skin taken from the site of injection for microscopic examination. The tissue was fixed in 10% formalin, embedded in paraffin and sections were stained with hematoxylin-eosin.

Three of 12 animals sacrificed at days 10 and 12 showed a pink coloured nodule at the injection site. Microscopic examination showed normally preserved epidermis and upper dermis. In the lower dermis and subcutaneous fatty tissue, a localized well circumscribed nodule, composed mainly of lymphocytes, was seen (Figure 1). Higher magnification (Figure 2) showed a dense collection of mature lymphocytes, few large histiocytes with large oval clear nuclei, and few plasma cells.

A recent study of the pharmacological activity of oriental hornet venom[6] showed that the venom possessed protease, hyaluronidase, released histamin from mast cells, caused hemolysis and was immunogenic. The antigenic effect of the venom might explain the clinical anaphylactic reaction attributed to the venom[7]. The similarity of pseudolymphoma of the skin to drug-induced pseudolymphoma is striking. Patients taking anticonvulsants, particularly diphenylhydantoin (Dilantin) and nephenytoin (Mesantoin) can develop lymphadenopathy which on microscopic examination may simulate lymphoma[8–10]. It has been suggested that this syndrome represents a drug-induced sensitivity resembling a serum sickness hypersensitivity reaction, or possibly a genetically determined enzymatic defect as seen in primaquine sensitivity[8,11]. The fact that venom injection to various animals did not show the pseudolymphoma reaction, whereas only C 57 black mice developed this reaction, supports the notion that this reaction is genetically determined.

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Acute Effects of Tolamolol on Renal Function in Hypertensive Patients[1]

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Summary. The renal haemodynamic effects of a single i.v. administration of tolamolol were studied in 9 hypertensive subjects. No change of GFR and ERPF was observed after tolamolol, while urine output decreased and urine creatinine concentration increased. A reduction of the heart rate was confirmed. Blood pressure was unchanged.

Tolamolol, a phenoxypropranolamine compound (Pfizer, UK-6558–01), is a new β-adrenergic blocking agent. Although preliminary studies have indicated that it exerts an antihypertensive action[4], there are no data available concerning its effects on renal function. This knowledge seems to be necessary before undertaking any further clinical investigations, since most antihypertensive drugs decrease the glomerular filtration rate (GFR) and the effective renal plasma flow (ERPF). The present study has been designed to examine the effect of intravenously administered tolamolol on renal function (GFR and ERPF) of hypertensive patients.

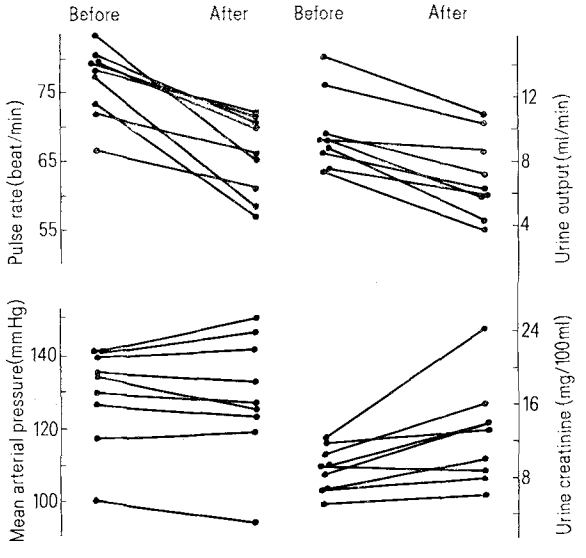

Fig. 1. Variations of different parameters in individual patients before and after tolamolol administration.

Material and methods. 9 hypertensive female patients (4 with essential hypertension, 1 with renovascular hypertension, 3 with pyelonephritis and 1 with nephritis) were examined. The age of the subjects studied was between 34 and 52 years (mean 43.11 ± 6.64 SD). At basal conditions their mean arterial pressure (MAP) ranged from 100.53 to 140.65 mm Hg (mean 129.57 ± 12.46 SD), GFR from 55.71 ml/min to 134.60 ml/min (mean 93.69 ± 22.99 SD) and ERPF from 227.08 ml/min to 600.28 ml/min (mean 410.35 ± 103.25 SD).

The patients were hydrated by administration of 1 l of water during the 60 min preceding the experiment. Thereafter each patient drank 200 ml of water every 20 min. Diatrizoate-I^{131} and hippuran-I^{125} were used for the measurement of GFR and ERPF respectively. Renal clearances were determined by continuous venous infusion of

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the radioactive tracers and by vesical catheterization. Doses of about 1.5 μCi of diatrizoate-I^{131} and 3.0 μCi of hippuran-I^{125} per kg of body weight were dissolved in 500 ml of saline. A priming dose of 100 drops per min was administered i.v. to all patients for 10 min, after which the individual dosage was adjusted to give the same plasma concentration for all patients having different renal function. This was verified by checking the constancy of the body radioactivity by external counting over the precordial area. Another scintillation counter, similar to the type now being used to measure GFR by external counting[5], was collimated over the bladder to verify whether the emptying of the bladder through the catheter was total. A sufficiently constant radioactive concentration was reached 45–60 min after commencement of the venous infusion. At this moment the clearances were started. 2 basal clearances, each of 20 min duration, were carried out; thereafter in a period of 5 min 10 mg of tolamolol were injected i.v. to 5 patients and 15 mg to the other patients. 10 min after the end of the venous injection of tolamolol, 2 other clearances of the same duration were performed to assess the possible changes in renal function. Blood pressure and pulse rate were monitored every 2 min during the whole experiment. Radioactivity of plasma and urine was measured by a well-type counter and a multichannel analyzer. Urinary creatinine was determined by a Technicon autoanalyzer.

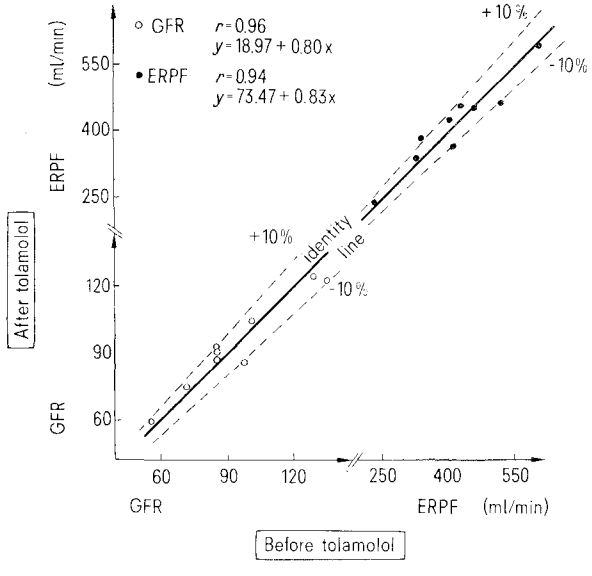

Fig. 2. Relationship between GFR and ERPF before and after tolamolol administration.

Results. The results obtained in each case are shown in Figures 1 and 2. Tolamolol induces a significant decrease of the heart rate. The mean pulse rate was 77 ± 5 SD beats/min before injection and 66 ± 6 SD ($p < 0.001$) after injection. Decrease of the heart rate was maximal 5 to 10 min after tolamolol administration. No significant variation of MAP was observed. MAP (mm Hg) resulted 129.57 ± 12.46 SD before and 128.90 ± 15.69 SD after tolamolol. A decrease of urine output and a consequent increase of urine creatinine concentration were found after using the β-blocker, in spite of the constant hydration of the patients studied. The mean urine output (ml/min) was 9.8 ± 2.3 SD before and 7.0 ± 2.5 SD after tolamolol ($p < 0.001$); the mean urine creatinine (mg/100 ml) resulted 8.7 ± 2.3 SD before and 12.6 ± 5.4 SD after ($p < 0.05$).

Finally, as far as the main purpose of this study is concerned, a remarkable stability of the renal function was observed after injection of the new drug. GFR (ml/min) was 93.69 ± 22.99 SD before and 93.75 ± 21.10 SD after; ERPF (ml/min) 410.13 ± 103.25 SD before and 413.88 ± 96.56 SD after tolamolol. No statistically significant differences were observed between the two clearances carried out after the tolamolol administration. No adverse side-effects were observed.

Discussion. After i.v. administration of tolamolol in hypertensive subjects, a significant fall of the heart rate was observed. MAP remained unchanged, as found by MILLER et al.[6] in patients with coronary heart disease. Our results seem to indicate that tolamolol induces a decrease of urine output (verified by the increase in urine creatinine concentration) without determining any variation of GFR and ERPF. This indicates an increased tubular reabsorption of water by some unknown mechanism(s). In contrast to this, other new β-blockers were recently found to cause a significant decrease of GFR and ERPF together with a marked lowering of urine output[7].

The stability of renal haemodynamic effects found after acute administration of tolamolol justify further clinical investigations on its chronic effects in relation to the renal function and arterial pressure.

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Inhibited Hormonal Induction of Hepatic Phosphoenolpyruvate Carboxykinase in Poly I:C Treated Mice, an Endotoxin-Like Glucocorticoid Antagonism[1]

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Summary. Corticosteroid induction of mouse hepatic phosphoenolpyruvate carboxykinase was inhibited by prior injection of poly I:C. Mice challenged with a lethal dose of endotoxin 4 h after administration of poly I:C could not be protected by a concurrent injection of hydrocortisone.

Gram-negative bacterial endotoxin and the synthetic double-stranded RNA polyriboinosinic-polyribocytidylic acid (poly I:C) are known to elicit similar biological effects, both toxic [2–4] and apparently beneficial[5–8]. Several of these effects are mediated by substances produced by cells within the treated animal.

Poly I:C and endotoxin are also known to elicit metabolic alterations in mice such as inhibition of corticosteroid induction of hepatic tryptophan oxygenase (TO)[9–10] and depletion of liver glycogen[10,11]. Endotoxin also inhibits stress induced synthesis of hepatic phosphoenolpyruvate carboxykinase (PEPCK)[12]. This metabolic im-