthma or rhinitis is maintained.

- The potency of corticosteroids varies between individual drug substances. Greater potency does not however necessarily equate with greater efficacy. All inhaled corticosteroids have the potential to cause systemic side effects, the frequency and severity of which will be dependent upon the dose and duration of treatment.
- Systemic effects of inhaled and nasal corticosteroids may occur, particularly at high doses prescribed for prolonged periods. Possible systemic effects with inhaled corticosteroids include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. In children receiving nasal corticosteroids at licensed doses growth retardation has been reported.
- It is recommended that the height of children receiving prolonged treatment with inhaled or nasal corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled or nasal cortisosteroid, if possible, to the lowest dose at which effective control of asthma or rhinitis is maintained. In addition, consideration should also be given to referring the patient to a paediatric specialist.
- Prolonged treatment with high doses of inhaled corticosteroids, or higher than recommended doses of nasal corticosteroids may result in clinically significant adrenal suppression. Additional systemic cortisosteroid cover should be considered during periods of stress and elective surgery.

It is important to emphasis that inhaled and nasal corticosteroids provide proven, effective control of asthma and rhinitis respectively and may, in some patients, remove the necessity for oral cortisosteroid therapy. The recognition that systemic effects may occur and that the lowest effective dose should be used, does not alter the favourable risk-benefit profile of these medicines.'

The article in the 1999 Pharmacology & Therapeutics journal, which set out the details of the MCA review on which the CSM advice was based, is lengthy but Dr Suvarna read out at the inquiry the following extract from the section entitled Hypothalmic-pituitary-adrenal axis suppression in children: Inhaled corticosteroids:

"Discussion. From the evidence reviewed in the previous sections, it is possible that HPA axis suppression may occur at currently licensed doses in children. However, the literature is far from consistent with a number of well designed studies showing no effect at licensed doses. However, children with severe, chronic asthma are increasingly being prescribed high doses of inhaled steroids to control their symptoms as an alternative to oral corticosteroids and possibly in the belief that it is a safe alternative with few systemic effects. At these high doses there is convincing evidence that significant adrenal suppression with clinically relevant sequelae occurs.

In children with early onset of asthma and hence early use of inhaled steroids systemic side effects are of particular concern. Alveolar development is probably complete by 18 months of age, after which lung and body growth occurs in a highly proportional fashion. Paediatric dosage recommendations however often apply to children 4 - 16 years of age and therefore there will be a great potential for systemic activity in very young children in whom blood volume is smaller. Assessment of the dose in terms of micrograms per squared meter per day as opposed to absolute

dose may therefore provide a more valid comparison amongst children of different ages and weights. As such, Prifits et al (1990)reported that although only one child in their study population was taking greater than 800 micrograms per day of inhaled Beclometasone, 13 were taking greater than 460 micrograms per squared meter per day which is considered the upper limit of the conventional adult dose. It is particularly important therefore that in children the dose is titrated to the lowest possible dose at which effective control of symptoms is maintained".

Warning of adrenal suppression in 1998 Current Problems in Pharmacology bulletin

Dr Shapiro's view was that the 1998 Current Problems in Pharmacovigilance bulletin highlighted adrenal suppression as an area of concern but was not suggesting that adrenal suppression actually happened.

Dr Thornton said that he did not read the 1998 bulletin that way and did not think that a merely theoretical risk was implied. He said that a GP would be expected to read this bulletin and that, even if it contradicted advice from other sources, it should give cause to consider a change in practice.

Dr Paton said that what was contained in the bulletin in Current Problems in Pharmacovigilance accorded with what he already understood and, as I understood his evidence, it did not tell him anything that he thought was new.

Dr Cochran said that the MHRA quoted no evidence to justify the statement in the 1998 bulletin regarding adrenal suppression. He said that he did discuss this with colleagues both within Glasgow and in other centres as the advice came from a national body and was contrary to his own understanding of the evidence at the time. He said that everyone he spoke to in the field agreed there was no evidence to justify the statement and that he did not consider that it gave any reason to change his prescribing policy. Dr Cochran specifically said that no studies were referenced in the relevant article.

Dr Suvarna said that in the case of the May 1998 bulletin a great deal of material had been reviewed, of which none in particular stood out, and so, for ease of reading, footnotes were left out. He said that the studies referred to were too numerous to include in a document such as this which is designed to be easily accessible and easily readable for general practitioners, hospital doctors and pharmacists so that they can very quickly take on board key safety messages. He also said that there is note at the end of the bulletin, 'Enquiries, Comments and Suggestions to Dr. A. Cave, Medicines Control Agency' and said that that was how an interested practitioner could get more information about an article contained in Current Problems in Pharmacovigilance. Dr Suvarna said that in the year July/August 2003 to the same time in 2004 the central inquiry point at the agency took something like 34,000 requests for information from the public.

I accept the point made by Dr Suvarna about not unnecessarily lengthening a document which is intended to be easily read and accessible. However, the absence of a footnote to this particular section in the bulletin did differentiate it from the first section to which there was appended such a footnote, albeit a relatively short one.

The more general matter of the adequacy of the safety message in the 1998 bulletin is dealt with as part of the considerations in the following section:

Publication of review in 1999 Pharmacology and Therapeutics Journal

Dr Suvarna said that the full text of the MCA's 1997 review was published in the Pharmacology and Therapeutics journal in 1999 and that this article contained a list of the material reviewed. He said that he thought that the review was published in this journal as it would have been unlikely to have been accepted for publication in journals such as the Lancet or the BMJ due to its length and because it was reviewing old information and explaining the position of the MCA and the CSM rather than presenting new information.

Dr Todd said that he had never seen the MCA review, which was published in the journal of Pharmacology and Therapeutics in 1999, and he said that this was an obscure journal. He also said that he was surprised that the MCA had not sent him a copy of this publication at the time in view of the correspondence he had been sending to the Agency.

Dr Paton said that he had never read or heard about the MCA being published in Phamacology and Therapeutics. He did not think he had ever heard of the journal and would not regard it as mainstream. He said that the contact that he would recognise as coming from the MCA consisted of the publications that were sent to his home and that he did not know that there was a fuller published article behind the bulletin.

The views of Dr Paton, Dr Todd and Dr Cochran regarding the contents of the review, as published in the 1999 Pharmacology and Therapeutics journal, were not before the inquiry, the publication itself being lodged after Dr Cochran gave his evidence and Dr Paton and Dr Todd stating that they had not been aware of its existence. It may very well be that the contents of this review would not have had an impact on their views on the validity or, in Dr Todd's case, the adequacy of the safety message which the MCA and the CSM intended to give in the 1998 Current Problems in Pharmacovigilance bulletin. They may already have been aware of all or most of the case reports or studies referred to in the 1999 review publication, although I did note that Dr Todd confirmed that one of the studies referred to in the review publication (Boe et al 1994 Eur Respir J 7, 2179-2184, which demonstrated that there were no significant differences in efficacy between 2,000 micrograms daily of fluticasone and 1,600 micrograms daily of beclomethasone but that fluticasone produced significantly more suppression of the HPA axis as asssessed by serum cortisol levels) was one which he would not have been aware of and that no representative would have told him about it. It may well be that any studies relevant to adrenal suppression may have produced results indicative of adrenal suppression which was in the category which Dr Paton and Dr Cochran considered to be benign or not clinically significant. On the other hand, there may have been, in the review, case reports or studies of which they were not previously aware. It is not for the inquiry to speculate on this matter.

However, the Current Problems in Pharmacology bulletin is the recognised publication of the MCA and the CSM and is the publication which was sent to all

relevant practitioners and it seems to me that at least the fact that the full MCA review was to be published should have been included in this document for the information of those clinicians who did wish to study the issue further.

I also consider that, for the benefit of all practitioners, certain of the concerns which were subsequently highlighted in the 1999 publication, such as the fact that there was increasingly a practice of prescribing high doses of inhaled corticosteroids for children and the particular concern relating to very young children whose asthma treatment commences at a very young age, should and could, appropriately and concisely, have been contained and highlighted in the 1998 bulletin .

Warning about prescribing of high doses of inhaled corticosteroids

Dr Suvarna said that the MCA carried out its 1997 wide-ranging pharmacovigilance review of all available evidence in relation to all inhaled and nasal steroids, looking at adrenal suppression and all other possible systemic effects, as a result of yellow card and literature reports of adrenal suppression and adrenal insufficiency, much of the evidence of harm relating to very high dose, unlicensed use of inhaled corticosteroids.

He said that the agency's responsibility is to regulate medicines and the pharmaceutical industry. He said that it was not the responsibility of the Agency to make judgements or recommendations about the practice of individual doctors. He said that the agency monitors 'the use of medicines in terms of the safety of those medicines' and that 'that includes licensed use and off licence use'. He said that it was recognised that it may be justified to use high doses. However, this was not something which the agency or the CSM could generally endorse or support. He said that such use is a matter for individual doctors and the Agency has no jurisdiction over or power to take action against off-licence prescribing.

However, Dr Suvarna confirmed that the agency might issue warnings which took account of the fact that they were aware that the practice had developed to use off licence doses in particular circumstances.

Indeed the inquiry was made aware of the fact that in October 2002, the agency's publication, Current Problems in Pharmacovigilance, contained an article entitled 'Inhaled corticosteroids and adrenal suppression in children' in which prescribers were 'strongly advised that the paediatric licensed doses of all inhaled corticosteroids should not be exceeded' and there was a reminder of what the licensed doses were, Dr Suvarna said that the reason for this was that, 'What was new in 2002 was the recognition that there may be a large amount of off licence use particularly in children which was producing problems and which were just going unrecognised and for these reasons it was considered appropriate to remind prescribers of the issue and of the licensed doses'

When Dr Leather spoke about Dr Todd's 1996 Lancet paper, he said that he thought what Dr Todd was doing with his patients reflected the change in practice of giving more patients higher doses of inhaled corticosteroids and that his publication raised the profession's awareness that they should not be complacent when using very high doses of inhaled corticosteroids.

Dr Suvarna said that Dr Todd's 1996 case study report was an important case series, which had to be reviewed in the context of all the other evidence. He said that it related to children who had been exposed to very high unlicensed doses of inhaled steroids and that this report offered some evidence of a serious concern relating to doses far in excess of the licensed doses in children.

It cannot be said that the increasing use of high doses of inhaled corticosteroids with children was a matter which was not recognised by the agency at the time of the MCA review, given the reference in the 1999 publication of the MCA review to the fact that 'children with severe, chronic asthma are increasingly being prescribed high doses of inhaled steroids to control their symptoms as an alternative to oral corticosteroids and possibly in the belief that it is a safe alternative with few systemic effects'.

Moreover, the 1995 BTS guidelines which were being referred to by the medical profession at that time specified doses of inhaled corticosteroids in the management of asthma in children under 5 years of age of up to 2,000 micrograms of inhaled steroids per day and indeed stated in the introductory pages that 'Stepping down the dose of inhaled steroids once asthma is controlled has been emphasisied in current guidelines but is often not implemented with the result that many well controlled patients are

overtreated with inhaled steroids.' The maximum dose recommended for children under 5 years in the new British Guidelines on the Management of Asthma, published in the February 2003 volume of Thorax, specified a maximum of 400 micrograms of inhaled corticosteroids daily, which is in marked contrast to the dosage five times higher which was in place as a guideline at the relevant time.

However, there was no reference in the 1998 Current Problems in Pharmacovigilance bulletin to the fact that any concern as such had been identified in relation to children increasingly being given doses in excess of the licensed amounts and there was no reminder that the profession should not be, as stated by Dr Leather, complacent when using such very high doses.

This seems to me to be a significant omission, given the concerns, which had been highlighted at that time by the MCA review, regarding the increasing use of high doses in children and the side effects of adrenal suppression which had been detected and which had been assessed by the agency as 'clinically significant'.

Potential of corticosteroids to cause adrenal suppression as a class effect

As I understood his evidence, Dr Todd did not regard the terms of the 1998 Current Problems in Pharmacovigilance bulletin as amounting to a warning particularly as it did not make any specific reference to fluticasone, which Dr Todd considered to be the drug which had the potential to do harm as it was being used in such high doses, in spite of its greater potency.

Dr Suvarna said that he understood that there was no specific reference to fluticasone in the May 1998 bulletin because the CSM's advice was that the potential for inhaled and nasal corticosteroids to cause systemic side effects was a class

effect, something which could be caused by any inhaled or nasal corticosteroid. He said that it would have been disproportionate to highlight one particular member of that class. His view was that, if you were to compare them dose for dose, the risk would be greater for fluticasone because it is more potent but once you take that into account there is evidence of clinically important adrenal suppression and other systemic effects occurring with the other products. He said that, at the time when the 1997 review was carried out, the MCA had received 28 reports of adrenal suppression or adrenal insufficiency on the yellow card database, 13 with beclamethasone and 15 with fluticasone.

From the evidence which was before the inquiry I accept the agency's reasoning for not considering it to be appropriate to draw attention to particular concerns about the use of one particular drug, in this case, fluticasone.

However, it seem to me that a reminder of the relative potencies of the various inhaled corticosteroids (and nasal corticosteroids if it was considered that high doses of these drugs were also increasingly being used) could quite simply have been referred to or specified in a table of the various drugs, with licence conditions regarding patient age and comparative dosage. This would also, of course have acted as a reminder not only of licensed doses and of the fact that fluticasone was more potent but also that it was not licensed for children under 4 years.

Dr Suvarna spoke of the importance of not diluting the key message by inserting too much information in a brief safety bulletin and also said that it would have taken up a 'fair amount of space'. However, it seems to me that, firstly, this message was of particular importance and was fundamental to one of the key issues, namely dosage and, secondly, that the insertion of a table, such as that which was included in the 1999 review publication, would not have been space consuming and would not have diluted the message but, rather, would have made it very clear and easily assimilated. I consider that it would have been reasonable, proportionate and, in all of the circumstances, appropriate to have included this information.

Notification of change in SPC for fluticasone

Dr Suvarna said that practitioners should be familiar with the licence conditions of medications, which are summarised in the BNF but said that they were not required to refer to the SPCs on a regular basis.

He said that the SPCs for all nasal and inhaled steroid products were changed after the agency's review. The inquiry's attention was drawn to the change in the SPC for fluticasone in 1998.

Dr Suvarna agreed that changing the SPC was not the most appropriate or effective way of communicating with the medical profession and said that publication in the Current Problems in Pharmacovigilance bulletin was the means by which the agency would bring its advice and information regarding changes in an SPC to the medical profession.

The changes to the SPC for fluticasone in 1998 included the following:

'Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is important therefore that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of the inhaled corticosteroid, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

Prolonged treatment with high doses of inhaled corticosteroids, particularly higher than recommended doses, may result in clinically significant adrenal suppression. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.'

However, there was no reference in the 1998 bulletin to the fact that these changes had been made to the SPC. This seems to me to be somewhat inconsistent with Dr Suvarna's point that the purpose of articles such as those in the Current Problems in Pharmacovigilance bulletins was to highlight these changes.

Conclusion

I have no doubt from the evidence before the inquiry that the MCA acted appropriately and timeously in 1997 when it became clear that there was a potential safety issue regarding the use of inhaled and nasal corticosteroids and a decision was taken to carry out a review of all available information and evidence on the subject.

I note that the overall evidence from the review was such that the CSM considered that it was appropriate to issue advice to practitioners and it is clear that steps were taken to do so, given the decision to issue a special bulletin of Current Problems in Pharmacovigilance. I am satisfied that the bulletin which was issued in 1998 was intended to draw the attention of the medical profession to the agency's concerns regarding aspects of the use of inhaled and nasal corticosteroids.

However, it does not seem to me, from the evidence which was before the inquiry and for the reasons set out previously, that the terms of the bulletin were sufficiently robust or comprehensive.

I also note that it was considered that the full review should be published in another journal so that it could be accessed by interested practitioners and I entirely accept the reason for publication in this particular journal and the fact that it was neither appropriate not practical to send out the full review to all practitioners.

However, I do consider that the fact that the full review was to be published should have been drawn to the attention of interested practitioners within the bulletin itself.

Dr Suvarna said that the communication of safety messages should be balanced, complete and given on the basis of all relevant information and expert assessment. That position is logical and reasonable.

He also said that the message given in 1998 following the agency's review was considered to be appropriate at the time given the level of evidence and in the light of the level of concern at the time.

I understand and fully accept as justified the concern of the agency that it would be counterproductive to unnecessarily precipitate regulatory action and thereby undermine confidence in important medicines.

I am very conscious of the fact that at the inquiry we have had the benefit of hindsight, given the information concerning cases of adrenal crisis which were reported in 2001 and 2002, including Emma's death.

However, I have come to the view, in the light of all the evidence before me including the fact that the MCA and the CSM did have safety concerns after consideration of the 1997 review, the indications of the increasing use of high dose inhaled corticosteroids in children, the extent of the complacency which existed at the relevant time within the medical profession regarding the safety of inhaled corticosteroids and the prevalence of the disease of asthma in the population, that this was an area where it was important that the safety warnings should be clear, compelling and effective and I consider that a stronger and fuller warning regarding the use of high dose inhaled corticosteroids, particularly for prolonged periods and particularly in children, than that which the 1998 bulletin contained, would have been appropriate at that time and, accordingly, is a fact which is relevant to the circumstances of Emma's death.

4. Protocol regarding authorisation for neuropathology examination

Emma's father, Stewart Frame, told the inquiry that he and his wife were telephoned by, he believed, a police officer and were told that it had not been possible to establish the cause of Emma's death. Emma's parents were given the option of accepting the post-mortem results, having Emma's body retained for further examination or having Emma's brain removed for further investigation, which could take six weeks. Mr and Mrs Frame understood that the procurator fiscal was satisfied that no further investigation was required and that the question as to whether there should be any further investigation was left to them to decide.

Mr Frame said that they decided that no further investigations should be done at that point. Mr Frame said that he and his wife made this decision very quickly. He said that this was not the most important thing for them at that time.

Dr Howatson said that at the time of the post-mortem examination he sought authorisation from the procurator fiscal for retention of the brain for a formal and

detailed neuropathology examination. He said that this was refused despite his professional advice that such an examination should be carried out.

Dr Howatson said that he thought, at the time of the post-mortem examination, that Emma had viral encephalitis. He said that specialist examination by a consultant neuropathologist of brain samples submitted at the time of the post-mortem examination showed no evidence of any convincing infective, hypoxic, ischaemic, metabolic or traumatic injury in the brain but that there was literature to show that a more complete examination detects pathology in the brain which otherwise would be missed.

He described the examination of the brain in his report as a "wholly inadequate examination", although he said in evidence that his language in the report was perhaps "a little bit intemperate". He said that he got perhaps 80 percent of what was available. He said that there was a risk that a viral encephalopathy may have been missed because areas where lesions etc might have been may not have been examined.

In spite of this, and based on all the other evidence available, Dr Howatson was satisfied with the diagnosis of adrenal insufficiency as the cause of Emma's death.

Nevertheless, it is very unfortunate that this area of investigation was not fully explored in order that as much as possible of any remaining doubt about the diagnosis of death be excluded. Indeed, Mr Holmes in his submissions referred to the fact that only about 10 percent of the brain substance had been sampled and that it is recognised that limited examinations can miss encephalopathic or inflammatory changes elsewhere.

It may very well have been that, even if they had been given Dr Howatson's views on the inadequacy of his examination without further tests being carried out, Mr and Mrs Frame would nevertheless have expressed the wish that there should be no further examination. This is a matter which was not explored at the inquiry.

However, it seems to me from the evidence which Mr Frame gave, and which I had no hesitation in accepting, that the contact made with the family regarding this matter was in itself inadequate and inappropriate.

After I had heard the evidence of Mr Frame and Dr Howatson in connection with this matter, I inquired of the procurator fiscal as to whether any evidence was to be led in relation to the existence of any protocol or details of the standard procedures which are followed in situations of this kind. The procurator fiscal told me that it had not been his intention to lead any evidence in relation to this point but he said that he would make inquiries with a view to considering whether such evidence might be available for the assistance of the inquiry. Mr Houston subsequently, and very helpfully, lodged with the inquiry, with the consent of all the parties, an affidavit signed by him as the procurator fiscal at Lanark, in which it is stated that:

"There is an established protocol by the Procurator Fiscal, who has control of the remains in a death which has been reported to him, to the effect that retention of organs of the deceased after a post-mortem for the purposes of further detailed

examination is at his discretion and solely upon his authorisation and in accordance with any reasonable wishes of the next-of-kin and the Procurator Fiscal is not obliged to state his reasons for the refusal of such consent."

I do not intend to make any comment in relation to the matter of the procurator fiscal not being obliged to state his reasons for the refusal of such consent. However, I do consider that, given the evidence before me in relation to the matter of authorisation for a full neuropathology examination, procedures in respect of ascertaining the "reasonable wishes of the next of kin" require to be put in place.

I therefore recommend that the following proposals be considered by Crown Office, when deciding whether and, if so, what procedures might be put in place.

Firstly, I do not consider that it is appropriate that a matter of such sensitivity should be discussed in a telephone call to the bereaved family. It seems to me that a meeting

with a suitably trained representative of the procurator fiscal should be offered to the family of the deceased person.

Secondly, it is clearly essential that all of the appropriate information regarding the medical advice and recommendation and the reasons for any such recommendation should be provided during the course of any such discussion in order that the family might make an informed decision. It seems to me that this information may be obtained from the appropriate medical authorities and relayed by the procurator fiscal's representative to the family of the deceased. Alternatively, in the event that the procurator fiscal's representative considers him or herself to be insufficiently qualified to enter into a meaningful discussion about the medical recommendation, a meeting with the person making the request for the organ retention, or someone acting on his or her behalf, should be offered to the family.

5. The British Guidelines on Asthma Management 1995 Review and Position Statement

Guidelines on asthma management were drawn up in 1995 by a committee of paediatricians, specialist and general physicians and nurses and were published in the February 1997 volume of Thorax, which is the journal of the British Thoracic Society. Thorax is not a periodical that general practitioners would normally receive. This particular issue of Thorax was sent to all general practitioners.

The guidelines consist of text and eight summary charts. Within the text of the guidelines, under the heading "Gaining Control and the Stepwise Approach to Management", is stated the following:

'The importance of gaining control of asthma is re-emphasised, abolishing symptoms as soon as possible and optimising peak flow by starting treatment at a level likely to achieve this. This approach is most likely to gain and maintain the patient's confidence in the treatment and the health professional, and enhance compliance with treatment and outcome. Current understanding of the mode of action of steroids would support a strategy of starting with oral steroids or moderately high dose

inhaled steroids. Once control is achieved the dose of steroid can be reduced. It is therefore recommended that many patients who need anti-inflammatory therapy should be started on inhaled steroids on a dose of 400-500 micro-grams twice daily for beclomethasone or budesonide or 250 micro-grams twice daily for fluticisone (half these doses for younger school children). ...

Stepping down the dose of inhaled steroids once asthma is controlled has been emphasised in current guidelines but is often not implemented with the result that many well controlled patients are over treated with inhaled steroids."

Chart 6 in the guidelines related to "Management of asthma in children under 5 years of age". There was a copy of chart 6 on the wall of Dr Shapiro's surgery and on the wall of the nurses' treatment room at his practice.

The chart is headed with the following note:

"Starting out:

Patients should start treatment at the step most appropriate to the initial severity. ..."

Step 2 on chart 6 relates to "Regular inhaled preventor therapy". It specifies a dosage of beclomethasone or budesonide up to 400 micrograms or fluticisone up to 200 micrograms daily.

Step 3 on chart 6 relates to "Increased dose inhaled steroids". It specifies beclomethasone or budesonide increased to 800 micrograms or fluticisone 500 micrograms daily via a large volume spacer.

Step 4 on chart 6 relates to "High dose inhaled steroids and bronchodilators". It specifies a dosage of inhaled steroids (up to 2mg/day) and other treatment as in step 3. There is no specified differentiation between beclomethasone and budesonide on the one hand and fluticisone on the other.

Under the "Stepping down" section of chart 6 is stated: "Regularly review the need to decease treatment and step down as indicated. Monitor all changes in treatment by clinical review."

Within the text of the guidelines under the heading "Inhaled Steroids" reference is made to the possibility of side effects. The side effects to which specific reference is made are impaired growth in children and osteoporosis.

Also under this heading fluticisone is stated to be "as effective as beclomethasone dipropionate and budesonide at half the dose when given by equivalent delivery systems.". and it is also stated that "fluticisone should be included in the guidelines as an alternative inhaled steroid at half the doses recommended for beclomethasone and budesonide when given by metered dose inhaler".

At the time when the 1995 guidelines were published, the summary of product characteristics for Flixotide accuhaler specified doses of Flixotide for children over four years. The maximum dosage for children between 4 and 16 years was 50-100

micro-grams twice daily. Accordingly, the guidelines allowed for treatment of a class of patients for which the drug was not licensed and at dosages considerably in excess of the licensed dose.

Dr Thornton said that the 1995 guidelines approved the use of higher initial doses of steroids than had previously been thought appropriate. He confirmed that in places the guidelines recommended off-label dosages.

He said that the guidelines may be criticised in that they specify a dose of inhaled steroids of up to 2 milligrams per day, without pointing out the difference between fluticasone and the other inhaled corticosteroids. He said that, nevertheless, the difference was made clear at steps 2 and 3 and elsewhere within the text.

Dr Thornton's view was that a dose of fluticasone exceeding 1,000 micrograms daily would not be considered appropriate by any practitioner who was properly conversant with the guidelines.

I have previously set out my view in this matter as regards the extent to which Dr Shapiro's was influenced by the guidelines when he decided upon the the dose of fluticasone to prescribe for Emma. Nevertheless, it does seem that it would appear that his initial interpretation of the terms of the BTS guidelines did contribute to Dr Shapiro's confidence in prescribing high dose fluticasone for Emma.

As Dr Thornton said, the charts included in these guidelines were kept in a handy position for easy reference during patient consultations. No doubt this was a reason for the publication of the charts. Accordingly, it was important that such documents intended for quick and easy reference should be accurate. It seems to me, from all the evidence before the inquiry that chart 6 was insufficiently specific when it did not differentiate between fluticasone and the other inhaled corticosteroids at step 4 and in all of the circumstances of this case I consider that this was a fact which was relevant to the circumstances of Emma's death.

6. Notification of outpatient appointments at Yorkhill to referring general practitioners

Mrs Dougall submitted that, in terms of section 6 (1) (d) of the Act, there was a defect in the system of working which contributed to Emma's death, namely a failure in communication and follow-up between Dr Shapiro and the consultant respiratory staff at Yorkhill. In particular, she said that there was failure on the part of Dr Shapiro to follow up the non-issue of clinic appointments and a failure on the part of Yorkhill staff to follow up apparent non-attendance at clinic appointments.

Evidence was given to the inquiry regarding the delay in the issue of a first appointment for Emma and the lack of a specialist follow-up appoiintment for Calum.

Specifically in relation to the failure of the first referral of Emma to Yorkhill, Dr Shapiro said that his recollection was that when he phoned Yorkhill in January 1999 about his January 1998 referral, he was told that Emma's appointment had been changed by a parent, then an appointment was cancelled by the hospital then another was cancelled by the parent as Emma was 'well'. Dr Shapiro never

discussed this matter with Emma's mother. The clinic attendance records on Emma's medical records from Yorkhill are incomplete and the only appointment noted is the first one attended by Emma.

Mr Frame said that he and his wife would have taken a first referral to Yorkhill very seriously and were not aware of any such appointment. He said that his wife was very diligent about making and keeping appointments and he could not imagine any circumstances in which the appointment would have been forgotten or cancelled, although he could not say this with absolute certainty. Mr Frame thought that it was possible that the family did not receive notification of the appointment as they moved house in April 1998.

It is clearly unsatisfactory that Emma was not seen by a specialist after the first referral and that no clear explanation is available as to why this occurred.

Dr Cochran said that if a patient failed to attend his clinic, he wrote directly to the parents and sent a copy of the letter to the GP so that both were aware of the situation. He said that, if an appointment was cancelled by the parents, it would not be noted in the records as they would have gone through the appointments office. If the Hospital cancelled an appointment, a replacement would be given. However, he was not aware of any policy in Yorkhill of informing GPs when patients failed to attend clinic appointments.

Dr Paton said, in relation to a further appointment which he should have had with Calum but which did not take place, that if a patient did not attend the practice was that a letter would be sent to the patient, but not to the referring general practitioner. He said that, in Calum's case, there was no note on file to say that he failed to attend and that no letter had been written about a failed appointment. He said that this was clearly a problem within the hospital system.

Dr Paton said that, if a patient did not get an appointment it would take a while for the referring GP to work out as the GP would write, would know that there was a waiting list and would probably 'get a bit lost as to where you are in the system and it is not as tight as you would like in that sense,.'

There was clearly some breakdown in communication at the time of Emma's first referral to Yorkhill but it does not seem to me the delay in Emma attending for her appointment contributed to her death. There was no evidence before the inquiry to suggest that an earlier appointment for Emma would have resulted in different advice being given to Dr Shapiro to reduce or discontinue the prescription of fluticasone.

However, the evidence which was given in relation this matter did highlight that there appears to be no system for ensuring that referring general practitioners are kept informed by Yorkhill regarding the appointments which they have requested, certainly prior to the appointment date.

There is clearly an expectation by general practitioners that there may be some delay before an appointment is given. Dr Shapiro said that, at the time when he referred Emma, Dr Paton's waiting list would often be seven or eight months. Dr Thornton said that the routine specialist outpatient appointment was in the order of

several months and it was understandable that it did not seem exceptional to Dr Shapiro that Emma had not been seen by a specialist during the first part of 1998.

Accordingly, while I do not consider that this is a section 6(1)(d) issue, I do consider that is it is a relevant fact in terms of section 6(1)(e). It seems to me that it would be relatively simple to have a procedure in place whereby, when an outpatient appointment is requested by general practitioners, the referral is acknowledged upon receipt together with notification to the general practitioner of the date offered for a first appointment or the likely time-scale within which an appointment will be offered and subsequent notification to the general practitioner when the appointment is isssued. Accordingly I would recommend that there be a review of the practice in Yorkhill relating to first referrals of a child in order to establish whether a staightforward system to achieve this might be put in place.

- **Review of practice in matters concerning prescribing and monitoring of inhaled corticosteroids**

Dr Donaldson said that he and his colleagues intended to complete and publish their study on the data on the children taking high doses of fluticasone who were recalled to Yorkhill after Calum's diagnosis. He was of the view that practice guidelines thereafter might be issued by the Chief Medical Officer to include counselling families whose children were on fluticasone and the other inhaled corticosteroids, both within and outwith licensed doses. He envisaged that this might involve a written plan, including the use of oral steroids when appropriate in the former case and synacthen testing and a written plan including the use of oral steroids and hydrocortisone injection where necessary in the latter case. Dr Donaldson said that he and his colleagues were concerned about putting families off giving inhaled steroids. He said that knowledge about side effects is now very widespread and that there will be few practitioners in Scotland who would prescribe outwith licence without thinking very carefully for fluticasone.

Dr Paton said that a policy of the specialist prescribing and keeping under review patients on high, off-licence doses of steroids is a very sensible one which he would now follow. However, he said that the question of monitoring adrenal function was less clear. He said that he thought that many centres around the UK, including Yorkhill, were trying to work out who actually needs adrenal function testing, when they need it, what form that testing should take and when the patient should be re-tested. He said that there was no clear protocol for this yet and that this was a matter of ongoing debate. He also said that different centres have different pressures and thought that choices were being made about patient management which differed from centre to centre.

Dr Thornton said that consideration should be given to methods to enable practitioners to keep pace with the rapid development of guidelines and to use them effectively in practice. He said that relevant guidelines in asthma management have been issued or updated in 1990, 1996, 1997, 1998, 1999, 2003 and 2004, that the latest BTS guideline on asthma management runs to 91 pages and even the quick reference guide contains 17 pages of flow diagrams and charts. He said that it was difficult for busy doctors to absorb all this rapidly changing information and to use it

consistently in the pressured environment of modern general practice. He said that in future, the development of GP computer systems to provide intelligent support for prescribing, that links diagnosis, patient's age, current guidelines and safety margins could assist general practitioners to keep pace with the rapid proliferation of guidelines and protocols in modern medicine and ensure appropriate guidance is available at the point of prescription and, if further developed, could highlight when off-label prescribing is about to occur and provide links to evidence, where it exists, that would support or counter the advisability of such action.

In his commentary to the *Todd et al 'Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom' (14),* Professor Russell said that '...it would seem sensible to try to identify those few individuals in whom adrenal suppression has occurred by assessing adrenal function. My suggestion would be that children on FP in doses greater than or equal to 1,000 microgrammes per day should have a low dose short ACTH stimulation test but the precise details of what should be done and to whom will depend on local practices and facilities.'

Dr Todd said that all clinicians should have access to the data, clinical studies and all other information lodged in support of a licence application. In response to this point, Dr Leather said that Glaxo had a medical information line, which was available to clinicians to ring to request data, and that Glaxo are currently about to make all of their clinical studies available on the internet, to include all data on file as well as published data. He said that the data for Flixotide would be appearing on the website during the course of the next year.

Dr Todd's concerns centred principally upon fluticasone and he also recommended that the 250 and 500 microgram devices for Flixotide should be withdrawn and that there should be a re-examination of all the clinical studies which were carried out for the initial licensing application for the drug in 1993. He said that the message that fluticasone is more potent and should be taken at half the dose had become confused by the fact that it is available in large dosage devices. Dr Leather said that many medicines were available in adult and paediatric doses and that the highest dose available is the only dose licensed to treat chronic obstructive pulmonary disease. He also said that since that time there have been many more studies in fluticasone carried out by Glaxo, their competitors and clinicians world-wide. He stated that the data supporting Flixotide is greater than at the time of launch and his view was that an independent review such as the Cochrane Review was preferable to a re-examination of original data as the Cochrane Review examines literature from around the world, frequently updates its review and would include the original data from the original submissions.

In relation to the question of differentiating between fluticasone and the other inhaled corticoseroids, Dr Donaldson said that he wanted to be clear that he was certainly not 'gunning for' fluticasone. He said that he thought it was 'important not to get skewed on fluticasone alone and to deprive children of a very helpful medication' but said that he thought it had to be taken into account that 'it is a highly lipophilic drug, it is very effective, it is more potent and it is one to watch perhaps even more carefully'. He also said that 'it appears that if you need to give high doses of inhaled steroid then fluticasone commonly does not give you cushingoid features, does not cause severe growth failure. It can happen but it does not appear to be common and

therefore it does seem to be, of the three drugs, probably the drug of choice to go outwith licence, with all the precautions that arise.'

Dr Paton said that there were particular features of fluticasone which may be important in producing the side effect of symptomatic adrenal insufficiency but he did not know if this was a fluticasone-specific effect or was a high dose class effect. He said that this was being resolved by assuming that anybody on any high dose steroids, is at risk from this particular side effect. His assessment was that in some patients you need a high inhaled potency if you are going to attain asthma control without having to move to oral steroids, which have other side effects. He said that one of the key perceived advantages of fluticasone was that it was a steroid which was to be used at doses of half the amount of beclamethasone and the formulations available allowed use of fluticasone more easily at higher doses, which assisted patient compliance. He said that, just at the time when fluticasone, a potent steroid which was closer to an oral steroid, became available the medical profession was changing how it used inhaled corticosteroids, being more free with them, as highlighted by the step down approach of using high starting doses, as detailed in the BTS guidelines, and that for reasons of convenience fluticasone became the drug used when potency was required and the medical profession was 'seduced, made complacent by the fact that it does seem to be a very safe drug within the licensed dose...'

Dr Leather said that fluticasone had a niche position in the treatment of severe asthmatics and that therefore the use of out of licence doses was disproportionately reported in fluticasone compared to other asthma therapies. In illustration of this, he referred to a graph, extracted from the Dinlink database of March 2002, which showed brand shares of inhaled corticosteroids prescribed to patients under 16. The graph shows patient/brand percentages measured according to dosage amounts. This was separated into columns for each of the inhaled corticosteroids for low dose (up to 799 micrograms of beclamethasone or equivalent), moderate (800-1499 micrograms of beclamethasone or equivalent) and severe (1500+ micrograms of beclamehtasone or equivalent). He interpreted this as showing that in patients with mild asthma, Flxotide was used in less that 20% of cases, that in patients with moderate asthma Flixotide became used more often, in approximately 50% of cases, and that 100% of patients with severe asthma were taking Flixotide. Dr Leather said that he thought the reason fluticasone was used at higher doses was because of analyses such as that carried out by the Cochrane review, which Dr Leather said has shown benefit at high dose, and the lead given by secondary care physicians who have studied the scientific information and publications such as the Cochrane review. He thought that the bulk of high dose prescriptions would be initiated in secondary care. Dr Leather said its more severe form asthma is a disease that still has significant mortality. He referred to the contents of the National Asthma Campaign Audits of 2001 and 2002 and the Scotland Asthma Audit Summary of 2001 (11,13&12 respectively) to highlight the relevant figures in relation to this and to the prevalence of the disease and said that these gave a measure of the workload and the suffering that asthma causes.

A great deal of information was provided to the inquiry about the comparative potency and efficacy of fluticasone, including issues of oral and lung bio-availability, plasma half-life, volume of distribution and accumulation potential. In relation to the

question of the particular use of fluticasone in high doses, it seems to me from the evidence that I heard that it may well be, and indeed seems reasonable to assume, that dosage is dependent upon the severity of the asthma but it may also be that confidence in the safety of this drug makes some prescribers more confident about prescribing it in higher doses in order to control symptoms quickly.

In relation to all the inhaled corticosteroids there are issues regarding the impact upon measurable effects arising from dosage availability of the various inhaler devices, the varying degrees of compliance with taking medication and the probably imponderable issue of the difficulty in assessing the variability of individual patients and their consequent susceptibility to side-effects.

These and others are issues for the medical profession to consider when clinical judgements are made as to whether inhaled corticosteroids should be prescribed, which inhaled corticosteroids should be prescribed and the doses at which they should be prescribed.

What does appear to be a matter of agreement is that caution should be exercised in the prescribing of inhaled corticosteroids and that there is still no consistent practice in matters relating to the precautions which should be taken when they are prescribed. The 2003 new British Guidelines on the Management of Asthma, are, of course, of considerable assistance with their clear prescribing steps and strong advice regarding the stage at which referral should be made to a specialist.

It certainly seemed from Dr Shapiro's evidence that the awareness of side effects has changed. He described as 'a whole sea change different' the 2003 new British Guidelines on the Management of Asthma, which specified a dosage maximum for children under 5 years of 400 micrograms, one-fifth of the maximum in the previous guidelines. He commented that you could not fail to respond to that guideline.

However, it does seem to me that there is a need for advice regarding best practice in relation advising on side-effects and in monitoring such side effects, including possible adrenal suppression, in addition to prescribing. The question of an appropriate requirement in relation to the issue of steroid cards, perhaps also in cases where inhaled corticosteroids are prescribed in licensed doses, should also now be considered.

Taking all of these factors into account, I am of the view that consideration should be given by the appropriate authorities to conducting a review of the practice of general practitioners and hospital specialists when prescribing inhaled corticosteroids, with a view to assessing whether it is appropriate to issue comprehensive guidelines in relation to prescribing, specialist referral, informing patients about possible side-effects, monitoring to detect side effects and ancillary matters such as the issue of steroid cards.

Concluding remarks

I am grateful to all who took part in this inquiry for their assistance in making the very wide ranging and complex issues which were raised at the inquiry as clear and accessible as possible.

Many questions were raised and many, sometimes conflicting, answers were given about the comparative efficacy, potency and safety of fluticasone, the drug prescribed for Emma, and the other inhaled corticosteroids. These are clearly not matters upon which an inquiry of this kind could or should come to any conclusions. These are matters for those who have expertise in the fields of pharmacology and medicine to consider and evaluate and thereafter to advise practitioners upon. It was clear from evidence led that knowledge and understanding in this area is continually expanding and developing and changing.

At the outset of the inquiry, Mr Frame said that it seemed that people have accepted very readily that Emma had been, as he understood it, the only child who had died and that she had almost become just a statistic. He said that the day before Emma died she was bright and healthy, a five year old girl who loved her life. Mr Frame wanted to be sure that the people who took the decisions could explain why they did so and to understand just how this drug was licensed and controlled and marketed to general practitioners. Mr Frame said he believed that Emma's death could have been prevented and he wanted to understand why it had not.

While the cause of Emma's death has been determined, it became apparent during the course of the inquiry that her death came about as a result of a combination of several circumstances. I hope that all the questions that Emma's parents had have been raised and addressed at the inquiry.

I am in no doubt that it was Emma's death that largely precipitated the dissemination of warnings to the medical profession, including particularly the issue of the article published by the Medicines Control Agency and Committee on Safety of Medicines in the October 2002 Current Problems in Pharmacovigilance bulletin and of the 'Dear Healthcare Practitioner' letter from GlaxoSmithKline in November 2002. It has been said that the complacency about the safety of these drugs has been shattered. I hope that, as a result, the deaths of other children may have been avoided.

However, many of the clinicians who gave evidence spoke of the importance of there not being, in the words of one of the specialists who was quoted at the inquiry an 'outbreak of steroid phobia'. Dr Paton sounded a warning about this when he described a girl with severe life threatening asthma whose father read in a newspaper that oral steroids were poison and she stopped taking them that day and was in hospital shortly thereafter.

I would hope that this determination relating to Emma's death does not precipitate any such situation. Asthma is a very serious, potentially fatal, condition and it has become a very prevalent one. All the doctors who gave evidence on the subject, were agreed that inhaled corticosteroids have represented a significant advance in the treatment of asthma and have transformed the quality of life of many asthma sufferers.

Mr and Mrs Frame and other members of Emma's family were present throughout the whole of these lengthy proceedings. It must have been a very difficult time for them. I would like once again to express my deepest sympathy to them for their tragic loss.