Clinical review

Recent advances

Cardiopulmonary resuscitation

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Coronary artery disease is the leading cause of death in most developed countries. In the United States alone, 500 000 deaths a year are caused by coronary artery disease, over half of which are due to sudden cardiac arrest.[1] Often cardiac arrest is the initial manifestation of coronary artery disease, so many of these patients if successfully resuscitated could have years of productive life remaining. Improvements in cardiopulmonary resuscitation therefore could have an appreciable impact on total mortality.

Recent advances in cardiopulmonary resuscitation

- Sudden cardiac arrest remains a major cause of death in developing countries
- Despite years of experience with cardiopulmonary resuscitation, survival after cardiac arrest continues to be quite low
- Automatic external defibrillators and bystander cardiopulmonary resuscitation improve survival after sudden cardiac arrest
- Doctors should identify and counsel those patients who are not candidates for cardiopulmonary resuscitation

Cardiac arrest outside hospital

Although cardiopulmonary resuscitation (CPR) has been practised for nearly 40 years, survival after cardiac arrest outside hospital remains low (table 1).[2-8] Most events are associated with underlying coronary artery disease, but only a minority of patients will have an associated acute myocardial infarction.[9] Holter monitor studies of patients who had a cardiac arrest outside hospital have found that most patients initially develop ventricular tachycardia before they progress to ventricular fibrillation. If untreated, cardiac rhythm deteriorates to asystole in several minutes.[10] The most important predictors of survival after cardiac arrest are whether the arrest was witnessed, the time from collapse to defibrillation, and the initial cardiac rhythm identified by emergency staff. Patients with asystole rarely survive.[5 11]

Automatic external defibrillators

Because two of the best predictors of survival of cardiac arrest are time to defibrillation and initial rhythm, decreasing the time to defibrillation will increase survival rates. Logistical problems, however, make this effort difficult. Paramedics trained in advanced life support are effective in improving survival but are not always rapidly available. To increase the availability of defibrillation, the automatic external defibrillator was developed. This device is designed for use by first responders not trained in advanced life support, such as firefighters, emergency medical technicians, and even lay people. The operator simply has to check that there is no pulse, place the device on the patient, and turn it on. It senses the cardiac rhythm, and if it identifies rapid ventricular tachycardia or ventricular fibrillation it delivers a countershock. Operators require little training as there is no need to identify rhythms.

Initial studies showed the safety of the automatic external defibrillator and that it significantly decreased time to defibrillation in comparison to defibrillation by paramedics.[12 13] In a randomised trial comparing emergency medical technicians using an automatic external defibrillator or a standard defibrillator, survival to discharge for patients in ventricular fibrillation was 16/63 (25%) with the automatic external defibrillator and 21/84 (25%) with a standard defibrillator.[14] In a controlled prospective study comparing early defibrillation by firefighters using an automatic external defibrillator with delayed defibrillation by paramedics, survival was 30% (84/276) in patients treated with an automatic external defibrillator and 19% (44/228) in those given standard defibrillation by paramedics ($P < 0.001$).[15] A recent meta-analysis of seven prospective studies of automatic external defibrillation found an 8.5% reduction in relative risk with early defibrillation by emergency medical technicians compared with basic life support alone.[16]

The American Heart Association has strongly endorsed equipping all emergency vehicles with the device,[17] and the International Association of Fire Chiefs has endorsed equipping every fire suppression unit in the United States.[18] A task force of the American Heart Association is working to expand the use of automatic external defibrillators to lay people by incorporating training into basic life support courses.

Table 1 Survival to discharge in studies of prehospital cardiopulmonary resuscitation (CPR) that included comparison of patients who received or did not receive cardiopulmonary resuscitation from bystanders

Study (year)	Location	Defibrillation time (min)*	Proportion given bystander CPR	No (%) surviving		
				Overall	Bystander CPR	No bystander CPR
Cummins (1988)[2]	Seattle	10.0	27	373/2043 (18)	196/726 (27.0)	177/1317 (13)
Spaite (1990)[3]	Tucson	4.7	28.9	25/298 (8.4)	13/86 (15.1)	12/212 (5.6)
Becker (1991)[4]	Chicago	16	28.0	33/2949 (1.3)	20/582 (3.4)	15/1479 (1.0)
Herlitz (1994)[5]†	Gothenberg	8.5	18	187/1660 (11.3)	77/303 (25.0)	110/1357 (8.0)
Wik (1994)[6]	Oslo	6.0	45	28/334 (8.4)	17/149 (11.4)	11/185 (5.9)
Crone (1995)[7]	Auckland	11.0	55	99/978 (10.1)	77/527 (14.6)	18/437 (4.1)
Gallagher (1995)[8]	New York City	12.4	32	30/2071 (1.4)	19/662 (2.9)	11/1405 (0.8)

*Mean time from collapse to first defibrillation.†Study included witnessed arrests only.

The device would be available at areas where there are high concentrations of people, such as sporting events, fairs, and airports.[19]

Bystander CPR

Each year, millions of people learn cardiopulmonary resuscitation techniques. Despite this, for many years there has been debate about whether cardiopulmonary resuscitation by bystanders improves survival. In controlled studies using multivariate analysis, bystander initiated cardiopulmonary resuscitation has been shown to more than double prehospital survival (table 1)[2-8]—but most patients with cardiac arrest do not receive this treatment. To identify the determinants of who receives bystander cardiopulmonary resuscitation, Litwin *et al* looked at survival according to location of collapse. Patients who had a cardiac arrest in public were more likely to have had their arrest witnessed and were more likely to have received resuscitation from bystanders than patients who had a cardiac arrest at home (69% *v* 49%). Survival among patients who had an arrest in public was much higher than that among patients who had an arrest at home (27% *v* 13%). After control for time to defibrillation and whether the arrest was witnessed, much of this difference could still be explained by the higher rate of resuscitation by bystanders given to patients who had an arrest in public.[20] Too often patients who have a cardiac arrest at home do not receive cardiopulmonary resuscitation from family members.

There has been some concern that cardiopulmonary resuscitation improperly performed by bystanders could be dangerous. Though several studies have shown that "good" bystander cardiopulmonary resuscitation is better than "poor" resuscitation, survival did not differ significantly between poor resuscitation and no resuscitation at all (table 2).[6 7 8 21] Two studies differentiated the quality of resuscitation by whether the bystander was performing only external chest compression or only artificial ventilation.[8 21] Survival in patients who received only external chest compression was significantly higher than in patients who did not receive resuscitation from bystanders; patients who only received artificial ventilation had survival rates similar to patients who did not receive bystander initiated cardiopulmonary resuscitation. Animal models have suggested that artificial ventilation during cardiopulmonary resuscitation may not be necessary.[22] Whenever possible, external chest compression and artificial ventilation should be provided together, but instructors may counsel potential rescuers who are not physically able to accomplish both manoeuvres on their own that doing external chest compression alone is reasonable and is far better than no resuscitation.

Basic life support

Initially it was thought that forward flow during external chest compression was due to direct compression of the heart between the sternum and vertebral column. Now it is thought that increased intrathoracic pressure leads to forward flow and cardiac filling occurs passively during the upstroke of compression. Several years ago investigators reasoned that active decompression on the upstroke would increase negative intrathoracic pressure and improve ventricular filling and therefore myocardial and cerebral blood flow. This led to the invention of the active compression-decompression device, which improved ventricular filling and coronary and cerebral blood flow in animal models and in experimental studies in humans.[23 24] Initial small randomised clinical trials with active compression-decompression found improved short term survival and a trend towards improved long term survival.[25 26] A recent large randomised trial, however, found no significant difference in survival to discharge from hospital after standard cardiopulmonary resuscitation and active compression-decompression resuscitation.[27] Routine use of active compression-decompression resuscitation cannot currently be recommended.

Interposed abdominal counterpulsation was devised with the idea that compression of the abdomi-

Table 2 Numbers (percentages) of patients surviving to hospital discharge in studies of prehospital cardiopulmonary resuscitation based on quality of resuscitation and whether external chest compression only or ventilation only was used

Study	Overall survival	Cardiopulmonary resuscitation			External chest compression only	Ventilation only
		Good	Poor*	None		
Van Hoeyweghen[21]†	255/3035 (8.4)	71/443 (16)	31/412 (7.5)	153/2180 (7)	26/263 (10)	1/51 (2)
Wik[6]	28/334 (8.4)	16/70 (23)	1/79 (1)	11/185 (6)	—	—
Crone[7]	99/964 (9.9)	64/330 (19)	13/197 (7)	18/437 (4)	—	—
Gallagher[8]	30/2071 (1.4)	14/305 (4.6)	5/357 (1.4)	11/1405 (0.8)	2/102 (2)	0/26 (0)

*Includes all patients given resuscitation that was not judged as "good quality," including those given external chest compression only and ventilation only.
†Long term survival defined as consciousness at 14 days.

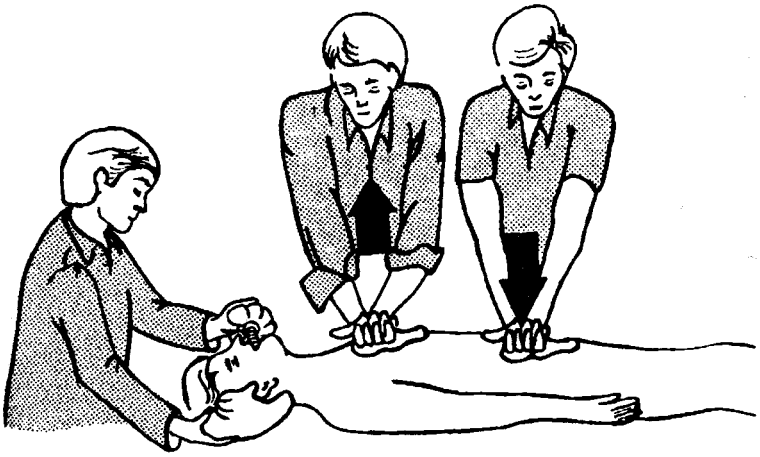

Fig 1 Interposed abdominal counterpulsation is designed to augment diastolic aortic pressure and improve blood flow.[29] Reprinted by permission of the American Medical Association

nal aorta would augment diastolic blood flow and thus improve forward flow (fig 1). Initial haemodynamic studies showed improved coronary and common carotid perfusion as well as improved cardiac output.[28] In a small randomised but unblinded study, interposed abdominal counterpulsation improved survival to discharge significantly.[29]

Circumferential chest compression with a pneumatic vest has also been studied as a more effective way of increasing intrathoracic pressure during external chest compression (fig 2). A preliminary study has shown improvement in haemodynamics and improved short term survival in humans,[30] and a multicentre trial studying long term survival is under way. Neither interposed abdominal counterpulsation or circumferential chest compression can currently be recommended for routine use.

Some experimental research has questioned the notion that external chest compression works by improving haemodynamics, claiming that there is minimal blood flow to the brain and heart during standard external chest compression.[31] Patients who receive cardiopulmonary resuscitation from bystanders are more frequently in ventricular fibrillation than patients who do not.[4 5 7] Although the mechanism of how external chest compression works remains uncertain, it may be partially explained by the maintenance of ventricular fibrillation until defibrillation can be provided. This may explain why techniques designed to improve haemodynamics, such as active compression-decompression, have not been shown to improve survival.

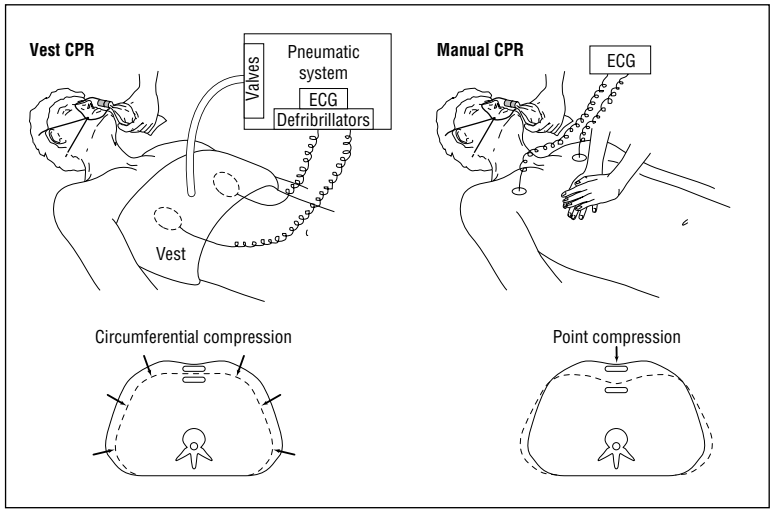

Fig 2 Circumferential chest compression is designed to increase intrathoracic pressure and improve blood flow.[30] Reprinted by permission of the *New England Journal of Medicine*

Advanced life support

Research in advanced life support has focused on pharmacological interventions. A study in 1989 found that high dose epinephrine (5 mg to 15 mg) improved haemodynamics and increased return of spontaneous circulation more than standard dose epinephrine (0.5 mg to 1.0 mg).[32] This led to the widespread use of high dose epinephrine, despite the absence of evidence of improved long term survival. In the last few years several randomised trials have failed to show improved long term survival with high dose epinephrine.[33-35]

Preliminary case series using magnesium sulphate and vasopressin in selected refractory cardiac arrests have shown promising results. Use of these drugs, however, remains experimental.[36 37]

A recent study of advanced life support in prehospital cardiac arrests found that such interventions by paramedics did not seem to contribute to neurologically intact long term survival.[38]

Cardiac arrest in hospital

Patients who have a cardiac arrest out of hospital are often relatively healthy, whereas patients who have an arrest in hospital often have concurrent illness. Studies in hospital have also shown that early defibrillation is important since patients with witnessed arrests, on cardiac monitors, and in ventricular fibrillation are more likely to survive cardiac arrest.[39] However, research efforts on improving survival after an arrest in hospital have focused on techniques such as active compression-decompression, interposed abdominal counterpulsation, and high dose epinephrine—with disappointing results, as mentioned previously.

Another focus of research has been the identification of subgroups unlikely to survive resuscitation. This task has been hampered by the fact that these researchers have yet to standardise definitions, as out of hospital researchers have done with the Utstein criteria (a formalised nomenclature that allows the comparison of research done in various settings without methodological heterogeneity[40]). In a recent review we showed that the heterogeneity of in hospital studies makes it difficult to compare data collected in different studies. Because patients with arrest in hospital often receive defibrillation before chest compression, researchers need to report survival for patients who actually receive external chest compression.[39] We have also proposed definitions that will enable researchers to compare survival of patients in various subgroups.[41]

Another major problem in identifying patients unlikely to survive resuscitation is the increasing use of "do not resuscitate" orders. While this is ethically appropriate it means that subjects with a particular diagnosis who receive cardiopulmonary resuscitation are a highly selected group. At the University of Virginia, for example, only one in eight patients with cancer who has a cardiac arrest receives resuscitation.[41]

Overall, less than a third of patients with cardiac arrest in hospital receive resuscitation.[39] The frequency of do not resuscitate orders should be reported in any study of in hospital cardiopulmonary resuscitation.

Despite these limitations, in our review of 68 studies, overall survival in hospital after cardiopulmonary resuscitation averaged 14% (range 0% to 28.9%); patients with coronary artery disease did better than average and those with metastatic cancer, advanced age, recent stroke, sepsis, and a dependent lifestyle did worse. We found no subgroup for which cardiopulmonary resuscitation was futile.[39] Predictive models such as APACHE II may be useful, but such models are not completely validated.[42]

Conclusion

Recent research on cardiopulmonary resuscitation has met with both disappointments and successes. Experience with active compression-decompression and high dose epinephrine has taught us that success in experimental models does not necessarily translate into improved long term survival in clinical studies. Improvements gained from changes in basic or advanced life support techniques are likely to be modest. Future clinical trials will need to be well designed and large enough to have sufficient power to detect a small difference in meaningful long term survival.

Early defibrillation and bystander cardiopulmonary resuscitation improve survival. Because sudden cardiac death is a large public health problem the impact of the increasing availability of automatic external defibrillators and wider training in cardiopulmonary resuscitation has great potential. Doctors should be advocates for early defibrillation programmes and cardiopulmonary resuscitation training in their communities. Finally, doctors need to counsel patients who are unlikely to survive cardiopulmonary resuscitation about the risks and benefits of the procedure.

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Lesson of the week

Persistent itching due to etherified starch plasma expander

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Etherified starch should be suspected as the cause of pruritus in patients who develop severe persistent pruritus after major surgery or other indications for use of a plasma expander

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Etherified (hydroxyethyl) starch is a plasma expander commonly used in the treatment of hypovolaemia due to surgery, trauma, sepsis, or burns. It is also used to prime cardiopulmonary bypass machines,[1] as a sedimenting agent to increase yields of granulocytes during leucapheresis,[2] and to improve the microcirculation and tissue oxygenation—for example, in the treatment of sudden deafness.[3-5] Severe persistent pruritus after the use of this artificial colloid was first reported by Parker *et al* in 1982.[2] Although 32% of patients who received etherified starch reported pruritus in a retrospective study,[4] few reports of this complication have been published in English.

We report three cases of pruritus induced by etherified starch after heart surgery that were seen by dermatologists from our department over four months. These cases show the importance of considering this diagnosis in patients who develop pruritus after major surgery.

Case reports

Case 1

A 75 year old woman was referred with a one year history of severe generalised pruritus that had begun three weeks after repair of a left ventricular aneurysm. Perioperatively she had been given amiodarone, perindopril, bumetanide, spironolactone, warfarin, ranitidine, and co-codamol. When she had first developed pruritus her cardiologists had suspected a drug reaction, but the pruritus had persisted after some of the drugs had been discontinued or changed. She was also thought to have scabies, but treatment for this was ineffective. On examination she had numerous excoriations on the trunk and limbs. The onset of the pruritus shortly after heart surgery suggested that something that she had been exposed to perioperatively might be responsible; the possibility that she might have received etherified starch was therefore considered. Her cardiothoracic surgeon confirmed that she had indeed received 500 ml etherified starch 6% (hetastarch, weight average molecular weight 450 000) postoperatively. Her pruritus remained after 20 months and was refractory to treatment, including oral chlorpheniramine and a potent topical corticosteroid. She was unable to tolerate topical capsaicin because it caused burning.

Case 2

A 56 year old man presented with a five month history of severe pruritus, which had begun four weeks after coronary artery bypass grafting. The pruritus was generalised but worse around the head and neck and severe enough to disturb his sleep. He was taking atenolol, diltiazem, lisinopril, isosorbide mononitrate, aspirin, and simvastatin, but he had been taking all of these drugs for at least a year before the onset of the pruritus. On examination his skin looked normal apart from excoriations. Pruritus caused by etherified starch was suspected, and inquiry showed that he had received 500 ml etherified starch 6% (hetastarch, 450 000 molecular weight) postoperatively. He had some relief from crotamiton 10% and hydrocortisone cream 0.25%, and the pruritus resolved after a total of eight months.

Case 3

A 63 year old man presented with a one year history of severe generalised pruritus, which had begun three months after coronary artery bypass grafting. The only drugs he was taking were aspirin and atenolol. The pruritus had not responded to potent topical corticosteroids, and he had become anxious about what might be causing him to itch. Inquiry showed that he had received 1000 ml etherified starch 6% (hetastarch, 450 000 molecular weight) intraoperatively. It was explained to him that the itching was likely to resolve spontaneously eventually, which it did, 20 months after it began.

Histopathology

Histopathology of the skin in all three cases showed the same changes to varying degrees. Paraffin sections showed some urticarial change, with dermal oedema, vessel dilatation, and increased numbers of mast cells. A few vacuolated macrophages were seen around vessels and nerves throughout the dermis. Some vacuoles stained faintly by the periodic acid-Schiff reaction. The vacuolated macrophages were much easier to see in epoxy resin sections of 1 μm stained with toluidine blue (fig 1), which give greater structural detail than paraffin sections of 3 μm. Electron microscopy showed that the vacuoles were largely empty apart from some clumped electron dense material at the periphery (fig 2); similar vacuolation was also seen in vascular endothelial cells. Some of the vacuolated macrophages were located next to mast cells, many of which showed partial or complete degranulation (fig 2).

Discussion

The main clue to the cause of our patients' pruritus was its onset in the first few weeks or months after major surgery. The clinical suspicion was supported by confirmation that they had received etherified starch and by histopathological evidence of storage vacuoles containing etherified starch in the skin.

Etherified starch solutions are heterogeneous, containing molecules with a wide range of molecular weights. The smaller molecules (< 50 000 molecular weight) are rapidly excreted by the kidneys, whereas

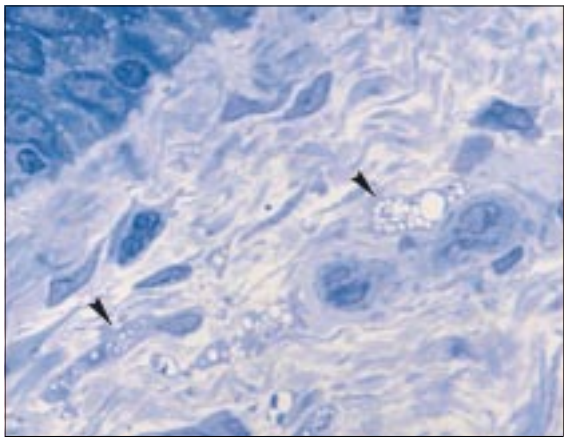

Fig 1 High power micrograph of skin showing vacuoles in macrophages (arrows) in dermis (toluidine blue stained section of 1μm thickness)

the larger molecules persist intravascularly until they are slowly hydrolysed or taken up by the mononuclear phagocyte system and other cells in various tissues.

The histopathological findings in our cases confirm the observations of others.[4-7] The foamy macrophages are usually difficult to detect in routine paraffin sections unless specifically searched for under high power.[5] The periodic acid-Schiff reagent, which stains some polysaccharides, may facilitate their detection by positive staining of their vacuoles,[5] but the staining may be weak, as in our cases, or absent.[6 7] The safest histological diagnosis is therefore based on detection of membrane bound vacuoles, predominantly in macrophages and endothelial cells, on electron microscopy.[5] Jurecka *et al* have shown that the electron dense material around the margins of the vacuoles stains positively with polyclonal serum containing antibodies to etherified starch.[5]

The mechanism by which storage of etherified starch induces pruritus is not yet fully understood. It does not seem to be an allergic hypersensitivity reaction mediated by the immune system as there is usually little or no inflammatory cell infiltrate[5] and the incidence of pruritus is dose related.[4] Whether macrophages, endothelial cells, keratinocytes, Langerhans cells, or other cells in which the starch molecules are deposited[5] release mediators that induce itching or whether there is a more direct effect on sensory nerve fibres is still uncertain. In our cases the number of mast cells was increased and mast cells were degranulated on electron microscopy, features that have not been seen in other studies.[5 6] However, the resistance of the pruritus to antihistamines suggests that it is not simply mediated by histamine.

In a retrospective study Gall *et al* found pruritus in 32% of 266 patients who received etherified starch for otological indications[4]; these patients received a minimum total volume of 2500 ml. The incidence of pruritus was related to the total dose of etherified starch and to its concentration and average molecular weight. The pruritus typically begins one to three weeks after administration and usually lasts six weeks to six months,[3] but it may last more than two years.[5]

The pruritus is generally refractory to treatment, including antihistamines,[3-5] ultraviolet B phototherapy,[6] and topical corticosteroids.[7] Topical capsaicin, which depletes substance P from sensory neurones, has been reported as being effective in individual cases.[6] However, it may be poorly tolerated, as in case 1, and would not be expected to alter the natural course of the pruritus.

As in our patients, the correct diagnosis may be considerably delayed[7] or the diagnosis could be missed because of lack of awareness of etherified starch as a cause of pruritus and because most patients will no longer be receiving the plasma expander when they present with itching. In 1992, 14 cases of pruritus of unknown cause after cardiopulmonary bypass grafting were reported, the itching beginning one to six weeks after heart surgery and lasting from four to 24 months.[8] Although the possibility that the pruritus was caused by etherified starch was not considered by the authors, in retrospect, the time course of the itching suggests this diagnosis. Etherified starch is often used to prime cardiopulmonary bypass machines and for postoperative volume replacement after grafting.[1] Light microscopy of skin was reported as showing normal results, but if high resolution light microscopy after resin embedding and electron microscopy were not performed the characteristic vacuoles could easily have been missed on routine histology.

In conclusion, etherified starch induced pruritus should be considered in the differential diagnosis of severe generalised pruritus and a history taken for possible exposure to this agent, such as during major surgery.

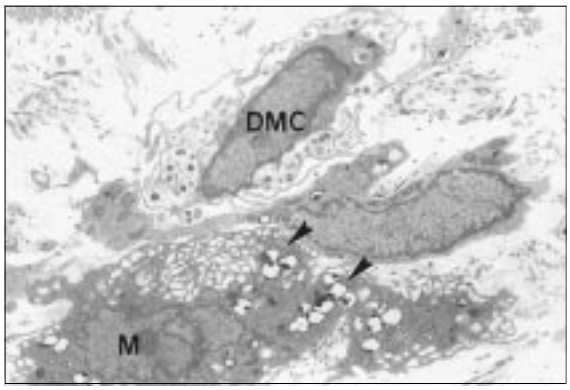

Fig 2 Electron micrograph of skin showing macrophage (M) containing membrane bound vacuoles (arrows) with electron dense material at margins. DMC=degranulating mast cell; bar=2μm

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