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CITRATE INTOXICATION

A CLINICAL AND EXPERIMENTAL STUDY

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For many years the sodium salts of citric acid have been used as anticoagulants in blood for transfusion. For the most part it has proved safe to infuse into humans the quantities of citrate contained in stored blood. However, as the rapid infusion of large volumes of blood has become a more frequent event, there have been several reports of citrate overdose in man. Citric acid forms weakly dissociated salts with divalent cations (Hastings *et al.*, 1934) and its untoward effects are generally attributed to the depression of ionization of such cations in the extracellular fluid, particularly calcium. The excitable tissues of the body are susceptible to such a depression, the effects on cardiac muscle being the most important.

Wexler *et al.* (1949) studied newborn infants with erythroblastosis receiving exchange transfusions of citrated blood. In the course of the transfusions the plasma citrate rose from normal levels of 2 to 3 mg. to 60 to 120 mg./100 ml. In some cases there was associated tetany or convulsions relieved by the infusion of calcium.

Electrocardiographic changes in the course of exchange transfusions were observed by Furman *et al.* (1951) in six infants, four of whom showed muscle tremors and two lengthening of the QT interval. These changes were reversed by intravenous calcium gluconate. Gustafson (1951) observed muscle tremors but no changes in the QT interval in eight infants receiving exchange transfusion. Ames *et al.* (1950) also failed to detect significant E.C.G. changes in infants with plasma citrate levels of up to 53 mg./100 ml.

In adults there have been two extensive investigations: those of Bunker *et al.* (1955) and Howland *et al.* (1957). The former workers studied 130 patients receiving citrated blood, generally in the course of surgery. They calculated the depression of plasma ionized calcium due to citrate from the measured total plasma calcium, protein, and citrate, using the equations of Hastings *et al.* (1934) and McLean and Hastings (1935). The calculated ionized calcium was used to correlate clinical and biochemical findings. At rates of blood infusion of about 500 ml. in 15 minutes the rise in plasma citrate and depression of ionized calcium was greater in those patients with liver disease than in the remainder. Thus, of the 28 patients in whom the calculated plasma ionized calcium fell below the normal range—that is, less than 0.8 mM/kg. H_2O —17 suffered from liver disease, 2 underwent surgery involving interference with liver

circulation (pancreaticoduodenectomy with portal vein resection, resection of thoracic aortic aneurysm), and 4 had resection of abdominal aortic aneurysms, the surgical details not being given. One patient underwent craniotomy under induced hypothermia to 25.8° C. Those patients with the lowest ionized calcium levels had associated hypotension, in some cases reversed by intravenous calcium chloride.

Howland *et al.* (1957) established normal values for plasma citrate in man (0.80 ± 0.8 mg./100 ml.) and in women (1.08 ± 0.9 mg./100 ml.). By infusion of acid-citrate-dextrose solution (A.C.D.) rapidly into patients they were able to show large increases in plasma citrate with accompanying lengthening of the QT interval, though without detecting tetany or hypotension. They also studied 77 patients receiving citrated blood under anaesthesia and found good correlation between the rate of blood infusion and the plasma citrate level, without, however, observing untoward effects from the raised plasma citrate.

Apart from the above reports, the literature of citrate intoxication in man includes a few incompletely documented cases in which citrated blood was implicated as a cause for cardiac dysrhythmia—for example, Hubbard *et al.* (1956) and Argent (1957).

In summary, it appears from the clinical reports that there may be a marked elevation of the plasma citrate level by the infusion of citrated blood under certain circumstances: in exchange transfusions in infants, and on other occasions when blood or plasma is infused rapidly, particularly in the presence of disease or impaired blood supply of the liver. The signs which have been attributed to citrate intoxication are muscle-twitching or convulsions in the unanaesthetized patient, E.C.G. changes, particularly lengthening of the QT interval leading to cardiac asystole, arterial hypotension resistant to further blood transfusion or pressor agents, and possibly prolongation of clotting-time.

It is surprising, in view of the widespread use of citrated blood and the above reports of toxicity, that the fate of infused citrate in humans is not yet completely known. Salant and Wise (1917), using the rather inexact method of citrate estimation available at the time, studied the fate of brief infusions of citrate into animals. They noted that of an infused dose 4 to 13% was excreted in the urine in rabbits, 30% in cats, and 40% in dogs. They confirmed the previously observed effects of muscle-twitching, convulsions, and cardiac and

respiratory arrest. They also noted that blood itself had little or no power to destroy citrate. Martensson (1940), using a similar infusion technique, found that in the rabbit 4 to 8% of a dose was excreted in the urine, in the cat 27 to 43%. From perfusion experiments he came to the conclusion that the liver had little or no ability to destroy citrate, the kidney a marked ability—results at variance with the work of Sjöström (1937), who obtained nearly complete clearance of citrate from the perfusate in one passage through the perfused liver, and at variance with observations of Bunker *et al.* in man. One conclusion which can be drawn from the animal experiments is that there is a marked species difference in the behaviour of infused citrate.

In this paper we present four clinical cases demonstrating greatly raised plasma citrate levels following the infusion of blood under various circumstances, and an account of some work on the elimination of infused citrate from the plasma in dogs and man.

Material and Methods

The blood used for transfusion was that supplied by the National Blood Transfusion Service. Each 540-ml. bottle contains 1.75 g. of citrate expressed as citric acid.

For the estimation of plasma and urinary citrate the method of Natelson *et al.* (1948) was used, modified to extend the range. Plasma citrate levels are reported as mg./100 ml. of citric acid. Plasma calcium was estimated

by the method of Sobel and Sobel (1939). It was found that plasma citrate levels of up to 250 mg./100 ml. did not interfere detectably with calcium estimation, provided the oxalated plasma was allowed to stand for 12 hours at 4° C. before centrifuging. Ionized calcium was calculated from the equations of Hastings *et al.* (1934) and McLean and Hastings (1935). It is realized that this method does not give precise values, but it gives the only measure of ionized calcium in the presence of citrate that is at present available.

Other biochemical estimations were made by methods previously reported from this laboratory (Wynn and Houghton, 1957; Wynn and Ludbrook, 1957). Blood samples were either arterial or were taken from a vein distant to the site of infusion.

The QT interval on the E.C.G. was corrected for heart rate by the formula $QT/\sqrt{R-R}$ and expressed as QTc.

A blood balance by a method of swab weighing was carried out on these patients undergoing surgery.

Clinical Investigation

Case 1

A man of 55 was operated on under induced hypothermia to 29.8° C. for an aortic thrombosis extending up to the level of the renal arteries. Early in the operation 2.2 l. of blood was infused in one hour (1.4 mg. citrate/kg./min.), exactly replacing blood lost. Systolic blood pressure fell from 240 to 100 mm. Hg (Fig. 1). It was noted that on the E.C.G. the QTc interval lengthened from 0.44 to 0.64 sec. (Fig. 2). Calcium gluconate (1 g.) was given at this stage intravenously. Arterial clamps were placed across the aorta above the renal arteries and on both common iliac arteries for some three hours during the resection of the affected aortic segment and insertion of a homograft. After release of the clamps there was further haemorrhage and 3.25 l. of blood was given in 1.4 hours (1.5 mg. citrate/kg./min.). Blood pressure became unrecordable in the extremities and remained so despite more than complete blood replacement and the infusion of noradrenaline. The QTc interval became lengthened to 0.70 sec., there was excessive oozing from the wound, and the patient died in ventricular fibrillation after receiving 7.5 l. of blood (26 g. citrate). The infusion of 2 g. of calcium gluconate during this latter period was without effect.

An arterial blood sample had been taken prior to the induction of hypothermia, and a further sample was taken during the second phase of rapid blood infusion. Analysis of these samples showed that during this latter period, when citrate was being given at the rate of 1.7 mg./kg./min., the citrate level rose to 140 mg./100 ml., the total calcium fell from 10 to 13.6 mg./100 ml., while the calculated ionized calcium fell from 1.2 to 0.35 mM/kg. H₂O. The plasma total protein, sodium, potassium, and chloride remained essentially unchanged. The blood pH fell from 7.44 to 7.32.

FIG. 1.—Changes in oesophageal temperature, blood pressure, QTc interval, plasma citrate, total and ionized calcium in Case 1. Amount of infused blood is shown in 0.5-litre blocks, and duration of aortic clamping and of noradrenaline infusion is indicated.

FIG. 2.—E.C.G.s (lead I) in Case 1 at various times after induction of anaesthesia (see Fig. 1). Note temporary lengthening of QT interval during rapid infusion of blood at 5.8 hours, and grosser changes from 10.1 hours.

It seemed probable to us that citrate intoxication played an important part in this patient's death. We therefore performed plasma citrate estimations on blood samples collected from other patients undergoing operation under hypothermia.

FIG. 3.—Changes in oesophageal temperature, blood pressure, and plasma citrate in Case 2. Amount of infused blood is shown in 0.5-litre blocks. Duration of aortic clamping is indicated.

TABLE I.—Summary of Observations on Case 2. Time Periods are Those Between Arterial Samples, Taken Before Blood was Given, Before Aortic Clamps were Applied, During Clamping, and After Release of the Clamps (See Fig. 3)

	Period Before Clamping (1-2 Hour)	Period During Clamping (2-4 Hour)	Period After Unclamping (2-4 Hour)
Citrate infused (g.)	1.75	5.5	5.5
Rate of citrate infusion (mg./kg./min.)	0.4	0.6	0.6
Arterial plasma citrate at end of period (mg./100 ml.)	11	41	13
Plasma citrate clearance* (% normal)	65	20	70

* See Discussion.

Case 2

A man of 35 had a syphilitic aortic aneurysm situated in the region of the eleventh to twelfth thoracic vertebrae. At operation the aorta was clamped above and below the aneurysm, at a level above the coeliac axis. From Fig. 3 and Table I it may be seen that, despite the fact that there was no period of rapid blood infusion, at the end of the period of aortic clamping the plasma citrate level had risen to 41 mg./100 ml., and immediately after release of the clamps to 48 mg./100 ml. During an equal period following release of the clamps with an identical rate of citrate infusion the plasma citrate fell to 13 mg./100 ml. The oesophageal temperature throughout remained close to 28° C.

Case 3

This patient was a woman of 44 with a thrombosis of the abdominal aorta extending up to just below the renal arteries. Under hypothermia (28° C.) a bypass homograft was inserted from the aorta above the coeliac axis to the left external iliac artery. By application of a Craford clamp to the aorta it was possible to perform the upper anastomosis without interrupting the aortic blood flow. During 30 minutes after the clamps were released 1,100 ml. of blood was infused (1.9 mg. of citrate/kg./min.). The

plasma citrate rose to 39.5 mg./100 ml. and the calculated rate of citrate removal from the plasma was 65% of normal (see Discussion). There was an associated lengthening of the QTc interval from 0.53 to 0.63 sec., but no significant hypotension.

Case 4

A man of 24 underwent partial hepatectomy for a haemangioma of the liver with associated cirrhosis. Induced hypothermia to 29.5° C. was used. Preoperatively the only defect in liver function detected was a bromsulphthalein retention of 25% after 45 minutes. In the course of the operation the hepatic artery was clamped for 90 minutes. During this period the blood pressure fell, and it remained

FIG. 4.—Changes in oesophageal temperature, blood pressure, QTc interval, and plasma citrate in Case 4. Amount of infused blood is shown in 0.5-litre blocks. Duration of hepatic arterial clamping and of noradrenaline infusion and time of injection of 10 ml. of 10% CaCl₂ are indicated.

TABLE II.—Summary of Observations on Case 4 (see Fig. 4)

	Pre-operative	15 min. After Clamping Hepatic Artery	15 min. After Unclamping Hepatic Artery	2½ hr. Later (1 hr. Post-op.)
Oesophageal temp. (°C.)	37	29.5	29.5	32
B.P. (mm. Hg)	120	85	50	110
Rate of citrate infusion (mg./kg./min.)	0	0.4	1.2	0.85
Plasma citrate (mg./100 ml.)	1.6	14.7	70	28.1
Plasma citrate clearance† (% normal)	—	42	23	42.5
Total plasma Ca (mg./100 ml.)	8.8	8.2	11.0	14.5*
Total plasma Ca (mM/kg. H ₂ O)	2.35	2.20	2.90	3.80
Calculated ionized Ca (mM/kg. H ₂ O)	0.90	0.70	0.50	1.30

* 45 minutes after CaCl₂ infusion. † See Discussion.

low for the remainder of the operation (three hours) despite complete replacement of measured blood loss and the infusion of noradrenaline (Table III and Fig. 4). An intravenous injection of 10 ml. of 10% calcium chloride was followed within a few minutes by a rise in B.P. to 110 to 120 mm. Hg.

Experimental Investigation

1. Citrate in Stored Blood and Plasma

It is known that in normal human blood the citrate ion is virtually confined to the plasma (Natelson *et al.*, 1947). In recently collected citrated blood it was possible to show that at least 98% of the added citrate remained in the plasma. In such blood at 4° C. there was, over a period of three weeks, a progressive fall in plasma citrate concentration to 92% of the original level, but whether this represents metabolic destruction of citrate or a movement into the red cells was not determined.

2. Metabolism of Infused Citrate

When citrate is infused intravenously over a brief period, and the plasma citrate level is measured at intervals following the infusion, there is a very rapid fall of plasma citrate during the first few minutes, which slows until the normal plasma level is regained after about 60 minutes (Mårtensson, 1940: Fig. 7). This rapid disappearance of citrate from the plasma is due to three mechanisms: distribution throughout at least the extracellular space, excretion in the urine, and metabolic destruction.

Bunker *et al.* (1955) observed, as we have, that the plasma concentration after a brief rapid infusion does not exceed that which would be attained if the infused citrate were rapidly distributed in the extracellular space.

In order to eliminate the distribution factor in experiments to determine the rate of metabolic destruction, we have used steady rates of infusion of A.C.D. It was judged that a steady state had been reached with regard to distribution when the plasma citrate and urinary excretion of citrate were constant in successive 10-minute periods. When this steady state is reached, the rate of clearance of citrate from the plasma (excretion plus metabolic destruction) equals the rate of infusion. If the rate of citrate infusion, the plasma citrate, and the urinary excretion of citrate is known, the rate at which citrate is metabolized may be calculated.

FIG. 5.—Relation in two dogs between rate of citrate infusion and plasma citrate concentration. Open circles: dog 1, normal body temperature. Open triangles: dog 2, normal body temperature. Closed triangle: dog 2, hypothermia to 28.5° C. (oesophageal) (see Table III). Each point represents mean value from three plasma samples taken at 10-minute intervals.

Relation of Plasma Citrate Level to Rate of Citrate Infusion.—In both dog and man the rise in plasma citrate was directly proportional to the rate of infusion (cf. Bunker *et al.*, 1955; Howland *et al.*, 1957) (see Figs. 5 and 6). At comparable rates of infusion (1 mg./kg./min.) the elevation of plasma citrate was much higher in the dog (20 mg./100 ml.) than in the human (12.5 mg./100 ml.) (Figs. 5 and 6).

FIG. 6.—Relation in a normal man between rate of citrate infusion and plasma citrate concentration. Each point represents mean value from three plasma samples taken at 10-minute intervals.

Urinary Excretion.—In the dog at widely differing rates of infusion more or less constant 44% of the infused citrate was excreted in the urine (limits 43 to 48%) (Table III). In normal unanaesthetized man under similar conditions only 18 to 20% was excreted, the remainder being presumably metabolically destroyed. The urine-plasma concentration ratio ranged from 74 to 100 in the dog and from 14 to 25 in the human.

Metabolic Destruction.—It follows from the above that, in man, metabolic destruction is more important as a means of removing citrate from the plasma than in the dog. For a given elevation of plasma citrate the rate of metabolic destruction in man is about twice that in the dog, weight for weight.

TABLE III.—Summary of Observations on a Dog Receiving Citrate at Differing, Though Steady, Rates of Infusion, at Normal Body Temperature and Under Hypothermia (see Fig. 5)

Sub-hepatic Temp. °C.	Citrate Infused (mg./kg./min.)	Plasma* Citrate (mg./100 ml.)	Citrate Excreted (mg./kg./min.)	Excreted %	Urine/Plasma Conc. Ratio	Citrate Destroyed (mg./kg./min.)
37.2	0.86	19.5	0.39	45	74	0.47
37.1	2.12	44.6	0.92	48	96	1.20
28.5	0.83	30.5	0.36	43	100	0.47

* These plasma figures are the mean values of determinations made on three samples obtained at consecutive 10-minute intervals. The values did not differ from the mean by more than $\pm 2.5\%$.

Effect of Hypothermia in the Dog.—This was studied in the dog by first determining the rate of metabolic destruction of citrate at normal body temperature, as described above, then repeating a previous rate of infusion in the same animal with its temperature lowered by surface cooling (Table III and Fig. 5). The results show that for the same rate of infusion the rise of plasma citrate was 65% greater in the hypothermic dog, and at equivalent plasma citrate levels the rate of metabolic destruction was 42% lower.

Effect of Hypothermia in Man.—It was not feasible to study this effect by steady infusion. Instead 1.5 g. of citrate was infused in 20 minutes and the fall in plasma citrate followed during the succeeding 40 minutes in three patients before and during hypothermia for carotid disobliteration. A typical result is shown in Fig. 7, demonstrating a similar qualitative effect of hypothermia in man to that in the dog.

FIG. 7.—Fall in plasma citrate concentration in a patient following the infusion of 1.5 g. of citrate in 20 minutes. Open circles: normal body temperature. Closed circles: hypothermia to 30 to 32° C. (oesophageal).

Discussion

In the previous section we have defined some of the factors which, during the transfusion of citrated blood, affect the removal of citrate from the plasma and govern its concentration therein. We have found that the rise in the plasma citrate level produced by a steady infusion of citrate is proportional to the rate of infusion. Bunker *et al.* (1955) and Howland *et al.* (1957) have also observed this straight-line relationship (in patients receiving citrated blood). At a citrate infusion rate of 1 mg./kg./min., the elevation of plasma citrate we obtained was 12.5 mg./100 ml. Calculations based upon the data of Bunker *et al.* give a figure of 11 mg./100 ml., and Howland *et al.* reported 8 mg./100 ml.

When the rate of blood transfusion is known, and has been of sufficient duration to allow a steady state to be approached, the difference between the observed and predicted plasma citrate levels allows us to calculate the approximate rate of plasma citrate clearance (excretion plus metabolic destruction) as a percentage of normal, using our results relating the rise of plasma citrate to the rate of infusion (Fig. 6).

With the use of this information it is possible to predict the approximate elevation of plasma citrate produced by a given rate of blood infusion, and to detect and roughly quantitate any defect in the rate of plasma citrate clearance in a patient.

It is difficult to define a dangerous plasma citrate level, but from the observations of Wexler *et al.* (1949), Bunker *et al.* (1955), and ourselves a level of 50 mg./100 ml., giving in a normal person a calculated plasma ionized calcium of about 0.5 mM./kg. H₂O, may be considered at least undesirable. In a normal adult this corresponds to a steady rate of citrated-blood infusion of about one bottle (540 ml.) per five minutes, a rate rarely achieved in practice. It is noteworthy, however, that Argent (1957) and Hubbard *et al.* (1956) have each published an account of a patient undergoing cardiac surgery, during which this rate was attained and in whom ventricular standstill and fibrillation occurred respectively, with reversion to normal rhythm by means of a calcium injection.

It would appear, then, that except at excessively rapid rates of blood infusion some defect in plasma clearance is necessary to produce dangerous levels of plasma citrate. In Fig. 8, in 27 of the 28 cases of which Bunker *et al.* give details, the plasma citrate level is plotted against the rate of citrate infusion and compared with the straight line we have derived for normal man—for example, Fig. 6.

FIG. 8.—Relation in man between rate of citrate infusion and plasma citrate concentration. Straight line: our experimentally determined line. Points represent 27 cases from Bunker *et al.* (1955). Open circles: survivors, plasma citrate clearance 60 to 120% of normal. Dotted circles: survivors, plasma citrate clearance less than 50% of normal. Closed circles: deaths.

denectomy and resection of portal vein, and cirrhosis of the liver with bleeding oesophageal varices. Five other points represent patients with a calculated plasma citrate clearance

of less than 50% of normal, while the points representing the remaining patients, many of whom suffered from liver disease, fall more or less along the line of normality.

In Fig. 9 points representing our four patients are similarly plotted. Case 1, in which the blood supply to the liver, kidneys, and lower limbs was impaired for some three hours, shows a gross deviation from normal, and the patient died in circumstances suspicious of citrate intoxication. Case 4, with a hepatic haemangioma and associated cirrhosis, shows a gross defect in plasma citrate clearance immediately after the hepatic artery had been clamped under hypothermia for 90 minutes. This patient had unexplained hypotension reversed by intravenous calcium chloride. From Cases 2 and 3 points are derived showing the effect of hypothermia alone—the plasma citrate clearances are between 65 and 70% of normal at 28° C., a figure consistent with that obtained in the dog for a similar temperature reduction (65%).

Case 4, with pre-existing liver disease, showed a rather lower plasma citrate clearance (42%) under hypothermia.

It thus appears that high plasma citrate levels are unlikely to occur with citrated blood transfusion in normal humans, except where the rate of transfusion is extremely rapid (greater than 1 pint (540 ml.) per five minutes in an adult, or during rapid exchange transfusion in infants). In metabolically abnormal patients, with liver disease, anuria (in view of the fact that some 20% of infused citrate is excreted), or rendered hypothermic, or when there is impairment of liver circulation or application of clamps to the thoracic or high abdominal aorta, the ability to clear the plasma of citrate may be so impaired as to make high plasma citrate levels a real danger.

The recognition of the signs of citrate intoxication presents a difficulty, for hypotension may be both the cause for and the effect of rapid transfusion, and, unless a blood balance has been kept, citrate intoxication may be overlooked. The E.C.G. changes from the hypocalcaemia produced by a high plasma citrate concentration—in particular lengthening of the QTc interval, progressing to asystole—may have many other explanations, from hypothermia to hyperkalaemia. Muscle-twitching or convulsions from hypocalcaemia do not appear to occur in the anaesthetized patient, and excessive oozing from the wound is more likely to be due to replacement of the blood volume with stored blood than to a citrate effect.

However, if there are good grounds for suspecting that a high plasma citrate level is the cause of otherwise unexplained hypotension or cardiac dysrhythmia, the logical remedy is the administration of calcium. We prefer to use calcium chloride rather than calcium gluconate, on the ground that the former is more completely ionized. The correct dose can be assessed only by the slow (0.5–1 ml./min.) intravenous injection of 10% calcium chloride, until a response is seen in the blood pressure or on the E.C.G., or until 10 ml. has been given.

Prevention is possible in planned surgical procedures when blood may have to be given rapidly, and when one or more

FIG. 9.—Relation in man between rate of citrate infusion and plasma citrate concentration. Numbered points represent Cases 1 to 4. Dotted circles: hypothermia alone. Closed circles: hypothermia plus impaired liver function. Triangles: hypothermia plus interference with liver blood supply. Note the change in scale of plasma citrate concentration.

of the circumstances which depress the rate of clearance of citrate from the plasma are present, by having available blood collected without the use of citrate. Heparin may be used—though this is often undesirable, particularly in vascular surgery—or blood may be collected over an ion-exchange resin (Walter, 1950). The use of commercial packs for the latter purpose has been satisfactory in our hands, though they are expensive and the blood may be safely stored for only about 10 days.

Summary

High plasma citrate levels occurred during the infusion of citrated blood into four patients undergoing surgery under hypothermia. One patient died with signs attributable to citrate intoxication.

A linear relationship between the rate of infusion of citrate and the rise in plasma citrate level was demonstrated in normal man and dogs. For each 1 mg. of citrate infused per kg. per minute the rise was about 20 mg./100 ml. in dogs and about 12.5 mg./100 ml. in humans.

By using a constant infusion technique it was shown that in dogs some 40% and in man some 20% of infused citrate was excreted in the urine, and the remainder was metabolically destroyed.

In both dog and man hypothermia to 28 to 29° C. was shown to reduce the rate of metabolic destruction of citrate by 30 to 40%.

From our findings it would seem that the infusion of citrated blood at less than about 1 pint (540 ml.) in five minutes in an adult is unlikely to cause a dangerous rise of plasma citrate, provided that the rate of citrate metabolism is not reduced.

Circumstances which impair citrate metabolism in patients are discussed.

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The Ministers of Agriculture and Health and the Secretary of State for Scotland have considered the revised Report of the Food Standards Committee on Copper. They accept the view of the Committee that the consumer will be adequately protected if limits for the copper content of foods which are consistent with good commercial practice are observed and that, in the absence of any new developments, it is unnecessary to give statutory effect to the recommended limits. With certain exceptions these are: beverages ready to drink, 2 p.p.m.; other foods, 20 p.p.m.

SOME AETIOLOGICAL ASPECTS OF CORONARY HEART DISEASE

AN INDIAN POINT OF VIEW BASED ON A STUDY OF 867 CASES SEEN DURING 1948-55

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In a few years' time two centuries will have passed since Heberden described the syndrome of angina pectoris, yet the aetiology of coronary heart disease remains undetermined. Western writers seem to believe that the so-called "material civilization" of the West is responsible for the increased incidence of this disease in their countries and that Asiatics are far less prone to fall victim to this malady. Arnott (1954) says: "Coronary heart disease is one of the main causes of disability and death in the United States, Canada, Britain, Northern Europe, Australia, and New Zealand, and these are all countries which, nationally speaking, derive more than 30% of the food calories from fat. On the other hand, areas like southern Europe, Africa, India, and the Orient in general have diets the fat of which contributes less, usually much less, than 20% of the calories. It is difficult to be certain that atheroma and coronary heart disease are much less in these countries. The extent and standards of medical, biochemical, and pathological work are, generally speaking, much inferior, while the vital statistics of the populations at risk are less clearly defined. Nevertheless, while the evidence is not of the same quality as in the materially more favoured countries, it is uniformly consistent with the conclusion that the diseases are comparatively very uncommon."

Views in an editorial in the *Lancet* (1955) on the subject of coronary disease are thus expressed; "Beside this we have to set the fact that clinicians with experience in the East have long held that the disease is rarer in Asiatics than in Europeans—to an extent that cannot be wholly explained by the Europeans having longer lives. Support for this opinion comes from pathological studies showing that the inhabitants of the Japanese island of Okinawa have little atheroma or coronary-artery disease. In Africa the post-mortem findings of Higginson and Pepler at Johannesburg indicate that severe atheroma is far less common among the Bantus than in American and European hospitals."

In India, publications on the incidence of coronary diseases have been rather few. In recent years prevalence of coronary disease has been pointed out by some Indian authors (Vakil, 1949, 1954; Malhotra, 1951; Samani, 1956). For the present communication we have collected the data of 867 cases of coronary disease seen by us, so that the readers in other countries may be presented with the available picture of this disease in India.

The presented data go to show that coronary disease forms a big group in the cardiac population of this part