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Blood Pressure in Hypertension

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Publications of the Staff

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Edsel B. Ford Institute for Medical Research

Titles and Selected Abstracts

Edited by G. B. Bluhm, MD

Cardiac lymphangioma and lipoma. D. T. Anbe and G. Fine. *Amer Heart J* **86**:227-35, Aug 1973.

The simultaneous occurrence of two cardiac tumors is rare. It is also unusual for benign tumors to be associated with arrhythmias. A case is reported of a 43-year-old Caucasian male who died while undergoing coronary arteriography. This patient, who had normal coronary arteriograms, had various arrhythmias, paroxysmal atrial and junctional tachycardia, sinus tachycardia, wandering pacemaker, frequent premature atrial contractions (atrial trigeminy), premature ventricular contractions and first degree A-V block. The postmortem examination revealed a thick

fibrous epicardium containing lymphangiomatous changes. There was also diffuse and focal (lipoma) lipomatous infiltration of the heart. The lipoma was in the right atrial wall. There was extensive diffuse fatty infiltration in the right atrium, sino-atrial node, inter-atrial septum and atrio-ventricular node. The fatty infiltration was moderate in the right ventricle and minimal in the left atrium. It is felt that there is a causal relationship between the arrhythmias and the lymphangiomatous and lipomatous infiltrations.

Abstracts

Immunofluorescent techniques as diagnostic aids. T. K. Burnham. *Cutis* 12:519-26, Oct 1973.

Three applications of immunofluorescent techniques as diagnostic aids are described: Among *Antinuclear factors (ANF)*, 15 separate and distinct nuclear immunofluorescent patterns were classified into three groups of diagnostic importance: 1. Patterns of major diagnostic importance—Peripheral fluorescence was seen in severe SLE, while speckles were mainly confined to scleroderma and Raynaud's disease; 2. Patterns of less but still helpful diagnostic importance; and 3. Patterns not associated with any specific disease. In direct cutaneous immunofluorescence, the three clinical applications of a positive "band" test in LE were: 1. Confirmation of LE in clinical

and pathologic non-diagnostic skin lesions; 2. Confirmation of a diagnosis of SLE in SLE patients without LE skin lesions; and 3. Severe disease and probably a poorer prognosis if the band was found in clinically normal SLE skin. In indirect immunofluorescence in bullous diseases, the "tubular" band of bullous pemphigoid and epidermal intercellular fluorescence (ICF) confirmed the diagnoses of bullous pemphigoid and pemphigus. However, some negative indirect tests were found in both these groups. Direct tests should therefore be performed in patients strongly suspected of having bullous pemphigoid or pemphigus if the indirect test is negative.

Characterization and significance of urinary fibrin degradation products. P. Cortes, E. V. Potter and H. C. Kwaan. *J Lab Clin Med* 82:377-89, Sept 1973.

Urine samples from patients with renal disease and proteinuria were examined for material which reacted with antisera to fibrinogen or its degradation products (FDP). Such material was found in samples from 9 of 24 patients and was characterized in 8 patients by immunodiffusion in agar gel, immunoelectrophoresis in cellulose acetate, electrophoresis in acrylamide gel with subsequent immunodiffusion in agar gel, and/or gel filtration with Sephadex G-200. All 8 urine samples contained FDP while none contained thrombin-clottable fibrinogen. The FDP were of early, late, and intermediate types in 5 samples, early and intermediate in 2 samples, and only late in 1 sample. Selectivity of proteinuria according to molecular size was determined in 9 patients by

gel filtration (Sephadex G-200) of urine and serum samples. Six of these patients had urinary FDP. The presence or absence of fibrin, fibrinogen, or FDP within glomeruli was ascertained by immunofluorescent observation of renal biopsies from 22 patients. Urinary FDP appeared to be related to nonselectivity of proteinuria rather than to the presence of fibrinogen or its derivatives within glomeruli. Both low selectivity and urinary FDP were found only in patients with severe proliferative and exudative glomerular lesions. Furthermore, improvement of the clinical course in 2 patients following initiation of steroid treatment was accompanied by increased selectivity of proteinuria and disappearance of urinary FDP.

Recurrent atrial flutter. Treatment with a surgically induced atrioventricular block and ventricular pacing. R. Garcia and E. Arciniegas. *Arch Intern Med* 132:754-7, Nov 1973.

Recurrent bouts of atrial flutter with rapid ventricular response were noted in a 52-year-old housewife with mild mitral stenosis and multiple drug intolerance to quinidine, procainamide, and propranolol. She required frequent cardioversions. Large doses of digitalis failed to convert the rhythm

to a more stable chronic atrial fibrillation. The incapacitating episodes of atrial tachyarrhythmia were successfully terminated following a surgical ligation of the AV conduction system and the implantation of a permanent left ventricular pacemaker.

Comparison of guanadrel and guanethidine. L. Hansson, A.V. Pascual and S. Julius. *Clin Pharmacol Ther* 14:204-8, Mar-Apr 1973.

Both guanadrel and guanethidine caused a statistically significant reduction of blood pressure when compared to placebo, but there was no significant difference between the two drugs, regarding antihypertensive potency. With guanadrel it was possible to achieve significantly more control of the blood

pressure throughout the day. There also were fewer complaints of early morning dizziness during the guanadrel period, and there was less diarrhea. The effects of both drugs on cardiac output and total peripheral vascular resistance were identical in the resting recumbent position and during tilting.

Abstracts

Effect of beta-adrenergic blockade on plasma volume in human subjects. S. Julius, A.V. Pascual, P. H. Abbrecht and R. London. (Introduced by Sibley W. Hoobler). *Proc Society for Experimental Biology and Medicine* **140**:July 1972.

A two-step autonomic blockade with the use of intravenous propranolol (0.2 mg/kg) and atropine (0.04 mg/kg) was done on 27 human male subjects from 18 to 26 years of age. Plasma volume, cardiac output, central venous pressure, plasma protein, and hematocrit were determined and total peripheral resistance calculated before and shortly after beta adrenergic and parasympathetic blockade. Plasma volume was determined by dye dilution method (Evan's Blue) and by calculations based on changes in plasma protein and

hematocrit. The study presents substantial decrease in plasma volume shortly after extensive beta adrenergic blockade. The decrease in plasma volume does not seem to depend on the influence of propranolol upon the cardiac output, total peripheral resistance and central venous pressure. Change in hematocrit after beta adrenergic is lesser than expected for the observed decrease in plasma volume determined by dye dilution and change in plasma protein. Mechanisms of the observations are discussed.

Parenteral long-acting corticosteroids: Effect on hypothalamic-pituitary-adrenal function. G. R. Mikhail, L. C. Sweet and R. C. Mellinger. *Annals Allergy* **31**:337-43, July 1973.

The extent of adrenal suppression during treatment with intramuscular triamcinolone acetonide was studied in 22 patients with dermatologic disorders or bronchial asthma. Sup-

pression was more marked when smaller doses of the drug were injected at two to four week intervals than when larger amounts were given every six weeks.

Serial hemodynamic observations in secundum atrial septal defect with special reference to spontaneous closure. M.R. Mody. *Amer J Cardiol* **32**:978-81, 1973.

Data on spontaneous closure of ventricular septal defect are well established. In contrast, information on spontaneous closure of atrial septal defect is less clearly defined. The authors present serial hemodynamic observations in secundum atrial septal defect and discuss spontaneous closure of this lesion. Forty patients with atrial septal defect of secundum type, diagnosed by cardiac catheterization, underwent repeat study 1½ to 14 years later to document the frequency of spontaneous closure. These 40 patients were classified in two groups of 20 each according to age. Group 1 comprised 20 patients who were less than

one year of age on the initial study and Group 2 comprised 20 patients who were older than one year on the initial study. Eleven of the 20 patients in Group 1 were noted to have spontaneous closure of the atrial septal defect on repeat study. The incidence of spontaneous closure was not necessarily related to the size of the defect. In contrast, none of the 20 patients in Group 2 had spontaneous closure on repeat study. Data indicate that atrial septal defect of secundum type diagnosed in the first year of life frequently closes spontaneously. If the defect is diagnosed after the first year, it is unlikely to close spontaneously.

Phase II evaluation of adriamycin in human neoplasia. R. M. O'Bryan, J. K. Luce, R. W. Talley, J. A. Gottlieb, L. H. Baker and G. Bonadonna. *Cancer*, **32**:1-8, 1973.

Four hundred and seventy-two patients with disseminated neoplasia were treated with two or more doses of adriamycin (14-hydroxydaunomycin), an antibiotic found in the fermentation products of *streptomyces peuceitius caesius*. Nineteen participating institutions from the Southwest Oncology Group (SWOG) reported objective remissions

in 118/472 patients with best results noted in lymphoma, sarcoma, and carcinoma of the breast. The response rate with higher doses was slightly better than with lower doses. However, patients were not allocated randomly into the dosage schedules, and doses were raised or lowered according to toxic effects. Consequently, these data do not

Abstracts

measure dose-response. They may simply mean that better responses were seen in patients classified with less advanced disease. It is concluded that adriamycin is an effective agent against some human neoplasms. Regressions occurred promptly with little or no hematopoietic toxic effects; severe toxicity or fatal toxicity from drug-induced hematopoietic toxicity was uncommon. The major limit-

ing toxicity associated with adriamycin therapy was cardiac, the exact etiology of which is not clear, but apparently is dose-related. No significant cardiac toxicity was observed in patients receiving less than 550 mg/m². A dose-response study is indicated particularly since significant cardiac toxicity appears to be cumulative and such a study is now in progress by members of the SWOG.

Effects of adenine nucleotides on NADH binding to mitochondrial malate dehydrogenase. N. R. Oza and J. D. Shore. *Arch Biochem* **154**:360-5, Jan 1973.

The effects of adenine nucleotides on initial velocity and NADH binding have been studied with the malate dehydrogenase reaction. ATP, ADP, and AMP were inhibitors competitive with NADH and uncompetitive with oxaloacetate but caused only 50-60% inhibition at saturating concentrations. Direct fluorescence titrations indicated that saturating con-

centrations of the adenine nucleotides displaced 50-60% of the bound NADH from enzyme — NADH complex. Adenine and adenosine had no inhibitory effect but ADP-ribose caused complete inhibition and NADH dissociation. The possible mechanistic basis for these results and their physiological implications are discussed.

Horse liver alcohol dehydrogenase - Amino groups and rate-limiting steps in catalysis. B. V. Plapp, R. L. Brooks and J. D. Shore. *J Biol Chem* **248**:3470-5, May 1973.

Picolinimidylation of one amino group per active site of horse liver alcohol dehydrogenase increases the turnover numbers of the enzyme approximately 10-fold and other kinetic constants up to 140-fold at pH 8. The picolinimidylated enzyme shifts the absorption maximum of NADH to lower wave lengths, indicating that the amino group that can be modified is probably not involved in the spectral shift observed when NADH binds to native enzyme. Product and dead-end inhibition studies at pH 8 indicate that the mechanism of the modified enzyme conforms to an Ordered Bi Bi and not to a rapid equilibrium random mechanism. Stopped flow studies show that NAD⁺ binds 10 times more slowly to the modified enzyme than to the native enzyme and that NADH binds at about

the same rate to both enzymes. Dissociation of NADH (5.6⁻¹) is rate-limiting for the reaction of NAD⁺ and ethanol catalyzed by the native enzyme but was too fast to measure (>200⁻¹) with the modified enzyme. The transfer of hydrogen from ethanol to NAD⁺ now controls the turnover (32 s⁻¹) with the modified enzyme as shown by a deuterium isotope effect of 4.8 in the steady state reaction. The maximum velocity of the reaction of NAD⁺ and ethanol is dependent upon a group with a pK of 7.2; this group's must be unprotonated for maximum activity and could be an imidazole. For the reaction of NADH and acetaldehyde, no isotope effect was observed and the turnover (550 s⁻¹) may be limited by isomerization and dissociation of the enzyme-NAD⁺ complex.

Carcinoid tumors of the appendix: Report of 35 cases. J. L. Ponka. *Amer J Surg* **126**:77-83, July 1973.

Appendiceal carcinoid tumors are not common, but are of interest because they are discovered more or less unexpectedly after appendectomy. In our series of 35 cases, the tumor was discovered most frequently during abdominal section for some other disease. Appendectomy during gynecological procedures and biliary tract procedures yielded the most of these tumors. Appendectomy alone would have been curative in 33 of the 34

surgically-treated patients. In one case, tumor was discovered incidentally at postmortem examination. Carcinoid tumors of the appendix tend to be slow growing and may spread through the muscularis to the serosa and regional lymph nodes. If a large appendiceal carcinoid is found with extension through the line of section or the regional lymph nodes, then right colectomy is advocated. Further long term study of this tumor is still in order.

Abstracts

In vivo analysis of lipid-protein in ratios in human muscle by differential x-ray absorption using ^{109}Cd photos. L. R. Preuss and F. P. Bolin. *Advances X-Ray Analysis* 16:111-23, 1973.

The combination of accuracy, speed and compactness makes the ^{109}Cd two photon absorptiometric method a promising possibility for the determination of fat-lean ratios in living subjects. The accuracy possible with this method promises to be of use in unraveling

some of the more difficult problems relating to body composition. In vitro work has been highly successful and various techniques are being explored for the application of the method to living subjects.

Clinical evaluation of 1,3-Bis(2-chloroethyl)-1-nitrosourea (BCNU; NSC-409962) with fluoxymesterone (NSC-12165) in the treatment of solid tumors. E. S. Reyes, R. W. Talley, R. M. O'Bryan and R. A. Gastesi. *Cancer Chemother Rep* 57(2):225-30, April 1973.

Sixty patients with solid tumors were given BCNU, a drug with alkylating properties. From previous clinical studies in a wide spectrum of tumors, a constant and unique feature of BCNU was the severe hematologic toxic effects which were delayed in onset and of a more prolonged duration than those which had been observed in other drugs. Since androgens have a possible myeloprotective action and are also known to stimulate erythropoiesis, the present clinical study was designed to determine if the hematopoietic toxicity of BCNU could be modified if the drug was used in combination with the anabolic androgen, fluoxymesterone. Patients were selected randomly for either of the two therapy programs, one group received BCNU alone, and the other group received BCNU

plus fluoxymesterone. The dosage employed of BCNU was 100 mg/m² for 2 or 3 days every 6 weeks, fluoxymesterone was given orally at a dose of 10 mg 3 times daily. Forty-seven of the 60 patients entered on study were evaluable for response to therapy. Six of the 47 had partial responses, 12 had no change in their status, and 28 had progression of their tumors. The six patients with partial responses were observed in four breast cancer patients, one patient with rectal carcinoma, and one patient with epidermoid carcinoma of unknown origin. Fifty-six patients were evaluable for toxicity. Hematopoietic toxicity essentially was the same for the two programs. Peak hematologic toxicity occurred between the fourth and sixth weeks with recovery usually by the sixth or seventh week.

Inhibition of primary ADP-induced platelet aggregation in normal subjects after administration of nitrofurantoin (Furadantin). E. C. Rossi and N. W. Levin. *J Clin Invest* 52:2457-67, Oct 1973.

The evidence indicating that platelets may play a role in the occurrence of certain thromboembolic phenomena has stimulated a search for inhibitors of platelet function. This report presents data to indicate that nitrofurantoin is a potent inhibitor of primary ADP-induced platelet aggregation. The addition of 10 μM nitrofurantoin to citrated platelet-rich plasma obtained from 12 normal subjects produced a $29 \pm 6\%$ (2 SD) inhibition of the velocity of platelet aggregation induced by 2 μM ADP. The inhibitory effect of nitrofurantoin demonstrated competitive kinetics in respect to ADP. The intravenous (180 mg) or oral (200 mg) administration of nitrofurantoin produced a

serum nitrofurantoin concentration ranging from 2.7 to 23 μM in 28 normal subjects. Platelet-rich plasma obtained from these subjects demonstrated inhibition of the velocity of ADP-induced platelet aggregation that correlated with the log of the serum nitrofurantoin concentration ($P < 0.001$). Collagen-induced platelet aggregation was also inhibited in a dose-related manner, and the bleeding time was significantly prolonged in the two subjects with the highest serum nitrofurantoin concentration. These studies indicate that nitrofurantoin in vivo inhibits platelet function to a degree that is proportional to the serum nitrofurantoin concentration.

Abstracts

Pseudomonas osteomyelitis. Radiologic features. N. I. Salahuddin, T. Madhavan, E. J. Fisher, F. Cox, E. L. Quinn and W. R. Eyer. *Radiology* **109**:41-7, Oct 1973.

Seven cases of *Pseudomonas* osteomyelitis were seen, all occurring in young black male drug addicts. The site of involvement was always adjacent to a septic arthritis or disc-space infection due to the same organism and included (a) lumbosacral spine, (b) cervical spine, (c) pubic symphysis, (d) ribs, (e) ischial tuberosity, (f) sacroiliac joint, and (g) hip joint. Radiologic features included narrowing of

joint spaces with bone destruction and sclerosis. The diagnosis was made by culture of the organism from the site of involvement in 6 cases and by blood culture in one. All patients were treated with immobilization and gentamicin 3 mg/kg intramuscularly. Radiologic and clinical improvement was noted in all.

The celiac artery compression syndrome: Does it exist? D. E. Szilagyi, R. L. Rian, J. P. Elliott and R. F. Smith. *Surgery* **72**:849-63, Dec 1972.

The contention, held by many, that association of an angiographically demonstrable stenosis of the celiac artery and a somewhat ill-defined set of clinical symptoms resembling intestinal angina constitutes a syndrome amenable to surgical correction is puzzling, since all fundamental physiologic and pathologic considerations would dictate that an isolated stenosis or even occlusion of the celiac artery should be semeiotically silent and clinically unimportant. Upon analyzing our clinical material during the last five-year period, we found no fully documented case of this syndrome. Of 157 celiac arteriograms performed both in search of cause for vague ab-

dominal symptoms and in the study of suspected abdominal diseases, 49.7% of the patients showed some degree of stenosis of the celiac axis, with a considerable range of variation in anatomical detail. No correlation could be found between the existence of celiac arterial narrowing, degree of narrowing, and presence of collaterals on the one hand and such symptoms and signs as abdominal pain and weight loss on the other. The conclusion is that narrowing of the celiac artery is of such common occurrence as to be a normal anatomical variant; its association with symptoms at present has no proved significance in the pathophysiology of the alimentary tract.

New ultrastructural evidence for virions in intradermal metastatic nodules of human breast adenocarcinoma. J. H. L. Watson, J. L. Swedo and R. W. Talley. *Compte rendu du 7^e Colloque international sur les tumeurs mammaires. Saint-Pierre-de-Chartreuse* June 1972. Pages 361-78.

The frequent discovery of the usual virus-like particles is reported for this tissue at all cytological locations except the nucleus. In addition, two other ultrastructural occurrences which could be related to viral activity are described. The first of these is related to head-and-tailed bodies which are found within the ducts or intracytoplasmic lumina of the cells. These bodies are identical in shape, size and morphology with many of the MT virions and B particles reported from mouse and human milks. The second relates to the discovery of a type of budding from the mem-

brane of the ducts in these cells of human mammary adenocarcinoma. Thus, it may be said that particles resembling the oncogenic RNA tumor viruses have been found in solid human mammary tumor as well as in human milk and that this is further ultrastructural evidence for the possibility that a virion may be active in human breast cancer. The discovery of a type of budding may be evidence for the same possibility, although no claim is made that either of the particles involved is oncogenic *per se*.

Listed by title only:

Infections that hospitalize the patient. F. W. Whitehouse. *Geriatrics* p. 9, July 1973.

Two minutes with diabetes. F. W. Whitehouse. *Medical Times*, **101**:35, Oct 1973 and **101**:143, Nov 1973.