Abstracts

Lipid-containing cells have been observed in the female mammary gland in a variety of conditions, namely, plasma cells mastitis, xanthomas, fat necrosis, and liposarcomas. The occurrence of lipid in the epithelial cells is normally associated with pregnancy and lactation and in these instances indicates a secretory activity. In carcinomas, this has usually been interpreted as a degenerative change and given little attention. This report is concerned with a case of mammary carcinoma in which lipid production by the tumor was the outstanding feature suggesting a secretory activity rather than a degenerative process.


The decrease in bone mass observed in osteoporosis results from an imbalance between bone formation and bone resorption and may arise in the following ways: (1) reduction in bone formation while bone resorption remains unchanged, (2) normal bone formation associated with increased bone resorption, (3) decrease in bone formation in addition to increased bone resorption, (4) an increase in bone formation with a greater increase in bone resorption, and (5) a reduction in bone formation greater than a decrease in bone resorption. It has been postulated by Albright and Reifenstein that post-menopausal or senile osteoporosis results from a decrease in bone formation while bone resorption continues normally. Recent studies using bone-seeking isotopes have, in contrast, suggested that bone formation is normal or slightly increased in this form of osteoporosis and that bone resorption instead is increased. Dietary studies in England and the United States indicate that patients with osteoporosis ingest less calcium in their diets as compared with their nonosteoporotic contemporaries. Therapeutic approaches including sex hormones, calcium supplements, vitamin D, high protein diet, and mobilization have been recommended. While relief of pain and improved retention of calcium have been demonstrated after therapy with anabolic hormones, as well as after the administration of calcium, there is little evidence of increased bone formation by roentgenographic and histologic studies.


Cholesterol concentrations in serum, liver and carcass, as well as acetate-1-C\textsuperscript{14} incorporation rates, were investigated in a comparative study on mice, rats, hamsters and guinea pigs, using a single standard basal diet supplemented in various ways with cholesterol and bile acids. When diets were supplemented with cholesterol, guinea pigs and hamsters accumulated large quantities of this sterol, whereas mice and rats were more refractory. In all species, cholesterol-containing diets inhibited incorporation of acetate-1-C\textsuperscript{14} into liver. None of the cholesterol or bile acid supplements had significant effects on carcass cholesterol concentrations in any of the species. Acetate-1-C\textsuperscript{14} incorporation into carcass remained unaffected in rat, mouse and hamster, but was inhibited in the guinea pig. Those bile acids that are present in the bile of a given species inhibited incorporation of acetate-1-C\textsuperscript{14} into liver cholesterol. Other bile acids had varying effects on cholesterol concentrations and synthesis rates. Hyodeoxycholic acid limited the accumulation of liver and blood cholesterol of animals fed atherogenic diets.

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Cancer chemotherapy, even with the crude, weak, toxic, and only fractionally effective methods which we have today, has a practical role in medicine. There will appear in Michigan this year, 2,950 likely candidates for treatment with the drugs now available on the general market. Since only about 1,000 of them will be seen by men specializing in this work, it is necessary, if 2,000 people are to obtain the very real help open to them, that physicians generally do their best to learn to utilize these drugs in a prudent and effective way. A table is included to indicate the kinds of neoplastic disease we have found responsive to chemotherapeutic and hormonal treatment, the agents we are now using in each of them, and an estimate drawn from published work and our own experience of the frequency with which one may expect a reasonably beneficial response to occur. Careful adjustment of regimen to the individual case is critical for drugs with a narrow therapeutic range. The proper use of chemotherapeutic agents is an art which can be achieved through long hard experience or, with less time and anxiety, through tutelage. At first, it is best for a man attempting to do this work to associate himself in some way with someone who has been practicing it. This can be done through thoughtful participation in the management of a series of one's patients with a consultant, while at the same time developing a knowledge of the literature on the agents concerned. Experienced chemotherapists are to be found associated with many hospitals in the state of Michigan. A considerably larger cadre needs to be developed, however. It is hoped that this estimate of the dimensions of the medical service we ought to provide in cancer chemotherapy, together with some clarification of its nature and purpose, will encourage additional physicians to interest themselves actively in the subject.


One thousand, three hundred and seventeen men, aged 40 to 65 years, who were working full time in the Detroit area were surveyed. A questionnaire, chest roentgenogram, and spirogram were obtained on each person. These men were divided into four categories: (1) no industrial exposure, 175; (2) industrial but no silica exposure, 598; (3) silica exposure for more than 20 years, normal chest roentgenogram, 404; (4) silica exposure for more than 20 years; roentgenogram showed silicosis in 140. A spirogram was obtained on each man from which were calculated the forced expiratory volume (FEV\textsubscript{i}); one-second forced expiratory volume (FEV\textsubscript{i}); the one-second forced expiratory volume as a percentage of the forced expiratory volume (FEV\%); and maximal midexpiratory flow (MMEF). All three measurements fall with increasing age and are adversely affected by bronchitis and cigarette smoking. Occupation appeared to have little effect on ventilation, there being no significant difference between the occupational groups except in relation to the FEV\textsubscript{i}.


The recognized association of rheumatoid arthritis with nodule formation, psoriasis, and certain types of chronic leg ulcers prompted a cooperative study to determine if deviations from the normal could be identified in uninvolved areas of the skin in patients with rheumatoid arthritis. Within the limits of the study including clinical examination, cutaneous testing, and microscopic studies, it was not possible to detect consistent changes in the skin which would differentiate the patients in this series who had rheumatoid arthritis from others in a similar age group. This investigation failed to demonstrate any structural or functional abnormalities of apparently normal glabrous skin which could be attributed to the presence of rheumatoid arthritis.


Sweat chloride measurements were made using induced heat to produce sweating in 83 white adults, divided into 35 control subjects and 48 patients with chronic bronchial disease.
**ABSTRACTS**

The mean sweat chloride level in the bronchitic group was significantly higher (49.5 ± 23.4) than that of the control group (35.7 ± 17.5). Clinical findings (pulmonary and gastrointestinal) and family histories in 9 bronchitic patients whose sweat chloride levels exceeded 71 mEq./L. (>2 standard deviations from the mean of the controls) suggested that these individuals had partial forms of cystic fibrosis. Changes in dietary salt intake with or without deoxycorticosterone altered sweat chloride concentrations in the control and bronchitic subjects tested, but not in one patient who had established cystic fibrosis. In view of the various factors which may alter concentration of sweat electrolytes in adults, correlation with clinical findings is needed before attributing an isolated instance of sweat chloride elevation to the presence of cystic fibrosis.


The chemical element, fluorine, has had a meteoric rise to prominence. It is not uncommon to use a fluorinated toothpaste or, perhaps, to take a vitamin pill containing a fluoride. Nonflammable fluorinated compounds are important to anesthesiologists, but why do the drug and chemical industries seem so determined to fluorinate steroids, tranquilizers, antiemetics, diuretics, and antipyretics as well as anesthetic compounds? A series of exploratory questions posed to three leading pharmaceutical and two chemical companies provided me with helpful information additional to that found in the literature. In summary, fluorination has provided us with a host of important beneficial compounds from plastic resins to drugs, insecticides, and anesthetic agents. Fluorine is flame-quenching and a stabilizer of molecular arrangement. Until, however, we can answer some basic pharmacodynamic questions, I believe unbridled enthusiasm solely “because it's fluorinated” is not presently warranted.


During the past four years at the Henry Ford Hospital 36 patients suffering from advanced ulcerative colitis have had intestinal continuity restored by ileo-rectal anastomosis after removal of all the colon and the upper third of the rectum. There were no deaths in the immediate postoperative period, but 3 patients died from complications incidental to the operation, none of which were attributable to anastomotic difficulties. One patient, age 70, with complicating carcinoma, died at four weeks from pulmonary and cardiac complications; one at three months from pulmonary embolus and one at eleven months following reoperation for recurring attacks of intestinal obstruction. A fourth patient who had a concomitant malignancy of the colon succumbed two years later from metastatic carcinoma. All these patients were autopsied and in no instance was there any breakdown of the anastomosis.


It is the purpose of this article to review briefly some modern knowledge of the nature of the osteoporoses essential for understanding them and to outline the nature of the dynamic cellular disturbance immediately causing them. The material is aimed at the clinician. Because of a quiet and recent revolution in our understanding of the osteoporoses much of the present text will be new to clinicians. A discussion of causes in the conventional sense is omitted, justification being that whatever they may be, they must turn the handles of the “faucets” described here to affect the skeleton. There is currently active interest, investigation, and discussion about the ultimate causes of some of the osteoporoses. Age, racial, dietary calcium, dietary protein factors and gonadal-adrenal interrelationships are invoked by various authorities to explain various osteoporoses. The outline of skeletal dynamic physiology given here represents the framework within which the ultimate causes of the osteoporoses must operate. Whether the cause is a mineral deficiency, a hormone imbalance, or something else, the immediate cause is an excess of resorption over formation. Skeletal balance is the “faucet” that must be turned by the ultimate cause to produce an osteoporosis, and which must eventually be re-turned by a pharmacologic agent to cure an osteoporosis.

The purpose of this study was to determine whether the small increase in abundance of N$^{15}$ normally found in nitrogenous compounds of biological origin is primarily due to mass discrimination in nitrogen metabolism, or to reproducible analytical errors. This problem was approached by repeatedly determining N$^{15}$ in the same series of nine amino acids, either purchased in chromatographically pure form or isolated from proteins of rat liver, dog serum, and six plant sources. Proteins and amino acids included in the study were selected on the premise that concentration or redistribution of N$^{15}$ might occur in such processes in urea formation, nitrogen transfer, or nitrogen fixation. Data for N$^{15}$ excess in a series of alkaloids were also secured. Standard deviations obtained in series of analyses were too small, and values for N$^{15}$ excess in the same amino acids isolated from different sources too variable, to permit interpreting the observed N$^{15}$ excess as a reproducible error. Distribution of N$^{15}$ in amino acids of the animal proteins studied resembled that observed when N$^{15}$-labelled amino acids or ammonium compounds are given. Differences between results for amino acids of animal and plant origin also supported the idea that the small excess of N$^{15}$ normally found is metabolically as well as statistically significant. Results for N$^{15}$ in amide nitrogen likewise supported this view. The smallest excess of N$^{15}$ occurred in amino acids from proteins of legumes, which fix nitrogen. In synthetic amino acids, the concentration of N$^{15}$ was more often below than above normal abundance.


A group of ten experiments was done wherein one cornea of each rabbit was inoculated with one of ten strains of Pseudomonas. These strains were isolated from human infections. In vitro antibiotic spectra had previously been done. The corneas were then treated with 100 μg/ml (1:10,000) solutions of polymyxin B and colistin sulfate. Slightly over 50 per cent of the total expected corneal damage was averted by continuous bathing of the cornea with either of these solutions. About 99 per cent of the final corneal damage occurred in the first week in both the treated and untreated animals. Final results showed no statistically significant difference in the effectiveness of the two drugs, weight for weight.


Flumethiazide and hydrochlorothiazide are two new potent diuretics. They each exhibit only weak carbonic anhydrase inhibitor effect, about 1/400 and 1/200, respectively, compared to acetazolamide (Diamox®). Using our experimental method on a mixed rabbit colony, the hydrochlorothiazide and flumethiazide groups and the controls showed no significant drop in intraocular pressure. The inability of these drugs to lower intraocular pressure probably can be correlated with their potency as carbonic anhydrase inhibitors. The tension-lowering effect of acetazolamide observed in this study is in agreement with the findings of previous investigators.


The urethras of 164 women were measured 496 times. Three methods of measurement were compared. Direct and radiographic measurements with a Foley catheter resulted in spurious and inconsistent impressions of shortening because the urethra telescoped over the catheter. The metallic bead chain method of mensuration was deemed most satisfactory because distortion of the urethra did not occur but measurement was approximate because of variable bead distribution; the error was estimated to be within the range of plus or minus 5 mm. No correlation between incidence, severity, or cure of stress urinary incontinence and a short urethra could be demonstrated.

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*Alkali-inactivation of the succinoxidase system and its reactivation ("Reconstitution")

This article is an inquiry into the experimental foundations of the claim that a complete, intact, and physiological respiratory chain can be reconstituted from soluble, purified succinic dehydrogenase and alkali-treated heart muscle preparations. It is shown that while the reconstructed system is in many respects quite similar to the original one as it occurs in heart muscle, there are important and precise chemical and biological differences between the intact system and the reconstructed one. Thus the process of reconstitution is not, in fact, a physiological process.


The activation of succinic dehydrogenase discovered by Kearney in 1955 is an intramolecular change in the enzyme which involves the transformation from a form of very low activity to one of very high activity. It is brought about by incubation with substrates and competitive inhibitors and other substances which combine at the active center. Originally, the activation was thought to be irreversible since on dialysis of the activated enzyme full activation remained. The recent advent of more efficient methods of removing small molecules from protein preparations, such as gel filtration on Sephadex, has permitted the demonstration that the activation process is, in fact, reversible. Both soluble and particulate preparations can be extensively deactivated by mere passage through a Sephadex column.


Of 26 patients with dissecting aneurysm of the aorta diagnosed from 1950 through 1962, 13 patients lived less than six weeks from the time of initial diagnosis. Of the other 13 patients, 2 had had successful operative repair of the aneurysm during the acute stage. The average survival of the remaining 11 patients was 26 months. Prognosis of this unselected group of patients was better than has been reported previously for this disease. No significant correlation could be found between survival of the patient and the presence of past hypertension, associated recognized cardiovascular disease, or site of intimal rupture.


Many surgeons do not like the term "heart failure". It would be nice if some other term could be devised. Consider the case of a man who has a systolic murmur over the aortic valve. He has mild stenosis, but as the years go by, it gets worse and the heart enlarges. He keeps on working and probably by this time he is getting some digitalis. Finally, the heart gets as large as it possibly can, the murmur becomes a little bit less harsh, and at this time, the ankles begin to swell. Now, we say there is "heart failure". We could more properly call the situation "heart success", because the heart has carried this man through four or five years of fighting against a bad situation, that of a tight aortic valve, which with luck, the surgeon could correct by direct-vision surgical procedures. The term "heart failure" has been used in regard to cases of constrictive pericarditis, although there is absolutely nothing wrong with the heart. The heart muscle is there just begging for the chance to open up and receive the blood from the pulmonary veins, and as soon as the constricting pericardium is removed, the myocardium immediately begins to function better. It may take a few weeks for it to get over its atrophy, but the muscle is good, and we may say that we have another example of "heart success".


Despite careful efforts to control the output of ultrasound emanating from the applicator tip, to negate the influence of heat generated by the probe tip and to render uniform the increment of radiation time, it is evident from the audiograms and histopathologic studies

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that there is great variability of response among experimental animals to ultrasound radiation. Pathologic changes varied from complete destruction of the organ of Corti to cloudy swelling of the hair cells, with maximum damage occurring beneath the area of the radiating applicator tip. Inner hair cells appeared to be more resistant to the destructive effects of ultrasound than were outer hair cells.


Highly purified preparations of reduced nicotinamide adenine dinucleotide (NADH) dehydrogenase from heart oxidize a number of NADH analogues and catalyze transhydrogenations between NADH and NAD analogues. Ferricyanide is the only satisfactory electron acceptor hitherto found. The dehydrogenase shows very little or no reaction with cytochrome c, menadione, lipoic acid and its derivatives, and coenzyme Q0. Various aspects of the kinetics of the purified dehydrogenase are described. The enzyme is competitively inhibited by NAD and its analogues. Amytal, antimycin A, cyanide, azide, and o-phenanthroline are not inhibitory. In both soluble and respiratory chain-bound preparations, the NADH-ferricyanide reaction is only slightly inhibited by organic mercurials under conditions that abolish electron transport to the respiratory chain. The enzyme is rather stable at neutral pH and at temperatures below 30°. At higher temperatures, at acid pH, and in the presence of organic solvents, rapid inactivation occurs, which is accompanied by the emergence of NADH-cytochrome reductase activity. Amytal is shown to interrupt electron transport on the oxygen side, not on the substrate side, of NADH dehydrogenase. The reasons that have given rise to the alternative interpretation in the literature are discussed.


The pleural esophageal stripe, as has been pointed out by others, is a neglected but useful landmark in the roentgenographic study of esophageal disease. Its use is most rewarding in chronic inflammatory disease of the esophagus in which mucosal aberration may be negligible and thickening of the wall, as appreciated by increased width of the stripe, may be the only indication of abnormality. The normal pleural esophageal stripe measurement is 3 to 5 mm. with the esophagus distended. In the presence of inflammatory disease, measurements up to 2 cm. were obtained. Malignant tumor, abscess, and ulceration may produce marked local deformity in addition to some diffuse thickening. Miscellaneous entities such as achalasia and esophageal varices produce less constant changes in the pleural esophageal reflections.


An adequate trial of conservative treatment should precede any use of steroids in rheumatoid arthritis. When steroids are used, a 60 to 70 per cent suppression should be the goal, rather than complete suppression. In addition to steroid therapy, the panelists discuss physical therapy, management of osteoarthritis, distinguishing features of degenerative articular disease versus rheumatoid arthritis of the hands, and the use of salicylates, phenylbutazone, chrysotherapy and antimalarials. Some laboratory tests for the rheumatoid factor are reviewed briefly, as well as the finding of uric acid crystals in synovial fluid of patients with gouty arthritis.


This paper is a review describing details of the catalytic and molecular properties of the various lactic dehydrogenases which occur in yeast and their genetic and cytological interrelations.

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ABSTRACTS

Megaloblastosis produced by a cytosine antagonist 1-β-D-arabinofuranosylcytosine.

Cytosine arabinoside induced objective, but temporary, decrease of tumor masses in three patients with lymphosarcoma and slight decrease in some lesions in two out of ten treated patients with disseminated carcinomatosis. In doses of 3 to 50 mg./Kg. given at varying intervals, cytosine arabinoside induced definite megaloblastic changes in the marrow of all patients studied. Mitotic abnormalities similar to those found in other megaloblastic anemias also occurred. Associated with bone marrow changes, depressions of hemoglobin, white blood cells and platelets in the peripheral blood were observed. The exact mechanism of action of cytosine arabinoside has not been elucidated. It is speculated that because of the close structural similarity between cytidylic acid, cytosine arabinoside could interfere with DNA synthesis.


An extensive study was undertaken during the past year to determine the effectiveness of colistin sulfate and seven sulfonamides (sulfisoxazole, sulfadimethoxine, sulfamoxole, N1-acetyl sulfanilamide, sulfadiazine, sulfamethoxine, and sulfathiazole) when used singly and in combination against 75 strains of gram-negative bacilli (Aerobacter, Alcaligenes, Bacterium anitratum, Escherichia, paracolobactrum, Proteus, and Pseudomonas). The chemotherapeutic agents were evaluated using both the disc and tube dilution procedures employing the following fluid and solid media: sheep’s blood agar, Mueller Hinton, Sulfonamide Resistant, and Trypticase Soy media. The drugs were used in concentrations of from 1.0 to 1,000 µg/ml of medium. The strains of Proteus were usually resistant to 1,000 µg or more of the individual drugs but proved to be highly sensitive to low concentrations of colistin sulfate in combination with any one of the sulfonamides. In many instances, there was a 50- to 100-fold decrease in the amount of each drug necessary to inhibit the organism when combinations of colistin sulfate and sulfonamide were used as opposed to the use of either one drug or the other. This demonstrated a marked synergistic effect. Strains other than Proteus were frequently sensitive to lower concentrations of colistin sulfate, and, therefore, the combination with sulfonamides usually demonstrated an additive effect rather than synergistic activity. The in vitro synergistic effect shown by the combinations of colistin sulfate with any one of the seven sulfonamides suggests the possibility of in vivo application of these regimens in the treatment of Proteus infections (i.e., septicemia, urinary tract, etc.).


A new intramuscular iron preparation, a colloid of iron, sorbitol, and citric acid, has been found to be nontoxic, well tolerated and clinically effective in the treatment of iron-deficiency states. The rapidity of absorption from muscle is a striking feature of pre-clinical pharmacological studies. Thirty-three patients received injections of iron-sorbitol. From a total of 386 injections (37,300 mg. iron), only 4 patients complained of unusual local soreness, and 3 were noted to have skin staining. No instance of a generalized reaction was observed. Four brief case reports were included to exemplify the use of iron-sorbitol in clinical practice. The clinical indications for the use of intramuscular iron were reviewed. These are: Chronic incorrectable blood loss, malabsorption states, intolerance to oral iron, and lack of patient cooperation.


Occasionally degenerative and mild inflammatory changes in the mesentery of the small intestine produce a mass. This may be manifest clinically as an asymptomatic abdominal mass, the nature of which is not determined by diagnostic studies. In other patients, abdominal pain of a nonspecific nature is present with or without a palpable abdominal mass. Two patients with this condition are reported. The gross appearance of the mass at surgery is diagnostic. It is largest at the root of the mesentery, has a mottled tan-yellow surface, and does not involve the small bowel itself. In considering the lesion, it seems noteworthy primarily to recognize it for its benign nature and to differentiate it from other conditions involving the mesentery. Biopsy is sufficient as a surgical procedure. The exact pathogenesis and nature of the lesion makes a specific term to identify it difficult. We prefer the term lipogranuloma, inasmuch as it seems to best describe it and avoids confusion with terminology used for other lesions with which it may be confused. The process does appear to be primary in the fat of the mesentery of the small intestine. This lesion is undoubtedly more common than heretofore reported. Mild forms involving the root of the mesentery are probably common and insignificant in appearance.