

resistance to the progress of dental caries than does a well calcified structure. In addition, the presence of interglobular spaces in the dentin increases the pain incident to the preparation of cavities for dental restorations. Thus the importance of efforts to reduce or eliminate this undesirable effect of artificially induced fever on tooth structure becomes quite apparent.

While the use of sodium fluoride injections and vital staining with alizarine have already provided means of inquiring into some of the biological processes associated with dental calcifications, controlled artificial fever would seem to offer another and somewhat different approach to the study of such physiological phenomena.

Further work, using the albino rat as the subject of artificially induced hyperpyrexia, is being carried on in order to observe the effects over a wider range and duration of temperatures, and in an attempt to lessen the undesirable effects by a preliminary increase of the available supply of materials concerned in the calcification process.

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Pathogenesis of Hemorrhage in Artificially Induced Fever.

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Every therapeutic agent of value has its potential dangers and hyperpyrexia is no exception to this general rule. Two of the most constant pathologic findings following induced fever in experimental animals and in human subjects are hemorrhage and acute parenchymatous degeneration of the liver. Hartman¹ has pointed out the similarity of these pathologic changes to those encountered following prolonged mild asphyxia, and has demonstrated that anoxia is a common accompaniment of artificially induced fever.

The mechanism underlying the hemorrhage following artificially induced fever has never been entirely satisfactorily explained. In the present study selected cellular and humoral factors important in the complex phenomenon of blood coagulation have been determined under experimental conditions in rabbits and during fever therapy in human patients. Total platelet counts have been correlated with

¹ Hartman, F. W., *J. Am. Med. Assn.*, 1937, **109**, 2116.

qualitative and quantitative studies of the megakaryocytes in serial marrow punctures; quantitative prothrombin and fibrinogen determinations have been followed by histopathologic studies of the liver. Fever was induced in the experimental animals with the radiotherm and in human subjects with the Kettering hypertherm.

Marked differences in the susceptibility of these several coagulation factors to fever were noted from individual to individual. During and following artificially induced fever in rabbits there was a decrease in total platelets in all instances, the lowest determinations being one-fourth to one-third of the pre-fever control values. More or less extensive megakaryocytic damage was apparent during the period of low platelet values and a prompt and rapid regeneration of new megakaryocytes always preceded the return of the circulating platelets to normal levels. A quantitative decrease in prothrombin and fibrinogen occurred in those animals in which liver damage was later found, and where no hepatic damage could be demonstrated no disturbance in prothrombin had been recorded.

Comparable observations were made in young adult patients, both male and female, normal except for some manifestation of gonorrhoeal infection. The efficiency and integrity of the liver were determined from time to time by the appropriate liver function tests and by variations in the icterus index. There was a pathologic retention of bromsulphalein dye in every subject immediately following induced fever together with a greater or lesser degree of chemical and clinical jaundice (highest icterus index was 70 units). The most marked decrease in prothrombin occurred during the 24-hour period following the fever treatment. Some decrease in prothrombin occurred in every fever patient studied, though in only one individual did the determination fall below the critical level of 35% of normal. In this individual who received 10 hours of hypertherm fever above 105°F without previous glucose fortification, the prothrombin reached a low point of 11% of normal and hematemesis occurred during that time. Quantitative fibrinogen studies in 2 subjects showed no variation from normal values. The circulating blood platelets were affected in all subjects, the maximum decrease being approximately one-sixth to one-fourth the control values, sometimes persisting for 48 to 72 hours post-fever. Epistaxis occurred in one individual on the day following fever therapy during this period of thrombocytopenia. A much slower tendency for megakaryocytic regeneration was noted in the human than in the rabbits' marrow.

On the basis of these studies, the sequence of events in the pathogenesis of hemorrhage in artificially induced fever may be reconstructed as follows: with the rise in temperature anoxia develops, a

rapid depletion of the liver glycogen occurs and definite histologic evidence of hepatic cell necrosis appears. The decrease in prothrombin, with or without a decrease in fibrinogen, may be correlated with the extent of liver damage. Any injury or destruction to megakaryocytes is reflected by a prompt proportionate decrease in the circulating blood platelets. Concomitant damage to the endothelial cells directly has not been demonstrated.

Whether hemorrhage will remain potential or become an actual fact in any given instance must depend upon the relative degree and interaction of the impairment which each of these 3 important coagulation factors suffers during a period of fever. The assurance of adequate glycogen storage in the liver should always be prerequisite to fever therapy, and a careful appraisal should be made of the megakaryocytic reserves in the bone marrow.

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Effect of Pectin Supplements on Avitaminosis A in Rats.*

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It is generally recognized that vitamin A is essential in preventing xerophthalmia and keratinization of the mucous epithelium of the body. This substance is also thought to play an important rôle in the synthesis of mucin by the body because a dehydration of the mucous membrane occurs as a result of avitaminosis A. Manville^{1, 2} has suggested that galacturonic acid plays a rôle in mucin formation. In view of the fact that the pectin molecule is composed of 8 molecules of galacturonic acid, it was thought that ingested pectin when fed in a vitamin A-free diet might retard the characteristic keratinization of the mucous epithelium. The object of this investigation was to determine whether or not pectin is effective in preventing or

* Contribution No. 317, Massachusetts Agricultural Experiment Station. Abstracted from A. Kobren, Thesis for Master of Science degree, Massachusetts State College, 1938.

¹ Manville, I. A., Address delivered at 41st annual convention International Apple Assn., Boston, Mass., 1936.

² Manville, I. A., *Science*, 1937, **65**, 44.