RES MEDICA
Journal of the Royal Medical Society

Contents

ISSN: 2051-7580 (Online) ISSN: 0482-3206 (Print)
Res Medica is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

Res Medica, Summer 2003
doi:10.2218/resmedica.v0i0.2003

RES MEDICA

Journal of the
Royal Medical Society

Summer 2003

ADJUNCTIVE THERAPY FOR PARTIAL SEIZURES IN ADULTS WITH EPILEPSY

CONFIDENCE. BY KEPPRA.

ADD-ON THERAPY STARTS WITH

Keppra® ▼

levetiracetam

CONNECTING EFFICACY WITH TOLERABILITY IN AN EASY-TO-USE AED[1]

KEPPRA® Prescribing Information:

Please read Summary of Product Characteristics (SPC) before prescribing.

Presentation: Keppra 250, 500 and 1,000 mg film-coated tablets containing 250, 500 and 1,000 mg levetiracetam respectively. **Uses:** Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in patients with epilepsy. **Dosage and administration:** *Adults and adolescents older than 16 years:* The initial therapeutic dose is 500 mg twice daily which can be started on the first day of treatment. Depending upon clinical response and tolerability can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increments or decrements every two to four weeks. *Elderly:* Adjustment of the dose is recommended in patients with compromised renal function. *Children (under 16 years):* Not recommended. *Patients with renal impairment:* Adjust dose according to creatinine clearance as advised in SPC. *Patients with hepatic impairment:* No dose adjustment with mild to moderate hepatic impairment. With severe hepatic impairment (creatinine clearance <70ml/min) a 50% reduction of the daily maintenance dose is recommended. **Contraindications:** Hypersensitivity to levetiracetam, other pyrrolidone derivatives or excipients. **Warnings and special precautions for use:** If discontinuing treatment reduce dose gradually. **Interactions:** Keppra did not affect serum concentrations of phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin or primidone. Drugs excreted by active tubular secretion could reduce the renal clearance of the metabolite. Levetiracetam 1,000 mg daily did not affect the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel). Levetiracetam 2,000 mg daily did not affect the pharmacokinetics of digoxin and warfarin and prothrombin times were not modified. **Pregnancy and lactation:** Should not be used during pregnancy unless clearly necessary. Breast-feeding not recommended. **Driving, etc:** Caution recommended when performing skilled tasks, *e.g.* driving vehicles or operating machinery. **Undesirable effects:** Incidence of undesirable effects considered to be at least possibly related in controlled clinical studies: *Very common* (>10%): asthenia, somnolence. *Common* (between 1%-10%): GI disturbances, anorexia, accidental injury, headache, dizziness, tremor, ataxia, convulsion, amnesia, emotional lability, hostility, depression, insomnia, nervousness, vertigo, rash, diplopia. For information on post-marketing experience see SPC. **Legal category:** POM. **Marketing authorisation numbers:** 250 mg x 60 tablets: EU/1/00/146/004. 500 mg x 60 tablets: EU/1/00/146/010. 1,000 mg x 60 tablets: EU/1/00/146/024. **NHS price:** 250 mg x 60 tablets: £29.70. 500 mg x 60 tablets: £49.50. 1,000 mg x 60 tablets: £94.50. **Further information is available from:** UCB Pharma Ltd., 3 George Street, Watford, Hertfordshire WD18 0UH. Tel: 01923 211811. medicaluk@ucb-group.com

Date of preparation: December 2002.

Reference: 1. Cereghino J et al. Neurology 2000;55(2):236-242.

UCB Pharma

UCB-K-02-29

Contents

Editorial

For the first time in recent memory, Res Medica has been published twice in a single academic year. A brief glance at the articles shows that those responsible for this are the members – the majority of the articles this time around have come from people involved with the society in some capacity.

We will always need material for the next issue. As the journal is written for and by the society, we welcome contributions from any of the members. This request extends especially to those members who, now qualified, are working away from Edinburgh. Your knowledge and experience may be invaluable to future doctors, as well as of great interest to your contemporaries.

We also need people to help produce the journal in years to come. Most of the current team are approaching their final year at Edinburgh. Anyone who thinks they can help out will be very welcome – look out for notice of committee meetings, or get in touch with one of us.

Enjoy the issue.

David Griffith
Editor

The Rise and Decline of Operative Obstetrics
Or, The Joys of a Peripatetic Obstetrician

Kenneth Chapman MB, ChB.(Edin), FRCOG, FRANZCOG, MMSA

My wife was giving birth to twins in one of the most prestigious London teaching hospitals. The first had been safely delivered and we awaited the birth of her second. "Hadn't you better get on with the other?" I said after about 5 minutes. "Check the lie and rupture the membranes or something". "Certainly not", was the reply. "Your consultant is one of the most famous in the country. He has had 102 publications and the meta-analysis convincingly shows that awaiting the resumption of labour is by far the safer plan". I sat on disconsolate. Finally after about an hour there was sudden activity. A trolley arrived and the labour ward sister informed me that it had been decided that my wife should have her second twin delivered by Caesarean section. "Fools, vagabonds, swine," I yelled as I was dragged away, protesting, by two burly porters.

I awoke and it was a dream. This has encouraged me to share with you the joys of a peripatetic obstetrician who spent more than 40 years practising obstetrics when obstetrics, particularly operative obstetrics, truly was an Art. Sadly this is no longer the case, although one could, if one had the necessary experience, still practise this kind of obstetrics in a developing country where the patient would bless you for having saved her child and for having preserved her from a feared Caesarean section. It is almost impossible to convey the sense of achievement, joy and wonder when, bathed in sweat, after a difficult rotational forceps or breach delivery, one stands gazing at a new creation and shares with the parents their varying emotions.

I entered the Edinburgh Medical School in 1948, in the last of a batch of ex-service men, when the new National Health Service was just beginning. The obstetric lectures in those days concentrated very largely on the mechanisms of normal and abnormal labour and the convolutions which the foetus went through during its passage to the outside world. These struck me as entirely rational, unlike much of medicine which we were then taught. It endeared the subject to me, so much so indeed that I wrote my Dissertation to the Royal Medical Society on an obstetric topic.

My appetite was further whetted when I did my normal deliveries (20 required in those days) in the Rotunda Hospital, Dublin. The teaching was good, but, after two deliveries in the hospital, all others were carried out on 'District' in the slums of Dublin. One experienced student would be sent out with one just starting his apprenticeship and, once there, they had to remain with the patient until she was safely delivered, the placenta was examined and risk of post-partum haemorrhage negligible. In those days the teaching was strictly "hands off the cord," and one waited until one thought that the cord had lengthened and the uterus had contracted and risen before using the uterus itself as a plunger to push the placenta out of the vagina. Now, as students, we found this waiting for completion of the third stage particularly irksome, especially as by this time we were usually tired and hungry. I had never heard of Brandt[1] or Andrews[2] who had written earlier about a method which, several years later, was to be developed into the system now used today and known as 'controlled cord traction.' I reasoned, however, that if the uterus were well contracted and I pulled on the cord, it

would usually deliver the placenta, with less pain for the patient and with greater speed and satisfaction for myself. I found that it worked well and, when my final obstetric viva came round, and I happened to be asked about 'conduct of the third stage of labour,' I had great pleasure in telling my Professor how I thought the third stage of labour should be managed. Sadly he did not agree with me and suggested that I should return in a few months to "resit the Final Examination!"

I finally passed and, after general medical and surgical house appointments, I proceeded to Bangour General Hospital in West Lothian. There, under the able tutelage of the late Dr Janet Worling, who, at that time, was Senior Registrar, I began my apprenticeship in Obstetrics in earnest. We are talking about operative obstetrics so I shall confine my discussion to this aspect of the subject, but will not describe the destructive operations which were still required from time to time in those days in cases of gross foetal abnormality, before ultrasound, amniocentesis and specialised laboratory investigations were available.

I learnt to determine head position by digitally examining the sutures. I became adept at giving chloroform anaesthesia with rag and bottle but, best of all, Janet Worling was magnanimous in allowing her Housemen to perform all the abnormal deliveries. This, for me, included at least twenty manual rotations and Haig Ferguson forceps deliveries. I learnt to grip the head by the narrower bitemporal diameter, to use the right hand for right occipito-lateral positionsand the left for left occipito-lateral positions. I learnt to use the spare hand abdominally to assist the rotation by exerting pressure on the anterior shoulder, and to prevent the foetus from rotating back to its original position until ready to apply the first forceps blade, which is done with the rotating hand still in situ.

Assisted breach deliveries by the Housemen under Janet Worling's supervision also took place from time to time. Although I modified her method of allowing the breach plenty of time to descend before commencing the delivery at a later date, in that I subsequently considered a very slow descent of the breach in the second stage of labour as indicative of borderline disproportion and, therefore, unsuitable for vaginal delivery. Nevertheless, after a year with her I had successfully delivered some eight or nine singleton breaches by myself without loss. She also introduced me to the art of internal version and, during my time at Bangour, I carried out three internal versions for prolapsed cord, also without foetal loss. This gave me tremendous confidence with any intra-uterine manipulation, for I learnt to identify the foetal spine and to distinguish the foot from the hand by feeling the heel. Obviously such manipulations required the presence of liquor amnii, although uterine relaxation could be achieved with chloroform.

After a further year spent at the Samaritan Hospital in London engaged in gynaecology I proceeded to Queen Charlotte's Hospital where I shall forever be indebted to Mr Joe Holmes, the Resident Obstetrician, who taught me to use Kielland's forceps. Although I could use manual rotation confidently, nevertheless I could not guarantee a perfect application of the forceps blades every time, particularly if I was rotating a persistent occipito-posterior, for there was always an urge for the head to rotate backwards when the forceps blades were being applied. Much has been written about the risk of Kielland's forceps producing horrific tears. I have never had any, which I attribute to the fact that I have always paid strict attention to the way the blades are applied:

- After catheterization first assemble the blades with the indicator buttons and pelvic curves facing the occiput.
- Then take the anterior blade and insert it into the vagina below the brow until the fenestration has disappeared from view whilst, all the time, keeping the handle pressed against the patient's opposite buttock.
- Thirdly, while keeping the leading edge of the blade tilted slightly towards the foetal skull, wander the blade over the brow (while still keeping the handle of the forceps pushed as far laterally as possible) until it sits snugly over the temporal bone of the foetus. Although many

student obstetricians find the application of the anterior blade difficult, in fact, if done properly, it is very easy.

- The posterior blade is the difficult one to apply. To achieve this insert the left hand and fingers in the hollow of the sacrum, and move them slightly to the left and upwards until the finger tips are above the sacral brim in front of the patient's right sacro-iliac joint. Next insert the posterior blade over the hand and fingers, which protect the maternal soft tissue from trauma, and then jiggle the posterior blade to the midline until it locks with the anterior blade. There may be some apparent asynclitism but, since it is a sliding lock, this can easily be corrected.
- Next depress the forceps handles until they are at an angle of 60° to the floor and slowly rotate the forceps by gripping the forceps handles at their proximal shoulders. The rotation can be made easier by grasping the whole handle between the proximal and distal shoulders with the other hand provided you insert the middle finger between the two handles to avoid compressing them.
- All these manoeuvres should have been performed between contractions.
- Check that the leading edges of the forceps blades are below and parallel to the lambdoidal sutures and you are ready to deliver the patient. You can now perform your episiotomy which needs to be a generous one.
- With the next contraction, or sooner if there is foetal distress, while keeping the handles initially at 60° to the floor you can exert traction on the proximal shoulders of the forceps, and I stress again, do not compress the handles between the proximal and distal shoulders.
- As descent occurs the hands will rise and, just before crowning, the blades can be removed and one hand used to deliver the head by grasping it in the bitemporal diameter while the other hand guards the perineum.

My Registrar appointment at the Whittington Hospital allowed me to become expert in all types of delivery without the need for supervision which I had had as a Houseman and Senior Houseman. Thus I became as adept at bringing down a posterior arm as in performing Lovset's Manoeuvre for delivering extended arms in breach deliveries and in using the Mauriceau-Smellie-Veit Method as an alternative to forceps for delivery of the after-coming head. In both of the latter cases however I prevented the head from popping out too quickly by using an assistant to exert pressure on the brow if the former method were employed or, if I was delivering with forceps, I would complete the delivery by grasping the forceps where they locked with one hand while exerting pressure on the foetal brow with the thumb of my free hand. In this way I was able to deliver breaches sufficiently expeditiously to prevent asphyxia but sufficiently gently to avoid tentorial tears and intracranial haemorrhage.

Delivery of the second twin also engaged my attention and I found that if it presented by the breach it was best and most safely delivered by immediate breach extraction, if transverse by internal version and breach extraction, and if presenting by the vertex, rupture of the membranes alone would sometimes suffice. If however contractions did not speedily resume syntocinon could be given or, alternately, internal version and breach extraction could be employed, although in these cases if most of the liquor had drained away, general anaesthesia and uterine relaxation obtained with halothane was advisable. Unlike cases where chloroform used to be used, some degree of post-partum haemorrhage often occurred, but this usually ceased once the halothane had been discontinued. As noted previously this type of intra-uterine manipulation intrigued me and I wrote a paper on its utilisation at Queen Charlotte's Hospital over the preceding 25 years[3]. I also dealt with no less than three cases of monoamniotic twin pregnancy during my time at the Whittington Hospital[4].

The Ventouse was beginning to be used during my sojourn at the Whittington and, although it never endeared itself to me, I found it useful to augment contractions in cases of foetal distress in the first stage of labour to rapidly obtain full cervical dilatation. On one occasion, when I thought the membranes were ruptured, I employed this method and achieved rapid

dilatation of the cervix and delivery of an unmarked infant. The membranes, as a matter of fact, were intact and I had used the membranes of the forewaters as a metreurynter. The Senior Registrar considered that it warranted further research[5] and it gained us the Whittington Hospital Research Prize for that year.

Finally, I also taught myself to apply the anterior blade of Kielland's forceps by the classical method so that I had this in my armamentarium should I ever come across a case where I could not apply the blade by the wandering method.

I am also grateful to the Consultants, the late Mr John Marshall Scott and Mr Richard Law, for encouraging me, when there was a real emergency, such as a ruptured uterus with the tear extending into the broad ligament, to immediately perform Caesarean hysterectomy without wasting precious minutes in trying to obtain their permission, something which nowadays, sadly, would not be acceptable. This reminds me of a telephone call I had two or three years ago from a Registrar in a famous London teaching hospital when I was still engaged in private obstetric practice. He had read a case report I had written about a patient with placenta praevia percreta whom I had managed safely a few years before where, besides Caesarean hysterectomy and repair of the bladder, I was forced to ligate both internal iliac arteries because of continuous heavy bleeding[6]. "And how did you get on?" I asked eagerly after I had answered many of his questions about a similar case of his. "Oh, the woman died," he replied ruefully. These tragic events are likely to become more common, even if the labour wards of our country are manned by inexperienced Consultants.

This then was the type of training and experience which one was likely to obtain in good obstetric departments in the United Kingdom in the 1950's and 1960's when operative obstetrics had reached its zenith. There were, of course, many where the training and teaching left much to be desired and, unfortunately, the quality of obstetric care is judged by the lowest common denominator. The result is that, in this litigious age in which we now live, the only 'safe' abnormal delivery, apart from simple 'lift-out' forceps, is Caesarean section. Even in the best obstetric departments, of course, one can see in hind-sight that, in certain circumstances, Caesarean section would have been the better option. One remembers particularly cases where women with occipito-posterior positions were allowed to labour for 48, or even 72, hours before being delivered by rotation and forceps extraction, sometimes still with a rim of cervix persisting. Such women were often so mentally traumatised that they never embarked upon a further pregnancy. The elderly primigravida was another case in point where Caesarean section was often the better option, while delivery of the breach with borderline disproportion was fraught with risk. For the latter scenario I subsequently developed a 'trial of breach' where I considered a prolonged first stage or delayed descent in the second stage of labour as indicative of disproportion.

When I moved to Iran I had full scope to practise the type of obstetrics which I loved. In the University of Isfahan one frequently had to deal with cases of ruptured uterus where the foetus was dead, and where the woman might have travelled on the back of a donkey for two or three days from a remote village after the local 'handy'

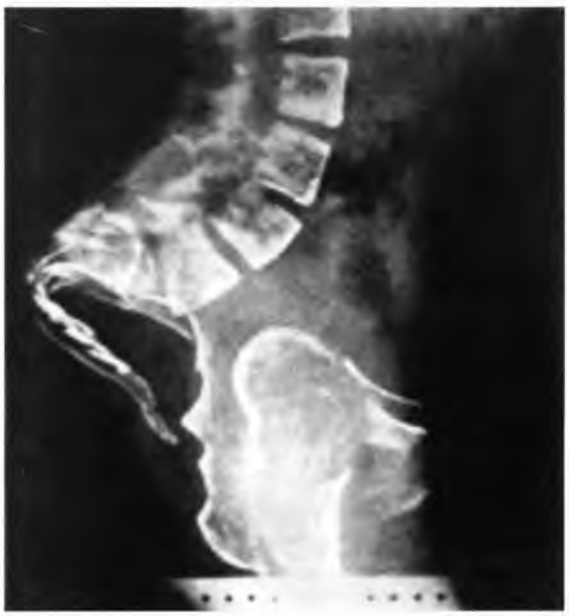

Figure 1. Lateral radiograph. Reproduction poor but showing characteristic osteomalacic sacral deformity.

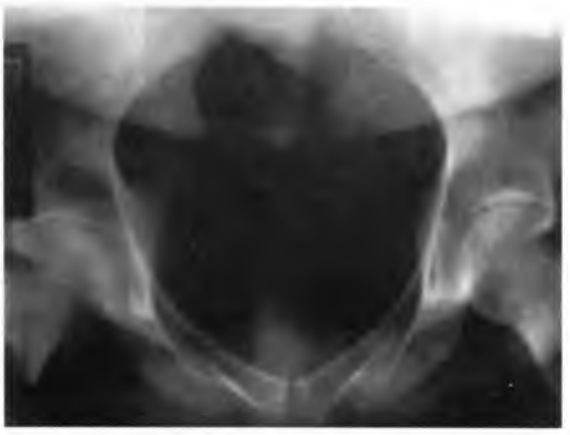

Figure 2. Radiograph showing anthropoid brim of woman who had an engaged brow in the second stage of labour.

woman had failed to deliver her. Such women, sadly, nearly always required Caesarean hysterectomy and it amazed me that I never lost such a patient, for blood was not usually available, unless supplied by a relative. These Iranian peasant women tolerated shock and degrees of anaemia which would have killed their European or American neighbours.

Osteomalacia, too, was common in those children and young women who had spent their developing years in dark, dusty factories making Persian carpets. Such women nearly always required Caesarean section, which was usually rendered difficult because the shape of the pelvis caused extreme dextro- or laevo-rotation and obliquity of the uterus [7](figure 1).

The ancient art of Braxton-Hicks[8] bipolar version was also used by me on three or four occasions in the second trimester where patients were bleeding heavily on account of major degrees of placenta praevia. Blood being unavailable and hysterotomy not wanted, I inserted two fingers through the cervix and placenta, and by careful manipulation with these, aided by external manipulation of the foetus with the free abdominal hand, I succeeded in grasping a foetal foot and pulling it out through the placenta, cervix and vagina. To this I would then attach a 0.5 kg weight. The half breach thus sat on the placenta and compressed it, bleeding ceased, labour commenced and three or four hours later the foetus and placenta would be delivered. The baby was usually dead or succumbed shortly after birth for in those days it was pre-viable. However, the woman's life was preserved and she had retained an intact, healthy uterus[9].

In Iran, too, my wife, Dr Roxana Chapman and I came across the first cases of Asherman's Syndrome or uterine synechiae which we had seen, caused, usually, by over-vigorous post-partum or post-abortal curettage, and presenting as secondary amenorrhoea. Diagnosis in those days was confirmed by hysterography; but division of the adhesions with sound or curette was less successful[10].

Moving later to New Zealand to establish an obstetric department in the hospital of a new town I had plenty of scope to practise good operative obstetrics and to save the patient, either from the hands of an inexperienced general practitioner, or from an eighty mile drive to the nearest obstetric department in a large city.

It was there too that my wife and I saw some cases which later stimulated us to write a paper on 'Premonition of foetal death', for we were able to show that a few women whose waking and sleeping hours centred around what they thought would be the death of their developing foetus actually did loose their unborn child. We were able to show that, in a very few carefully selected cases, the promise of elective Caesarean section just before term resolved the situation and provided them with a live baby[11].

Three years later we moved across the Tasman Sea to Sydney where we remained practising obstetrics (as well as gynaecology), privately, until the end of 1986. I was very busy performing about 250 deliveries a year and it was a joy to see many of the same patients year after year for their second, third or even fourth deliveries. The litigation plague had not reached Australia when we were there and I was able to show that secondary brows could be safely delivered by Kielland's forceps rotation and extraction and, by obtaining post-partum X-Ray pelvimetries with antero-posterior, brim, lateral, and outlet views, I demonstrated that they all had long oval

or anthropoid brims and that labour had commenced with the foetus presenting in the occipito-posterior position[12] (figure 2). One also saw abnormal cases from time to time in Australia, as well as New Zealand, which taxed one's ingenuity, and which were of sufficient interest to report[3,13-15] (figures 3 & 4).

We also collected many more cases of Asherman's syndrome in New Zealand and Australia, and had our first successes in treating such patients, in that they not only resumed normal periods but that some subsequently became pregnant. Thus we were able to show that it was of world-wide distribution and not confined to developing countries, as had been previously taught[16] (figure 5).

We returned to the United Kingdom in 1986 where I still maintained a private obstetric practice until about three years ago. Due to the fact that medical insurance refused to pay for obstetric confinements unless there were definite complications, most British patients preferred to use the National Health Service so most of my patients came from overseas. My greatest success was in presenting an Indian Minister's wife with a live child after she had had four pregnancies, no living children and a ruptured uterus on two occasions. I kept her at rest in bed from the 18th week onwards and had weekly and, later, twice weekly oblique ultrasounds to show the width of the lower segment at its junction with the bladder. It is likely that slight dehiscence occurred at the 20th week, but thereafter nothing

Figure 3. Triplet placentae with papyraceous twins attached.

untoward happened until the 31st week when a very large deficiency became obvious. I carried out immediate Caesarean section and delivered a live child who was lying in an intact amniotic sac which bulged through a hole in the uterus the size of a foetal head. I had taken the precaution of giving the mother weekly injections of dexamethasone from the 25th week onwards and I was happy to see that no respiratory complications occurred in the neonatal period[17]. Three years later the mother came to England for a holiday and brought her daughter to show me.

We had several more cases of Asherman's syndrome after returning to England and were able to show that two-stage hysteroscopic laser treatment of severe cases, where three- quarters, or more, of the uterine cavity had been obliterated by adhesions, allowed such patients once again to conceive and have live children[18]. My wife, Dr Roxana Chapman, is the laser surgeon and bears the credit, I merely subsequently delivered them.

Figure 4. Monoamniotic twin placentae with cord entanglement and true knot in one of them.

I continued to practise obstetrics, as I had always done, until I retired two years ago, not listening to purveyors of doom and, fortunately, was not involved in litigation. One interesting case which I remember was an abdominal pregnancy which masqueraded as an ovarian malignancy[19] (figure.6). My last

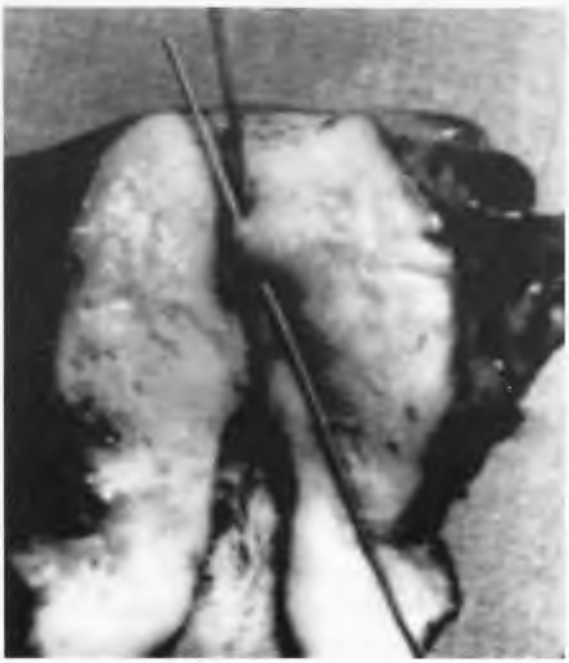

Figure 5. Opened uterus exhibiting a very thick fundal synechia.

Kielland's forceps rotation and extraction was performed on a westernised Arabian Princess who was highly delighted with the outcome. I should add that, for the last 30 years, I have performed all my Kielland's rotations and deliveries under pudendal nerve block, unless the patient happened to be under epidural anaesthesia at the time, and no patients have ever complained to me of pain in association with this type of anaesthesia.

The only vaginal complication which the modern obstetrician is likely to come across, and where advances have been made, is in the management of shoulder dystocia. Those interested should read the excellent monograph on this by O'Leary[20].

References.

1) Brandt ML. The mechanism and management of the third stage of labor. Am J Obstet Gynecol 1933; 25: 662 – 667.

2) Andrews CJ. The 3rd stage, Brandt placenta expression. Southern Med Surg 1940; 102: 605 – 608.

3) Chapman K. Internal version (a review of 118 cases) J Obstet Gynaecol India 1967; 17: 368 – 380.

4) Chapman K. Monoamniotic twins. Lancet 1974; 2: 1456.

5) Jones JB, Chapman K, Taylor RW. A new use for the Ventouse. Lancet 1963; 1: 1397 – 1398.

6) Chapman K, Chapman R. Placenta praevia percreta with bladder infiltration. J Obstet Gynaecol 1999; 19: 539 – 540.

7) Chapman K. Osteomalacia in Iran. J Obstet Gynaecol Br Cwlth 1971; 78: 857 – 860.

8) Hicks JB. On a new method of version in abnormal labour. Lancet 1860; 55, 2: 28-30.

9) Chapman K. Bipolar version in the management of haemorrhage from placenta praevia. Obstet Gynecol 1972; 40: 373 – 376.

10) Karimi R, Chapman K. Traumatic uterine synechiae. Irish J Med Sci 1974; 148: 319 – 324.

11) Chapman K, Chapman R. Premonition of foetal death. Stress Med 1990; 6: 43 – 45.

12) Chapman K. Aetiology and management of the secondary brow. J Obstet Gynaecol 2000; 20: 39 – 44.

13) Chapman K. Twin papyraceous foetuses in a triplet pregnancy. J Obstet Gynaecol 2000; 20: 317 – 318.

14) Chapman K .Failure to diagnose monoamniotic twin pregnancy by ultrasound but with fortunate outcome. J Obstet Gynaecol 1999; 19: 310 – 311.

15) Chapman K. Cervical pregnancy with hydatidiform mole. Acta Obstet Gynecol Scand 2001; 80: 657 – 658.

16) Chapman K, Chapman R. Asherman's Syndrome: a review of the literature and a husband and wife's twenty year world-wide experience. J Royal Soc Med 1990; 83: 576 – 580.

17) Chapman K, Meire H, Chapman R. The value of serial ultrasounds in the management of recurrent scar rupture. Brit J Obstet Gynaecol 1994; 101: 549 - 551.

18) Chapman R, Chapman K. The value of two stage laser treatment for severe Asherman's Syndrome. Brit J Obstet Gynaecol 1996; 103: 1256 - 1258.

19) Chapman K. Abdominal pregnancy masquerading as an ovarian malignancy. J Obstet Gynaecol 2001; 21: 194 – 195.

20) O'Leary JA. Shoulder dystocia and birth injury: prevention and treatment. .McGraw-Hill, Inc., New York, 1991.

Figure 6. A 7cm diameter haemorrhagic mass containing placenta, gestational sac and a 3cm embryo unidentified by preoperative ultrasound.

Is Affective Priming Possible?

Thomas C. Russ
Undergraduate Medical Student, University of Edinburgh
T.C.Russ@sms.ed.ac.uk

INTRODUCTION: This study is a replication of Murphy and Zajonc (1993), Jenner (2000), and Chalmers (2000) in order to test the affective priming hypothesis.
METHOD: University of Edinburgh students were shown short exposures of faces showing emotional expressions (affective primes) ranging from 12.5 ms to 44 ms. This was followed by a mask and then a neutral face which they were asked to rate for likeability on a scale from 1 to 5. Their recognition of the emotional face was tested by a separate experiment at each exposure time.
RESULTS: No affective priming effect was found either when there was no recognition of the affective prime above chance or when recognition was significantly above chance. However, the results do suggest that recognition of the polarity of emotion shown occurs before the recognition of the specific emotion.
CONCLUSION: This study does not support Murphy and Zajonc's (1993) affective priming hypothesis. The findings do suggest that the primary recognition of faces may be towards a positive/negative judgement with the identification of the specific emotion shown occurring later.

DUNCAN: There's no art
to find the mind's construction in the face.
Macbeth I iv

As King Duncan found out, the facial expression of an emotion is not so simple to interpret as it might seem. Even though 'emotion' is such a central concept to the human condition, it eludes precise definition.

What is an emotion?

William James (1884) answered this question by posing another: "Do we run from a bear because we are afraid or are we afraid because we run?" The first answer seems intuitively correct, but James' "thesis on the contrary [was] that the bodily changes follow directly on the perception of the exciting fact, and that our feeling of the same changes as they occur is the emotion" (James, 1884), i.e. we are afraid because we run away.

Furthermore James proposed that emotions were differentiated from each other by the physiological changes that 'caused' them. James' theory of emotion held a dominant position. until Cannon's (1927) claim that bodily changes in various emotions were not distinctive enough for James to be correct. However he did agree that it was the physiological changes that differentiated emotions from other states.

Following a dearth of research, the 1960s marked a period of change in the psychological attitude to emotions. Schachter and Singer (1962) synthesised James' and Cannon's theories and added a cognitive component. They suggested that the previously mentioned physiological changes result in a state of non-specific increased autonomic arousal. We then interpret this heightened arousal in the light of our situation *i.e.* social context, knowledge, and expectation. In effect they claim the emotional experience is a label given to a general physiological state which depends on a cognitive interpretation of the context the person finds themself in.

Schachter and Singer provided empirical evidence for their theory by injecting people with epinephrine and providing either pleasant, unpleasant or emotionally neutral situations, thus varying the mood reported by the participants.

Lazarus (1982, 1984) developed this school of

thought and provided evidence that emotions are dependent on the unconscious appraisal (*i.e.* interpretation) given to them. He goes so far as to say that "appraisal is a necessary as well as sufficient cause of emotion" (Lazarus, 1991, p. 352). In order to support his point he showed a film of a gruesome circumcision ritual with a narrative which either played up or played down the disturbing content of the film. The commentary significantly affected the subjects' autonomic responses and self-reports afterwards, leading him to his conclusion about the importance of appraisal.

Fundamental feelings or cognition the King?

Appraisal is still a major component contemporary psychological theory of emotion. However Zajonc (1980) has tried to turn the tide of cognitive psychology's influence in emotion by proposing that emotion and cognition are independent.

He first put forward this idea in 1980 by publishing a "rather speculative article" (Zajonc, 1984, p. 117) entitled "Feeling and Thinking: Preferences Need No Inferences". In essence his main question was whether we can "like something or be afraid of it before we know precisely what it is" (Zajonc, 1980, p. 154).

The paper referred to a large amount of empirical evidence involving the *mere exposure effect*— the phenomenon that repeated exposure to a stimulus "enhances [one's] attitude toward it" (Zajonc, 1968, p. 1), *i.e.* mere exposure to something can create a preference for it. Importantly however, this effect is still observed if the stimuli are presented subliminally, *i.e.* unconsciously (Kunst-Wilson & Zajonc, 1980). The participants will still prefer the stimuli they have already seen to new ones but will not be able to consciously differentiate between the new and old stimuli. More recently Murphy and Zajonc (1993) have investigated the phenomenon of *affective priming*, where "positive and negative affective reactions can be evoked with minimal stimulus input and virtually no cognitive processing" (p. 723). They found that sub-optimal exposure to an affective prime (facial expressions) could bias subjects' judgement of a neutral stimulus (Chinese ideograms) presented afterwards. The subjects were unable to recognise which face they had seen when presented with the face and a foil.

That preferences can be formed without any conscious recognition of the stimulus leads Zajonc to the conclusion that the emotional judgements (preferences) were formed without the involvement of cognition- in effect that affect and cognition are separate and partially independent systems, citing neuroanatomical separation of affect and cognition in support of his theory.

The debate in the psychological literature between Lazarus and Zajonc is quite involved and slightly confusing. They both base their theories on different definitions of emotion and they both admit that neither position is disprovable: "...the question contested here cannot be fully resolved unless we have a full understanding of consciousness" (Zajonc, 1984, p. 118); "...at this stage of theory, knowledge and methods, Zajonc can no more prove that cognition is not present in any emotion, much less before it occurs, than I can prove it is present" (Lazarus, 1984, p. 126).

Surely a feasible hypothesis would be that affect is primary, i.e. preferences can be formed without the involvement of cognition, but they seldom are. This fits in with Zajonc's explanation and also with Lazarus' dual neural pathways (sub-cortical and indirect, via the cortex). If cognition (which would react after affect) contradicted the emotional reaction, the cognitive reaction would predominate, as Lazarus' gruesome film experiment suggests. In other words, they could both be correct.

How do our faces relate to our emotions?

There is not room here to discuss theories of why we express our emotions in our faces. However, cross-cultural data suggest that there is universal expression of a number of so-called basic emotions (e.g. Ekman and Friesen, 1971; Ekman, et al. 1987; Ekman, 1992a, 1992b). These basic emotions including at least happiness, anger, fear, surprise, sadness, and disgust (Ekman, 1984), though there is some discussion about exactly how many and which emotions should be included. Ekman (1992) uses 'basic' in terms of having a biological basis, as well as combining to form more complex emotions. He cites

evidence of "different patterns of autonomic activity for the emotions of anger, fear, sadness and disgust" (p. 552), echoing James' original theory from 1884. He suggests that happiness or contempt wouldn't have distinct patterns of ANS activation because "it is unlikely that any specific pattern of motor activity [for such emotions] would have been relevant to survival. ... [However,] I do expect to find distinctive patterns of central nervous system activity marking each of the basic emotions" (p. 552).

A currently popular theory of the relation between emotions and facial expression is the *facial feedback hypothesis*— that "expressive behaviour plays a role in activating and regulating emotion experience" (Izard, 1990, p. 488). This idea dates back to Darwin (1872) ("even the simulation of an emotion tends to arouse it in our minds").

Where is emotion found in the brain?

An attempt has been made to describe the nature of emotions and their relation to cognition and an explanation of facial expressions of emotion has been touched on. Unfortunately there is not room for a thorough discussion of the neuroanatomical and neurophysiological findings regarding emotion. Therefore the discussion will be confined to two areas: the Papez circuit and recognition of disgust.

The most famous neural theory of emotion must be the Papez circuit (Papez, 1937). This derives from Broca's (1878) structural definition of 'le grand lobe limbique' (limbus = rim *(latin)*) and a distinction between the more primitive medial cortex and the lateral (neo-)cortex involved in thought processes and sensory/motor functions. The Papez circuit explains "the subjective experience of emotion in terms of the flow of emotion through a circle of anatomical connections from the hypothalamus to the medial cortex and back to the hypothalamus" (LeDoux, 1998, p. 87). Papez thought of the sensory inputs to the thalamus being split into a stream of thought and a stream of feeling.

The former was directed to the neocortex to form perceptions, thoughts, and memories and the latter was directed to the hypothalamus to form emotions. The cingulate cortex was where affective flavouring was thought to be given to everyday events.

MacLean (1949) took this model further and explained our frequent inability to adequately describe our emotions with the idea that the emotional 'visceral brain' and the 'word brain' used different languages. In 1952 he renamed the visceral brain the limbic system (harking back to Broca, 1878) to avoid confusion with the physiological concept of 'viscera'.

People with Huntington's disease or even merely the gene for it show impairments of emotion recognition with severe specific impairment of recognition of disgust (Sprengelmeyer et al., 1996; Gray et al., 1997). This differential impairment of different basic emotions (a similar situation occurs for fear with damage to the amygdala) gives weight to the theory that there are separate neural systems for the recognition of certain emotions.

Pathologically Huntington's disease is characterised by atrophy of the caudate nucleus and putamen (collectively, the striatum) and, to a lesser extent, the globus pallidus. There is also dilation of the lateral and third ventricles and frontal lobe atrophy (Cotran et al., 1999). This pathological data, along with the specific impaired recognition of disgust in those with Huntington's disease, implicates the basal ganglia and specifically the striatum in the recognition of disgust. Similarly impaired recognition of disgust is seen in obsessive compulsive disorder and Gilles de la Tourette's syndrome with co-morbid obsessive-compulsive behaviour (Sprengelmeyer et al., 1997) adds weight to the involvement of the fronto-striatal region in the mediation of disgust. Furthermore, fMRI studies have added even more support to the involvement of the striatum and the anterior insula in the recognition of disgust (Phillips et al., 1997; Phillips et al., 1998).

Method.

Participants

Twelve undergraduate students (8 female and 4 male in 12.5ms conditon or 7 female and 5 male in 25ms and 44ms conditions), mean age = 23.2 (12.5ms); 20.9 (25ms); 20.9 (44ms).

Materials and apparatus

Faces were from Ekman and Friesen's (1976) selection (Happy: PE, JB, JM, SW; Angry: EM, WF, NR, SW; Disgusted: JB, WF, JM, MO). Masking ideogram was constructed to provide optimal masking of the mouth and eyes of the primes. (Editor's note. To reproduce these would have infringed copyright. Instead, we took our own pictures. See figure 1).

Procedure

The participant was shown the twelve neutral faces in a random order preceded by a 12.5ms, 25ms, or 44ms exposure to an affective prime and a 30 ms ideogram mask. After each face the participant was asked to give a rating for how much they liked the face from 1 ('not at all') to 5 ('quite a bit'). They were asked to respond within the first few seconds of seeing the face. This was carried out on three separate occasions so that each face could be rated after priming with each emotion but the effect of the memory of seeing the same face earlier in the experiment would be minimised.

In each trial four of the faces followed happy primes, four followed angry primes and four followed disgusted primes. Each participant saw one of six arrangements of primes in relation to neutral faces (e.g. faces A to D primed with happy on one day, then angry, then disgusted or faces A to D primed with angry on one day, then happy, then disgusted etc.)

After each session the participant was shown exposures of the twelve primes (for an appropriate duration), each followed by the mask, and after each one asked to identify the emotion (out of happy, angry, or disgusted). This was to test recognition of the emotions of the primes.

Results.

Figure 2 shows mean correct identification of specific emotions and emotion polarity (*i.e.* recognising angry or disgusted as 'negative'; happy was the only 'positive' emotion). At 12.5 ms exposure neither emotion nor polarity could be identified above chance. At 25 ms exposure happy and angry, but not disgust, and positive and negative polarity were recognised above chance. At 44 ms only happy and negative polarity for angry were recognised above chance.

Figure 3 shows the mean 'likeablilty' rating of a neutral face following affective primes at 12.5 ms exposure. As can be seen there is no significant difference between rating of the faces. In other words, no affective priming effect was seen.

Figure 4 shows the mean number of misidentifications of angry or disgusted (the negative emotions). At 12.5 ms there is no difference in misidentification to positive or negative, at 25 ms there is a significantly higher number of misidentifications to the other negative emotion for angry and disgusted. This remains at 44 ms for disgust, but not angry.

Figure 5 shows misidentification of happy primes. Again, at 12.5 ms, there is no difference in positive or negative misidentifications. At 25 and 44 ms there is a significantly lower misidentification to negative emotions.

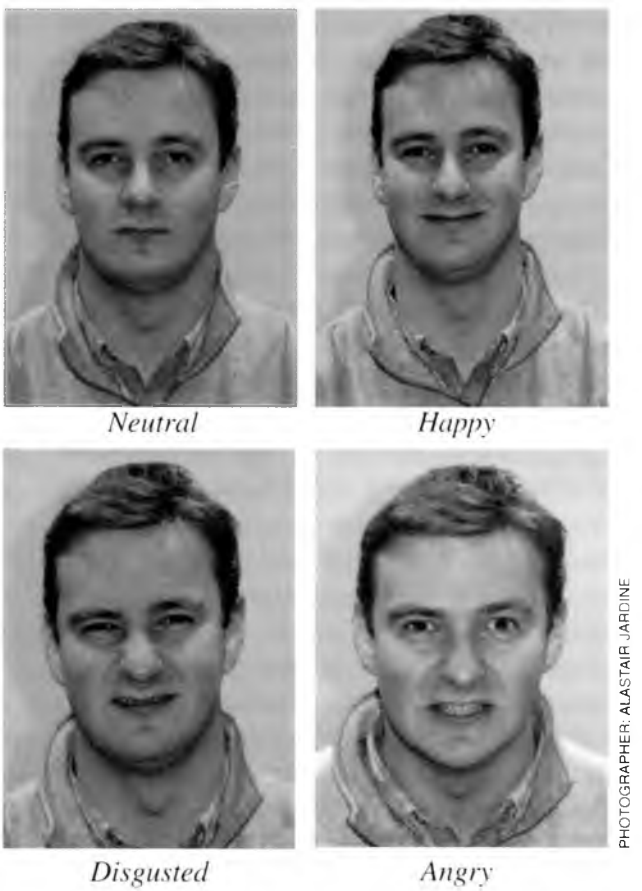

Figure 1. Reconstructions of the images used.

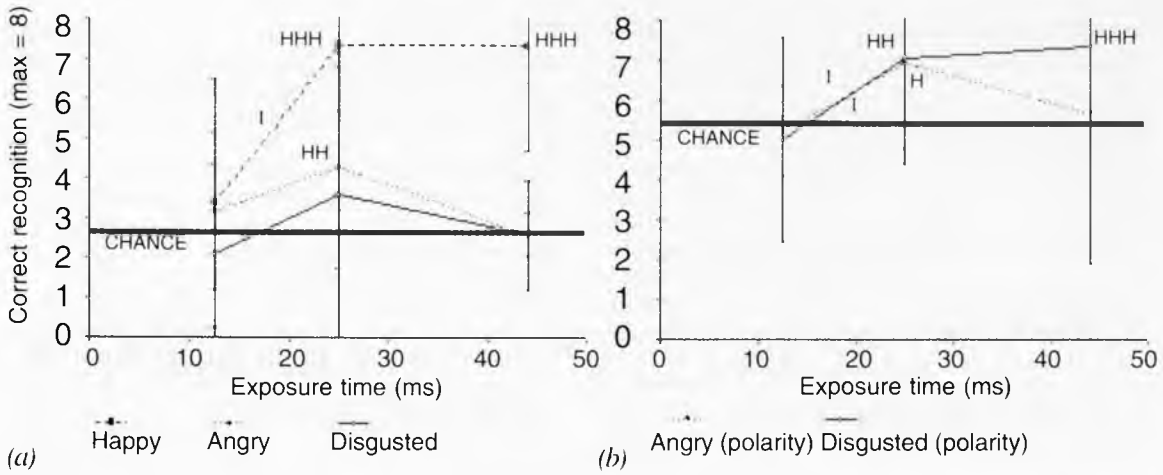

Figure 2 Mean correct recognition (± 2 SD) of individual emotions (a) and emotions categorised by polarity (b) at exposure times of 12.5, 25 and 44 ms. H = identification significantly above chance (H p < .05, HH p< .01, HHH p< .001). I = significant difference in identification between exposure times (I p< .05).

Discussion.

This study has found no evidence of affective priming with or without recognition of facial primes. Subliminal presentation of an affective stimulus before a neutral face failed to bias a judgement of likeability of the face.

Jenner (2000) and Chalmers (2000) found that happy was correctly identified by 29 ms exposure and anger and disgust were only correctly identified at 53 ms exposure. In the present study the results were not dissimilar: happy was correctly identified by 25 ms exposure and angry and disgust were not correctly identified above chance at 44 ms (the longest exposure time used), except for angry at 25 ms exposure (this identification was not evident at 44 ms). However the polarity of both angry and disgust were identified significantly above chance at 25 ms exposure and the polarity of disgust was correctly identified significantly above chance at 44 ms. Figure 2 summarises these findings.

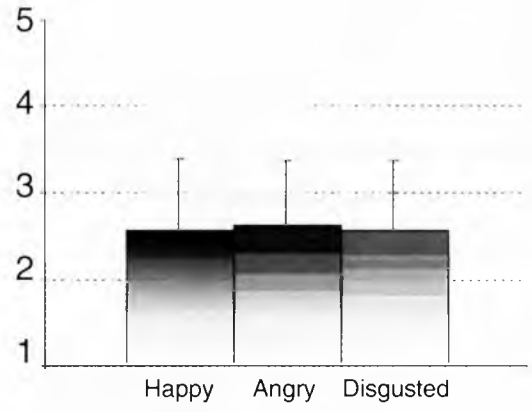

Figure 3. Mean rating of neutral face following affective primes (+ 2 SD). Rating was on a scale of 1 (don't like face at all) to 5 (like the face quite a bit).

It was noticed that angry primes were often mistaken for happy, possibly because of the bared teeth of half of the angry primes being mistaken for a smile. It is possible that the negative polarity in angry primes wasn't correctly identified at 44 ms because of this. Too little data in this experiment (12 subjects each identifying 12 primes) could possibly also play a part.

Furthermore, as the exposure time increases the number of errors which attribute the wrong polarity to disgusted primes decrease, leaving most of the errors to be errors of specific emotion but with the correct polarity being identified. At 12.5 ms exposure time there is no significant difference in the number of errors identifying the prime as the wrong polarity or the correct polarity for either angry or disgusted primes. By 25 ms exposure, the number of errors misidentifying the polarity of the emotion has decreased leaving a significant difference between misidentifications of the correct polarity and those of the wrong polarity. This continues at 44 ms exposure for disgusted primes but not for angry primes. Overall for angry primes there is no significant relationship between type of errors

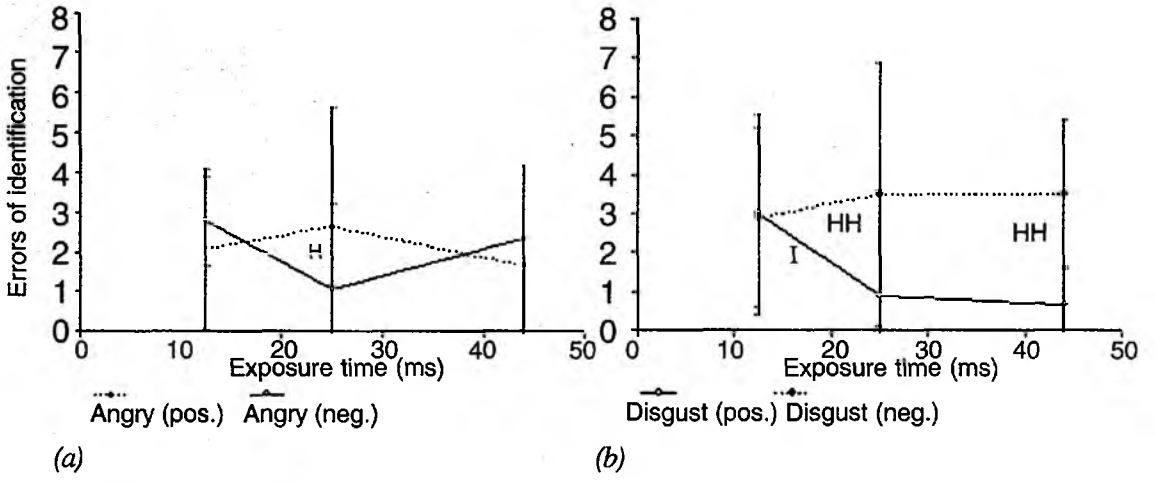

Figure 4 Mean number (± 2 SD) of misidentifications of angry (a) or disgusted (b). The polarity of the misattributed emotion is given in brackets. H = significant difference in identification between emotions (H $p < .05$, HH $p < .01$). I = significant difference in identification between exposure times (I $p < .05$).

and exposure time. These results are shown in Figure 4.

These findings, along with those for happy primes (Figure 5), suggest that the primary recognition of faces could be a positive/negative evaluation with recognition of the specific expression (happy, angry, or disgusted) coming in. at a longer exposure. The lack of such an effect for angry primes could be partly because of misrecognition of bared teeth as smiles, as mentioned above.

There are obviously weaknesses to this study, not least the number of subjects and the paucity of neutral faces available to rate (there are only 14 in the Ekman and Friesen (1976) series).

It would have been useful to analyse the rating of individual neutral faces when primed positively and negatively. Another positive emotion (*e.g.* surprise) would allow more useful comparisons of recognition of polarity.

In conclusion, this study does not support Murphy and Zajonc's (1993) findings and suggests that conscious exposure to affective primes, at least up to 44 ms, does not affect judgements of preference either. However it does suggest that recognition of polarity of emotion of a facial expression may occur before recognition of the specific emotion shown by the prime.

Acknowledgements.

I would very much like to thank my supervisor, Dr. T.K. Pitcairn, whose help was invaluable. I would also like to remember Richard Lazarus, a great psychologist, who died recently.

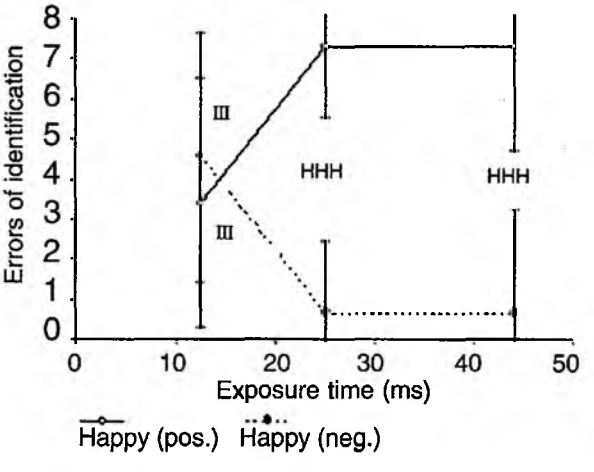

Figure 5. Mean number (± 2 SD) of misidentifications of happy primes. The polarity of the misattributed emotion is given in brackets. H = significant difference in identification between emotions(HHH $p < .001$). I = significant difference in identification between exposure times (III $p < .001$).

References.

Broca, P. (1878). Anatomie comparée des circonvolutions cérébrales. Le grand lobe limbique et la scissure limbique dans le série des mammifères. *Revue Anthropologique*, Ser 21 21, 385-498.

Cannon, W.B. (1927). The James-Lange theory of emotions: A critical examination and an alternative theory. *American Journal of Psychology*, **39**, 106-24.

Chalmers, E. (2000). Emotion, Cognition and Awareness: Is Affective Priming Possible with Suboptimal Stimulus Exposures? *Unpublished Undergraduate Dissertation,* University of Edinburgh.

Cotran, R.S., Kumar, V., Collins, T. (Eds.). (1999). *Robbin's Pathologic Basis of Disease,* 6th ed. Philadelphia, London: WB Saunders.

Darwin, C.R. (1872). *The Expression of the Emotions in Man and Animals.* London: Murray.

Ekman, P. (1972). Universals and cultural differences in facial expressions of emotion. In: Cole, J. (Ed.). *Nebraska Symposium on Motivation*, 207-283. Lincoln: University of Nebraska Press.

Ekman P. (1984). Expression and nature of emotion. In: Scherer, K., Ekman, P. *Approaches to Emotion*, 319-343. Hillsdale, NJ: Erlbaum.

Ekman P. (1992a). An argument for basic emotions. *Cognition and Emotion*, **6**, 169-200.

Ekman P. (1992b). Are there basic emotions? *Psychological Review*, **99**, 550-553.

Ekman P., Friesen, W.V. (1971). Constants across cultures in the face and emotion. *Journal of Personality and Social Psychology*, **17**, 124-129.

Ekman P., Friesen W.V. (1976). *Pictures of Facial Affect.* Palo Alto: Consulting Psychologists Press.

Gray, J.M., Young, A.W., Barker, W.A., Curtis, A., Gibson, D. (1997). Impaired recognition of disgust in Huntington's disease gene carriers. *Brain*, **120**, 2029-2038.

Izard, C.E. (1990). Facial expressions and the regulation of emotions. *Journal of Personality and Social Psychology,* **58**, 487-498.

James, W. (1884). What is an emotion? *Mind*, **9**, 188-205.

Jenner, A. (2000). Emotion, Cognition and Awareness: Is Affective Priming Possible with Subliminal Stimulus Exposures? *Unpublished Undergraduate Dissertation,* University of Edinburgh.

Kunst-Wilson, W.R., Zajonc, R.B. 1980). Affective discriminations of stimuli that cannot be recognised. *Science*, **207**, 557-558.

Lazarus, R.S. (1982). Thoughts on the relations between emotion and cognition. *American Psychologist,* **37**, 1019-1024.

Lazarus R.S. (1984). On the primacy of cognition. *American Psychologist,* **39**, 124-129.

Lazarus R.S. (1991). Cognition and motivation in emotion. *American Psychologist*, **46**, 352-367.

LeDoux, J.E. (1998). *The Emotional Brain.* London: Phoenix.

MacLean, P.D. (1949). Psychosomatic disease and the 'visceral brain': recent developments bearing on the Papez theory of emotion. *Psychosomatic Medicine*, **11**, 338-353.

MacLean P.D. (1952). Some Psychiatric implication of physiological studies on frontotemporal portion of limbic system (visceral brain). *Electroencephalography and Clinical Neurophysiology*, **4**, 407-418.

Murphy, S.T., Zajonc, R.B. (1993). Affect, Cognition and Awareness: Affective Priming with Optimal and Suboptimal Stimulus Exposures. *Journal of Personality and Social Psychology*, **64**(5), 723-739.

Papez, J.W. (1937). A proposed mechanism of emotion. *Archives of Neurology and Psychiatry*, **38**, 725-743.

Phillips, M.L., Young, A.W., Senior, C. *et al.* (1997). A specific neural substrate for perceiving facial expressions of disgust. *Nature*, **389**, 495-498.

Philips, M/L, Young A.W., Scott, S.K. *et al.* (1998). Neural responses to facial and vocal expressions of fear and disgust. *Proceedings of the Royal Society of London– Series B: Biological Sciences*, **265**, 1809-1817.

Schachter, S., Singer, J.E. (1962). Effects of elaborative processing on implicit and explicit memory for new associations. *Psychological Review*, **69**, 379-399.

Sprengelmeyer, R., Young, A.W., Calder, A.J. *et al.* (1996). Loss of disgust: Perception of face and emotions in Huntington's disease. *Brain*, **119**, 1647-1665.

Sprengelmeyer R., Young A.W., Pundt, I. *et al.* (1997). Disgust implicated in obsessive-compulsive disorder. *Proceedings of the Royal Society of London. Series B: Biological Science*, **264**, 1767-1773.

Zajonc, R.B. (1968). Attitudinal effects of mere exposure. *Journal of Personality and Social Psychology,* **9**, 1-27.

Zajonc R.B. (1980). Feeling and thinking: preferences need no inferences. *American Psychologist*, **35**, 151-175.

Zajonc R.B. (1984). On the primacy of affect. *American Psychologist*, **39**, 117-123.

Help!

We need articles for future issues. If you have a BSc project or an SSM which you'd like to see in print, or if there is a topic which interestes you enough to write about it, please get in touch with us.

Probing Fistulae in the G.I. Tract

Paul J Jenkins, Medical Student, University of Edinburgh
Pradip K Datta, Consultant Surgeon, Caithness General Hospital

Introduction

Fistulae are commonly encountered in general surgery. A fistula is an abnormal connection between two epithelial surfaces (figure 1). It can connect two hollow viscera together, or can connect a hollow viscus to the skin. In this way they can either be visceral and internal, or cutaneous and external. The connection between the surfaces is usually lined with granulation tissue.

A sinus is a granulating track from a source of infection to the surface. Sinuses can develop into fistulae if inadequately treated.

A fistula occurs as a complication of many different diseases, and from a variety of causes:

Congenital - tracheo-oesophageal fistula
Acquired - traumatic, e.g. rectovaginal fistula following labour
- neoplastic - carcinoma
- inflammatory - Crohn's Disease
- infective - diverticulitis
- fistula-in-ano
- iatrogenic - surgical (post-op)
- radiation

> "A fistula is an abnormal connection between two epithelial surfaces. It can connect two hollow viscera together, or can connect an hollow viscus to the skin. Gastro-intestinal fistulae are a surgical challenge."

Tracheo-Oesophageal Fistula

Tracheo-oesophageal fistula is most commonly found with oesophageal atresia as a **congenital abnormality**. It results from incomplete separation of the larynx and trachea from primitive foregut. In 85% of cases the upper end of the oesophagus ends in a blind sac. The upper end of the lower portion of the oesophagus communicates with the trachea at the level of T4. In 50% of cases there has been maternal hydramnios, and in many cases there are other congenital malformations.

Babies with this condition suffer cyanosis, choking and feeding problems. Regurgitation from the blind oesophageal sac leads to aspiration and pneumonia. This condition is distinguished from obstruction by the presence of choking rather than vomiting. Confirmation of the diagnosis is obtained by the failure to pass a soft catheter. Opaque x-ray contrast medium injected through the catheter shows the sac.

Emergency surgery is necessary within 24 hours

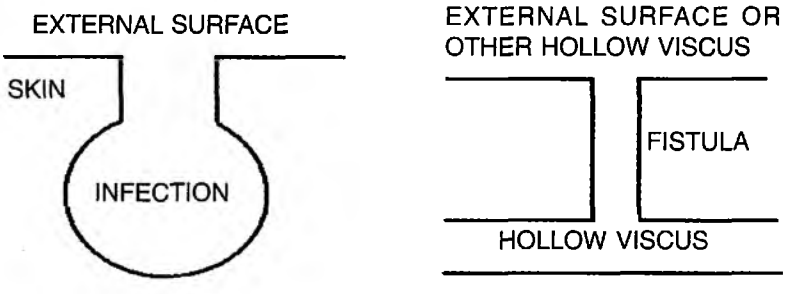

Figure 1. Examples of fistulae

to disconnect the oesophagus from the trachea and perform an end to end anastomosis with the free end of the oesophagus. In expert centres mortality is less than 10%.

In older patients, tracheo-oesophageal fistulae most commonly occurs in advanced **carcinoma of the oesophagus**. The tumour erodes the trachea. The condition should be obvious when a patient with dysphagia complains of severe coughing episodes on trying to swallow any food. This leads to aspiration pneumonia. The original diagnosis is confirmed by upper GI endoscopy which is followed by bronchoscopy.

Treatment is of the underlying condition. In very advanced disease the palliative insertion of a stent is the treatment of choice.

Abdomen

Gastrojejunocolic fistulae most commonly arise from a carcinoma of the stomach eroding into the transverse colon or vice-versa. This results in severe diarrhoea, foul gas being discharged, and the vomiting of formed faeces. Other symptoms of gastric carcinoma are present such as anaemia, asthenia and cachexia. The onset is extremely rapid.

Gastrojejunocolic fistulae are also a complication of posterior retrocolic gastrojejunostomy, and may also occur from chronic anastomotic peptic ulceration.

Anastomotic fistulae are usually cutaneous and present with bowel contents discharging through the wound several days post-operatively.

Pancreatic fistulae (cutaneous) commonly occur after operation on the pancreas for trauma, after Whipple's or after pancreatic necrostsectomy for severe acute pancreatitis and external drainage of a pseudocyst. The pancreas can enter a hypersecretory mode and can secrete as much as 2 litre of juice per day. Therefore, close attention must be paid to fluid balance in such patients. The patient should undergo an ultrasound scan to ensure there are no pancreatic fluid collections, but otherwise should heal rapidly. If the pancreatic duct has been disrupted, then distal pancreatectomy should be undertaken.

Aortoduodenal fistula is an uncommon complication of abdominal aortic aneurysm surgery. Patients commonly present months or years after operation with haematemesis or melaena. Urgent operation should be carried out to separate the duodenum from the graft, close any holes in the duodenum and remove the graft.

Crohn's Disease is a major cause of intestinal fistulae. It causes granulomatous transmural inflammation followed by axillo-inflammatory bifemoral graft. Approximately 25% of patients develop fistulae at some point, the anus being a common area. Crohn's presents with chronic diarrhoea, abdominal pain, weight loss and a spectrum of extra-abdominal symptoms. Fistulae are external or internal. External can be enterocutaneous or perianal. Internal fistulae are enteroenteric, enterocolic, enterovaginal and enterovesical. Confirmation of fistulae can be demonstrated with contrast studies. Abscesses must be drained and enterocutanous fistula can result from Crohn's disease through the same mechanism. Treatment depends on the level of the fistula. Those with low output (<1 litre/day) will heal by secondary intention. Those with high output must be surgically repaired with excision of the affected bowel loop. Steps must be taken

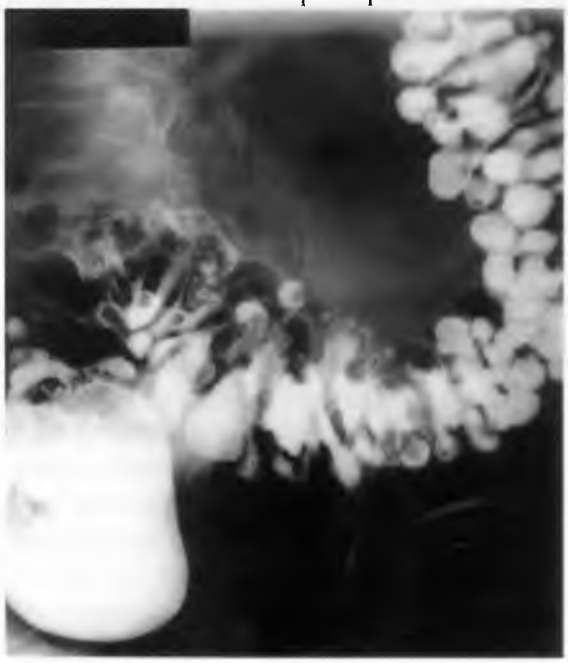

Figure 2. Barium enema showing severe diverticular disease

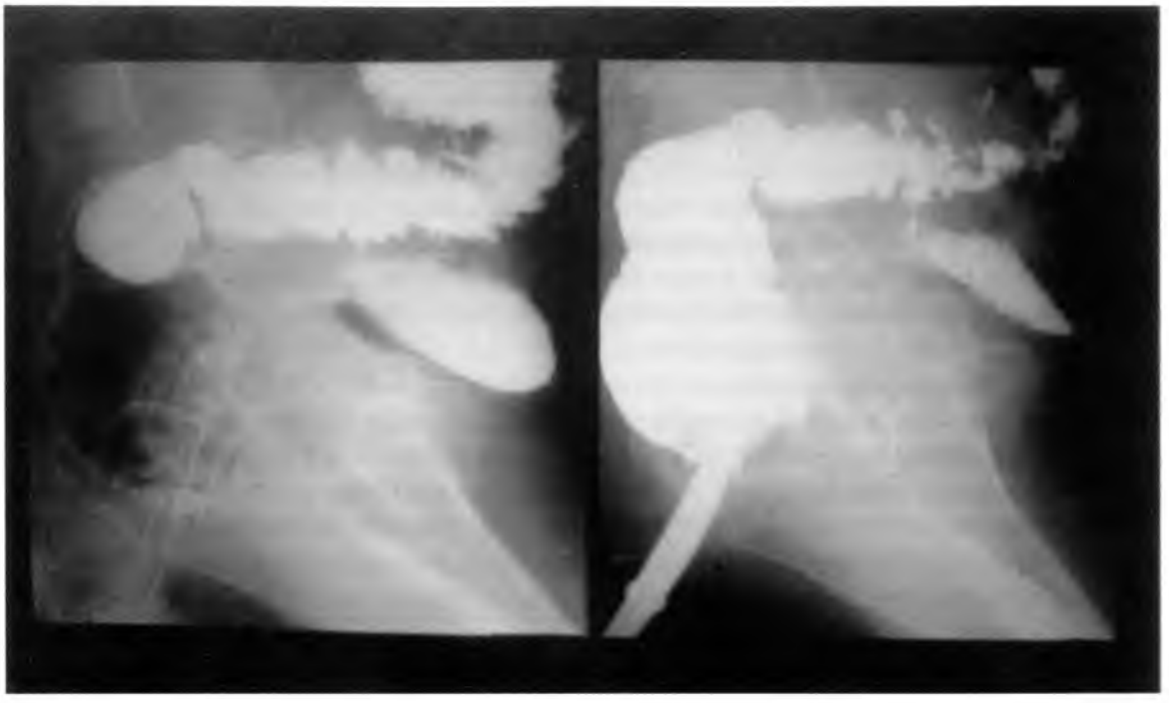

Figure 3. Lateral view of a barium enema, showing a vesicoclic fistula

to protect the surrounding skin from intestinal juices.

Diverticulitis is a condition with recurrent infection of diverticula in the wall of the colon (figure 2). These can form into pericolic abscesses. Rupture can occur into the peritoneal cavity. Alternatively, adherence of the inflamed colon to adjacent organs may result in fistulae between the colon, bladder, small bowel, skin or vagina. Fistulae occur in 2% of patients with diverticular disease, but are much more common in severe disease. Fistulae are present in 20% of patients requiring operative treatment. A history of recurrent left iliac fossa pain, with a swinging fever and leukocytosis, along with symptoms and signs of fistulation should point to diverticulitis as the cause of fistulation. Vesicocolic fistulae occurring through diverticular disease are tend to result in pneumaturia, whereas though arising through neoplasia more often give rise to faecaluria. Treatment of diverticulitis is with fluids and antibiotics (Metronidazole and Gentamycin), with drainage of any intra-abdominal abscesses.

Vesicocolic fistulae (figures 3 & 4) are most commonly found in Crohn's disease, diverticulitis and colonic carcinoma. This results in intractable cystitis and pneumaturia. Investigation is with MSU, barium enema, sigmoidoscopy, colonoscopy and cystoscopy. Intra-venous urography should be carried out to rule out obstruction or fistulae higher up the urinary tract.

Treatment is by laparotomy, with excision of the affected bowel loop, anastomosis, and repair of the bladder wall.

Fistula-in-Ano results from the rupture of anal subcutaneous and submucosal abscesses. These abscesses arise within glands in the anal wall and spread along tissue planes. They are inadequately treated by incision and drainage alone. The abscess may spread to the skin as a sinus with chronic discharge of pus. The sinus eventually will communicate with the anal canal higher up. Such fistulation occurs in 30% of abscess. An internal opening in the anal canal communicates with one or more openings in the perianal skin. The internal opening of the fistula may be felt on rectal examination. Fistulae are classified by their level and the structures of the anal canal they traverse. They are classified as subcutaneous, submucous, low anal, high anal, ano-rectal, and pelvirectal. Those entirely beneath the ano-rectal ring can be treated by the insertion of a probe, and incising down onto the probe to lay

Figure 4. Barium enema showing air in urinary bladder

open the fistula. The track is then laid open and left to heal by secondary intention. This has no effect on faecal continence as the external sphincter remains intact. In higher fistulae, the track can only be opened to the ano-rectal ring. A ligature is thus passed through the upper track and left for 2 to 3 weeks for scar tissue to form.

Goodsall's Rule is useful if the location of the internal opening is not obvious. *"If the external opening lies anterior to a line drawn transversely through the centre of the anus, the tract passes radially through a straight line towards the internal opening. If the external opening is posterior to the line, the track curves in a horseshoe manner to open into the midline pesteriorly".*

Gastro-intestinal fistulae are a surgical challenge. The best outcome is obtained by a multi-disciplinary approach between the surgeon and the gastroenterologist with help from the radiologist for diagnosis and the dietician for overall management.

Bibliography.

Wakelin SJ, Crofts TJ. Gastroduodenal disorders. In Garden OJ et al eds. Principles and Practice of Surgery, pp239-61. Edinburgh: Churchill Livingstone, 2002. Ref ID 434. Reprint: Not in file.

Garden OJ. The Pancreas. In Garden OJ et al eds. Principles and Practice of Surgery, pp262-91. Edinburgh: Churchill Livingstone, 2002. Ref ID 435. Reprint: Not in file.

Dunlop MG. Intestine and Appendix. In Garden OJ et al eds. Principles and Practice of Surgery, pp318-49. Edinburgh: Churchill Livingstone, 2002. Ref ID 436. Reprint: Not in file.

Dunlop MG. Anorectal Conditions. In Garden OJ et al eds. Principles and Practice of Surgery, pp350-67. Edinburgh: Churchill Livingstone, 2002. Ref ID 437. Reprint: Not in file.

Colonic Diverticular Disease. Current Problems in Surgery 2000; 37: 463-508. Ref ID 438. Reprint: Not in file.

An engraving entitled: "Melbourne Place and Victoria Terrace from George IV Bridge"

Matthew H Kaufman

Professor of Anatomy, Honorary Librarian of the Royal Medical Society

Section of Anatomy, College of Biomedical and Clinical Laboratory Sciences, University of Edinburgh, Hugh Robson Building, George Square, Edinburgh, EH8 9XD

I thought that the members of the Society might be interested in learning about an "engraving" that hangs rather inauspiciously on one of the walls of the Society's Library in Bristo Place (figure 1). This item is of interest in several regards, but principally because no copy of it is available in the Reference Collection of the Royal Commission on Ancient and Historical Monuments of Scotland (RCAHMS) in Bernard Terrace, Edinburgh. A detailed analysis of its features, however, reveals that this image is in fact a photograph of a very rare etching. The original is an anonymous etching that measures 23.9 by 41.3cm including the fine border line around it. It is based on a drawing by the architect George Smith (located in the Daniel Wilson scrapbooks, Vol 1, p 78, in the Library of the National Museums of Scotland). It is likely that

Figure 1. Etching dating from 1835, entitled: "Melbourne Place and Victoria Terrace from George IV Bridge," being the architect's proposal for this area of George IV Bridge.

the photograph was carefully hand-colored to enhance its overall appearance. What is particularly intriguing about it is that it is an architect's impression of what he envisaged this area should look like, rather than a view of the real scene. It was apparently submitted to a meeting of the Plans and Works Committee of the City Improvement Commissioners on 25 August 1834. The minutes of this meeting are located in the City Archives. The overall plan was approved on 12 February 1835. Melbourne Place was named after the 2nd Viscount Melbourne, who was Prime Minister from 1835-41, on 10 December 1835. He was also the premier at the accession of Queen Victoria. Victoria Street and Victoria Terrace were named after the heir to the throne on 6 October 1836. It was suggested on 20 October 1836: *"That an engraving of Melbourne Place should be displayed in as many public places as possible."*

This item is of interest because of the architectural details displayed. One of the most obvious features is that only the buildings located on the northern side of Victoria Street and Terrace are shown. All of the buildings on the western side of George IV Bridge, principally the Public Library and the buildings on the southern side of Victoria Street are absent. Those on the northern side of Victoria Street that front onto Victoria Terrace, at a higher level, to the west of the narrow passage known as Fisher's Close, are seen because the majority of them were of a considerably earlier construction. It is of interest that George IV Bridge was originally termed King George IV Bridge, was designed by Thomas Hamilton (1784-1858) and dates from 1829-32. It is curious that earlier maps of this area (e.g. the map of about 1831 published by Peter Brown and Thomas Nelson in the Map Collection of Edinburgh University Library) appear to show numerous small buildings on the south side of what was subsequently termed Victoria Street.These were demolished during the subsequent City Improvement Acts.

A careful inspection of the individual buildings along the northern side of Victoria Terrace would appear to indicate that relatively little has changed since the preparation of this engraving. It should be noted, however, that some of the detailed features of the premises that belonged to the Melbourne Place tenements block that were located in Victoria Terrace, were not included when these buildings were subsequently erected (figure 2). This includes the balcony associated with the second floor, and the central window of the fourth floor. More particularly, when built,

the end of the tenement block was at right angles to Melbourne Place, and had three rather than five windows on each floor, as shown in the etching. On the southern side of Victoria Street, no buildings are shown. The Highland and Agricultural Society's Museum is clearly seen in the 1852 Ordnance Survey Map, as well as in the 1846 Directory Map of this area, on the corner of the southern side of Victoria Street and George IV Bridge. John Henderson had originally designed this building (the plans are dated 31 July 1836, for a seedsman, Charles Lawson) but it was only built some years later. The upper floors of this building are now used to house theArt Library. The Dean of Guild Court approved the plans for this building on 19 September 1837. A number of other properties are also shown at intervals along the southern side of this street as it descends in a westerly direction towards the West Bow and the Grassmarket in these two maps.

Figure 2. Similar view of the southern end of the Melbourne Place tenements to that shown in Figure 1, in 1965, shortly before it was demolished. Crown copyright, RCAHMS.

The Public Library is not shown, and is in any case a much later addition to George IV Bridge, being designed by Sir George Washington Browne, and dates from 1887-90. Similarly, India Buildings, constituting 1-6 Victoria Street, dates from 1864, was designed by David Cousin, and is consequently not present in this engraving. More recently, the building that was formerly the Highland and Agricultural Society's Museum has been incorporated into the Public Library. The headquarters building of the Bank of Scotland is clearly seen in the distance, at the top of the Mound, at the northern extremity of Bank Street. The former headquarters building of the Bank of Scotland moved from Bank Close in 1805, to the head of Bank Street in about 1812. This imposing building was designed by Richard Crighton, but was later expanded in about 1846 by the architect David Bryce. Bank Street runs continuously in a north-westerly direction into North Bank Street. Other readily recognisable buildings are also seen where the Lawnmarket crosses George IV Bridge where it runs into Bank Street, such as the building that includes Deacon Brodie's Tavern. According to Grant (1880-3, Volume 1, p. 123), the County Hall building located almost directly opposite Melbourne Place, and presenting fronts to the Lawnmarket and St Giles, on the eastern side of George IV Bridge, consisted of a "very lofty portico [with] finely-fluted columns. The first building on this site was erected in 1817 and contained several spacious and lofty court rooms with apartments for the Sheriff and other functionaries employed in the business of the county." J. McIntyre Henry designed the Midlothian County Buildings, which succeeded them, and these date from 1900-05. In this etching, the earlier building is discreetly hidden by a wall, as the original County Hall building was considered at that time to be rather unsightly. The side of the County Chambers had inadvertently been exposed by the demolitions undertaken to make way for George IV Bridge.

Figure 3. View of the eagle rescued from the central gable above the fourth storey of Number 7 Melbourne Place and now located in the Society's premises in Bristo Place.

The present building of the National Library of Scotland is of only relatively recent construction, dating from 1956, and was built in a Classical-modern style. Reginald Fairlie designed it. The colonnaded building on the far right of the engraving, along the eastern side of George IV Bridge where the National Library of Scotland is now located, although a prominent feature of the drawing, was in fact never erected. It was designed by W. H. Playfair (1790-1857) but was considered too expensive to build. The original architect's drawings of this building are located in the Special Collections Section of Edinburgh University Library.

Clearly when the Royal Medical Society moved from their first hall at number 11 Surgeon's Square, the buildings in Melbourne Place had not only been built in a style similar to that shown in this etching, but were all well established. The architect George Smith designed these tenements along Melbourne Place. Jane Girdwood and others bought the land on which they were built from the Improvement Commissioners. They then petitioned the Dean of Guild Court, and the Warrant that enabled them to build these premises was granted on 17 May 1836. While the original architect's drawings for the Victoria Street end and other parts of the Melbourne Place tenements are available for analysis in the City Archives, the plans for Number 7 are not present. Accordingly, it is not possible to establish whether the central gable above Number 7 contained any sculptural embellishment on the original plans, although the impression is gained that this is unlikely to have been the case.

Of greater interest to present members of the Society, is the fact that there appears to be no evidence of an eagle with spread wings (Figure 3) surmounting the central gable of what shortly afterwards became the Society's premises at Number 7 Melbourne Place (Figure 4). The reason for this is straightforward. It was a feature that did not appear in the original architect's drawing, but was probably added as an embellishment to enhance the dignity of these properties when they were eventually built. It is unlikely that the eagle that surmounted the central gable of these premises had any other significance. This union of sculpture and architecture had been suggested by George Smith (1793-1877) in a lecture to the School of Arts in August 1827 (Anon, 1827).

Reference to Gray is particularly instructive in this regard, as he indicates that the Society purchased Number 7 from its original owners, and that the Society first occupied their New Hall in 1852. According to Gray: *"Melbourne Place was a recent City Improvement when the Society removed there"* (Gray, 1952, p.205). He continued: *"Dr George [sic] Wilson, ... in his Memorials of Edinburgh in the Olden Time* (Wilson 1848, Volume 1, 172), *indicated that ... Old Bank Close ... was demolished in 1834 to make way for it. The Old Bank, now known as the Bank of Scotland, which gave the ancient alley its name, carried on all its business in the close."* According to this source: *"The antique mansion that formed the chief building in this close, excited very great and general attention from the time that it was exposed to view in opening up the approach to George Forth's Bridge, until its demolition in 1834, to make way for the central buildings of Melbourne Place, that now occupy this site."* Gray (1952, p. 206) continued: *"... Messrs. James and John Grey, the owners of the building purchased by the Society ... were established in Melbourne Place towards the end of 1837."* Messrs. J. & J. Grey were the proprie-

tors of the *North British Advertiser* and a number of short-lived publications such as *Grey's Monthly Record* and *Grey's Weekly Record* (Gray, 1952, p. 206).

The antique mansion referred to here was Robert Gourlay's House that dated from "1569" (Gray, 1952, p.206, citing Wilson, 1848, Volume 1, p. 172), although Wilson (1848, Volume 1, 173-4) indicated that this house bore the date "1588". This somewhat later date coincides with the date that he and his wife, Helen Cruik, received a Royal Mandate from the King at Dumfries to build this house.

Two of the principal features that are evident in this engraving, however, are the gas fittings that illuminate all of George IV Bridge, and the iron railings that are shown along the western boundary of this thoroughfare. Almost identical railings are still seen at intervals along the western side of George IV Bridge. Mr. Thomas Hamilton had designed both these railings and the gas lamps, and the Committee in due course accepted his proposal. It appears that the subsequent cost of the railings and the gas lamps was £226-15-0. John Paterson of the Edinburgh Foundry made them. In order to prevent the iron railings from rusting, an extra charge of £10 was made by the Foundry so that they could be exposed to oil while they were still hot. It is clear that this treatment was extremely effective, as these railings still show no evidence of rust.

Reference to the detailed Ordnance Survey Maps of this area is particularly instructive, in that they provide information on the approximate date of construction and first appearance of the principal buildings displayed – if they were built. Confirmation of the relevant dates of many of the buildings seen in this engraving and their architects are available from the various books and other items of reference in the Edinburgh Room of the Public Library on George IV Bridge (see e.g. Anon (undated)).

Figure 4. Frontage to Number 7 Melbourne Place in 1965, shortly before it was demolished, showing the Society's main entrance doorway, flanked on either side by shops. The Society's premises consisted of five windows on the first, second and third floors. The eagle, with spread wings, is mounted on the central gable above the fourth storey. Crown copyright, RCAHMS.

Acknowledgements

I am indebted to Dr. J. Rock for his invaluable advice on the interpretation of the photograph of this etching, and to the staff of the Edinburgh Room, Edinburgh Public Library, George IV Bridge and the Edinburgh City Archives for their assistance.

References

Anon (1827). School of Arts. *The Scotsman*, 15 August 1827, column 4, 519 [report of a lecture delivered in the School of Arts].

Anon (undated). Buildings *of Special or Architectural Interest: Descriptive List: City of Edinburgh.* Edinburgh: RCAHMS – Scottish Development Office, St. Andrew's House.

Grant, J. (1880-3, but these volumes are undated). *Cassell's Old and New Edinburgh: Its History, its People, and its Places.* 3 Volumes. London, Paris and New York: Cassell, Petter, Galpin and Co., Volume 1, 116, 123.

Gray, J. (1952). *History of the Royal Medical Society 1737-1937.* Edinburgh: University Press.

Wilson, D. (1848). *Memorials of Edinburgh in the Olden Time.* 2 Volumes. Edinburgh: H. Paton; London: Simpkin, Marshall, and Co. [the author was Sir Daniel Wilson, not George Wilson, as stated by Gray (1952)].

Statins: More than Cholesterol Reduction

Rameen Shakur BA (Hons) MPhil (Cantab.)

Introduction.

This article contains information from a talk given by the author at the RMS on 14/01/03, entitled: Statins and Immuno-modulation: A New Frontier. Statins represent one of the major successes of cardiology in the secondary prevention of coronary artery disease. This article attempts to understand the very molecule which makes many quake in their boots, cholesterol, and how basic science research continues to find novel methods in which statin therapy can participate.

> "Currently the most potent treatment for hyperlipidaemia are the HMG-CoA reductase inhibitors or statins."

Large scale epidemiological studies in the general population, especially through the Framingham Heart study, the largest and most comprehensive medical study in the history of cardiology and some would say in modern day epidemiology, has identified several risk factors pertinent to the development of cardiovascular disease. The study based in the small town of Framingham on the outskirts of Boston, Massachusetts in the USA, has provided the means for risk assessment and public health targets in the prevention of coronary artery disease. Some of these risk factors for coronary artery disease include age, hypertension, hypercholesterolaemia, diabetes, and cigarette smoking [1]. However, one factor that has proved to be, and continues to be, one of the great successes of 21st century medicine has been the introduction of the HMG-CoA reductase inhibitors. Yet, to better comprehend this "magic drug" one has to appreciate the drug's target, that of cholesterol.

Cholesterol.

Cholesterol is a ubiquitous alicyclic compound, a member of the lipid family, which is distributed in both free and esterified forms throughout the body. Cholesterol can exist in a number of different structural isomers, from having a single hydroxyl group at C-3 to having an unsaturated centre between the C5 and C-6 atoms (see figure 1). Physically, cholesterol like other lipids is hydrophobic except for a single hydrophilic OH group, attached to which are several hydrophobic rings.

Given the hydrophobic nature of cholesterol, it is therefore surprising that the concentration of cholesterol in the plasma of healthy people is usually 150-200mg dL^{-1}. The high level of solubility of cholesterol in blood is attributed to the formation of protein-lipid complexes, called lipoproteins (ie. LDL and VLDL) which through the aid of apo-lipoproteins are able to bind and hence dissolve large amounts of cholesterol within blood. Physiologically, approximately 30% of the total circulating cholesterol in the human body occurs as free cholesterol, whilst the remainder exists as cholesterol esters attached to plasma lipoproteins.

Cholesterol is a vital biological molecule, playing an essential role in the architecture of the cell membrane, by providing rigidity but also fluidity for the flipping of lipids on the cell membrane. Cholesterol is also the precursor for the steroid hormones such as the sex hormones Oestrogen and Testosterone, and the cortico- and mineralocorticosteroids such as cortisol and aldosterone respectively. Cholesterol is also

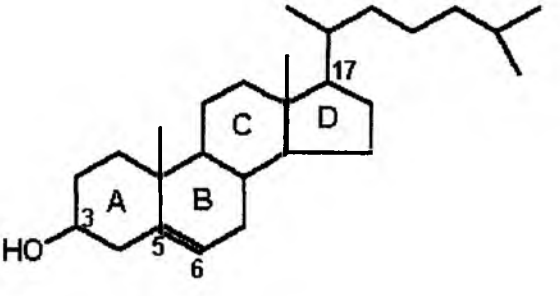

Figure 1 . The chemical structure of Cholesterol.

abundant in bile salts, allowing the process of emulsification for fat metabolism.

Cholesterol Synthesis - The Mevalonate Pathway.

The derivation of cholesterol can either be through diet or through de *novo* biosynthesis, which accounts for 45% of the cholesterol in the body. Whilst biosynthesis in the liver and the small intestines accounts for 10% and 15% respectively; other major synthetic sites include the adrenal cortex and reproductive tissues. The synthesis of cholesterol occurs in the cytoplasm and results from the reduction of the high energy bonds of ATP and Acetyl-CoA (ACT-CoA). As the pre-cursor in the cholesterol pathway ACT-CoA is converted to mevalonate via the formation of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA). This critical early step is rate-limiting in cholesterol synthesis and is regulated by the enzyme HMG-CoA reductase.

Upon successive phosphorylations of mevalonate and its intermediates an activated isoprenoid molecule, Isopentenyl Pyrophosphate, (IPP) is produced. Through the subsequent condensations of IPP to farnesyl pyrophosphate (FPP), and through the catalysis of the NADPH-requiring enzyme, squalene synthase, squalene is produced. It is the cyclisation of squalene to Lanosterol that produces the end product of cholesterol.

Cholesterol regulation.

The level of cholesterol synthesis can in part be regulated through the dietary intake of cholesterol and so the cellular level of cholesterol is maintained through the following independent but interacting mechanisms:

1) Cholesterol levels act as a negative feedback inhibitor for HMG-CoA reductase. Additionally, during times of excess, there is decreased expression of the HMG-CoA reductase gene resulting in low levels of mRNA for translation of HMG-CoA reductase.

2) The activity of HMG-CoA reductase is varied through covalent modification. This is achieved through either phosphorylating or dephosphorylating the enzyme, whereby phosphorylation of the enzyme reduces its activity. Phosphorylation is stimulated in context to the levels of cAMP in the body, under the hormonal control of insulin and glucagon. Increases in cAMP lead to the activation of the cAMP-dependent protein kinase, PKA, which in turn results in the phosphorylation and an increase in the activity of the phosphoprotein phosphatase inhibitor-1 (PPI-1). PPI-1 inhibits the activity of numerous phosphatases of which HMG-CoA reductase is one. It is through this method that hormones such as insulin, which causes a decrease in cAMP levels, leads to the activation of cholesterol synthesis.

3) Finally, both LDL and HDL receptor-mediated transport can also regulate plasma cholesterol levels. This process is based on the active uptake of excess hepatic cholesterol from the liver into the serum through LDL . Cholesterol in plasma membranes can be later extracted and esterified by HDL in the peripheral tissues. Cholesterol is finally excreted in the bile either in the form of bile salts or as free cholesterol.

HMG-CoA reductase inhibitors - Statins.

Currently the most potent treatment for hyperlipidemia are the HMG-CoA reductase inhibitors or statins. In 2000, statins were the second most popular drug in terms of sales , with sales of $15.9 billion - up 21% from 1999.[2]

Statins are HMG-CoA reducatase inhibitors, inhibiting the rate limiting enzyme HMG-CoA reducatase which conducts the breakdown of HMG-CoA to mevalonate, vital for the synthesis of cholesterol and isoprenoids further downstream in the pathway.

Statins are used extensively in current medical practice as a proven method of lowering blood lipid levels. Through numerous clinical trials this class of drugs have demonstrated their benefit in greatly reducing cardiovascular morbidity and mortality, as well as in the primary and secondary prevention of coronary disease in patients with and without coronary artery disease [3-9].

In addition to these clinical trials further *in vitro* and *in vivo* findings suggest that statins, through their highly effective lipid lowering abilities have other pleiotropic effects, in particular anti-inflammatory properties.[3]

Statins: Anti-inflammatory Properties.

An association between statin treatment and an anti-inflammatory response can be defined from markers of acute inflammation, including cytokines, C reactive protein (CRP) and white cell count. Needless to say, all the above factors are also indicative of being in a higher coronary risk factor group[10].

Further analysis into the schematic scenario of the atherosclerotic process allowed a definite conclusion that the evolution of atherosclerotic lesions involves an interaction between four major cell types: endothelial cells (ECs), smooth muscle cells (SMCs), macrophages, and lymphocytes. It has since been suggested that statins may interfere directly with several key mechanisms necessary for the involvement of different cellular elements in all the steps of atherogenesis.

The effect of Statins on endothelial function.

Since the observation that endothelial dysfunction arises early in the presence of elevated cholesterol levels [11] several experimental studies began to explore the effects of statins on preserving endothelial function. As a result it has shown that statins can alter the bioavailability of nitric oxide (NO) through the posttranslational up regulation of endothelial NO synthase (eNOS) mRNA and the decrease of superoxide anion production within vascular endothelial cells.[1] production within vascular endothelial cells[12].

Atherosclerosis over vascular endothelium having activated the endothelium has also been shown to increase the expression of adhesion molecules such as ICAM-1, VCAM-1 and E-selectin, vital for the extravasation of leuokocytes. Using a rat model Katoh *et al.* [13] showed how a particular statin (Fluvastatin) can reduce the expression of soluble ICAM-1. This result was also seen in hypercholesterolaemic patients, where there was also a reduction in the level of soluble P-selectin[14]. In addition statins have also been shown to inhibit the monocyte-endothelial interaction stimulated by oxidised LDL[15]. It is thought that oxidised LDL is able to be chemotactic for monocytes and human T lymphocytes[16], through inducing the expression of factors such as MCP-1 by both human endothelial cells and smooth muscle cells [17].

The effect of Statins on T-cell function.

It has been demonstrated that statins inhibited the Interferon-g (IFN-g)-mediated induction of class II major histocompatibility complexes (MHC II) on antigen presenting cells, including human monocytes/macrophages [18]. More recently, evidence by Weitz-Schmidt has also indicated that the statins Lovastatin and mevastatin selectively block the lymphocyte function associated antigen-1 (LFA-1). LFA-1 is involved in the adhesion of leukocytes to the

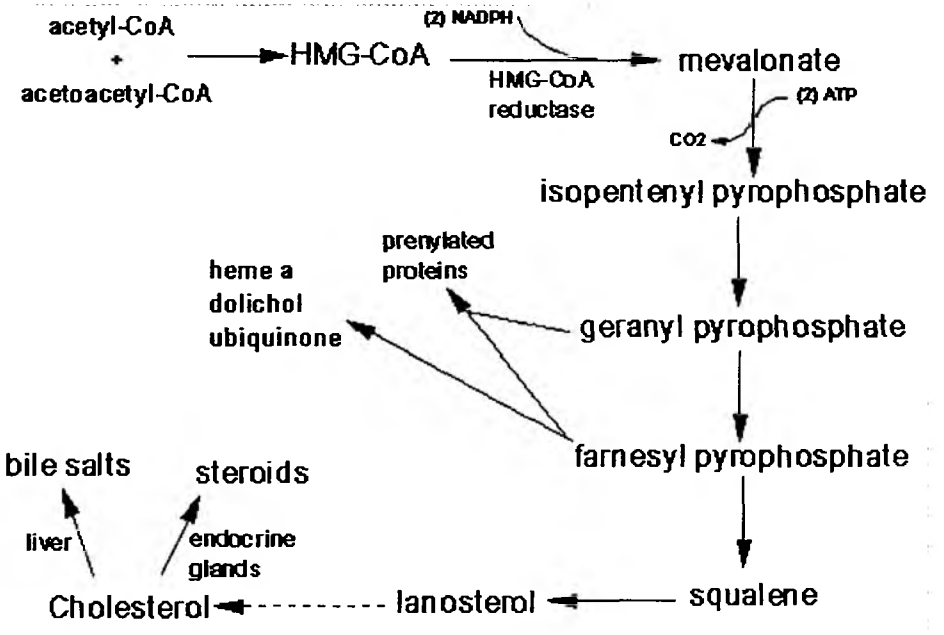

Figure 2. The Cholesterol synthesis pathway.

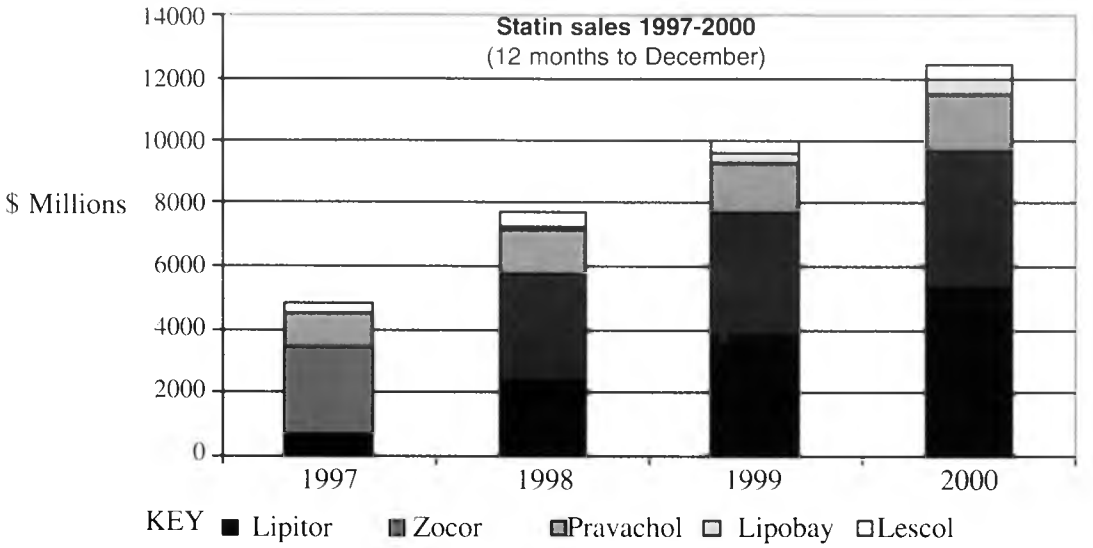

Figure 3. Statin sales 1997-2000.

binding molecules ICAM-1 and also in the process of lymphocyte re-circulation and effective T cell activation by antigen presenting cells. Statin-induced LFA-1 inhibition resulted in a decrease in lymphocyte adhesion to ICAM-1 and impaired T-cell co-stimulation [19].

As research continues into these and the other pleiotropic effects of statins, we can expect a new generation of cholesterol reduction drugs which are able to target a number of the secondary downstream products in the mevalonate pathway, which play an integral part in the inflammatory process.

The author has no conflict of interest, no financial support from the pharmaceutical industry.

References.

1) **Pearson TA, Futaki V.** Executive summary. 27th Bethesda Conference: matching the intensity of risk factor management with the hazard for coronary artery disease events. J Am Coll Cardiol. 27:961 (2000)

2) International Medical sales report. 1997-2000.

3) **Maron D. J, Fazio. S, & Linton, M.F.** Current Perspectives on statins. Circulation. 101. 207-213 (2000)

4) **Vaughan, C.J, Gotto, A. M & Basson, C. T.** The evolving role of statins in the management of atherosclerosis. J. Am. Coll. Cardiol. 35. 1-10 (2000)

5) **Pederson, T. R.** Statin trials and goals of cholesterol lowering therapy after Acute Myocardial Infarction. Am. Heart Journal. 138. 177-182 (1999)

6) **Pederson T R, Kjekshus J, Berg K, Haghfelt T, Faergeman O *et al.*** Randomised trial of Cholesterol lowering in 4444 patients with coronary heart disease: the scandanavian simvastatin study (4S). Lancet. 344: 1383-89 (1994)

7) **Waters D, Schwartz G, Olson G A.** The Myocardial Ischaemia reduction with acute cholesterol lowering (MIRACL) trial: a new frontier for statins? Current control trials in cardiovascular medicine. 2: 111-114 (2001).

8) **Cannon C P, McCabe C H, Bentley J, Brawnwald E.** Early statin therapy is associated with markedly lower mortality in patients with acute coronary syndromes: Observations from OPUS Timi-16. J Am Coll Cardiol: 87; 334A (2001).

9) **Sepherd *et al.*** (West of Scotland Coronary Prevention study (WOSCOPS): NEJM: 333. 1301-7. (1995).

10) **Ridker PM, Cushman M, Stampfer M J *et al.*** Inflammation. aspirin and the risk of cardiovascular disease in apparently healthy men. NEJM. 336:973-9 (1997)

11) **Vita J A, Treasure C B, Nabel E G *et al.*** Coronary vasomotor response to acetylcholine relates to risk factors for coronary artery disease. Circulation. 81:491-7(1990)

12) **Laufs U, La Fata V, Plutzky J, Liao JK.** Up-regulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. Circulation. 97: 1129-35 (1998).

13) **Katoh M, Kurosawa Y, Tanaka K, Watanabe A, Doi H, Narita H.** Fluvastatin inhibits O2- and ICAM-1 levels in a rat model with aortic remodelling induced by pressure overload. Am J Physiol Heart Circ Physiol. 281: H655-60 (2001).

14) **Romano M, Mezzetti A, Marulli C *et al.*** Fluvastatin reduces soluble P-selectin and ICAM-1 levels in hypercholesterolemic patients: role of nitric oxide. J Investing Med. 48: 183-9 (1999).

15) **Berliner JA, Territo MC, Sevaian A *et al.*** Minimally modified low density lipoprotein stimulates monocyte endothelial interactions. J Clin Invest. 85: 1260-6 (1990).

16) **Mc Murray HF, Parthasarathy HF, Steinberg D.** Oxidatively modified low density lipoprotein is a chemoreactrant for human T lymphocytes. J Clin Invest. 92: 1004-8 (1993).

17) **Cushing SD, Berliner JA, Valente AJ *et al.*** Minimally modified low density lipoprotein induces monocyte chemotactic protein 1 in human endothelial cells and smooth muscle cells. Proc Natl Acad Sci USA. 87: 5134-8 (1990)

18) **Kwak B, Malhaupt F, Myit S, Mach F.** Stains as a newly recognised type of immunomodulator. Nat Med. Dec; 6: 1399-1402 (2000).

19) **Weitz-Schmidt G, Welzenbach K, Brinkmann V *et al.*** Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. Nat Med. 7: 687-92 (2001).

Book Review

Davidson's Principles and Practice of Medicine, 19th edition

Marion A Simpson
4th year medical student, University of Edinburgh College of Medicine
M.A.Simpson@sms.ed.ac.uk

The first edition of *Davidson's* appeared in 1952; an almost pocket-sized volume which promised to concentrate on common disorders and everyday problems illustrated by an account of the applied anatomy and physiology of the relevant system. The textbook has come a long way since then, but remains true to its original ideals.

As a fourth year student at Edinburgh University, the *alma mater* of Sir Stanley Davidson, I can claim to be on intimate terms with the previous edition of the textbook, and I must confess to having been sceptical about the merits of a re-write. My doubts were quashed, however, when I began to investigate the new volume. Beneath its chic black cover, the book has undergone a radical structural reorganisation: it now comprises two discrete sections, *Principles of Medical Practice* and *System-Based Diseases*. The first does just what it promises, dealing with general principles such as infection and immune failure, critical care, and frail older people; topics which weave an overarching thread through every medical specialty but which are seldom addressed in isolation. The second discusses the clinical features and management of diseases under headings such as *Cardiovascular Disease* or *Blood Disorders,* fully in keeping with the system-based approach adopted by most 21st century medical schools. The structure of each chapter is broadly similar; there is a brief revision of the functional anatomy and physiology of each system, the investigations which might usefully be employed, and a large section on the major clinical manifestations of disease of the system, before moving on to details of specific diseases. The emphasis on symptomatology as a starting-point resonates with the fashionable problem-based approach to clinical medicine.

One of the most praiseworthy new features of this edition is the double-page spread on clinical examination preceding each of these system-based chapters. Illustrated with a human figure and a flow diagram of a scheme for examination, these provide a summary of the salient clinical features of disease of each system; very helpful for developing a logical examination sequence and invaluable for OSCE revision.

Changes in layout are not the only new aspects of the 19th edition. Several sections have appeared *de novo*, including a chapter dedicated to *Diabetes Mellitus* and one on *Clinical Genetics*. The opening chapter on *Infection and Immune Failure* has also been rewritten and expanded, with a large section on tropical and international health reflecting the enormous popularity of the textbook with students and doctors as far afield as India and South Africa. The book clearly demonstrates a willingness to move with the times; the chapter on *Drug Therapy* features a section dealing clearly and succinctly with some important aspects of evidence-based medicine, and throughout the book there are recent journal references and useful web addresses.

Having used Davidson's myself I may be liable to take for granted its many strengths; it would be remiss of me not to mention the clear and logical layout, pithy and relevant information (with plenty of information boxes to highlight the most salient points), well-chosen photographs and beautiful illustrations. These were features of the previous edition too; now they have been developed further, creating an even more polished and accessible volume.

Editorial Committee

Editor - David Griffith
Secretary - Paul Masson
Praeses - Thomas Russ
Ordinary Members
Joanne Sells
Ian Baxter

RMS Council, 265th Session

Senior President	David Cavanagh	*Publicity Convenor*	Mayank Madhra
1st Junior President	Joanne Sells	*Library Convenor*	Lucy Khan
2nd Junior President	Paul Jenkins	*Computing Convenor*	Jacob Grinfeld
3rd Junior President	Thomas Russ	*Entertainment Convenor*	Andrew MacKenzie
Senior Secretary	Iain Munro	*Editor,* Res Medica	David Griffith
Junior Secretary	Andrew Cotton	*Annual Dinner Convenor*	Michelle Arora
Business Convenor	Christopher Cartlidge	*Treasurer*	Dr Chris Thompson
House Convenor	Julia Critchley	*Permanent Secretary*	Mrs Elizabeth Singh
Museum Convenor	Neil McKenzie		

RMS Calendar, Summer Term 2003

Tuesday 22nd April	Cardiac Surgery - Mr P. Mankad
	Psychoanalysis - Mr T Russ
Tuesday 29th April	Annual Debate, with the Diagnostics Society
Tuesday 6th May	Locomotor Tutorial - Mr T White
	Alternative Medicine - Miss J Sells
Tuesday 13th May	Annual Extraordinary General Meeting
Tuesday 20th May	Valedictory Address - Mr D Cavanagh
Tuesday 27th May	Money in Medicine - Dr B O'Neill
Tuesday 3rd June	PRHO Survival Guide - Dr P Mills
Tuesday 10th June	Neuroanatomy Tutorial - Dr F Kristmundsdottir

NB: Some of these may be subject to change - please check in the RMS nearer the time. Also, there will be two tutorials run for final year medical students - dates are yet to be confirmed.

The Royal Medical Society
Student Centre, 5/5 Bristo Square, Edinburgh, EH8 9AL
Tel./Fax. (Office): 0131 650 2672
Tel. (Students): 0131 650 2671
E-mail: enquiries@royalmedical.co.uk
http://www.royalmedical.co.uk

ISSN 0482-3206
Printed by Highland Printers