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Quebec Beer-Drinkers' Cardiomyopathy: Biochemical Studies

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THE present paper is an attempt to correlate the main biochemical findings with the clinical symptoms and other laboratory data in the patients who developed cardiomyopathy. The total data available from clinical chemistry may appear sparse, but it must be remembered that the patients were admitted as individual emergency cases to eight different hospitals and there was therefore no systematic approach at the onset of the epidemic. However, as the similarity of the disease pattern became evident, it was possible to establish a more precise protocol of laboratory investigation from which significant trends appeared.

Each of the hospitals involved had sufficient laboratory facilities for thorough biochemical investigations. Owing to the variation in analytical procedures from one institution to another, some of the data had to be adjusted for proper comparison, whenever this was feasible. At the conclusion, a simple statistical analysis was attempted for some of the tests. Other scattered data are mentioned when suggestive of the underlying pathology. Fortunately, a follow-up has been available on some patients and this is also summarized here.

METHODS

Because circulatory abnormalities were consistently found in these patients, the possible influence of these abnormalities on the results obtained by liver function tests were tentatively appraised by correlating abnormal biochemical findings with the degree of centrilobular liver cell necrosis found in the liver sections examined from autopsies of 15 fatal cases. On the other hand, the liver sections obtained by biopsies on survivors were useless for all practical purposes because they were obtained from these patients at a time when their clinical and biochemical findings were improving. All histological material was examined by pathologists who were not informed of the other findings from the clinical laboratory. The criteria used for evaluating centrilobular necrosis were those suggested by Ellenberg and Osserman.[1] The method used for estimating the degree of liver damage was that of Sherlock[2]:

Grade A—centrilobular stasis with evidence of degeneration adjacent to the centrilobular vein.

Grade B—centrilobular and sinusoidal stasis with evidence of degeneration involving the internal one-third of the lobule.

Grade C—degeneration involving more than one-third of the lobule.

According to the observations made by Popper,[3] possible errors of interpretation due to autolytic processes after death were considered in the above classification.

In order to evaluate the effect of shock on the overall picture revealed by the liver function tests, an attempt was also made to correlate the latter with levels of blood pressure. Fortunately, repeated and precise measurements of arterial pressure were available, especially when shock or severe hypotension was present and patients were under close observation in intensive care units. As for the dates and times of the collection of blood for laboratory tests, these generally were obtained from the attending nurses' notes. With these data on hand, the patients were classified into three distinct groups according to the arterial blood pressure at the time of blood collection or in the hours immediately preceding: (a) a *normal group* showing stable systolic pressure at 120 mm. Hg or more, and diastolic pressure at 80 mm. Hg or more; (b) a *severe shock group* whenever the blood pressure could not be obtained; (c) a *hypotensive group*—all other cases.

RESULTS

Biochemical Findings on Admission

The results of various liver function tests are summarized in Fig. 1. Most tests were abnormal, some more so than others.

The serum bilirubin was abnormally high in 22 out of 32 patients and the serum cholesterol was outside the normal range in 6 out of 27 (from 79 to 251 mg. per 100 ml.). Comparison of serum alkaline phosphatase values was more difficult because of the variety of techniques used by the laboratories involved, but generally the results appeared to be within normal limits. The prothrombin time, which was performed in 34 cases, was below 80% in 27, and below

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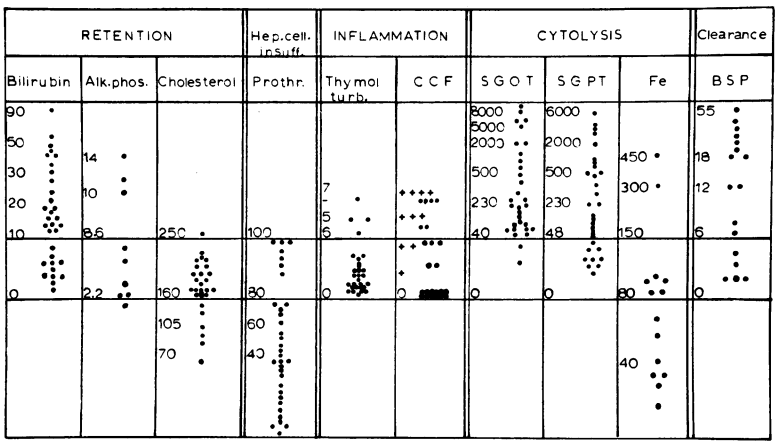

Fig. 1.—Tests of hepatic function.

40% in 16 others. Flocculation tests were normal except for: (a) increased thymol flocculation in two of nine patients who had the test; (b) increased thymol turbidity in 5 of 28 patients tested, and (c) an increased cephalin-cholesterol flocculation in 6 of 25 patients so tested.

TABLE I.—ELECTROPHORESIS OF SERUM PROTEINS IN 13 PATIENTS PERFORMED IN THREE INSTITUTIONS

	Mean Results		*Normal values*
Total proteins	*6.32 g. per 100 ml.*	*± 0.77**	*6.0-8.0 g. per 100 ml.*
Albumin.....	46.4%	± 6.5	57 - 63%
Alpha-1 globulin...	7.2%	± 1.9	2 - 5%
Alpha-2 globulin...	11.8%	± 2.3	8 - 10%
Beta globulin.....	15.0%	± 4.0	10 - 12%
Gamma globulin...	19.5%	± 5.2	14 - 16%

*1 standard deviation.

The electrophoretic pattern of serum proteins, available in 13 cases, shows an amazing similarity, as indicated by the low standard deviations (Table I). There is a general trend towards hypoalbuminemia while the accompanying hyperglobulinemia does not show an elevation of any specific pattern or fraction.

In contrast with the former, the serum enzyme tests show marked changes. Serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) were abnormally high in 30 of 31 patients: over 1000 units SGOT in 22.5% of the patients, and over 1000 units SGPT in 25.7%. Other enzyme determinations were performed at random: (a) lactic dehydrogenase (LDH) was abnormally high in 22 of 25 patients with values over 2000 units in 36.8%; (b) ornithine carbamyl transferase (OCT), highly specific for liver damage, was high in two of four patients tested; (c) isocitric dehydrogenase (ICDH) was also abnormally high in six of nine estimations (in three patients as high as 4000, 9610 and 62,470 units respectively); (d) phosphocreatine kinase (CPK) was estimated only once and was found to be within normal limits; (e) a single adolase determination showed an abnormally high result.

Other tests included: (1) bromsulphalein — increased retention in 14 of 17 patients; (2) serum iron (five normal, seven low or very low, and two high); (3) serum magnesium (all within normal limits in the few tests performed); and (4) the Westergren sedimentation rate (under 5 mm. in one hour in the majority of cases). The hemoglobin and erythrocyte counts were in the high normal range as a rule.

Attempts to detect thiamine deficiency by direct measurement of the vitamin were not successful since assays could not be performed immediately after sample collection. However, serum lactic and pyruvic acid assays made on 12 patients showed highly abnormal values: 30.3 ± 15.8 mg. per 100 ml. and 5.2 ± 2.5 mg. per 100 ml. respectively. In order to eliminate the influence of factors other than thiamine deficiency, such as hypoxia and shock, a means of predicting pyruvic acid values from the values found for lactic acid has been suggested.[4] Normally both values (measured and predicted) should agree closely, and any deviation found

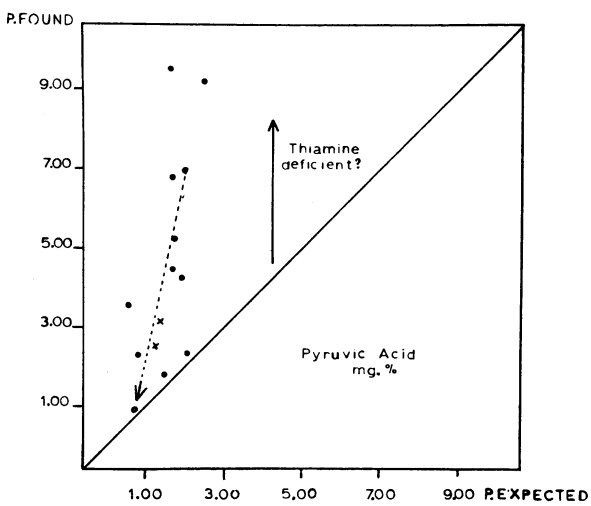

Fig. 2.—Serum pyruvic acid (actual and calculated). Values above the solid line represent an abnormal pyruvic-lactic acid ratio. Values joined by the dotted line indicate results of the test on admission and after treatment.

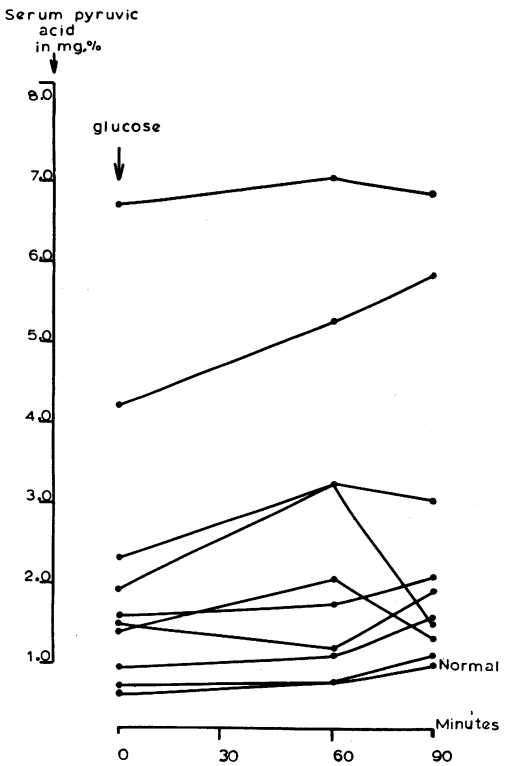

Fig. 3.—Pyruvic acid tolerance tests—serum pyruvic acid levels *before* and 30, 60 and 90 minutes *after* the administration of glucose.

is an indication of the degree of thiamine deficiency present. The deviations found in the few cases that were studied are shown in Fig. 2.

Other institutions involved in the present survey approached the problem of detecting thiamin deficiency by means of the pyruvic acid-tolerance test using a load of glucose (Fig. 3). Blood pyruvic acid (normal fasting: 0.5-1.0 mg. per 100 ml.) does not usually exceed 1.3 mg. per 100 ml. under glucose stimulation. Here again, abnormal levels were found.

Finally a gross attempt to correlate the above values with symptoms of thiamin deficiency was not successful, and this suggests some other etiological factor which might have interfered with the normal metabolism of pyruvate and lactate.

At the time of admission the significant biochemical findings therefore were: (a) hyperbilirubinemia (in the majority of cases); (b) a significant increase in most serum enzyme levels (especially SGOT and SGPT); (c) hypoprothrombinemia; (d) normal flocculation tests; (e) a relative polycythemia, and (f) a significant increase of both circulating pyruvate and lactate.

Follow-up

In February 1967, 30 patients were seen at periods varying from 9 to 13 months after admission to hospital.

All hemoglobin levels had returned to normal, except in one patient (18.3 g. per 100 ml.) With only one exception (48 μg. %), serum iron levels had reached normal values. Serum enzymes were normal except in four patients, but in these the values of SGOT and SGPT were below 150 units. The serum bilirubin was still slightly increased in two patients but normal in all others. Protein-bound iodine values were all normal. Radioactive iodine (^{131}I) uptake was low in two subjects (8% and 9%), increased in one (40%) and normal in all others.

Correlation Between Biochemical and Anatomical Findings (Fig. 4)

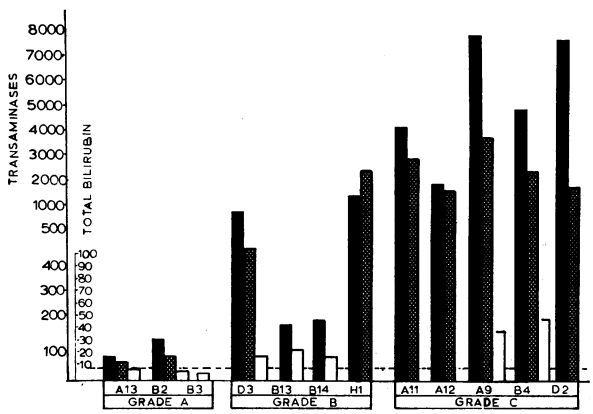

Fig. 4.—Correlation between biochemical values (solid blocks for SGOT; shaded blocks for SGPT, and clear blocks for total serum bilirubin) and degree of liver necrosis.

Because the state of the hepatic cell is best reflected by the transaminase and bilirubin values,[2] these are considered in relation to each anatomical group in Fig. 4: the trend is from normal to increased values progressing through groups A, B and C (Sherlock[2]), respectively. Although we are dealing with a rather small series, there appears to be a definite correlation between biochemical findings and the degree of centrilobular necrosis.

Correlation Between Biochemical Findings and Blood Pressure Levels (Figs. 5 and 6)

Here again some correlation appears to exist between arterial blood pressure and the liver function tests. Normotensive patients (Fig. 5) had total bilirubin and transaminase values within normal limits, while the "shock" group (Fig. 6) had increased values. As for the intermediate

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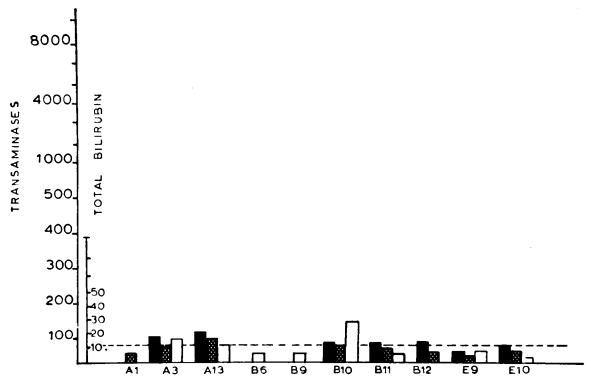

Fig. 5.—Biochemical values in normotensive patients. (Solid blocks for SGOT; shaded blocks for SGPT, and clear blocks for total serum bilirubin.)

"hypotensive group", no definite pattern could be found.

In some patients, serum total bilirubin and transaminase were measured on several occasions during the course of the present study; in general, these values were inversely related to the level of the blood pressure.

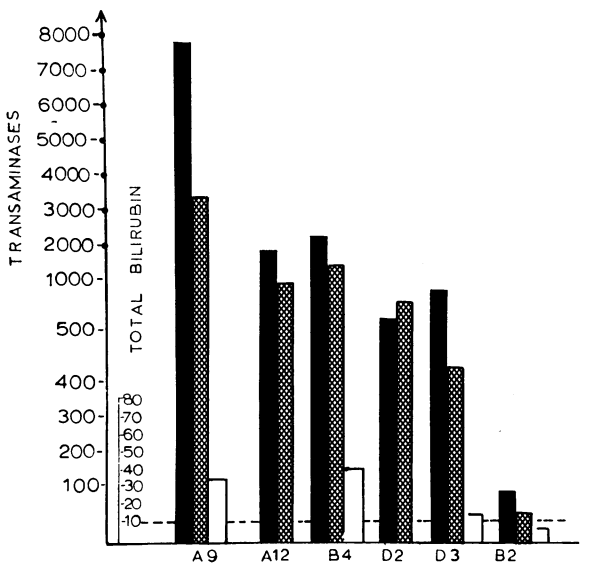

Fig. 6.—Biochemical values in patients in shock. (Solid blocks for SGOT; shaded blocks for SGPT, and clear blocks for total serum bilirubin.)

DISCUSSION

What is the origin of the increased serum enzyme levels? Do these increases result from the myocardial degeneration itself? It is possible that the myocardial necrosis which is known to be present could increase the levels of the enzymes to a certain extent, but it is improbable that they could cause such marked increases as those observed in the present series. Even if these enzymes were of myocardial origin, it still remains to be explained why myocardial lesions of similar extent are compatible with normal transaminase values in some cases. A reasonable conclusion, in our opinion, is that cardiac involvement was merely an accessory source of serum enzyme elevation.

As mentioned previously, the degree of hepatic centrilobular necrosis correlates well with the enzyme values. Other liver function tests (e.g. serum bilirubin, prothrombin time) also parallel serum enzyme values. OCT and ICDH enzymes, essentially hepatic in origin, also showed marked elevation. (Other scattered data, such as lactic—hydroxybutyric dehydrogenase (LDH/HBDH) ratio greater than 1.8 in all cases, in which both tests were performed simultaneously, also point to hepatic involvement.)

Although the essential effect of shock on the liver function tests, and especially on serum enzyme levels, has already been mentioned, the anomalies found in the present series are nevertheless more accentuated. Richman, Delman and Grob,[5] studying liver function tests in 173 cases of right heart failure of all types, report transaminase (SGOT and SGPT) values between 40 and 80 units in 80% of the patients, with a maximum of 1250 units. Shields and Shannon,[6] reviewing 1900 transaminase (SGOT) determinations performed during two years at the Harrisburg Polyclinic Hospital, found only four cases exceeding 1000 units among cardiac patients showing no hepatic pathology. Killip and Payne, during a period of 30 months, found only 17 cases of pure cardiopathy with the serum glutamic oxaloacetic transaminase exceeding 500 units, among which only five were over 1000 units with a maximum of 6570 units.[7]

The general tendency to polycythemia, as revealed by high-normal hemoglobins and erythrocyte counts, suggests a specific etiological factor although the influence of shock and dehydration cannot be ignored. Similarly, the anomalies found in pyruvic and lactic acid levels may be related to some specific factor affecting their metabolism, other than thiamine deficiency which, in the present series, could not be directly implicated. The association of lactic-acid acidosis with shock has been demonstrated.[7] However, it is a provocative thought that some etiological factor may have induced acidosis by a direct effect on the metabolism of pyruvate, with resultant accumulation of lactate.

Summary The main biochemical abnormalities involved in the present study have been reviewed. The most important disturbances were found in the serum enzyme levels, and their probable predominant hepatic origin is discussed. Various arguments favour the hepatic origin

of these disturbances due to two hypoxic factors: passive venous congestion secondary to right heart failure, and, predominantly, decrease of hepatic arterial blood flow due to shock. Follow-up studies showed that most liver function tests returned to the normal range. Other biochemical anomalies suggest the possibility of a specific etiological factor which might have acted via interference with pyruvate metabolism.

Résumé On a fait une compilation des principales analyses biochimiques effectuées par les divers laboratoires impliqués dans cette étude. L'observation la plus remarquable est l'augmentation des enzymes sériques. Leur origine hépatique est discutée. Des contrôles subséquents montrent que la plupart des épreuves de fonction hépatique redeviennent normales. Diverses autres observations suggèrent l'existence possible d'un facteur étiologique spécifique exerçant son action principalement sur le métabolisme de l'acide pyruvique.

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Quebec Beer-Drinkers' Cardiomyopathy: Electrocardiographic Study

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THE cardiac syndrome which struck Quebec beer drinkers several months ago revealed a number of interesting clinical and laboratory findings. To encounter such a large series, of almost epidemic proportions, in a relatively short time, is rather rare and indeed facilitated the precise description of this pathological entity which was hitherto unrecognized. It was thought that a special study of the electrocardiographic changes would be interesting because these were remarkably constant from one patient to another, varying only with the severity of the disease. By studying the electrocardiograms of 45 patients, we were able to observe major and rapidly evolving changes, which are reported here and compared with the observations made by different investigators on cardiomyopathy occurring in alcoholics.

The speed with which the pathology manifested itself in some of these patients is striking because the electrocardiograms substantiated the clinical and radiological findings in that they showed that the disease had begun only a few months before. In a few patients we had a chance to compare the electrocardiographic examinations made on admission with some recorded a few months previously when the patients had been investigated for other conditions. An example is shown in Fig. 1A and 1B, which demonstrate some rapid changes occurring in a 44-year-old patient.

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ADMISSION FINDINGS

The cardiac rate averaged 115 per minute, with a range of 90 to 160 per minute.

Arrhythmias were rare. There were isolated extrasystoles, i.e. one or two per tracing, in only two patients. The PR interval was found normal in all patients except in: (1) a case of atrial flutter in a patient who died 48 hours later, and (2) a case of nodal tachycardia in a patient who died the day of admission. One case of second-degree atrioventricular block occurred during treatment of a patient who survived; apparently due to digitalis, the block became first-degree two days after discontinuation of digitalis and eventually disappeared.

The P wave showed anomalies with significant frequency. Although the P axis in the limb leads remained within normal limits, varying between +30° and +90°, the axis in the precordial leads deviated towards the left and varied between 0° and −30° in 35 patients. The P waves generally had a peculiar pattern and were considered pathological in 28 cases. Five patients presented with a pattern characteristic of left atrial hyper-