I-B LONG-TERM EFFECTS OF ORAL VERAPAMIL THERAPY IN PATIENTS WITH AND WITHOUT HEART FAILURE. Jack Ferlinz, MD and Constantino T. Gallo, MD; Cook County Hospital, Chicago, IL

It is still unresolved what are the sequelae of long-term oral verapamil(V) administration to patients(pts) with or without congestive heart failure(CHF).For this purpose,30 pts were treated with oral V(80-160 mgs tid), and studied with clinical and serial M-mode echocardiographic(ECHO)examinations over a 1 year period.Twenty-one non-CHF pts had coronary artery disease(Group I),while 9 CHF pts had various forms of cardiomyopathy(Group II).V produced a sustained decrease in blood pressure in both groups(P<0.05).In Group I,14 pts(67%) obtained a good relief of angina pectoris,but 4(19%)did not improve,and 3(14%) developed new ischemic events(1 death,1 MI,1 unstable angina).In Group II pts,the long-range improvement in CHF symptoms was achieved in only 3 pts(33%),2(22%)did not improve,but in 4 pts(45%) V had to be withdrawn because of overt clinical deterioration.ECHO evaluations were performed at 0,1,4,8,and 12 months.LV function as measured by ECHO did not deteriorate in either group of pts despite the intrinsic negative inotropic activity of V, possibly because of the afterload reduction produced by the drug.While ECHO data do not suggest increased LV dysfunction even in pts with CHF,long-term therapy of CHF pts with V should be attempted only with great caution because clinical deterioration might result.

I-D DISPARITY BETWEEN CLINIC (CBP) AND AMBULATORY BLOOD PRESSURE (ABP) IN RESPONSE TO ANTIHYPERTENSIVE THERAPY. D.J. Fitzgerald MB,K. O'Malley MD PhD, E. O'Brien MB.The Blood Pressure Clinic and Dept Clinical Pharmacology,Royal College of Surgeons in Ireland Dublin.

The disparity between CBP and ABP recording may be important in studying the response to antihypertensive therapy.Trimazosin (T) and propranolol (P) were compared in 24 hypertensive subjects (diastolic CBP 90-110 mm Hg) in a double blind placebo controlled study.Each drug was administered in incremental doses twice daily over 12 weeks to a maximum of T 400 mg and P 320 mg daily or until diastolic CBP decreased to less than 85 mm Hg. ABP was recorded using a non-invasive portable recorder (Remler) over a single day during each phase of the study.CBP was recorded using a random-zero sphygmomanometer.T and P exerted comparable reductions in CBP (T-16/-10 p<.01,P-25/-14 p<.001),analysis of variance showing no significant differences between drugs.In contrast the decrease in mean ABP was more marked during with P (-26/-12 p<.001) than with T (-8/-4 p<.05) for systolic (p<.001) and diastolic (p<.01) recordings.The differences between drugs persisted throughout the 13 hours of ABP recording.

In conclusion,CBP may not reflect changes in ABP induced by antihypertensive therapy.

III-C AZTREONAM EXCRETION IN HUMAN MILK. Fleiss, M.D.,* R. Devlin, Ph.D., G. Richaud, M.D.,* M. Stern, B.A.* and J. Gordon, M.D.,* U.C.L.A. School of Public Health, Los Angeles, CA, and The Squibb Institute for Medical Research, Princeton, N. J.

Blood and milk concentrations of aztreonam, a monobactam antimicrobial agent, were determined in 12 healthy, lactating subjects. Simultaneous milk and serum samples were collected at periodic intervals following intravenous or intramuscular administration of 1 Gram dose of aztreonam and analyzed for aztreonam by an agar diffusion, microbiological assay using E. coli. Milk concentrations were found to be much lower than serum concentrations at all time points after both routes of injection. Peak milk concentrations averaged 0.3 ± 0.1 and 0.2 ± 0.1 ug/ml after I.M. and I.V. injections respectively. Peak serum concentrations averaged 42.6 ± 4.0 and 126.2 ± 17.1 ug/ml after I.M. and I.V. injections respectively. $AUC_{0\rightarrow\infty}$ and Cmax values for aztreonam in milk were less than 1% of those in serum after both injection routes. Tmax values averaged 6 to 7 times longer in milk than in serum after I.M. and I.V. injections respectively. A 5kg nursing infant ingesting one liter of milk per day would consume a maximum of 0.4% of the theoretical dose of aztreonam for children (15 mg/kg).

A41 ANAGRELIDE, A NEW AGENT FOR LOWERING PLATELET COUNT IN A SELECTIVE CONTROLLED, DOSE-RELATED MANNER. J.S. Fleming* and W.J.R. Taylor, Bristol-Myers Company, Pharmaceutical Research and Development Division, Syracuse, New York and Evansville, Indiana.

Anagrelide, a potent, orally active inhibitor of blood platelet aggregation presently undergoing clinical evaluation lowers platelet count in normal human subjects during multiple dose treatment. First regarded toxic side effect, this finding has now been cast in a new light as a result of recent mechanistic studies. When relatively high amounts are administered chronically, platelet counts drop precipitously after about four days of dosing. However, during this period, platelet survival is only moderately shortened and bone marrow toxicity is not observed. A theoretical model based on the assumption that anagrelide modulates the budding process of platelets from megakaryocytes is consistent with the data obtained from actual human studies. This suggests that anagrelide, aside from being a potentially effective antithrombotic agent, may be particularly useful in clinical conditions where excessively high platelet counts are a problem such as polycythemia vera and essential thrombocythemia. Because the fall in platelet count is both dose-related and reversible, it should be possible to titrate individual patients to a desired level of platelet count.