Abstracts of Recent Publications of the Professional Staff of the Henry Ford Hospital and the Edsel B. Ford Institute for Medical Research

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ABSTRACTS OF RECENT PUBLICATIONS OF THE PROFESSIONAL STAFF OF THE HENRY FORD HOSPITAL AND THE EDSEL B. FORD INSTITUTE FOR MEDICAL RESEARCH


An investigation was made of the effect of several dietary factors on total mouse liver cholesterol and beta steroids. It was found that increasing the amount of dietary cholic acid, added to a ration containing cholesterol, increased the deposition of liver cholesterol and beta steroids up to a limiting concentration. The addition of dihydrocholesterol, to diets containing cholic acid and cholesterol, significantly decreased liver cholesterol and beta steroids. If increasing amounts of cholic acid were added to a ration containing constant amounts of dihydrocholesterol and cholesterol, there were significant decreases in liver cholesterol and beta steroid concentration. Under all conditions, total liver cholesterol and beta steroid concentrations were parallel, indicating the absence of dihydrocholesterol deposition. Total beta steroids were determined by a new procedure employing the reaction of anthrone and digitonin in the presence of sulfuric acid.


It is known that the toxicity of 3-acetylpyridine (3-AP) and pyridine-3-sulfonic acid is increased by nicotinic acid deficiency in dogs. The two compounds have been considered as antimetabolites of the vitamin for this reason. It was suggested that if these compounds act by blocking the synthesis of Coenzymes I and/or II or by displacing the niacinamide moiety of these substances, the urinary excretion of N1 methyl nicotinamide, one of the chief products of niacin metabolism, should be altered. The addition of pyridine-3-sulfonic acid to the diets of normal and niacin depleted bitches did not effect the excretion of N1 methyl nicotinamide or, the Coenzyme I and II content of the erythrocytes.

Feeding of 3-AP to normal bitches receiving complete or niacin deficient diets resulted in greatly increased excretion of N1 methyl nicotinamide. That the substance excreted in increased amount was N1 methyl nicotinamide was confirmed by isolation and identification.


When 3-acetylpyridine (3-AP) is fed to dogs, large amounts of N1 methyl nicotinamide (NMeN) appear in the urine. This finding might be interpreted as evidence that 3-AP, acting as an antimetabolite, displaces nicotinamide from its
nucleotides, prevents its incorporation therein, or alternatively that 3-AP is biologically oxidized to nicotinic acid and is thus, in a sense, a provitamin. These conjectures were tested by feeding 3-AP containing an excess of C\textsuperscript{13} in the Carbonyl group. NMeN excretion increased markedly. The atom per cent excess of C\textsuperscript{13} in the additional NMeN excreted was 59 per cent as great as in the injected 3-AP. In a comparable experiment nicotinic acid tagged with C\textsuperscript{13} in the carboxyl was fed in amounts necessary to produce a similar increase in NMeN output. The atom per cent excess of isotope in NMeN was 46 per cent as great as in the ingested precursor. It was concluded that 3-AP is biologically oxidized to nicotinic acid to an extent sufficient to account for all of the increase in NMeN output observed after its ingestion.


It has been shown that after the administration of 3-acetylpyridine (3-AP) to the dog only about 10 per cent of the administered antimetabolite can be accounted for as N\textsuperscript{1} methyl nicotinamide. Inasmuch as the benzene analog, methyl phenyl ketone is metabolized to methyl phenyl carbinol glucuronide and hippuric acid, and a small amount of unaltered methyl phenyl ketone excreted, one might expect by analogy to find after 3-AP administration increased urinary excretion of all the normal metabolic end products of niacin metabolism as well as excretion of methyl beta pyridyl carbinol, its glucuronide, and unaltered 3-AP. The urinary excretion of these substances was investigated after the administration of 3-AP. It was found that the administration of 3-AP to the bitch resulted in increased urinary excretion of nicotinic acid, N\textsuperscript{1} methyl nicotinamide, and glucuronic acid. The administration of methyl beta pyridyl carbinol resulted in an excretion pattern similar to that observed in the case of 3-AP metabolism. No urinary methyl-beta-pyridylcarbinol or 3-AP could be detected after the administration of these substances. Between 20 and 30 per cent of injected 3-AP and methyl-beta-pyridyl-carbinol could be accounted for by increased urinary excretion of N\textsuperscript{1} methyl nicotinamide and nicotinic acid.


To determine the site of metabolism of 3-acetylpyridine (3-AP) both \textit{in vivo} and \textit{in vitro} studies were necessary. It was demonstrated that the metabolism of 3-AP by the adult bitch is not altered by feeding sulfathalidine. Canine blood cells metabolized 3-AP, while blood plasma was inactive. Canine liver and kidney slices rapidly metabolized 3-AP, while muscle slices were inactive. The metabolism of 3-AP by canine liver and kidney slices was inhibited by 2 X 10\textsuperscript{-8} M iodoacetic acid. 2 X 10\textsuperscript{-8} M cyanide did not inhibit the metabolism of this substance in liver but was effective in kidney. Homogenates of liver, kidney, and muscle did not metabolize 3-AP. These findings permit the suggestion that oxidation of 3-AP to nicotinic acid may involve systems requiring Coenzyme I, and that this accounts for the increased toxicity of 3-AP during niacin deficiency.

Eighteen previously reported cases of amyloid deposition in the lower respiratory tract have been reviewed. Ten of these cases were proved only at autopsy and the eleventh and twelfth only after pneumonectomy. In none of these cases was there evidence of amyloid deposition elsewhere in the body and they all must be assumed to be instances of primary amyloid deposition. A nineteenth case is added to this category and its progress recorded.

ACTH AND CORTISONE IN SURGERY. BROCK E. BRUSH. Recorder of the Columbia Medical Society, March 1954.

When a new medicinal or hormonal agent is introduced it usually goes through phases of evaluation. ACTH and cortisone, like antibiotics, should never be used as a substitute for well proven conservative principles of surgery. These hormones should never be administered in the presence of an undiagnosed abdominal condition. The greatest application of ACTH and cortisone is in the crisis of acquired hypersplenism and thyrotoxicosis. Acute non-suppurative thyroiditis, anogenital pruritis and orthopedic conditions are well established indications for their use. ACTH and cortisone are being evaluated for many surgical diseases and a clearer picture of their indications and contraindications will be possible with further experience.


Many patients with so-called “silent” gall stones have been advised by the medical profession that there is no need for surgical treatment and that they will probably not have trouble in the future; “just follow a diet and be careful.” We have reviewed 100 consecutive operations on the biliary tract in patients over the age of 65, in an attempt to evaluate the various procedures which are available and to determine what may be expected from surgical treatment in this age group. Elective gallbladder surgery is preferable to awaiting the inevitable complications arising from untreated cholecystitis. The increase in morbidity and mortality caused by the complications of gallstones is such that all physicians should urge cholecystectomy at an early and opportune time, before a serious situation develops. Cholecystostomy is the procedure of choice in the acutely ill and poor-risk patient with gallbladder disease. It should be used when it is necessary to operate on a patient with acute cholecystitis in whom complete and satisfactory visualization of the entire biliary tree has been rendered impossible by the inflammatory process.

TOXICITY OF ISONICOTINIC ACID HYDRAZIDES IN PULMONARY TUBERCULOSIS; TOXICITY OF ISONIAZID AND IPRONIAZID USED ALONE AND IN COMBINATION WITH STREPTOMYCIN OR P-AMINO-

Information available at the present time concerning the toxicity of isoniazid (isonicotinic acid hydrazide) has shown it to be a relatively safe agent for the treatment of pulmonary tuberculosis. Side-effects encountered among 42 patients receiving iproniazid and 35 patients given isoniazid show the former drug to be clearly the more toxic. Combinations of iproniazid with streptomycin or with p-aminosalicylic acid (PAS) appear more toxic than iproniazid used alone. Termination or interruption of therapy, or reduction in dosage because of toxicity, was necessary for 45% of those receiving iproniazid and only 9% of those taking isoniazid. While the majority of reactions to these compounds, particularly isoniazid, are minor, potentially serious effects include (a) mental changes, (b) peripheral neuropathy, (c) severe muscular spasms, and (d) hemoptysis. Attention is directed to one case of encephalitis and one sudden death, possibly related to administration of iproniazid. "Withdrawal" symptoms have been observed in 64% of 14 patients whose iproniazid therapy was abruptly terminated; these were not relieved by substitution of isoniazid. Isoniazid has proved to be a safe drug for therapeutic use. Iproniazid is considered too toxic for general use.


A spontaneous mammary pericanalicular fibroadenoma developed in a female albino rat of the Sprague-Dawley strain. Grossly the tumor was a hard, white, homogenous, lobulated, encapsulated, palpable mass. Six months after complete removal, no recurrence was indicated. Some investigators consider benign tumors incapable of further growth by transplantation. Small pieces of the present tumor, 2 ml thick by 3-4 ml in diameter, were implanted subcutaneously along the milk line of albino female rats. Of the transplants, 4 of 4 in the first, 5 of 6 in the second, 6 of 8 in the third, and 3 of 4 in the fourth generation continued to grow into large tumors. Increase in the size of transplant was not evident for 4-7 wk after transplantation. If no increase was evident after 8 wk, no growth occurred later. Histology of the tumors remained the same in each generation.


In female dogs, the relative amounts of benzoate metabolized by the two routes involving peptide linkage with glycine and ester linkage with glucuronic acid were not altered by growth hormone or testosterone propionate, and the latter hormone also failed to influence the course of metabolism of phenylacetate in this respect. These hormones were investigated because they produce nitrogen storage in which formation of peptide linkages is involved.

Chemical inactivation of viruses has been demonstrated in blood plasma without material changes in the plasma proteins. The most effective virucides have been found to belong to the following classes of compounds: (1) mustards, (2) imines, (3) conjugated unsaturated ketones, (4) alkyl oxides, (5) acetophenones, (6) alkyl sulfates and (7) lactones. Certain of these compounds, when added to plasma, are rapidly converted by hydrolysis to relatively nontoxic end-products. To date, the screening of approximately 400 chemicals for antiviral action in plasma has yielded only 7 that seem acceptable. Of these, beta-propiolactone shows the most promise from the standpoint of virucidal activity, biochemical properties and toxicity.


During the course of multiple myeloma most patients exhibit a tendency to bleed. One would expect a megakaryocytopenia in a disease characterized by anemia of the myelophic variety. A study was undertaken to review the occurrence of thrombocytopenia in a series of 58 histologically proved cases of multiple myeloma. Megakaryocytopenia is consistently present in the marrow of patients with multiple myeloma. Thrombocytopenia occurs in the majority of patients with multiple myeloma and is a major cause of abnormal bleeding in myeloma patients.


During the past thirty years there has been an increasing conservatism in arriving at the decision to remove tonsils and adenoids. While this has been accentuated by the advent of chemotherapy, the trend was evident even before that. In our own clinic, whose composition would reflect that of an average office practice in the middle economic stratum, the ratio of tonsillectomies to outpatients fell from 1:20 in 1936 to 1:50 in 1952. Results were appraised as to the effect on frequency of upper respiratory infection, abdominal pain, bronchitis, sinus infection, asthma, appetite and nutrition, and recurrent vomiting. From a follow-up study of 598 cases, and from a review of several conditions thought to be influenced by tonsillectomy and adenoidectomy, it is concluded that the procedure remains a highly beneficial one in the properly selected case.


The importance of careful study of the lungs in patients having symptoms of cerebral neoplasm has long been recognized. The lungs are often involved by
metastasis from tumors in other organs, and primary pulmonary tumors are frequently the site of origin for cerebral metastases. A review of more than sixty-five hundred autopsies performed at this hospital, plus a study of surgical specimens, reveals that the brain was secondarily involved by malignant tumors of various types in ninety-four cases, either by metastasis or extension. Fifty-three per cent of pulmonary cancers in which the necropsy included study of the brain were found to have cerebral metastases. There is increasing evidence that a solitary cerebral metastasis, once considered a contraindication to a definitive surgical attack upon the primary site of growth, may occasionally be removed successfully along with the primary, with resultant prolongation of the life of the patient.


Calibration and dispensation of colloidal\textsuperscript{198} Au solutions are frequently carried out by remote pipetting and by pressure transfer in plastic tubing through which its progress may be observed. Such a method is described.


The occurrence of nervous system involvement as a complication of infectious mononucleosis has been recognized with increasing frequency in recent years. Despite its low incidence, nervous system involvement ranks high among the causes of death in infectious mononucleosis. The occurrence of nervous system involvement as a serious complication in a small percentage of cases of infectious mononucleosis is stressed. Three such cases are reported, in which the neurologic manifestations took the form of an acute polyradiculoneuritis. Sheep hemagglutinins were demonstrated in the cerebrospinal fluid in one case. The heterophile agglutination test in the diagnosis of infectious mononucleosis is discussed, and some difficulties are mentioned. The nature of the Guillain-Barre syndrome is discussed briefly.


Suggested procedures for direct grouping of the ABO system of human blood groups are presented. Test-tube, slide-well and flat-slide methods comprise the direct grouping procedures. Confirmatory tests for checking the direct methods are also presented in detail. The latter include: reverse blood grouping; repetition of direct procedures with sera from additional sources; utilization of anti-AB serum; and subgrouping of A and BA. Several tables depicting the interrelationships of the various ABO systems of antigens and antibodies are presented. A discussion has been given of the possible effects on the methodology of grouping the ABO system of (1) use of immune grouping sera; (2) transposition of procedures utilized in the detection of unrelated blood groups and (3) recent in-
vestigations into the basic nature of the ABO antigen-antibody system.


An abstract from the Am. Rev. Tuberc. 69:216, 1954 embodying substantially this same material was published in the Henry Ford Hospital Medical Bulletin 2:39, 1954.


This experiment was designed to study the effect on hearing and on inner ear morphology, of obliterating the periotic duct and endolymphatic sac. Operations to obliterate these structures were performed on a series of seven sound conditioned cats. Destruction of the endolymphatic sac failed to create cochlear dysfunction or histological changes in the membranous labyrinth. Surgical blockage of the periotic duct was associated with a moderate rise in Reissner's membrane in two ears. At the present time we do not believe that the evidence from our work and that of Uyamo prove that blocking the periotic duct causes dilation of the endolymphatic system. Tests of cochlear function will be done by the method of recording evoked strychnine spikes from the auditory cortex in response to the onset of pure tones.


Treatment by resection of the aortic bifurcation and grafting is a very recent addition to the methods of management of abdominal aortic aneurysms. A report is given of a case of atherosclerotic abdominal aortic aneurysm that was treated with resection of the aortic bifurcation and replacement by homologous graft. During a period of observation of eight months, the result of the operation remained excellent.

*From Edsel B. Ford Institute for Medical Research.