Serum Lipid Changes in Relation to Pain

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Serum cholesterol and beta-lipoproteins have long been known to be reduced following myocardial infarction (Dodds and Mills, 1959; Frederickson, 1969; Tiblin and Cramer, 1963; Watson et al., 1963). Dodds et al. demonstrated a transitory fall in lipid factors maximal during the first week, then rising to a peak 3 to 6 weeks later. The factors responsible have remained untraced. Suggested causes have included dietary changes, ‘stress’, and heparin (Frederickson, 1969; Bestermann, 1958) but the work of Watson et al. (1963) and Walker et al. (1957) show that neither dietary changes nor heparin are relevant to the fall. ‘Stress’, far from producing a fall, has been shown by several workers (Grundy and Griffin, 1959a, b; Pinter et al., 1967; Rahe and Ransom, 1967; Wolf et al., 1962) to produce an elevation in both these lipid fractions.

We wish to present evidence that the pain itself is the dominant factor in the reduction of serum beta-lipoproteins and cholesterol following myocardial infarction and other organic lesions.

DESIGN OF THE STUDY

The investigation was divided into three parts—

1. Patients diagnosed as having myocardial infarction and coronary insufficiency on conventional criteria were studied for beta-lipoprotein and cholesterol changes during and after pain at 12- to 24-hour intervals for seven days (37 cases).
2. Patients with comparably severe abdominal pain, mostly cases of renal colic, were similarly studied (21 cases, 17 renal colic).
3. Taking preoperative admission as an accepted example of ‘stress’, blood samples were taken and compared with postoperative samples both with and without pain over one week (22 cases).

PROCEDURE

In all patients blood samples were taken within a few hours of admission and immediately preoperatively from those awaiting surgery. Further samples
### Table 1. Mean lipid values in patients with myocardial infarction (22 cases)

| Time          | Beta-lipoproteins | Total cholesterol |
|---------------|-------------------|-------------------|
|               | A Lowest lipid level within 48 hrs of admission | A Lowest lipid level within 48 hrs of admission |
|               | A + 48 hrs | A + 96 hrs | A + 120 hrs | A + 48 hrs | A + 96 hrs | A + 120 hrs |
| Mean values % | 69       | 78         | 82         | 87         | 82         | 78         | 79         | 81         |
| Change from A | significant rise (0.05 > P > 0.01) | significant rise (0.05 > P > 0.01) | very significant rise (P < 0.001) | not significant rise (P > 0.05) | not significant rise (P > 0.05) | not significant rise (P > 0.05) |

### Table 2. Mean lipid values in patients with coronary insufficiency (15 cases)

| Time          | Beta-lipoproteins | Total cholesterol |
|---------------|-------------------|-------------------|
|               | A Lowest lipid value within 48 hrs of admission | A Lowest lipid value within 48 hrs of admission |
|               | A + 48 hrs | A + 96 hrs | A + 120 hrs | A + 48 hrs | A + 96 hrs |
| Mean values % | 78       | 88         | 92         | 89         | 91         | 89         |
| Change from A | significant rise (0.05 > P > 0.01) | very significant rise (P < 0.001) | not significant rise (P > 0.05) | not significant rise (P > 0.05) | not significant rise (P > 0.9995) |
were taken daily in the non-fasting state (10.00 a.m.) for seven days. Complaint of pain was assessed on admission and followed by pain charts (Keele, 1948). Blood was allowed to clot, and serum separated by centrifugation which was then analysed within 72 hours of taking the specimen. Serum beta-lipoproteins were estimated turbidometrically (Walton and Scott, 1964) and serum total cholesterol colorimetrically (Klungsoyr et al., 1958). Strict quality control was observed throughout the procedures.

PRESENTATION OF DATA
Each of the patients investigated constituted a longitudinal study of serial lipid changes. Thus, each served as his own control, and serum lipid values during or closely related to the event of pain were compared to values during the post-pain period. This is a more sensitive method than contrast studies for detecting significant changes (Mason, 1968).

The duration of pain in each of the groups differed markedly. Patients with pain of long duration (more than 24 hours) had at least two serum samples available for lipid analysis where the trend of lipid change during pain could be easily seen, whereas those with a shorter pain duration (less than 12 hours) had only the initial lipid sample taken during or in close proximity to the pain. In the latter, serial lipid changes could therefore only be assessed post hoc.

Both beta-lipoprotein and cholesterol values are expressed as a percentage of the highest level reached during the first week after admission for each patient. Such proportional representations are an accepted method of presentation (Tiblin and Cramer, 1963) where a wide range of lipid values is encountered.

STATISTICAL ANALYSIS OF DATA
Student's 't test' for independent samples was used to compare the lowest lipid value reached during the first few days after admission to lipid values at fixed time intervals thereafter, extending to the end of the first week. Thus, the probability of low values occurring close to the period of pain is compared to the purely chance occurrence of low values at this time. This shows a clear trend of lipid changes for each group of patients, especially the changes that occur in the post-pain period (see Tables).

FINDINGS
Group 1. Patients with myocardial infarction had pain lasting for a mean of 48 hours, of which 36 hours occurred after admission. The mean values of beta-lipoprotein levels in these patients fell sharply during the duration of pain, reached lowest levels at the end of the period of pain, and rose to high
Table 3. Mean lipid values in patients with abdominal pain (21 cases)

| Time          | Beta-lipoproteins | Total cholesterol |
|---------------|-------------------|-------------------|
|               | $A$ Lowest lipid value within 24 hrs of admission | $A + 24$ hrs | $A + 48$ hrs | $A$ Lowest lipid value within 24 hrs of admission | $A + 24$ hrs | $A + 48$ hrs |
| Mean values % | 76                | 88                | 92              | 85              | 92              | 94              |
| Change from $A$ | significant rise (0.01 > P > 0.001) | very significant rise (P < 0.001) | significant rise (0.01 > P > 0.001) | very significant rise (P < 0.001) |

Table 4. Mean lipid values in patients undergoing surgery (22 cases)

| Time          | Beta-lipoproteins | Total cholesterol |
|---------------|-------------------|-------------------|
|               | $A$ Lipid value 24 hrs before operation | $B$ Lowest lipid value within 72 hrs after surgery | $B + 48$ hrs | $B + 96$ hrs | $A$ Lipid value 24 hrs before operation | $B$ Lowest lipid value within 72 hrs after surgery | $B + 48$ hrs | $B + 96$ hrs |
| Mean values % | 94                | 65                | 74              | 76              | 93              | 79              | 78              | 76              |
| Change from $B$ | not significant rise (P > 0.05) | significant rise (0.05 > P > 0.01) | very significant fall (P < 0.001) | very significant fall (P < 0.001) |
levels by the end of the first week. A rise of beta-lipoproteins was increasingly significant at 96 and 120 hours after the lowest value during the first 48 hours after admission ($P < 0.001$). Cholesterol changes showed a similar trend, but did not achieve significant rises in the post-pain period (Fig. 1a and Table 1).

Patients with coronary insufficiency had a much shorter duration of pain (mean 9 hours), persisting for only 3 hours after admission. Mean beta-lipoprotein levels in these patients similarly had a significant rise at 48 and 96 hours after reaching lowest levels at 12 hours after admission ($P < 0.001$). Cholesterol values did not show a similar response in these patients, and were not significantly changed (Table 2).

**Group 2.** Patients with renal colic and other forms of severe abdominal pain had a mean pain duration of 20 hours, 12 hours of which persisted after admission. Beta-lipoprotein levels fell sharply during this period, reaching the lowest levels simultaneously with the end of pain, and rose significantly at 24 and 48 hours after the lowest recorded levels ($P < 0.001$). Cholesterol changes were similar, and also reached significant rises after pain ($P < 0.001$) (Fig. 1b and Table 3).
**Group 3.** Patients under stress awaiting surgery (Fig. 2 and Table 4) had preoperative beta-lipoprotein levels significantly higher than values reached at the end of the postoperative week. During the period of postoperative wound pain mean beta-lipoproteins reached their lowest levels at 48 hours after surgery. This level was significantly lower than beta-lipoprotein levels 96 hours later. Cholesterol levels showed a similar significant difference when comparing ‘stress’ levels to values at the end of the postoperative week, but did not show any rise after the postoperative pain period.

**Longitudinal Studies**

The lipid pattern is very clearly seen in the longitudinal study of individual cases—

*Case (i)*, Male (C.L.) aged 46, admitted with a history of severe chest pain, and with the ECG and enzyme changes of an acute myocardial infarction (Fig. 3a). Serum beta-lipoproteins fell rapidly during the duration of pain, and steadily rose during the next four days. One week later he had further severe
chest pain without fresh ECG or enzyme changes, clinically diagnosed as a further episode of myocardial ischaemia (Fig. 3b). His beta-lipoproteins fell again during the period of pain, and rose within 4 to 5 days to the high levels reached previously. This high level was sustained a week later. Serum total cholesterol values behaved similarly, but less markedly.

Case (ii). Male (J.W.) aged 54, admitted with severe abdominal pain, due to anicteric biliary colic (Fig. 4a). Serum beta-lipoprotein levels during the persistence of pain fell to 56 per cent of that several days later, when pain-free. At the beginning of his second and third weeks after admission with two further bouts of severe abdominal pain, his beta-lipoproteins fell to similar levels, rising promptly to high levels when pain-free (Fig. 4b, c). Three months later, at elective cholecystectomy, a stone in the gall-bladder was found. Hepatic and common bile ducts were patent. Preoperative beta-lipoprotein levels were very much higher than the levels found during the period of postoperative pain. At the end of the first postoperative week his beta-
Fig. 4. Case (ii). (a) Admission with biliary colic. (b, c) Further episodes of colic. (d) Admission for cholecystectomy.* = lipid value expressed as a percentage of highest value in first week (see text). Bold line = β-lipoprotein values. Broken line = cholesterol values. Hachured portion = episodes of pain.
lipoproteins had risen to levels as high as after his previous episodes of pain (Fig. 4d).

*Retrospective Diagnosis of Pain*

Other significant observations consisted of cases in which pain was diagnosed retrospectively by the unexpected findings of low beta-lipoproteins.

*Case (a).* Male, aged 60, had a severe myocardial infarction, the pain lasting for four days. During this time beta-lipoproteins were low (420 mg %), rising by the seventh day to 600 mg per cent. On the ninth day a routine beta-lipoprotein sample was found to be surprisingly low (310 mg %), and on questioning, the patient revealed that the day before he had had a further episode of chest pain lasting several hours, which he had 'forgotten' to report. A pleural effusion was seen on his chest X-ray, and a diagnosis of pulmonary infarction accepted. On the fifteenth day, now free of pain for several days, his beta-lipoproteins had risen to 575 mg per cent.

*Case (b).* Male, aged 40, with uretic stone, admitted with haematuria, severe loin and hypogastric pain lasting one and a half days. Initial beta-lipoproteins were 385 mg per cent, rising to 510 mg per cent on the third day. On the seventh day they fell to 400 mg per cent. It transpired that he had had severe abdominal pain again on the fifth and sixth days after admission, but had omitted to mention this. On the fourteenth day his beta-lipoproteins were 520 mg per cent.

**DISCUSSION**

The patient's complaint of pain provides clinical evidence of great value despite the difficulties that attend its definition. Among the many parameters of pain studied, verbal complaints still remain the most reliable (Hilgard, 1969; Merskey and Spear, 1967).

Many years ago Cannon (1915) emphasised that pain is the most powerful experience shared by man and animals, and observed biochemical reactions in response to pain and emotional changes. But neither Cannon nor subsequent workers separated the experience of pain from other forms of 'stress'. Since pain is characterised by its unpleasant sensory quality from non-painful stress such as occurs with acute anxiety, this difference might be expected to be reflected in a distinctive biochemical pattern. Such a pattern, however, will often be obscured by its underlying pathology. Only if the same type of biochemical change occurs with pain produced by very different forms of pathology (for example, cardiac infarction and renal colic) can such changes be attributed to the experience of pain itself.

Very little work has been designed to sort out these factors. Shenkin (1964)
studied the effects of pain on plasma corticoids, finding these elevated in comparison with pain-free levels, but no data were presented regarding the timing of these observations in relation to the experience of pain. His findings are similar to those found in patients with non-painful stress (Mason, 1968; Burston and Russ, 1965). Alexander (1962) attempted to demonstrate different psychogalvanic responses in patients experiencing physical and psychogenic pain. Such responses, however, were so non-specific as to be very difficult to interpret.

Birke et al. (1965) made serial plasma lipid observations on patients suffering from burns. They noted a marked fall in cholesterol and in both low and high density lipoproteins starting on the first day, and reaching its greatest extent on about the tenth day. They attributed this fall to exudative changes with plasma protein loss. McNamara et al. (1972) confirmed early fall in plasma cholesterol and lipoprotein following war-wounds in American troops in Vietnam. Here there was a marked transient rise in free fatty acids and triglycerides in fracture cases that was associated with the occurrence of fat embolism. This was followed by a fall in the cholesterol. The cholesterol was noted to fall from the first day in cases without fracture.

Werner (1969) in his observations of serum protein changes following partial gastrectomy noted a fall in total proteins mainly due to decreased albumen in the first three postoperative days accompanied by a fall in both alpha and beta-lipoproteins and in total serum lipids. He suggests that these changes are due to loss of exudate into the wound with temporary failure of the liver to replace the protein loss. These and later workers make no reference to any pain experienced by their patients.

It is clearly of importance to distinguish these beta-lipoprotein and cholesterol changes with pain from those produced by (a) non-painful 'stress', (b) the vascular exudative factor.

(a) By performing the same lipid investigations on a group of patients preoperatively and postoperatively, non-painful stress was separated from postoperative pain. We found, in agreement with previous workers, that the serum cholesterol and beta-lipoproteins were higher with preoperative stress than at the end of the postoperative week. Both cholesterol and beta-lipoproteins constantly fell while pain was being experienced, the beta-lipoproteins appearing to be more closely related to pain than the cholesterol.

(b) The exudative factor is minimal in cases of pain in renal or biliary colic. Yet in these cases, the fall in lipids was as marked as in those of myocardial infarction in which an exudative factor might be significant. Moreover, the duration of this beta-lipoprotein fall appeared to correlate with the severity and duration of the pain in all cases, including those of renal colic.
CONCLUSION

A marked fall in serum beta-lipoproteins and cholesterol is associated with the experience of pain, regardless of the pathology underlying it. This fall is in marked contrast to the lipoprotein changes from stress or anxiety; it has been found so constant as to be useful as a diagnostic test of the experience of pain of organic origin. We suggest that pain itself is an important factor in the fall in plasma beta-lipoproteins and cholesterol found by those who have previously investigated the effects of trauma, myocardial infarction and post-operative changes.

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