

## $\beta$ Endorphin release in patients after spontaneous and provoked acute myocardial ischaemia

Keith G Oldroyd, Kath Harvey, Christina E Gray, Graham H Beastall, Stuart M Cobbe

### Abstract

**Background**—In animal models of circulatory shock and heart failure concentrations of the endogenous opioid peptide  $\beta$  endorphin are raised and opioid receptor blockade improves haemodynamic variables and survival. This study was performed to identify whether acute myocardial ischaemia provokes the release of  $\beta$  endorphin in humans.

**Methods**—Observational study in a university cardiology centre. Serial measurements of  $\beta$  endorphin made by specific radioimmunoassay were correlated with other clinical and neuroendocrine variables that were measured prospectively. Fifty five patients with acute myocardial ischaemia and 26 patients undergoing elective coronary angioplasty of the left anterior descending coronary artery were studied.

**Results**— $\beta$  endorphin concentrations were raised above the upper limit of normal in 31/42 (74%) patients with confirmed myocardial infarction, 3/13 (23%) patients with unstable angina, and 10/24 (42%) patients after coronary angioplasty. There was no evidence of myocardial release of  $\beta$  endorphin. There were significant positive correlations between  $\beta$  endorphin and the concentrations of adrenocorticotrophic hormone, cortisol, and arginine vasopressin. In patients with acute myocardial ischaemia there was a significant positive correlation between the peak concentrations of creatine kinase and  $\beta$  endorphin but no correlation with visual analogue scores of the intensity of chest pain. The highest  $\beta$  endorphin concentrations were seen in patients whose clinical course was complicated by the development of heart failure.

**Conclusions**— $\beta$  endorphin release is a component of the neuroendocrine activation associated with myocardial ischaemia/infarction.

Guillemin *et al* showed in 1977 that rats release  $\beta$  endorphin concomitantly with adrenocorticotrophic hormone (ACTH) from the pituitary into the circulation in response to a range of stressful stimuli.<sup>1</sup> Shortly after this, co-release was confirmed in humans.<sup>2,3</sup> It has been known for over half a century that the cardiovascular system is extremely sensitive to exogenous opioids<sup>4</sup> and thus it was postulated that  $\beta$  endorphin release might be a pathogen-

etic factor in the haemodynamic derangements present in shock states. Animal models of circulatory shock have since been used to confirm  $\beta$  endorphin release after canine haemorrhagic<sup>5,6</sup> and endotoxic shock<sup>7,8</sup> and after both in primates.<sup>9</sup> Plasma  $\beta$  endorphin concentrations were much higher in dogs with experimental chronic heart failure than in control animals.<sup>10</sup> In humans, plasma  $\beta$  endorphin concentrations rise in response to insulin-induced hypoglycaemia,<sup>11</sup> intense physical exercise,<sup>12</sup> and surgery,<sup>13</sup> and they are raised in some patients with heart failure.<sup>14</sup> There are no published data on the response to myocardial ischaemia or infarction.

### Patients

#### METHODS

To allow some clarification of the relation between the duration and severity of myocardial ischaemia and the release of  $\beta$  endorphin we studied two groups of patients.

#### Study 1

Fifty five consecutive patients admitted to the coronary care unit of Glasgow Royal Infirmary with a clinical diagnosis of acute myocardial ischaemia were studied. Myocardial infarction was confirmed by the presence of at least two of the three standard criteria: a compatible history of chest pain, typical evolving electrocardiographic changes, and an increase in the concentration of creatine kinase to above twice the upper limit of normal. Patients without these features but with evidence of ischaemia were considered to have unstable angina. Daily clinical examinations were performed and when there was evidence of pulmonary congestion radiological confirmation was sought. Cross sectional echocardiography was performed on day three, and where image quality allowed, we calculated the ejection fraction using apical two and four chamber views and a modified Simpson's formula.<sup>15</sup> Serial blood samples were taken from the time of admission to six weeks after discharge. Patients were asked to quantify the intensity of their chest pain on a 100 mm non-calibrated linear visual analogue scale cued with "very mild" and "very severe".

#### Study 2

Twenty six consecutive patients undergoing percutaneous transluminal angioplasty of the left anterior descending coronary artery were studied. Simultaneous aortic and coronary venous blood samples were taken for  $\beta$  endorphin and lactate estimation immediately before

Department of  
Medical Cardiology,  
Royal Infirmary,  
Glasgow  
K G Oldroyd  
S M Cobbe

Institute of  
Biochemistry, Royal  
Infirmary, Glasgow  
K Harvey  
C E Gray  
G H Beastall

Correspondence to Dr Keith  
G Oldroyd, Department of  
Medical Cardiology, Royal  
Infirmary, 10 Alexandra  
Parade, Glasgow G31 2ER.

Accepted for publication  
25 July 1991

the first balloon dilatation ( $T_0$ ) and at 2 ( $T_2$ ) and 10 ( $T_{10}$ ) minutes after the end of the procedure. Electrocardiographic leads I, II, III, aVR, aVL, and aVF were recorded continuously during each dilatation.

*Assays*

$\beta$  Endorphin was measured by "in-house" radioimmunoassay after extraction from plasma by  $C_{18}$  Sep-Pak cartridges. The assay uses an  $^{125}I$ -tracer and double antibody separation. The primary antiserum showed only 2% cross reactivity with human  $\beta$  lipotrophin (Peninsula Laboratories) during formal testing and <0.01% with  $\alpha$  endorphin,  $\gamma$  endorphin, [leu]enkephalin, [met]enkephalin, ACTH, and dynorphin. The within batch coefficient of variation is 13.7% at a mean concentration of 3.2 pmol/l, improving to 2.3% at 42.5 pmol/l. Between batch precision is 5.8%, 5.3% and 4.9% at concentrations of 5.7, 10.2, and 43.7 pmol/l respectively. The normal range (mean (2SD)) of this assay in 60 volunteers sampled at 0900 hours is 2.5–7.2 pmol/l. The standard deviation of repeated measurements calculated by the method of Bland and Altman<sup>16</sup> is 0.5 pmol/l.

ACTH was measured by radioimmunoassay in unextracted plasma according to the method of Nicholson *et al*<sup>17</sup>: normal range at 0700–0900 hours <17 pmol/l. Cortisol was measured in a direct, solid-phase radioimmunoassay system<sup>18</sup>: normal range at 0700–0900 hours 280–720 nmol/l. Arginine vasopressin was extracted from plasma by  $C_{18}$  Sep-Pak cartridges and measured by radioimmunoassay.<sup>19</sup> Lactate was measured by a commercially available enzymatic assay (Boehringer Diagnostica). All samples for peptide assay were taken into chilled lithium heparin tubes with trasylol (1000 units/ml) added as a peptidase inhibitor for the  $\beta$  endorphin samples. After immediate separation in a refrigerated centrifuge 2 ml volumes of plasma for  $\beta$  endorphin assay were acidified with 0.5 ml 2M hydrochloric acid and flash frozen in either a dry ice/methanol bath or liquid nitrogen. All samples from individual patients were assayed in the same batch.

STATISTICAL ANALYSIS

The distribution of the data derived from this study were assessed by calculating the standardised coefficients of skewness and kurtosis. All of the variables were significantly skewed and so group values were expressed as medians with inter-quartile ranges. Groups were compared by Wilcoxon signed rank and Mann-Whitney U tests as appropriate. Univariate linear regression analysis between variables was performed by calculating Spearman rank correlation coefficients. For calculations we used a version of Statgraphics (STSC Inc) on a personal computer.

Results

STUDY 1

Fifty five consecutive patients (37 male, aged 37–75) admitted to the coronary care unit with acute myocardial ischaemia were studied.

Raised plasma concentrations of  $\beta$  endorphin were detected in 31/42 (74%) patients with confirmed myocardial infarction (peak 12.0 (6.9–26.0) pmol/l) and in 3/13 (23%) patients with unstable angina (peak 4.5 (2.7–7.0) pmol/l) (fig 1). The highest concentration recorded was 98.8 pmol/l and occurred in a patient who subsequently developed cardiogenic shock and died. Figure 2 shows the time course of the change in  $\beta$  endorphin concentration for all 55 patients. There were no significant differences in  $\beta$  endorphin concentrations at any time point between patients who had and had not received thrombolytic therapy. The 12 patients with myocardial infarction who developed cardiac failure in hospital had a higher peak  $\beta$  endorphin concentration than those with an uncomplicated course (29.2 (9.9–51.5) v 9.6 (3.8–22.4) pmol/l (fig 1).

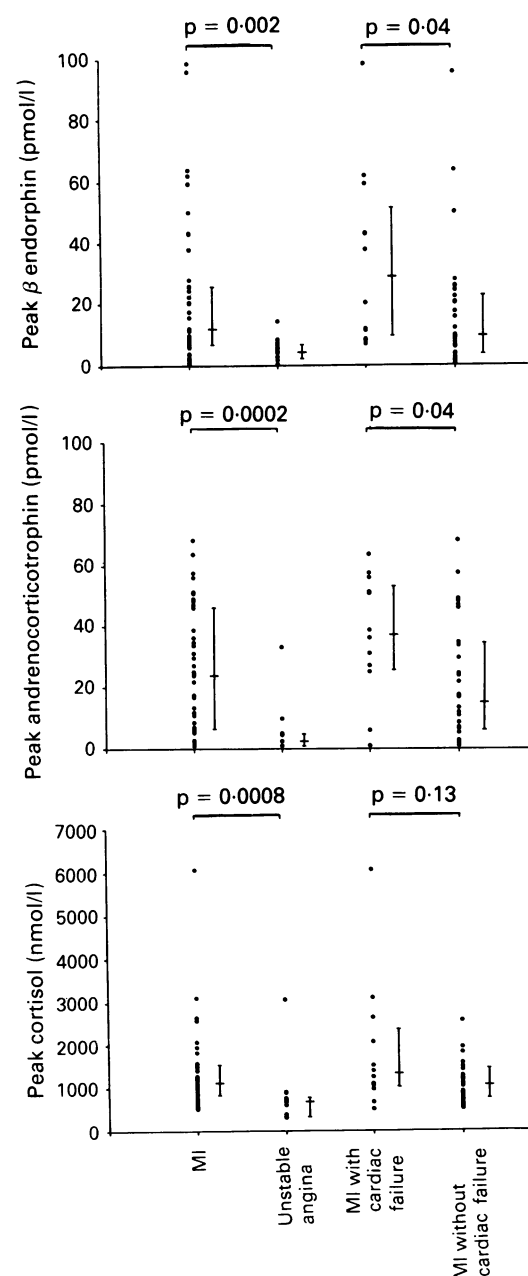


Figure 1 Peak concentrations of  $\beta$  endorphin, adrenocorticotrophic hormone, and cortisol in 55 patients with acute spontaneous myocardial ischaemia. Individual values are given with respective medians and interquartile range bars. MI, myocardial infarction.

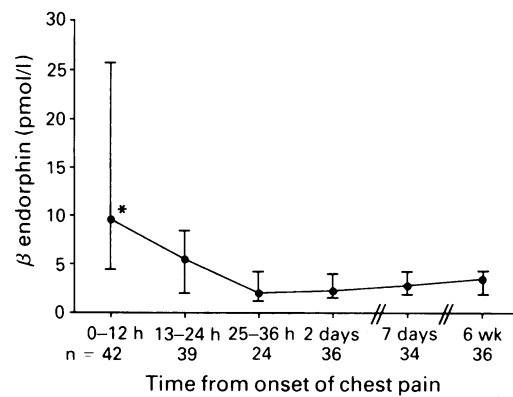


Figure 2 Serial median (interquartile range)  $\beta$  endorphin concentrations in 55 patients with acute spontaneous myocardial ischaemia. \* $p < 0.001$  v all other time points.

#### Correlation between $\beta$ endorphin and other neuroendocrine and clinical variables

Simultaneous measurements of other components of the hypothalamo-pituitary-adrenal axis provided a similar pattern of results to  $\beta$  endorphin. Thus peak ACTH and cortisol concentrations were 24.2 (6.6–47.0) v 2.5 (1.0–4.8) pmol/l and 1088 (824–1516) v 654 (323–742) nmol/l respectively for patients with myocardial infarction and without (fig 1). The highest concentrations of both  $\beta$  endorphin and ACTH were usually seen on admission and both returned to normal within 24 hours of admission in most patients (fig 2). Overall there was a good correlation between peak  $\beta$  endorphin and ACTH ( $r = 0.58$ ,  $p = 0.00001$ ), cortisol ( $r = 0.68$ ,  $p = 0.00001$ ) and glucose ( $r = 0.50$ ,  $p = 0.001$ ). Roughly equimolar concentrations of  $\beta$  endorphin and ACTH were seen, usually simultaneously, in 38/55 (69%) subjects. In 15 of these both were within the normal ranges (five with myocardial infarction) and in 23 one or both were raised. Several patients, however, showed a considerable difference between the concentrations of these

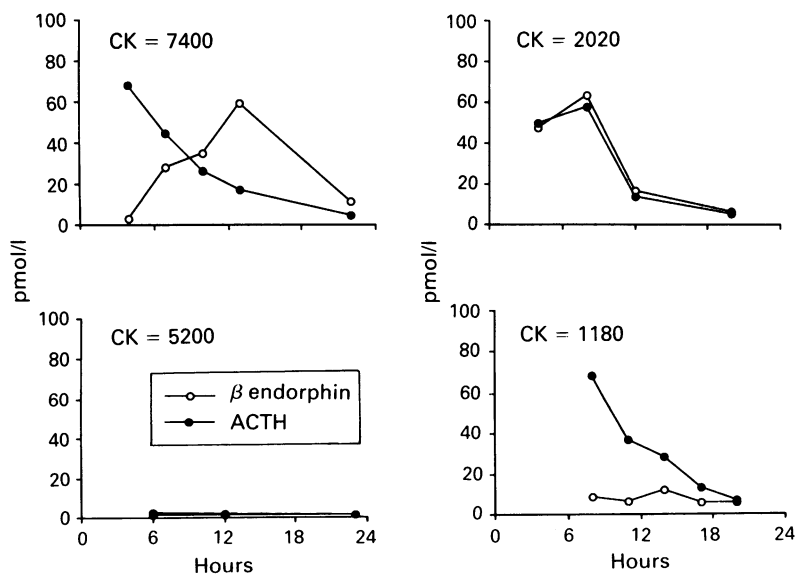


Figure 3 Individual patterns of  $\beta$  endorphin and adrenocorticotrophic hormone (ACTH) release in four patients with acute myocardial infarction. CK, creatine kinase (IU/l).

two related hormones. In 12 (22%) peak ACTH was higher than normal and was 2–18 fold higher than the peak  $\beta$  endorphin concentration. In five the opposite pattern was seen, with peak  $\beta$  endorphin being 2–8 fold higher than peak ACTH. Figure 3 shows individual examples of these patterns.

The peak concentration of arginine vasopressin in patients with myocardial infarction was significantly higher than in patients with unstable angina (9.0 (3.3–17.8) v 1.0 (0.8–2.9) pg/ml ( $p = 0.0002$ )) and considering all patients peak arginine vasopressin correlated well with peak  $\beta$  endorphin ( $r = 0.59$ ,  $p = 0.001$ ).

Peak concentrations of  $\beta$  endorphin and creatine kinase were positively correlated (fig 4) and there was a negative correlation between the time from onset of symptoms to peak  $\beta$  endorphin concentrations ( $r = -0.38$ ,  $p = 0.005$ ). Though pain is a stimulus to  $\beta$  endorphin release, there was no significant correlation with pain scores. These were virtually identical in the patients with and without myocardial infarction (78 (65–86) v 76 (63–86)) and those with and without cardiac failure (79 (57–84) v 78 (67–86)).

No significant correlations were seen with age, Norris score, ejection fraction on day three, and systolic or diastolic blood pressure or heart rate on admission.

#### STUDY 2

All 26 patients had a technically successful angioplasty. In three patients concentrations of  $\beta$  endorphin in the great cardiac vein were  $> 1.0$  pmol/l (2SD of the measurement error) higher than those in the aorta. But overall concentrations in the aorta and great cardiac vein were similar at both time points. There was thus no consistent evidence of any myocardial release and accordingly only the concentrations in the great cardiac vein are reported. At  $T_0$  only two patients had  $\beta$  endorphin concentrations  $> 7.2$  pmol/l (upper limit of normal): one of these had an episode of severe angina during transfer to the catheter laboratory and the other had a difficult arterial cannulation. Both of these patients were excluded from further analysis.

Before angioplasty the  $\beta$  endorphin concentration was 3.2 (2.4–4.9) pmol/l rising to 4.5 (3.4–13.8) pmol/l at  $T_{10}$ ,  $p = 0.002$ . The concentrations changed by  $> 1.0$  pmol/l in 16 patients: in 14 (58%) concentrations rose and in two (8%) they fell. At  $T_{10}$  10/24 (42%) patients had concentrations  $> 7.2$  pmol/l. The percentage change for all 24 patients was 62 (14–193)%. In the 14 patients showing increases in  $\beta$  endorphin the percentage change was 158 (73–248)%. The peak concentration of  $\beta$  endorphin after angioplasty was 4.6 (3.4–16.0) pmol/l, significantly lower than after myocardial infarction ( $p = 0.02$ ).

#### Correlation between $\beta$ endorphin and other neuroendocrine and clinical variables

As in the patients with spontaneous myocardial ischaemia, significant positive correlations were found between concentrations of  $\beta$  endor-

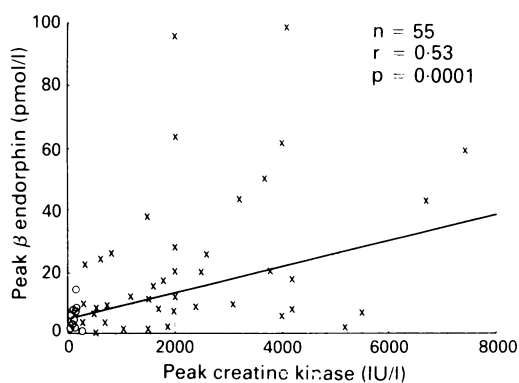


Figure 4 Correlation between peak concentration of  $\beta$  endorphin and creatine kinase in 55 patients with acute myocardial ischaemia. x, myocardial infarction; o, no myocardial infarction.

phin in the great cardiac vein and concentrations of ACTH ( $r = 0.85$ ,  $p = 0.0001$ ) and cortisol ( $r = 0.72$ ,  $p = 0.001$ ). No correlation was apparent between simultaneous measurements of  $\beta$  endorphin and lactate concentrations in the great cardiac vein ( $r = 0.06$ ,  $p = 0.76$ ) but there was a weak positive correlation with lactate extraction ( $r = 0.43$ ,  $p = 0.047$ ). There was a significant negative correlation between  $\beta$  endorphin concentration and the total duration of balloon occlusions ( $r = -0.69$ ,  $p = 0.0009$ ) but no correlation with the maximum ST segment deviation recorded during angioplasty ( $r = 0.002$ ,  $p = 0.99$ ).

### Discussion

$\beta$  Endorphin and ACTH have a common origin for pituitary pro-opiomelanocortin. They are stored together in the secretory granules of the pituitary corticotrophs and are co-released in response to stressful stimuli.<sup>20</sup> The unexpected dichotomy seen in some of our patients has, however, been described in other disease states.<sup>21,22</sup> This absence of molar unity may be related to the different plasma half-lives of  $\beta$  endorphin,  $\beta$  lipotrophin, and ACTH<sup>23,24</sup> and also to inter-individual variation in the post-translational processing of the precursor<sup>25,26</sup> which follows the application of a stressful stimulus.

Which component(s) of the stimulus of myocardial ischaemia provoke(s)  $\beta$  endorphin release and which if any are important in determining the pattern of the neuroendocrine response? In the patients with acute myocardial infarction and therefore prolonged periods of coronary artery occlusion there was a weak correlation between  $\beta$  endorphin concentrations and creatine kinase, a marker of ischaemic damage. There was a negative correlation between the duration of ischaemia (assessed from patient symptoms) and  $\beta$  endorphin concentrations. This latter finding suggests that  $\beta$  endorphin is released as a single pulse at the onset of myocardial ischaemia with the highest concentrations being found the earlier the patient is seen. In the angioplasty patients, in whom the period of coronary artery occlusion was much shorter, there was again only a weak correlation between  $\beta$  endorphin and a biochemical marker

of ischaemia and no correlation at all with the electrical evidence of ischaemia. The persistence of a negative correlation with the duration of ischaemia (balloon inflation time) in this second patient group is consistent with the release of a single pulse of  $\beta$  endorphin—in this case within minutes of the ischaemic stress being applied. In the patients with unstable angina, myocardial ischaemia was present but there was virtually no  $\beta$  endorphin release. Thus overall there is no convincing evidence that the  $\beta$  endorphin release is primarily determined by either the duration or the objective severity of the ischaemic insult.

What of the patient's perception of the ischaemic insult? Despite widely differing  $\beta$  endorphin concentrations, pain scores in the patients with myocardial infarction and unstable angina were virtually identical and overall there was no correlation between these scores and  $\beta$  endorphin concentrations. Visual analogue scales are a relatively crude method of assessing pain perception and it is possible that more complex techniques might have revealed a closer relation between perceived pain and  $\beta$  endorphin release. However, alternative stimuli such as nausea, transient blood pressure fluctuations, or the degree of activation of the autonomic nervous system might be involved.

There is good evidence that  $\beta$  endorphin release has a pathophysiological role in certain disease states and is not just an epiphenomenon. In various animal models of circulatory collapse including anaphylaxis,<sup>27</sup> hypovolaemia (haemorrhage),<sup>28,29</sup> and septicaemia,<sup>30,31</sup> naloxone and a range of other opioid receptor antagonists produce improved haemodynamic performance and substantial improvements in survival. A predominantly central mode of action is suggested by the lesser effects of analogues unable to cross the blood-brain barrier. Peripheral effects, however, may be important. Thus direct intracoronary infusion of naloxone in normal dogs results in dose-dependent increases in developed tension, left ventricular dP/dt, cardiac output, and blood pressure that are not reproducible with the inactive (+)-isomer.<sup>32,33</sup> The critical dependence of the response to naloxone on the presence of pituitary derived endorphins has been confirmed by Holaday *et al* who gave intracerebroventricular injections of naloxone to rats subjected to hypovolaemia. The dramatic recovery of blood pressure seen was completely abolished by prior hypophysectomy.<sup>34</sup>

There are relatively few studies of the effects of opioid receptor blockade in primary cardiac disease. In a canine model of chronic cardiac failure plasma concentrations of  $\beta$  endorphin were much higher than in control animals and the intravenous administration of nalmafene, a potent opioid receptor antagonist,<sup>35</sup> resulted in a further rise in  $\beta$  endorphin as well as increases in ACTH; catecholamines; mean arterial pressure; cardiac output; left ventricular dP/dt; and regional blood flow to the myocardium, skeletal muscle (quadriceps), and kidney. Sympathetic blockade abolished these effects, suggesting that the beneficial effects of opioid antagonists

in this model are mediated via the sympathetic nervous system.<sup>10</sup> In subsequent studies this group showed that the action of naloxone was preserved in anaesthetised animals, indicating that the effects were not related to removal of the antinociceptive action of the endogenous opioids.<sup>36</sup> Physiological concentrations of  $\beta$  endorphin selectively stimulate aldosterone secretion in dogs and could have a role in the modulation of sodium balance after myocardial infarction and in heart failure.<sup>37</sup> Also in a canine model it has been shown that the systemic and coronary vasoconstriction which follows the intracerebral administration of the opiate agonist fentanyl is mediated via the release of arginine vasopressin.<sup>38</sup> Our data showing a correlation between  $\beta$  endorphin and arginine vasopressin concentrations are consistent with this finding.

There are several anecdotal reports of improvements in blood pressure in patients with septicæmic<sup>39</sup> and cardiogenic shock<sup>40,41</sup> after the administration of intravenous naloxone. A recent double blind controlled study showed some benefit of naloxone in septicæmic shock.<sup>42</sup> Naloxone and some other opioid receptor ligands have another property that might be of relevance in cardiovascular disease. They showed antiarrhythmic activity in rats subjected to coronary artery ligation.<sup>43</sup> Interestingly,  $\beta$  endorphin at concentrations in the pmol/l range provokes a range of arrhythmias, mainly atrial, in isolated perfused rat hearts.<sup>44</sup> The arrhythmogenic action of  $\beta$  endorphin in this model is naloxone-reversible, but in most animals the concentrations of naloxone required to show cardiac electrophysiological and/or antiarrhythmic effects greatly exceeds the concentrations at which complete opioid receptor blockade would be expected. Thus it is likely that these effects are non-specific and unrelated to opioid receptor antagonism.<sup>45,46</sup>

We have shown, for the first time, that  $\beta$  endorphin release is a component of the neuroendocrine activation associated with myocardial ischaemia/infarction. The demonstration of a pathophysiological role in these particular clinical syndromes must await the results of further studies.

KGO is a British Heart Foundation junior research fellow.

- Guillemin R, Vargo TM, Rossier J, et al.  $\beta$ -endorphin and adrenocorticotropic hormone are secreted concomitantly by the pituitary gland. *Science* 1977;197:1367-9.
- Nakao K, Nakai Y, Oki S, Horii K, Imura H. Presence of immunoreactive  $\beta$ -endorphin in normal human plasma. A concomitant release with adrenocorticotropic hormone after metyrapone administration. *J Clin Invest* 1978;62:1395-8.
- Mullen PE, Jeffcoate WJ, Linsell C, Howard R, Lees LH. The circadian variation of immunoreactive lipotrophin and its relationship to ACTH and growth hormone in man. *Clin Endocrinol* 1979;11:533-9.
- Gruber CM, Robinson PI. Studies on the influence of morphine, papaverine and quinidine upon the heart. *J Pharmacol Exp Ther* 1929;37:429-49.
- Bruckner UB, Lang RE, Ganten D. Release of opioid peptides in canine hemorrhagic hypotension: effects of naloxone. *Res Exp Med* 1984;184:171-8.
- Vargish T, Beamer K. Hemodynamic effects of naloxone in early canine hypovolemic shock. *Circ Shock* 1985;17:45-57.
- Bone RC, Jacobs ER, Potter DM, et al. Endorphins in endotoxin shock. *Microcirculation* 1981;1:285-9.
- Evans SF, Medbak S, Hinds CJ, et al. Plasma levels and biochemical characterisation of circulatory [met]-enkephalin in canine endotoxin shock. *Life Sci* 1984;34:1481-6.
- Gurll NJ, Reynolds DG, Holaday JW. Evidence for a role of endorphins in the cardiovascular pathophysiology of primate shock. *Crit Care Med* 1988;16:521-30.
- Liang C-s, Imai N, Stone CK, Woolf PD, Kawashima S, Tuttle R. The role of endogenous opioids in congestive heart failure; effects of nalmafene on systemic and regional hemodynamics in dogs. *Circulation* 1987;75:443-51.
- Nakao K, Nakai Y, Jingami H, et al. Substantial rise of plasma  $\beta$ -endorphin levels after insulin-induced hypoglycaemia in human subjects. *J Clin Endocrinol Metab* 1979;49:838-41.
- Carr DB, Bullen BA, Skrinar GS, et al. Physical conditioning facilitates the exercise-induced secretion of beta-endorphin and beta-lipotropin in women. *N Engl J Med* 1981;305:560-3.
- Smith R, Besser GH, Rees LH. The effect of surgery on plasma  $\beta$ -endorphin and methionine-enkephalin. *Neurosci Lett* 1985;55:289-92.
- Kawashima S, Fukutake N, Nishian K, Asakuma S, Iwasaki T. Elevated plasma  $\beta$ -endorphin levels in patients with congestive heart failure. *J Am Coll Cardiol* 1991;17:53-8.
- Starling MR, Crawford MH, Sorenson SG, Levi B, Richards KL, O'Rourke RA. Comparative accuracy of apical biplane cross-sectional echocardiography and gated equilibrium radionuclide angiography for estimating left ventricular size and performance. *Circulation* 1981;63:1075-83.
- Bland JM, Altman DG. Statistical method for assessing agreement between two methods of clinical measurement. *Lancet* 1986;i:307-10.
- Nicholson WE, Davis DR, Sherrell BJ, Orth DN. Rapid radioimmunoassay for corticotrophin in unextracted human plasma. *Clin Chem* 1984;30:259-65.
- McConway MG, Chapman R. Development and evaluation of a simple, direct, solid-phase radioimmunoassay of serum cortisol from readily available reagents. *Clin Chim Acta* 1986;158:59-70.
- Morton JJ, Connell JMC, Hughes MJ, Inglis GC, Wallace ECH. The role of plasma osmolality, angiotensin II and dopamine in vasopressin release in man. *Clin Endocrinol (Oxf)* 1985;23:129-38.
- Owens PC, Smith R. Opioid peptides in blood and cerebrospinal fluid during acute stress. *Baillière's Clinical Endocrinology and Metabolism*. 1987;1:415-37.
- Jeffcoate WJ, Rees LH, McLoughlin L, et al.  $\beta$ -endorphin in human cerebrospinal fluid. *Lancet* 1978;ii:119-21.
- Hinds CJ, Evans SF, Varley JG, Tomlin S, Rees LH. Neuroendocrine and cardiovascular changes in septic shock: effect of high-dose corticosteroid therapy. *Circ Shock* 1985;15:61-72.
- Aronin N, Wiesen M, Liotta AS, Schussler GC, Krieger TD. Comparative clearance rates of  $\beta$ -endorphin and  $\beta$ -lipotropin in humans. *Life Sci* 1981;29:1265-9.
- Liotta AS, Li CH, Schussler GC, Krieger DT. Comparative clearance rate, volume of distribution and plasma half-life of human  $\beta$ -lipotropin and ACTH. *Life Sci* 1978;23:2323-30.
- Imura H, Kato Y, Nakai Y, et al. Endogenous opioids and related peptides: from molecular biology to clinical medicine. *J Endocrinol* 1985;107:147-57.
- Shiomi H, Watson SJ, Kelsey JE, Akil H. Pretranslational and posttranslational mechanisms for regulating  $\beta$ -endorphin-adrenocorticotropic hormone of the anterior pituitary lobe. *Endocrinology* 1986;119:1793-9.
- Amir S. Opiate antagonists improve survival in anaphylactic shock. *Eur J Pharmacol* 1982;80:161-2.
- Faden AI, Holaday JW. Opiate antagonists: a role in the treatment of hypovolemic shock. *Science* 1979;205:317-8.
- Vargish T, Reynolds DG, Gurll NJ, et al. Naloxone reversal of hypovolemic shock in dogs. *Circ Shock* 1989;7:31-8.
- Holaday JW, Faden AI. Naloxone reversal of endotoxin hypotension suggests role of endorphins in shock. *Nature* 1978;275:450-1.
- Faden AI, Holaday JW. Naloxone treatment of endotoxin shock: Stereospecificity of physiologic and pharmacologic effects in the rat. *J Pharmacol Exp Ther* 1980;212:441-7.
- Caffrey JL, Gaugl JF, Jones CE. Local endogenous opiate activity in dog myocardium: receptor blockade with naloxone. *Am J Physiol* 1985;248:H382-8.
- Lechner RB, Gurll NJ, Reynolds DG. Intracoronary naloxone in hemorrhagic shock: dose-dependent stereospecific effects. *Am J Physiol* 1985;249:H272-7.
- Holaday JW, O'Hara M, Faden AI. Hypophysectomy alters cardiorespiratory variables: central effects of pituitary endorphins in shock. *Am J Physiol* 1981;241:H479-85.
- Dixon R, Howes J, Gentile J, et al. Nalmafene: intravenous safety and kinetics of a new opioid antagonist. *Clin Pharmacol Ther* 1986;39:49-53.
- Sukamoto S, Stone CK, Woolf PD, Liang C-S. Opiate receptor antagonism in right-sided congestive heart failure. *Circ Res* 1989;65:103-14.
- Güllner H-G, Gill JR Jr. Beta-endorphin selectively stimulates aldosterone secretion in hypophysectomised, nephrectomised dogs. *J Clin Invest* 1983;71:124-8.
- Pasyk S, Grekin RJ, Walton JA, Pluta W, Pitt B. Mechanism of opiate mediated systemic and coronary vasoconstriction [abstract]. *Am J Cardiol* 1982;49:940.
- Peters WP, Johnson MW, Friedman PA, Mitch WE. Pressor effect of naloxone in septic shock. *Lancet* 1981;i:529-32.
- Dirksen R, Otten MH, Wood GJ, et al. Naloxone in shock. *Lancet* 1980;ii:1360-1.
- Higgins TL, Sivak ED. Reversal of hypotension with

- naloxone. *Cleve Clin Q* 1981;48:283-8.
- 42 Roberts DE, Dobson KE, Hall KW, Bruce Light R. Effects of prolonged naloxone infusion in septic shock. *Lancet* 1988;ii:699-702.
- 43 Sitsapesan R, Parratt JR. The effects of drugs interacting with opioid receptors on the early ventricular arrhythmias arising from myocardial ischaemia. *Br J Pharmacol* 1989;97:795-800.
- 44 Lee AYS, Zhan CY, Wong TM. Effects of  $\beta$ -endorphin on the contraction and electrical activity of the isolated perfused rat heart. *Int J Pept Protein Res* 1984;24:525-8.
- 45 Brasch H. Influence of the optical isomers (+)- and (-)-naloxone on beating frequency, contractile force and action potentials of guinea-pig isolated cardiac preparations. *Br J Pharmacol* 1986;88:733-40.
- 46 Oldroyd KG, Hicks MH, Cobbe SM. The class III antiarrhythmic effects of opioid receptor ligands are not receptor mediated [abstract]. *Eur Heart J* 1990;11:400.

*Br Heart J* 1992;67:235

## PLANTS IN CARDIOLOGY



*Senecio jacobaea* L. *Flora Danicae* Hafnia: Möllerus, 1787: volume 6; plate 944.

### Dietary pulmonary hypertension

The idea that certain plants could produce pulmonary hypertension seemed so unlikely that I began to wonder just how this discovery had been made. The story began in Iowa in 1884 when a new disease of horses with hepatic

cirrhosis was traced to the ingestion of *Crotalaria sagittalis* (Leguminosae) the native species of the rattlebox plant which was grown as green manure to improve the sandy soil. In 1921 *C. spectabilis* was introduced from India and it caused many outbreaks of disease among farm animals in the southern United States. Lesions in cows, pigs, goats, chickens, and horses included subendocardial haemorrhage, thickened pulmonary alveoli, pulmonary oedema, anaemia, and renal and hepatic disease. *Senecio* (Compositae) also caused equine cirrhosis in South Africa in 1920, while in North America the tar weed *Atalaya* (Sapindaceae), alsike clover *Trifolium* (Leguminosae), and *Amsinckia* (Boraginaceae) caused it too. A recent human epidemic of cirrhosis in India followed the accidental ingestion of *Heliotropium* (Boraginaceae). All these different genera and families contain pyrrolizidine alkaloids.

But none of these studies of natural or induced disease reported cardiac hypertrophy or pulmonary arterial disease. However, in 1955 Schoental and Head produced pulmonary infarction in rats with *Crotalaria*. Then in 1961 the breakthrough came when J J Lalich in Madison showed that rats fed *Crotalaria* seed or its alkaloid monocrotaline developed acute pulmonary arteritis. He went on to pioneer the crucial long term study. The rats developed intimal and muscular thickening of the pulmonary arterioles, dilated pulmonary arteries and right ventricular hypertrophy. In 1967 Kay, Harris, and Heath in Birmingham were the first to measure the right heart pressure in treated rats and confirm pulmonary hypertension. Later it was shown that the British plant, ragwort, *Senecio jacobaea*, sold in health stores for coughs and colds, produced pulmonary hypertension in rats. Meanwhile Bras and his colleagues had discovered that cirrhosis in Jamaican children was caused by hepatic veno-occlusive disease and they showed that the histology of their patients was identical with that of animals with *Crotalaria* and *Senecio* poisoning. Jamaican children often drank "bush-tea" made from these plants. But pulmonary hypertension has never been found in patients with veno-occlusive cirrhosis. Maybe only rats are susceptible. Donald Heath has recently looked back over his 25 years work on dietary pulmonary hypertension (*Circulation Research* 1991;25: 973-74).

Again, as with sweet clover disease of cattle (*British Heart Journal* 1991;66:181), a leguminous plant introduced from abroad for farming purposes has led via veterinary medicine to an important cardiovascular discovery.

A HOLLMAN