ties needed for rapid imaging of the whole skeleton. A large eluate volume may contain a number of oxidants which could lead to a poor labelling yield. It should therefore be realised that any decrease in bone uptake or degradation in image quality of a bone scan might result from such poor labelling of the preparation rather than its instability after the labelling had been carried out.

The results shown in table 2 suggest that there is no significant change in bone or soft tissue uptake between the standard preparation and those which have been stored at room temperature for 2 h before injection. It is a clear advantage to the user in being able to label the diphosphonate some hours before injection as occasional delays in patient arrival and other scheduling problems are sometimes unavoidable. As a delay of up to 4 h between labelling and injection does not affect bone uptake, 99m-Tc-MDP provides great flexibility of use in this respect.

The results of the pH study are summarized in table 3 from which it can be seen that the most marked changes occur at very low and very high pH values. The only variable in these experiments was pH as the weight ratio of MDP to SnF_2 was kept constant.

At low pH (1.5–2.0) a low Sn(II) concentration would be desired because of the competition which exists between Tc^{7+} and Sn^{2+} cations for the complexing sites of the MDP molecule. At this pH, Sn^{2+} ions are in excess and will result in some of the 99m-Tc not being able to bind onto the MDP molecule. Low uptake by the thyroid indicates that very little of the added free 99m-TcO_4^- is left in the unreduced state as excess stannous ions should lead to complete reduction.

Labelling efficiency depends on pH, and a high yield is obtained as shown by TLC (93.25±2.71%). This is probably due to the solvent system not being able to separate the bone complex from any hydrolyzed reduced technetium or other colloidal complexes which remain as a single entity at the origin on the TLC strip. A slight increase in liver and spleen activity indicated presence of some colloids.

At high pH (13.0–14.0) a high Sn(II) concentration is desirable for which 2 explanations may be given: either the reduction of 99m-TcO_4^- is rather slow at high pH and a high concentration of the Sn(II) reductant is advantageous, or part of the hydrated technetium oxide is incorporated in a tin hydroxide colloid. At this pH, bone localisation is considerably reduced, and most of the activity appears to reside in the blood and soft tissues. This may account for the high soft tissue concentration seen during the early stages in development of the bone kit and poor labelling yield as shown in the chromatography results (16.11±1.17%).

Other pH values studied (9.6–10.0 and 1.5 → 14.0 → 6.5) showed no change in bone uptake compared to the standard pH value (6.4–6.7) although slight increases occurred in soft tissues. The tissue distribution pattern was consistent with images obtained using a gamma camera. The maximum labelling yield occurs at pH = 6.4–6.7.

These findings indicate that regular monitoring and pH control should be performed on all 99m-Tc-labelled diphosphonate compounds particularly when they are intended for administration into patients such as in routine bone scanning.

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The influence of hyperosmolality on heart function

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Summary. Hyperosmolality produces a reduction in myocardial water content, an increase in ventricular stiffness and coronary blood flow, and a decrease in ventricular performance. The alterations of myocardial dehydration and ventricular stiffness are more pronounced in glucose-induced, and those of ventricular performance in urea-induced hyperosmolality.

Osmolality is an essential physical property of the organism, comparable to temperature in significance. As well as hyperosmolar diabetic coma, diagnostic or clinical treatment with hyperosmolar solutions can account for hyperosmolality of the blood[1–3]. In such cases serum osmolality may rise to, or even above, 400 mOsm/l[1,2]. The effect of glucose- and urea-induced hyperosmolality was, therefore, investigated on heart function.

Methods. 32 mongrel dogs of both sexes, weighing 16–26 kg, were anaesthetized with pentobarbital (30 mg/kg) and used to obtain Starling's heart-lung preparations.

The following parameters were measured: cardiac output and coronary blood flow directly (the latter through a cannula tied into the coronary sinus); blood glucose[4], urea nitrogen[5], osmolality (Knauer's semimicroosmometer), haematocrit and oxygen content; left ventricular water content by drying to constant weight; left ventricular pressure by a p23Db Statham gauge through a rigid catheter introduced into the apex and registered on a Hewlett-Packard recorder (Type 1061C); left ventricular passive elastic modulus (characteristic of the diastolic stiffness of ventricular wall) by the modified[6] method of Diamond and Forrester[7].

In order to measure the components of passive elastic modulus and cardiac output over a wide range, the haemodynamic variables were determined at 4 different levels of aortic pressure (40, 80, 120 and 160 mmHg).

After initial determinations, 2 groups of dogs (13–13 animals) were treated either with glucose or urea added to the blood dropwise until the respective doses of 0.5–1.0 and 0.4–0.8 g/kg b.wt was reached. Haemodynamic determinations were made at each stage. The experiment was then concluded in 6 preparations of each group, and the heart was removed for assessment of myocardial water content. In the remaining 7 preparations of both groups, the normal osmolality was reestablished and, after haemodynamic assessment the heart was removed for measurement of myocardial water content. In further 6 preparations, repeated haemodynamic determinations were carried out without altering the blood osmolality, in order to detect the probable occurrence of spontaneous changes. The results were examined statistically using Student's t-test and regression analysis.

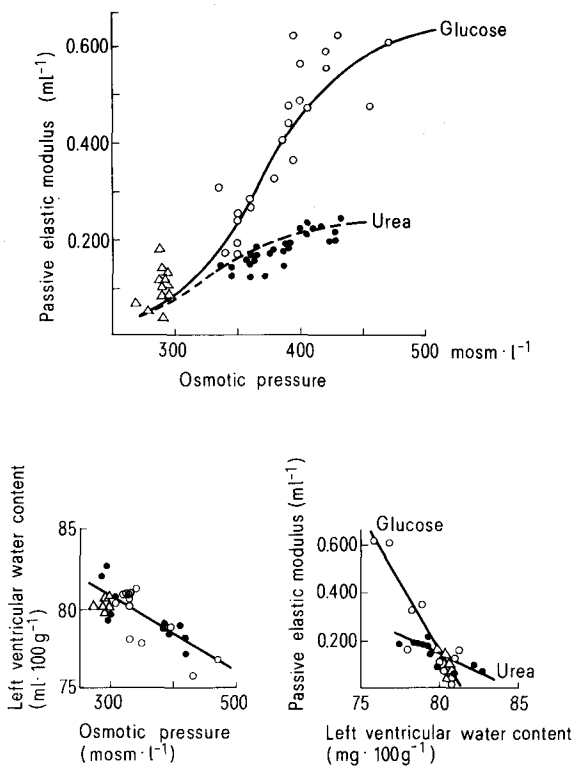

Fig. 1. Correlations between blood osmotic pressure and left ventricular passive elastic modulus; blood osmotic pressure and myocardial water content of the left ventricle; myocardial water content of the left ventricle and left ventricular passive elastic modulus. Solid circles indicate the value of control; open circles those of glucose-induced hyperosmolality and open triangles those of urea-induced hyperosmolality.

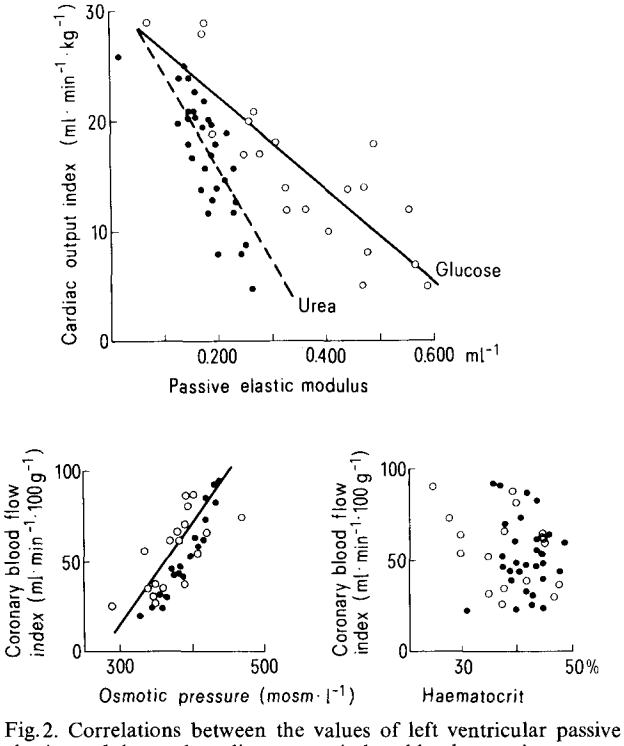

Fig. 2. Correlations between the values of left ventricular passive elastic modulus and cardiac output index; blood osmotic pressure and coronary blood flow index; blood haematocrit and coronary blood flow index. Symbols as in figure 1.

Results and discussion. The value of the passive elastic modulus rose considerably, when the osmolality of the blood elevated above 340 mOsm/l (blood glucose level above 600 mg/100 ml, or the blood urea nitrogen level above 100 mg/100 ml). The rise in the value of the passive elastic modulus was proportional to the increase in osmolality, but was more pronounced under hyperglycaemic than under hyperuraemic conditions. The highest blood osmolality tested was 470 mOsm/l, produced by levels of either 3000 mg glucose, or 440 mg urea for 100 ml blood (figure 1).

The decrease in water content of the left ventricular muscle was indirectly proportional to the increase of blood osmolality. On correlating the water content of left ventricular wall with the respective passive elastic modulus, the slope of the regression lines differed significantly ($p < 0.01$), depending on whether glucose or urea was responsible for the alterations. This fact suggests that increase of the passive elastic modulus, i.e. decrease of left ventricular compliance during glucose-induced hyperosmolality is due primarily to dehydration of the myocardium (figure 1).

The cardiac output decreased during increased left ventricular afterload under the hyperosmolar conditions. This decrease showed a close correlation with the rise of the passive elastic modulus in both groups but the decrease was more pronounced during hyperuraemia than during hyperglycaemia. This fact suggests that in hyperuraemia the decrease in cardiac output was due to some other effects, in addition to the disorder of the ventricular compliance (figure 2).

Coronary blood flow was markedly increased in hyperosmolality. This increase could be correlated with osmolality but not with the haematocrit (figure 2). These changes were reversible on reperfusing with blood of normal osmolality. In the control preparations, no spontaneous alterations were observed during the 60 min perfusion period.

Similar results to ours have also been reported by Templeton et al.[8] who found an increase of ventricular stiffness during hyperosmolality. However, the close correlation between ventricular stiffness and myocardial dehydration was not established. We conclude that, in diabetics, hyperosmolality by influencing ventricular compliance may be partly responsible for the development of heart failure in hyperosmolar diabetic coma.

The difference between glucose- and urea-induced phenomena, observed in this study and by other authors[9–12], could easily be explained by the easier intracellular penetration of urea[10,13]. However, the severe cardiac symptoms in uraemia seem to be due to a direct cardiac injury by urea rather than to alteration of myocardial compliance.

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