SIGNIFICANCE OF PEROXIDASE IN EOSINOPHILS

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Peroxidase-bearing granules are the primary component and product of eosinophils. The physiological significance of eosinophils is, therefore, considered to be related to the ability of this cell to synthesize, store, and transport peroxidase and to release the peroxidase-positive granules into body fluids by a lytic process that is controlled by hormones, by variations in the histamine-epinephrine balance, and by several other stimuli. Peroxidase occurs not only in eosinophils, but also in neutrophils and blood platelets; but it is not present in most cells of animal tissues.

The purpose of this work is to consider, as a working hypothesis, that the function of eosinophils is to produce, store, and transport peroxidase to catalyze oxidations. Many of the aerobic dehydrogenases that catalyze reactions in which hydrogen peroxide is produced are involved in protein catabolism. Therefore, relations between eosinophils and several normal and pathological conditions of increased protein catabolism are emphasized, and also the significance of peroxidase in eosinophils and other leukocytes to H_2O_2 produced by irradiation is considered.

The functions of eosinophils and peroxidases are difficult to establish experimentally, because other leukocytes and platelets contain peroxidase, and because several peroxidatic reactions can be catalyzed by hemoglobin and cytochromes (335), and because catalase, which decomposes H_2O_2, is present in erythrocytes and other cells, thereby preventing accumulation of H_2O_2 (616). In addition, catalase can act as a peroxidase in oxidation of alcohols (247) and large amounts of catalase cause purely oxidative effects, in contrast to the predominance of peroxidase activity when only small amounts of catalase are present (558). Furthermore, Keilen and Hartree have suggested that catalase may have a peroxidative function in most cells instead of preventing accumulation of H_2O_2 (74).

PEROXIDASE GRANULES

The eosinophil is one of the few types of cells which contain peroxidase and is the only cell which has its cytoplasm filled with large peroxidase-positive granules which are widely dispersed upon lysis of the cell. One function of eosinophils is the synthesis and storage of peroxidase within a cell and the release of this enzyme when and where it is needed for use by other cells. Eosinophils, thereby, resemble mast cells in having a significant function in extracellular metabolism. The peroxidase-positive granules of neutrophils are not widely dispersed upon lysis of the cell and would probably function primarily in intracellular metabolism.

Eosinophils appear to have a direct relation to oxidative enzymes. Spitzers,

1897, showed that the eosinophil granule is rich in iron and plays a significant part in the process of oxidation of iron-containing nucleoproteid (514). Winkler, 1908, was the first investigator to recognize both oxidase and peroxidase in eosinophils and, with less activity, in other granulocytes. He also demonstrated a strongly oxidative reaction with eosinophils from gonorrheal pus (514).

Granules of eosinophil leukocytes give positive peroxidase reaction with a variety of staining methods (137, 253, 325, 349, 514, 580, 627). Agner (7) gives an extensive review of the literature on the presence of peroxidase in leukocytes, the discovery of the "peroxidatic" reaction by Klebs, 1868, and Strive, 1872, and the reaction of granules in leukocytes to form indophenol blue from a mixture of a-napthol and the Nadi reagent. Another school of investigators (319) warns that the so-called "oxidase reaction" obtained by use of alpha napthol demonstrates a "special affinity of granules in leukocytes to napthol", but is misleading, for it "does not indicate the presence of oxidase nor . . . of lipid" and is merely a napthol reaction. Woodward (631) points out that many authors doubt the occurrence of peroxidase in animal tissues. Weinkler, 1907, found Nadi-positive granules in the cytoplasm of myeloid cells, but not in lymphocytes (7). Agner (7) determined that this Nadi reaction was due to a peroxidase by extracting verdoperoxidase from "leukocytes" in empyemic fluid. He found that the verdoperoxidase content of the "leukocytes" represented 1 to 2 per cent of the dry weight, which is 6 times the yield of peroxidase reported for the richest part of horse-radish root (7).

Brandenburg, 1900, using guiac resin-blue stain, found that bone marrow, pus, and leukemic blood gave a positive reaction for an iron and phosphorus-containing enzyme but that the thymus, lymph nodes, and spleen were negative (6). Agner's (6) review includes an excellent summary of opinions on whether the reaction is due to an oxidase or to peroxidase, and he concludes from the formation of indophenol blue, which can be provoked by peroxidatic reactions, that it is evident that the Nadi-reaction in leukocytes is conditioned by verdoperoxidase and that the verdoperoxidase occurs only in myeloid cells. Maehly (359) believes that myeloperoxidase, which is now considered about the same as verdoperoxidase (563), occurs in all myelogenic leukocytes but especially in granules of eosinophils.

Eosinophils have large, heavy granules when stained by Sato and Sekiya's method (137, 224), and younger myelocytes have fewer granules than later stages (224). Diggs, Sturm, and Bell (137) state that both eosinophils and neutrophils give a strongly positive reaction by Sato and Sekiya's method, but that eosinophils are laked, and the granules of basophils differ in their reaction from that of other methods. Carvalho, 1949, found that a modification of the peroxidase reaction stained granules of eosinophils specifically (46).

Granules of eosinophils are also peroxidase-positive when stained by Graham's

method and are large and closely packed in the cytoplasm as are the granules of eosinophils stained with eosin by Wright's method, thereby indicating that the peroxidase is present in the granules rather than in the cytoplasm. Eosinophils have deeply staining, round, glistening granules when stained by Moschkowski's method for peroxidase, in contrast with the staining of the cytoplasm in neutrophils which appears as a "compact brown mass" due to density of reaction (342). The peroxidase reaction of isolated granules has been investigated by only a few hematologists. The general principle involved in isolating the peroxidase granules is first to isolate and lyse the eosinophils; then the granules are separated by differential centrifugation in various media (39, 176). However, in studies on isolated granules it also is necessary to consider that the enzyme may be adsorbed to the surface of the granule, that the positive reaction represents a diffusion, or that the enzyme may be limited to either the outer or inner region of the granule.

Peroxidase in Cells

Neutrophils, myelocytes, myeloblasts and endothelial leukocytes, as well as eosinophils, give the peroxidase reaction with Goodpastur's staining method (580). Peroxidase granules in neutrophils are decreased whenever toxic granulation is present (627). Basophils are also considered to be peroxidase positive (253). The cytoplasm of neutrophils contains large quantities of glycogen (46) and is not filled with large peroxidase-positive granules. The peroxidase in neutrophils appears to be free throughout the cytoplasm, in contrast with the localization of peroxidase within the granules of eosinophils. Neutrophils, which have a greater ability to ingest particles than eosinophils (46), can digest microorganisms and foreign particles of small size, because, as shown by Rebuck, 1947, Feissinger, 1923, and others, the cell contains many enzymes such as proteolytic types, lipases, nucleotidase, and phosphatase (46). Eosinophils which have a very limited, if any significant, phagocytic functions, are mobile and motile and are adapted to conveying peroxidase granules to a given site where, following cytolysis, the peroxidase-bearing granules are scattered so that each granule becomes a peroxidase-distributing center. Other differences in the function of eosinophils and neutrophils have been mentioned. For example, certain eosinophils of turtles do not react to injections of turpentine and nucleic acid as do the heterophils (496).

The presence of peroxidase in monocytes has not been established, and Kracke (326) states that there is no agreement on the reaction of monocytes to peroxidase staining, but he (326) holds that those monocytes with visible granulation are peroxidase-positive. Kracke (326) also points out that the myeloblast is negative following Sato and Sekiya's stain for peroxidase.

Peroxidases in Animals

Several peroxidases are found in mammals and other vertebrates: myeloperoxidase, now considered to include verdoperoxidase (563), lactoperoxidase, and salivary peroxidase. The leucocytes that contain myeloperoxidase (563) may also be the source of lactoperoxidase, which can form the same enzyme-substrate compounds as myeloperoxidase, and might be formed from peroxidase granules released from neutrophils and eosinophils. Eosinophils and neutrophils occur in interstitial tissue of the mammary gland (372, 374). Lactoperoxidase can oxidize tyrosine and differs in this function from horse-radish peroxidase (446).

Distribution of Eosinophils

Eosinophils occur and have a wide distribution in the body fluids and organs of all vertebrates with the exception of certain fishes (481). A thorough review of the early literature on eosinophils was given by Schwarz in 1914. Opie (417) gives an excellent review of the literature on the origin and distribution of eosinophils in various tissues of higher vertebrates and the relation of these cells to nutrition. Ringoen (481) gives a thorough review on the phylogeny and morphology of eosinophils and their granules. Speirs (551) reviews the more recent literature on eosinophils and includes consideration of their relation to antigen-antibody reactions and to hypersensitivity.

Eosinophils may occur normally, as tissue eosinophils, in the loose connective tissue of structures under conditions similar to the occurrence of mast cells (43, 373, 597). The widespread distribution of eosinophils in the blood and other body fluids and tissues places these cells in the class with mast cells and other "free connective tissue cells" (371). Thus, these cells normally occur in the tissue fluid in loose connective tissue in the human mammary gland, lungs, and omentum and are numerous in the areolar connective tissue of the guinea pig, mouse, and rat and always occur in greater numbers than the other granular leukocytes in the lamina propria of the small intestine (373) and form constituent elements of the mucosal stroma throughout the gastrointestinal tract (481). Other investigators report that these cells are present in bone marrow and lymphoid tissue, especially in the thymus, lymph nodes, and spleen, and that they are found occasionally in the omentum and lungs (481). Eosinophils are abundant in lactating mammary glands (481), in the stroma of the mammary gland in guinea pigs, and also in the interlobular tissue of mammary gland of lactating rats (353). This cell also occurs in connective tissue of the human breast and may occur in the submucous connective tissue of the gastroenteral and respiratory tracts (181, 481). However, DaFano (125) states that he has never found true eosinophils in normal connective tissue of the mouse, while Fawcett (181) states that

eosinophils are not nearly as numerous in the subcutaneous tissue of man as in this site in the rat, where these cells are 25 times as numerous as in the circulating blood of this mammal.

Eosinophils are numerous in peritoneal fluid (42, 225, 427, 481) and in the omentum (481) and occur in the loose subpannicular connective tissue on the back of the rat in the ratio of 2 eosinophils to 3 mast cells (42). Large numbers of eosinophils occur in the peritoneal fluid of both normal and tumor-bearing hamsters (305). The fact that eosinophils occur in loose connective tissues suggests that tissue eosinophils may arise by transformation of undifferentiated mesenchymal cells, but Maximow and Bloom (373) hold that most of the tissue eosinophils are eosinophil leukocytes which have emigrated from blood vessels and become established in the connective tissue, the exception being those in the connective tissue of the mucosa of the intestine, "where special conditions prevail". Ewing (178) holds that physiologically eosinophils "are celomic tissue cells, finding their natural habitat in the tissues and not in the blood." It is necessary in evaluating numbers and distribution of eosinophils in tissues to recognize the fact that the usual fixation and staining methods used for tissues routinely imbedded in paraffin do not usually permit identification of these cells. In addition, some cells that stain with eosin may be other types, such as histiocytes (46), eosinophilized epithelial cells (578), Russell bodies or Charcot-Leyden crystals (481). The two forms of lactoperoxidase have been described, Lactoperoxidases A and B, which differ in reactions with dopa, spectrophotometric constants, and electrophoretic mobility (466). Perhaps these differences are due to difference in percentages of peroxidase derived from leukocytes and bacteria.

Verdoperoxidase, which occurs in a very high concentration in empyemic fluid from tuberculous patients (7) and in chloroma, also comes from leukocytes (511). Neutrophils contain as much as 2 per cent by weight of verdoperoxidase (584). Agner (6, 7) in his excellent reviews on the early literature on verdoperoxidase in leukocytes mentions that one important function ascribed to this enzyme is the detoxication of bacterial toxins (359). Verdoperoxidase, which is now held to be the same as myeloperoxidase (563), is considered by Agner (7) to be a slightly modified form of peroxidase and to react less vigorously as a peroxidase.

Leucocytes are also considered a source of peroxidase in saliva. Nickerson, Kraus, and Perry (412) found that polymorphonuclear cells, chiefly neutrophils, accounted for the peroxidase positive cells in saliva sediment, and that peroxidase could not be demonstrated in the streptococci in saliva. These authors also maintain that the serous acinar cells are a rich source of peroxidase. Peroxidase has been reported by Dempsey, 1944, as being a normal component of thyroid cells and having a possible function in the formation of thyroxin (86); however, Glock attributes the effect to hemoglobin (631). The cytochrome system is considered

the source of oxidative energy for synthesis of the thyroid hormone by Schachner, Franklin, and Chaikoff, 1943 (86).

Iron in Granules

The presence of iron in granules of eosinophils substantiates the occurrence of peroxidase because peroxidase is one of the iron oxidases found in mammals. However, literature on the amount of iron and the form in which it occurs in granules of eosinophils is controversial. Eosinophilic granules have been considered to be formed from hemoglobin or products of its breakdown (326, 480); Stachastnyi, 1905, and others hold that eosinophilic granules are derived from the products of degenerating erythrocytes (481). Barker reported that granules of the horse are 11 per cent iron (326), compared with hemoglobin, which contains about 0.34 per cent (41, 616). Wislocki and co-workers (628) found that human eosinophils "contain no iron stainable by the Turnbull blue method"; but Barker, 1894, reported iron in human granules (481). Petry, 1908, mentioned that eosinophil granules have a function in iron metabolism (481) and that granules in the horse have a high iron content (83). Eosinophils have also been considered phagocytes (37, 481) of hemoglobin or products of its breakdown, which substances form the eosinophilic granules in the cytoplasm (326).

Cytochrome c oxidase, which is also an iron-porphyrin-protein, has been reported in eosinophils. The amount of the total iron in peroxidase, therefore, cannot be readily distinguished from the amount in cytochrome c oxidase. The finding of large quantities of cytochrome in eosinophils convinced Amano that these cells probably transport or store cytochrome (602). Whether the cytochrome c oxidase in eosinophils is limited to the mitochondria of the cytoplasm, or possibly to mitochondria within or to other parts of the granules (10), has not been determined.

Cytochrome c oxidase has been reported in the granules of eosinophils (10, 622). It has not been determined whether this enzyme has functions which are limited to the development of granules, or whether it is present in sufficient quantities in granules of matured eosinophils and has a function in extracellular metabolism. Cytochrome c is associated with succinoxidase and cytochrome oxidase systems (264). The chief localization of cytochrome oxidase in mammals is in mitochondria (376), and the entire succinoxidase system is also practically exclusively localized in mitochondria (425). Use of labeled cytochrome c has shown that the cytochromes in nuclear and microsomal fractions were adsorption but that only 10 per cent of the cytochromes found in mitochondrial fractions was due to adsorption (40). If cytochrome oxidase is a significant product in granules, the eosinophils may have a function of readily stimulating erythropoiesis by releasing granules that increase the cytochrome oxidase activity after stimulation of hema-

topoiesis induced by such stimuli as low oxygen tension, hemorrhage, and feeding cobalt (512). Cowdry, 1914, reported numerous mitochondria in some eosinophils and none in others (480), and at least 3 investigators have reported structures resembling cristae of mitochondria in some granules of eosinophils (437); however, Pease (437) does not believe that granules in the earliest myelocytes contain mitochondrial structures or that the eosinophil granules develop from mitochondria.

The function of eosinophils would not appear to be the storage and transportation of iron per se because iron is present in hemoglobin and myoglobin and also occurs in various combinations with certain plasma proteins (109). When large amounts of hematin form from disintegration of hemoglobin, portions of the hematin combine with albumin (247). Protoheme, the pigment of myoglobin (247), is present in muscles, while ferritin is the form once held to be stored in the reticulo-endothelial organs (639).

The protein to which the iron protoporphyrin is attached determines the method of functioning in biological oxidations (203). Peroxidases and catalases differ significantly from hemoglobin and cytochrome. Blood and muscle hemoglobin reversibly combine with oxygen in the ferrous state without being oxidized to the ferric state, and the cytochromes catalyze processes by undergoing rapid oxidation and reduction between ferrous and ferric states (204), whereas peroxidases and catalases are now considered to have a more complicated oxidation process than electron transfer and to function by undergoing higher oxidation states. The higher oxidation states, represented by Fe^{V}_{per}, Fe^{VI}_{per}, and Fe^{IV}_{mb}, are considered to be due to oxidation of the iron atom itself or to electron or hydrogen atom abstraction from the porphyrin ring system (203).

The origin of peroxidase-containing cells from cells in the bone marrow is significant in view of the concentration of protohematin and hematin synthesis in hematopoietic tissue. Disintegration of erythrocytes in the bone marrow or spleen might be important as a source of hematin for synthesis of peroxidase. Eosinophil granulocytes, as well as neutrophils and platelets, normally develop in the bone marrow (283, 342) in adult mammals.

Lipids

Lipids have been reported in the granules of eosinophils by a number of investigators. Wislocki and co-workers (628, 629, 630) concluded that the granules of eosinophils are lipoidal since they stained deeply and uniformly with sudan black B. Fawcett (182) also reports that these granules stain intensely with sudan black due to a coating of lipid, and Sehrt found that they stained readily with Sudan III (629). Bacsich (26) used Sudan III for staining lipoid granules in leukocytes, and Sheehan (527) used sudan black in 70% alcohol. Discombe (138) states that

granules of eosinophils, as well as those of neutrophils, may be lipoid. However, Lillie and Burtner (349) attribute sudanophilia of leukocytes to a possible chemical combination of the dyes instead of true stain of lipids; in addition, they concluded that the oxidase reactions were not due to presence of fatty acid peroxides. Baillif and Kimbrough (28) report that the shell of the granules of eosinophils stains with sudan black, whereas the core does not. Sections under the electron microscope show that granules of eosinophils may comprise two separate pieces with a lumen like the core of an apple (518). Vercauteren, 1951, in a study of isolated granules, demonstrated that the surface layers are composed of phospholipids and that protein is present in the interior of the granule (46). The basophil is considered by some hematologists to be an abnormal eosinophil which failed to mature because the younger forms of eosinophils sometimes contain basophilic granules (83).

Other Substances in Granules

Eosinophilic granules have been reported to contain numerous substances, such as arginine, choline, nucleic acids, organic bound phosphate, and pentoses (605). Petry, 1908, found that these granules in the mouse contain 11 per cent iron, give xanthoproteic, oxidase, and peroxidase reactions, are soluble in concentrated alkali and in warm acetic acid, that neither trypsin or autolytic enzymes would digest the granules and that these granules do not give a fat reaction (481). Polysaccharides are probably present in tissue eosinophils in the mucosa of the human appendix since both the granules and the cytoplasm gave a positive periodic acid-Schiff (PAS) reaction (630). Eränkö (167) was unable to stain the granules with PAS, but the cytoplasm took the stain.

Histamine

Eosinophils are often considered a source of histamine (604) because a definite increase in their number occurs in conditions of parasitism and foreign protein reactions. However, no definite correlation has been established between the blood histamine level and the number of blood eosinophils (107). Usually, eosinophile counts and histamine levels are concomitantly high, but an increased number of eosinophils may be present with a normal level of histamine in the blood (107). Certain authors hypothesized that the eosinophils play an important part in the detoxication of histamine, and Vercauteren designated an antihistaminic substance obtained from isolated eosinophil granules 'antihistiminicum' (350). Lindahl (350) reports that an antihistaminic substance was obtained from eosinophils by Vercauteren's procedure. The active antihistaminic effect of this substance was thought to be due to the presence of phospholipids. Other investigators also hold that eosinophilia is a defense mechanism and that the chief function of

the eosinophil is to combat formation of excess histamine (604), while Janeway (283) states that eosinophils remain a mystery and "their function is unknown".

The fact that histamine occurs in practically all tissues in mammals (41, 107, 245, 252, 597) indicates the probable validity of the claims that this substance occurs in eosinophils (226, 325) at least in physiological traces. Indeed, some investigators (226) claim that normal eosinophils contain about 160 mg of histamine to 10^9 cells and that one third of the histamine content of all the blood elements in chronic myelocytic leukemia is within the eosinophils. Code (107) states that it is questionable whether eosinophils ever carry appreciable quantities of histamine. Kovacs, 1950, holds that instead of releasing histamine, as was originally thought, eosinophils "do not contain histamine, but perhaps histaminase" (283). Code (107) points out the importance of checking the potassium content of extracts to avoid mistakenly attributing the similarity of the potassium response for that of histamine.

Several pathological conditions indicate that eosinophils do not contain histamine. A fall in histamine content follows an influx of eosinophils into a tissue which has a high mast cell and a high histamine content (474). A bovine eosinophilic granuloma contained very little histamine (474), whereas an extremely high histamine content (1290 μg/g) has been found in a mastocytoma of a dog (617). Eckert and Totterman (155), after making a series of observations on patients "with severe eosinophilia, both relative and absolute", concluded that all the evidence obtained contradicts the possibility of histamine being essential in eosinophils. Vaughn (604) suggests that eosinophils transport histamine or a similar toxic substance "from the bone marrow to the tissues for inactivation" and that the clinical syndrome known as eosinophilic infiltration of the lungs may possibly be explained by this concept. Rogers (159) states that eosinophils have been suggested as the cells which manufacture or carry histamine and in this capacity probably initiate sloughing of skin homografts in man. He strongly favors "the hypothesis that eosinophilia is telltale evidence of an 'ill-defined allergic response' taking place in the tissues".

Functions of Peroxidase

The precise biochemical function of peroxidase has not been established, but this enzyme is known to use peroxide to oxidize many inorganic and organic substances (204). Peroxidase catalyzes oxidation of many phenols and aromatic amines in presence of peroxides (41). Peroxidase systems catalyze oxidation of oxaloacetate, keto-malonate, and dihydroxytartrate (309). In the presence of a number of H_2O_2-producing enzyme systems, such as xanthine oxidase or D-amino-acid oxidase, peroxidase can oxidize manganese^{++} and, thus, in the presence of oxalic acid in either orthophosphate media, involve a cycle of oxidation and reduction

(308). In the presence of hydrogen peroxide, peroxidase catalyzes the oxidation of ascorbic acid, epinephrine, tyrosine, many diamines, such as O-phenylenediamine; phenolic substances, such as guaiacum; aromatic monoamines, such as aniline; and indicators, such as phenolphthalein (370). The method and products of oxidized phenols remain obscure (624); phenols are also converted into arylsulphuric acid and arylglucuronides. Oxidation products of many phenols oxidize ascorbic acid (96).

Leukopenia and secondary pernicious anemia, occurring when linoleic acid is present in the diet of rats, have been attributed to oxidative breakdown of unsaturated fatty acid (232). Tappel (576) states that the hematin catalyzed oxidation of unsaturated fatty acids may occur in many types of oxidation of unsaturated fats in vivo under pathological conditions, with formation of H_2O_2 as a probable causative factor (232). Linoleic acid is oxidized by isolated mitochondria from rat liver, and it is also known that the unsaturated fatty acids are oxidized by the same mechanism as the saturated fatty acids (307). Tappel (575) states that the postulated mechanism of lineolate oxidation initiation involves a dual reaction of lineolate peroxide with hematin catalysts, and that hematin compounds appear to be very general peroxidative catalysts with a low order of specificity relative to the structure of the peroxide group or the molecule of which it is a part.

The functions of peroxidase and catalase differ in several ways from that of other iron oxidases. Cytochrome oxidase can catalyze oxidation of organic substrates by molecular oxygen, but peroxidase and catalase cannot (247). Peroxidases differ in function from hemoglobin and myoglobin in that peroxidase, as well as catalase, appears to form higher oxidation states, whereas the ferrous state of the hemoglobins combines reversibly with oxygen (203).

Peroxidase can act on extremely low concentrations of H_2O_2 (161), but the presence of hydrogen peroxide in living matter is considered doubtful (161). The presence of peroxidase in leukocytes and platelets and the controlled hormonal release of these granules from eosinophils might have a function in catalysing oxidations in extracellular fluids, whereas catalase, which occurs in all cells, is held to destroy H_2O_2 formed intracellularly. Peroxidase in dispersed granules of lysed eosinophils would appear to have a supplementary, extracellular function in those tissue fluids in which H_2O_2 is formed by extracellular metabolism of aerobic dehydrogenases in normal or in pathological conditions.

Peroxidases appear to be especially important in conditions in which there is catabolism of amino acids and purines, because several of the aerobic dehydrogenases produce H_2O_2, which may in turn combine with peroxidase to oxidize other compounds produced during, or as a result of, protein catabolism. This process has been recognized in studies on tryptophane oxidase, which oxidizes trypto-

phane to formylkynureinine (563) by using H_2O_2 formed by xanthine oxidase. It is possible that lactoperoxidase may also use H_2O_2 produced in reactions catalyzed by xanthine oxidase, an enzyme that occurs in milk (563).

Hydrogen peroxide is formed in reactions catalyzed by several aerobic dehydrogenases, which function in catabolism of purines and amino acids. Xanthine oxidase dehydrogenates hydrated forms of hypoxanthine to xanthine and xanthine to uric acid (563, 592, 616). Uricase, in the presence of O_2, converts uric acid to allantoin with formation of H_2O_2 (563, 592), in most mammals but not in snails, Dalmatian dogs, and primates (616). D-amino acid oxidase and L-amino acid oxidase function in the oxidative deamination of amino acids. Of these enzymes L-amino acid oxidase is the more important physiologically for it deaminates dietary, or L-amino, acids (245), while D-amino acid oxidase acts on unnatural, or D-amino, acids (616). Monamine oxidase (tyramine oxidase) deaminates primary amines forming aldehydes, ammonia, and hydrogen peroxide (563, 616). Diamine oxidase in the presence of gaseous oxygen catalyzes the oxidation of "substances containing two or more $—NH_2$ groups, with the conversion of the $—CH_2NH_2$ group into —CHO" (335). Diamine oxidase is also believed to act on other substances, such as histamine (335).

The distribution of aerobic dehydrogenases (592) that produce H_2O_2 during steps of protein catabolism is important in considering significance of peroxidase in leukocytes. Xanthine oxidase occurs in the liver of man, in milk, in several organs in the ox, and in rat blood (563); but it is absent from the liver of the hedgehog and dog (616). D-amino acid oxidase is present in most animal organs, especially the kidneys and liver (335, 563). L-amino-oxidase is also present in the liver and kidney (245); however, uricase is present in the liver, spleen, and kidney of most mammals but is absent in the liver of primates and the Dalmatian dog (616). Mono-amine oxidase occurs in the liver, and in the kidney, intestine, brain, placenta, and lung in vertebrates and is also found in invertebrates (563), whereas diamine oxidase has widespread distribution (563). Histidase, in higher animals, occurs only in the liver (563).

The liver is an organ in which most of the aerobic dehydrogenases produce H_2O_2 (245). The concentration and retention of peroxidase in the spleen becomes especially significant. Myeloperoxidase, which has a concentration of about 1.0 per cent in leukocytes (563), is abundant in the spleen (41). Leukocytes, which are retained in splenic sinusoids, contain peroxidase-positive granules, as indicated in imprints of the spleen of hamsters stained by Graham's peroxidase method (305). The liver is in direct contact with the spleen via the portal vein and receives a much higher concentration of peroxidase than most other organs, except the bone marrow, where the peroxidase-containing cells are formed.

Peroxidase occurs in eosinophils, neutrophils, and platelets, but it does not

occur in other cells, whereas catalase is present in all cells. The function of peroxidase in granules of eosinophils would, therefore, probably be related to catalysis of peroxidatic reactions in intercellular tissue fluids or other body fluids.

Peroxidase and Catalase

Peroxidase granules in eosinophils and neutrophils might supplement or replace some of the peroxidatic reactions of catalase. For example, castration in young adult male mice or adrenalectomy decreases activity of catalase, while testosterone injected into females increased the level to that of males (3). The function usually ascribed to catalase is decomposition of hydrogen peroxide; for example, one molecule of catalase has been considered capable of decomposing 2,640,000 (41) to 5,000,000 (335) molecules of H_2O_2 at 0° C.

Catalase, present in all cells, including hepatic cells (616), has been credited with having several oxidative and peroxidative functions. McClendon (376) states that "catalase is probably a peroxidase in vivo". Coupled oxidation, rather than decomposition, of the H_2O_2 has been considered a significant function of catalase (297) in all cells. Catalase in liver cells is present in 1000 times the amount necessary for decomposition of the usual content of H_2O_2. Catalase, in the presence of H_2O_2 oxidizes ethanol to acetaldehyde (11). Ribose-5-phosphate is oxidized by catalase in a system that slowly generates H_2O_2, such as glucose, glucose-oxidase (191). Catalase in the presence of H_2O_2 can also peroxidatively oxidize alcohols (36, 95, 96).

Catalase from the liver can act as a peroxidase to couple various substances such as epinephrine or tyrosine with catechol, but peroxidase can not act as a catalase to decompose H_2O_2 without a second substrate (577). Although the main function of catalase is considered the protection of cells from toxic effect and H_2O_2 (297), such as protection of the oxidation system from excessive H_2O_2 produced by enzymes that convert L-tryptophan to kynurenine (318), catalase from the liver may have other functions, such as a role in bile pigment formation, a process that has been demonstrated in vitro (306).

Greater resistance to some inhibitors may indicate that peroxidase can replace catalase under conditions in which catalase is inhibited and peroxidase is not. Goldacre and Galston (216) reported 2,4-Dichlorophenol (DCP) did not inhibit peroxidase, cytochrome oxidase, or hemoglobin at a concentration of 2×10^{-6} *M*, but that catalase was reversibly half-inhibited at this concentration. Lemberg and Legge (343) demonstrated that ascorbic acid causes inhibition of catalase by accelerating the destruction of the enzyme by H_2O_2 with production of bile pigment haemoprotein. Sulfanilamides and sulfapyridine also have an anticatalase activity in man (106). Two of the four centers for attachment of enzyme inhibitors to catalase are acted upon by azide and cyanide groups and the re-

maining two by phenol and H^+ (417). Inhibition of catalase is also suggested as a possible cause of the formation of Heinz bodies in erythrocytes (74).

Increased or sporadic function of an organ or of pathological conditions may also require supplementation of peroxidases from leukocytes. Xanthine oxidase activity in the breast increases many times during pregnancy (346). The infiltrations by eosinophils and neutrophils in the mammary gland during pregnancy and lactation may catalyze oxidations utilizing H_2O_2 produced by this enzyme (373). Absence of catalase in blood and liver, muscle and bone marrow has been reported (571), and is a condition which is considered to be due to a recessive gene (408).

Protein Catabolism

One concept of the function of the eosinophil is that this cell plays an important part in protein metabolism. Heidenhain in 1888 believed that eosinophils were more numerous in the intestinal mucosa of normal than of starved animals and that these cells play a part in nutrition. His view was upheld and amplified by several later investigators. Vaughn (604) states that Rous found that in dogs a meal rich in protein was followed by a much greater increase in eosinophils in the lymph than after a carbohydrate meal. Ringoen (481) cites several writers who hold that the most satisfactory explanation of eosinophilia rests on the basis of chemotaxis which is, in all probability, correlated with "a reaction against the toxic products of autogenous or parenteral foreign proteins". This idea is supported by Hajos and Mazgon's idea that "eosinophils function in desensitization" (481) and by Vercautern's (605) holding that eosinophilic granules play a part in detoxication of histamine.

The literature affords very little direct evidence as a basis for explaining the functions of eosinophils. Beattie and Dickson (37) incidentally indicate a nutritive function for these cells by stating that eosinophils "are fragile, and readily break down, with scattering of their granules", and Wintrobe (627) says that since "eosinophilia is characteristic of allergic disorders . . . it is held that eosinophils are concerned in the disintegration and removal of protein". Liebman (348) ascribes to eosinophils a secretory function which is "connected with protoplasmic, probably protein, breakdown" in eggs of the salamander, Triturus viridescens; and he states that eosinophils are the only leukocytes found in these eggs after the neutrophils have disappeared.

The literature on changes in the numbers of eosinophils is often difficult to evaluate because many investigators are contented with blood levels, while others may include both tissue and blood values without distinction in discussing results obtained. Most of the explanations of the cause of tissue (local and/or blood) eosinophilia involve hormonal, toxic, or other effects of necrosis (37, 407, 470), or

foreign protein reactions, including anaphalactic, histaminic, hypersensitive or allergic, inflammatory, and other reactions (37, 159, 240, 315, 377, 549). Rogers, 1953, (159) strongly favors the idea that eosinophilia is strong evidence of an " 'ill-defined allergic response' " in the tissues, and suggests that this cell "carries or manufactures histamine" (159).

Lymphopenia

One important condition in which protein catabolism is increased is the lysis of large numbers of small lymphocytes. Many normal and pathological conditions cause concomitant changes in lymphocytes and eosinophils; however, the significance of the parallel effects has not been determined. It is possible that the rapid and extensive lysis of lymphocytes increases the formation of hydrogen peroxide by the aerobic dehydrogenases which act on purines and amino acids and that a factor produced during protein catabolism causes lysis of eosinophils; however, the same, as yet unknown, mechanism that causes the lysis of small lymphocytes may also cause eosinophils to disrupt and release their granules.

The dependence of eosinophilia on protein degradation is shown by the effects of fasting (214, 277), ACTH, and/or cortisone (116, 133, 255, 328, 390, 421, 552); gestation and/or parturition in hamsters (301), in several stocks of mice (234), and in women (332).

A high carbohydrate diet decreases, while a high protein diet increases eosinophils. When fasted dogs were realimentated with an isocaloric protein diet, both capillary resistance and number of eosinophils rapidly returned to normal. Increasing the protein to a high level hastened the return to normalcy, while a diet high in carbohydrate tended to stabilize capillary permeability and eosinophils at the fasting levels (623). Apparently protein as such was not responsible for the increase in eosinophils, for Vartiainen and Apajalahti (603) found during 6 hours after feeding proteins to 24 healthy test subjects that casein (0.5 g/kg body weight) and tyrosine (0.6 g/kg) produced a fall of 33 and 86 per cent, respectively, 4 hours after ingestion, while gelatin (0.5 g/kg) had no effect on blood eosinophil counts. It has been shown that the eosinophil and lymphocyte counts fall in fasting dogs, but rapidly return to normal upon realimentation with high protein but not with high carbohydrate diet (623). Feeding quantities of liver, especially raw calf's liver, increased eosinophils 10 to 74 per cent (480).

A number of observers hold that since eosinophils are credited with playing a part in the "disintegration and removal of protein" (627) the presence of foreign or abnormal protein, such as products of destruction of lymphocytes which Bunting (83) holds are "specifically chemotactic for eosinophils", induces eosinophilia.

Protein leakage, one of several changes in allergical reactions, is considered to occur before infiltration of eosinophils (597). This tenet is supported by numerous

observations which indicate that many, if not all, antiphlogistic agents, such as cortisone and ACTH (520), which cause conditions of increased capillary permeability to return to normalcy, reduce the accompanying eosinophilia.

The fact that eosinophils are not present in unusual numbers at the site of allergic reaction until after hyperemia and consequent protein leakage have appeared (597, 604) indicates that the function of the eosinophil is to combat, rather than cause, the allergic reactions (107, 325, 597, 604, 627). Most observers state that they believe eosinophilia is characteristic of, or related to, allergic disorders (37). However, Vaughn (604) holds that the release of "histamine or some similar toxic substance . . . in abnormal quantities" results in eosinophilia of the blood. He points out that histamine is released during antigen-antibody proteolysis, which is associated with "proteolysis by intracellular trypsins". Many pathological processes, such as post-febrile states, allergic states, cancer, round worm infestations, and many therapeutic reactions have sufficient degree of breakdown of foreign, normal, and abnormal protein in the tissues to "allow release of histamine to be postulated", which he thinks would account for the accompanying eosinophilia (604). Egg albumin, hemoglobin, erythrocyte suspensions, and a mixture of hemoglobin and an erythrocyte suspension repeatedly injected produced a definite increase in blood eosinophils (480). Injection of peptone and protein caused local eosinophilia, but injection of amino acids had no effect (53).

Cortisone and ACTH

Cortisone is a strong eosinopenic and lymphocytopenic agent. Most agents that deplete lymphocytes and lymphoid tissue also deplete eosinophils (116). ACTH has been shown to deplete both eosinophils and lymphocytes (459) through its stimulation of the adrenal cortex to produce adrenal corticosteroids, chiefly cortisone (283), which has a lytic action on lymphocytes. Chronic cortisone treatment definitely depleted the eosinophils, as well as the lymphocytes and lymphoid tissue, in hamsters (116, 305). Thus, it is not surprising that Kovács, 1950, found that blood eosinophils are depleted by administration of adrenal corticosteroids or corticotropin (283).

Peritoneal eosinophils appear to be much less sensitive to the action of certain hormones than circulating eosinophils. Subcutaneous and intraperitoneal injections of cortisone, hydrocortisone, epinephrine, and histamine had little effect on the number of eosinophils in the peritoneum of mice previously pretreated with horse serum, but produced a marked peripheral blood eosinopenia within 3 hours (427). Speirs, 1952, found that administration of cortisone caused morphological changes with cytoplasmic budding and fragmentation of eosinophils in the peritoneum of rats, and these fragments were engulfed by free phagocytes (427).

Ham (297) suggests that cortisone produces eosinopenia by causing these cells to leave the blood vascular system and, presumably, to invade the connective tissues, while Padawer and Gordon (420) state that throughout the period of the developing eosinopenia following injection of cortisone or epinephrine, the peripheral blood contains a marked increase in fragments of eosinophils. Kramar, et al. (328) hold that during cortisone increase (the first phase of stress response is presumably associated with ACTH discharge) capillary resistance rises and the eosinophil level falls in normal and adrenalectomized animals; at withdrawal of the cortisone the capillary resistance drops precipitously, and eosinophilia supervenes.

A group of investigators report that irrespective of the kind of stress or agent used, including cortisone, 3 to 4 hours elapsed before a significant fall in eosinophils occurred in normal animals. Love obtained eosinopenia in adrenalectomized animals within 10 minutes after stress, which apparently was considered due to a non-cortisone, humoral agent (574). Keleman and co-workers (298) found that subcutaneous injection of 500–600 mg/kg of salicylates decreased the eosinophil number 10 to 30 per cent 4 hours later in rats, while others report that sodium salicylate inhibits inflammation in rats (601).

Little is definitely known about the mode of action of agents which destroy eosinophils in vivo. Apparently, the problem with regard to the action of cortical steroids is whether or not the substance acts directly or indirectly on the eosinophils. Some investigators point out the fact that cortical steroids are ineffective in vitro (574), but are effective in vivo, thereby indicating an indirect action (222, 574). Gordon (222) suggests that the results of work by Meuhrcke and co-workers in obtaining eosinopenia in defibrinated human blood in vitro by addition of cortisone and their finding that heparin apparently blocks this action of cortisone are evidence of a direct action of cortisone. However, Speirs circulated cortisone through preparations of the isolated liver and found that the steroids thus obtained had no effect on eosinophils either within the isolated system or within the animal (222).

Since many, if not all, agents which favor production of eosinopenia are antiphlogistics, it may be in order to consider disturbance of glycolysis as a contributing factor in eosinopenia. It has been shown that substances commonly used in treating rheumatism, such as acetylsalicylic acid, adrenocorticotropin (ACTH) monoiodoacetic acid, phlorizin, and salicylic acid, effectively inhibit reduction of triphenyltetrazolium chloride in isolated cornea. From these observations the investigators concluded that the antirheumatic and antiphlogistic effects of these substances are related to their disturbing glycolysis, which is important in development of inflammation, for 'forapin', a phlogistic substance, enhanced the activity of dehydrases in the cornea in situ (322).

Stimulation of protein catabolism was considered one of the properties of "the cortical hormone" by Long, Katzin, and Fry in 1940. Since then, cortisone or ACTH has been found to increase protein catabolism (312, 436) to produce a negative nitrogen balance (275, 358, 482) and to increase purine in the urine (356). Not only does cortisone increase protein catabolism, but it is also believed to decrease protein anabolism. Cortisone has been reported by Skipper, 1951, to inhibit incorporation of labeled formate into RNA and DNA in the viscera of mice (270).

A greater negative nitrogen balance is caused by ACTH and cortisone than by salicylates in children having their second or third attacks of rheumatic fever. However, the serum amino acid-level was increased 2 to 18 hours after injection of 25 mg of cortisone into rabbits (146). Production of lymphopenia and depletion of lymphoid tissues has been considered a source of the protein catabolized by administration of cortisone or ACTH, and Needham (409) supports this idea by stating that lymphoid tissues may furnish the main, if not the entire, source of protein depleted by cortisone. Other investigators (321) have suggested that one specific function of ACTH is mobilization of protein from lymphoid tissue (321). The use of adrenal cortical substance has been considered a sensitive method for mobilization of protein from lymphoid tissue (202). Carbohydrate administration does not modify the mobilization of protein from lymphoid tissue after treatment with ACTH (166). The mechanism by which cortisone and ACTH effect lymphoid depletion has not been determined. Engel (166) asks "Why do certain tissues, such as lymphoid tissue, respond so much more actively in protein metabolism than others?"

Epinephrine

In order to evaluate effects of epinephrine, ACTH, or cortisone on the number of eosinophils in the blood, it is necessary to recognize the counterbalancing, or antagonistic, effects of histamine and epinephrine (238, 490) and the opposite effects of these two substances on eosinophils (490). Injection of histamine stimulates release from the medulla of the adrenal of epinephrine (564), which reduces the number of eosinophils (215), but adrenalectomy in rats increases histamine content in the liver, lung, and gastrointestinal tract (573). Furthermore, ACTH, as well as cortisone, has an ameliorating effect on excessive histamine in allergical reactions (459, 460, 490). It is also necessary to consider that localization of eosinophils in several organs as well as increased lysis or decreased production of the cell (420) can cause eosinopenia. Since fluctuations in the level of circulating eosinophils may result from nonspecific stress, as well as from variations in normal adrenocortical function (215), precautions should be taken in evaluating the significance of changes in the eosinophil level following administration of these substances.

Epinephrine reduces both eosinophils and lymphocytes and may cause an eosinopenia (215), which is not prevented by hypophysectomy and, thereby, not considered to be due to increased ACTH augmenting corticoid production (520). Glaser (212) states that occasionally epinephrine may induce eosinopenia; Broch and Haugen (76) hold that the effects of epinephrine on eosinophil counts are too variable to be used as a reliable clinical test. Tyler, 1950, points out that epinephrine injections produce a transitory peak increase of 50 to 300 per cent in eosinophils, as well as in lymphocytes and polymorphonuclears, in man within about 15 minutes which is missed in counts made an hour after injection (548). Epinephrine also decreased eosinophilia in allergical patients, and in mice and rats infected with Trichina spiralis when adrenals were present; however, epinephrine did not cause eosinopenia in mice pretreated with ascorbic acid but did cause eosinopenia in mice pretreated with saline (24).

Serum from rats previously stressed for four hours by injection of epinephrine reduced the eosinophil count 50 per cent within 30 minutes after injection into normal rats (574). Injections of 50 μg of ACTH produced an average decrease of eosinophils of 87 per cent in mice previously stressed by injection of epinephrine. However, it is admitted that in normal mice mild stress of epinephrine injections produced a great decrease in the number of circulating eosinophils. A temporary rise in eosinophil count sets in after 7 hours of the stress-produced eosinopenia. The fact that injection of adrenal cortical hormones produced eosinopenia proportional to the dosage supports Selye's (520) contention that "the effect of adrenaline upon the eosinophils is mediated by the adrenal cortex". It has also been suggested that epinephrine has a direct but less powerful effect on the adrenal cortex of man than ACTH (64) and that its effects are mediated through rapidly increased production of ACTH (573). Epinephrine is thereby considered by certain investigators to be a type of humoral regulator of ACTH release (212). However, epinephrine is also considered to have a direct effect on causing eosinopenia as indicated by epinephrine causing eosinopenia in hypophysectomized animals (520), and this hormone alone may occasionally induce eosinopenia (212). Patients with hypopituitary activity are unable to secrete ACTH, and usually have a decreased eosinophil count following injections of epinephrine or conditions of stress (573). There is such close relationship between the eosinophil count and hypophysical and/or adrenocortical function that changes produced in the number of eosinophils following administration of either epinephrine or ACTH solution are the basis for tests to determine the presence of hypopituitaryism or hypoadrenocorticism. The procedures, with variations, for making the ACTH-Eosinophil test and the Ephinephrine-Eosinophil test are described by Talbot, Sobel, McArthur, and Crawford (573), and have been adapted to use in pre- and postoperative surgery by Roche, Hills, and Thorn (488).

Dispersion of the peroxidase-containing eosinophil granules may have a func-

tion in inactivating epinephrine. Lysis of eosinophils is a source of increased peroxidase and catalase titer of the blood of rabbits reported by Vacca, one hour after an injection of adrenalin (522). In addition, contraction of the spleen caused by adrenalin (547) increases the number of eosinophils and neutrophils in the blood. Eosinopenia has been reported in splenectomized rats after injection of epinephrine, but changes in neutrophils or lymphocytes were not observed (520).

Peroxidase in the presence of H_2O_2 can oxidize epinephrine, and other amines (249). In vitro experiments have shown that the horseradish peroxidase-H_2O_2 system destroys the pressor action of epinephrine (254) and that epinephrine was oxidized, as was shown by Szent-Györgi (254). Leucocytes of a crab (Cancer pagurus) contain a phenolase, which is capable of catalyzing the oxidation of adrenalin; however, it was reported that active phenolases of this type were not found in animals of any other phylum and, further, that the enzymatic capability of many phenolases to oxidize epinephrine is doubtful since the cytochrome oxidase system can catalyse catechol derivatives (50). Martin (370) also states that in vivo oxidation of epinephrine by phenolases is uncertain.

There are numerous other means of inactivating adrenalin. Blaschko, Richter, and Schlossman (62) describe the activity of an enzyme, adrenaline oxidase, which occurs in the liver, kidney, and intestine. The cytochrome oxidase system can oxidize epinephrine (194) as can polyphenoloxidase. In addition, adrenalin is inactivated by conjugation, which is probably the chief physiological method used by the body (624). Blaschko and Schlossmann (62) state that polyphenol oxidase, cytochrome oxidase, or peroxides in a phosphate buffer at pH 7.3 can inactivate adrenalin and form a red substance that is probably adrenochrome.

Fever

Fever may also increase peroxidase activity by increasing protein catabolism. Pyrexia increases protein catabolism and thus increases utilization of proteins as well as carbohydrates and fats (37). Fever of 1°, which increases basal metabolism 7 per cent, increases the amount of urea, ammonia, and nitrogenous bodies excreted and causes rapid utilization of carbohydrate in the liver and muscle, resulting in a state of inanition with increased metabolism of proteins and fats (90). The cause of the heat is considered to be accelerated oxidation. There is also loss of appetite with diminished food intake, impaired digestion, and excessive catabolism. Tissue protein, especially that of the muscles, is rapidly catabolized, and the nitrogen balance speedily becomes negative (607).

Great increases in extracellular oxidation outside the mitochondrial-cytochrome system may be a cause of pyrexia or excess body temperature. For example, the energy in oxidation of the tricarboxylic cycle to CO_2 and H_2O_2, which occurs in the mitochondrial-cytochrome system, is converted to the formation

of ATP, and stores about 686,000 calories (616). Several groups of investigators (271) estimate that the passage of one pair of electrons forms 3 moles of ATP and that this figure represents conversion of 60–65 per cent of the energy of oxidation to energy in the phosphate bond. Oxidations in fluids or cells where this conversion does not occur would not form ATP, and the energy would be released as heat. Mitochondria occur in granulocytes (46), and these cells might convert energy to ATP within the cytoplasm; however, extracellular oxidations, which occur in body fluids, probably would not convert energy to formation of high energy phosphate bonds. A systematic or extensive increase in extracellular oxidation could, thereby, cause fever. There are other changes produced by fever which may affect the number of eosinophils (520).

Peroxidase from eosinophils and neutrophils, by infiltration and subsequent disintegration in exudates, may also have a function in protein catabolism. Removal of injurious material by phagocytic cells has been attributed to the presence of proteolytic enzymes in these cells (387), and a greater amount of amino acids has been found in pleural fluid in inflamed conditions than occurred in the serum of the dog (387). Thus Menkin's (387) results confirm the observations of other investigators that "proteolysis is very active in exudates" and produces many split products.

Differences in protein catabolism, necrosis, and proteolysis, which occur at the margins and within the stroma of various tumors (305), may also be related to differences in extent of eosinophil infiltration. Eosinophils infiltrate certain uterine carcinomas in great numbers (586), mast cell tumors of the dog and horse and granulomas of the cat (450), neoplasms of the digestive tract (53, 481), and certain bone tumors (179). Kappis, 1907, reported blood eosinophilia of 33.6 to 35.5 per cent and numerous eosinophils infiltrating necrotic areas of a carcinoma of the lung. Others report eosinophilia up to 48.28 per cent for patients with carcinoma of the neck, cervix uteri, colon (481), and other sites.

Whether the tumor stimulates blood eosinophilia or merely attracts these cells from the blood stream so that they infiltrate the tumor is still debated (481). Murray (407) suggests that "the absolute eosinophil count may be a valuable test" to differentiate a malignant from an infectious process. Contrarily, Ringoen (481) states that "malignant tumors rarely produce eosinophilia" while Simon, 1906, holds that "hypereosinophilia is probably more common in carcinoma of the uterus than in any other form of malignancy" (481).

Scarlatina

Increased protein catabolism, which is caused by various factors, may be a factor in the very pronounced eosinophilia usually observed in scarlet fever. Protein catabolism is altered when there is an acute, diffuse glomerular nephritis,

which develops in 84 per cent of the cases of scarlet fever (90). An increase in adrenergic substances, which also increases protein catabolism, has also been found in the blood of 17 of 26 cases. Hypersensitiveness, which has been considered the cause of arthritis due to tissues of the joints being sensitive to a toxic product, would also evoke an eosinophilic response. Another possible cause of eosinophilia may be the increased breakdown of amino acids released following increased activity of plasmin. Group A hemolytic streptococci produces an activator, streptokinase, for plasminogen, the inactive form of the active proteolytic enzyme, plasmin (453), an enzyme which lyses fibrinogen and fibrin (41).

Peroxidase may function in inactivation of the scarlet fever toxin as well as in catalyzing oxidations of purines and amino acids. Scarlet fever toxin is a protein which is stable to the action of trypsin and pepsin and contains amino groups essential for its toxicity (247). Reaction of eosinophils may be important in this relation because granules of eosinophils, which are not digested by tryptase (326), may furnish peroxidase to inactivate the toxin. The inactivation process may be similar to the one described by Pappenheimer, 1948, who holds that the toxin of diptheria is a globulin-like protein which combines readily with iron-porphyrins and that this combination may form a respiratory enzyme (247). Agner (8), after reviewing the literature, states that crude diphtheria toxins are detoxified by peroxidases in the presence of H_2O_2 ; however, under similar conditions, purified toxin was not detoxified. Agner (8) noted that an intermediate product of oxidation of uric acid might react with diphtheria toxin to detoxify it. Hydrogen peroxide, a product of several steps in oxidation of uric acid (592), might be this intermediate agent. In addition, peroxidase in the presence of hydrogen peroxide inactivated Rh-antibodies in serum in vitro (610).

Foreign Protein Reaction

Anaphylaxis is another condition in which eosinophilia (501) and a rapid increased protein catabolism occur. Bronfenbrenner, 1944, considered that anaphylaxis was due to activation of serum tryptase (597). Bergmann and Fruton, 1941, found that the peptide linkages containing the carboxyl group of either arginine or lysine are acted upon by trypsin, while chymotrypsin acts on "peptide linkages involving the carboxyl group of tyrosine and phenylalanine" (249). Trypsin is considered to act more rapidly on the ester linkage —CO—OR than on the peptide linkage and requires —NH —CHR′ —CO— part of a molecule which must be derived from a diaminomonocarboxylic acids (arginine, lysine) or from norleucine and histidine (335). Cathepsin II, which is homospecific with trypsin (335), requires that basic sidechains of arginine and histidine for action (247).

Increased histamine increases extracellular protein catabolism through increasing capillary permeability. The eosinophilia which occurs after the bite of the

black widow spider (224, 326) has been related to histamine release since urticaria is one of the symptoms (378) but it may also be a response to direct or indirect effects on the six proteins of the venom (403) or to lytic effect of venom on plasma or other proteins. Eosinophilia is also caused by injecting the toxin of the flannel moth (Megalopyge urens Berg) into rabbits (375).

Mechanical stimulation of a lesion of urticaria pigmentosa incited eosinophilia (450). The release of histamine from greatly increased numbers of mast cells in the skin in urticaria pigmentosa may be the cause of eosinophilia observed in this condition and also the cause of eosinophilia in eosinophilic granulomas. An increase in histamine was reported by Macdonald in four cases of eosinophilia (458). Mast cells, which are abundant in eosinophilic granuloma (450), are considered an ideal condition for the development of marked tissue eosinophilia (450). Horseradish peroxidase in the presence of H_2O_2 partly destroys the irritating properties of poison ivy allergents (97). Peroxidase has also been considered to inactivate RH-antibodies (610).

Parasites

There are several direct and indirect causes of decomposition of protein in parasitic infestations. Thus, not only the parasite, but other effects of the infestation, such as hemorrhage, infiltration and necrosis of leukocytes, and fever increase extracellular protein catabolism.

Eosinophilia occurs in the later stages in most parasitic infestations by intestinal worms, amebiasis, filariasis, and trichaniasis, especially after cyst-formation in the muscles (56), in infestations of the lung by mites of the genus Tyroglyphus (37), and by the larvae of Ascaris (324) which pass into pulmonary alveoli. Eosinophilia in infestations may be as high as 80 per cent eosinophils of the total number of leukocytes and is also accompanied by an increase in the other white cells (224). In echinoccocus disease the eosinophils often reach 50 per cent of the white count, while in trichinosis they may reach an absolute count of 15,000 per mm^3 and may represent as much as 85 per cent of the white count (627).

Protein decomposed by necrosis is probably one of the most important stimuli for the local tissue eosinophilia in some parasitic infestations around living microfilaria in the ciliary body, vitreous or optic nerve. Death of the parasites or of only a segment of a single worm, produces a granulomatous reaction which, in some cases, becomes necrotic, and eosinophils form compact masses around the dead part (324). Necrosis of the muscle around some parasites (4), such as trichina larvae, is a contributing factor for eosinophilic infiltrations.

Several other pathological changes produced by parasites alter protein metabolism. Formation of a lymph thrombus, induced by the adult worm or debris (in filiariasis) or disintegration of the parasite (324), produces edema, with eo-

sinophils and other leukocytes infiltrating the focalized regions of edema and necrosis in the retina and in the lesions of infantile toxoplasmic retino-chloroiditis (320). Hemorrhage and leukocytic infiltrations also augment the foreign protein reaction in migration of Ascaris larvae into the lung, a process that causes fever, hemorrhages and broncho-pneumonic areas, and sometimes eosinophilia (625).

Increases in extracellular fluids are produced by parasites. The blister found in dracunuliasis is believed to appear when the Guinea worm's head reaches the epidermis (324). It is believed that an increased protein destruction is causally related to the profound systemic symptoms which precede the appearance of local hyperemia and small, red papules by some 24 hours, by the formation of the characteristic 2 to 7 cm blister beneath which the head of the worm lies, and through the small necrotic center of which the blister fluid containing serum, fluid excreted by the worm, lymphocytes, plasmacytes, and many eosinophils exudes. The subcutaneous, fibroblastic sheath in which the female worm lies is surrounded by a zone densely infiltrated with eosinophils, lymphocytes, and plasmacytes (324). The 4 to 5 cm Calabar, or fugitive, swellings which develop in the body skin during the course of loliasis, or infection by the loa loa, or 'eye worm', is usually accompanied by "a high peripheral eosinophilia" (324). The death of an eye worm (in loaiasis) causes abscess formations infected by bacteria, a condition that further augments extracellular protein catabolism (324).

A high local and/or peripheral eosinophilia apparently is characteristic of infestation by worms, especially round worms, and is generally conceded to be a response to putrefactive processes occasioned by death of the worm, to fluid excreted by the parasites, and/or the allergic or necrotic reaction caused in the surrounding tissues. Oxidation changes might also be a causative factor for eosinophilic changes in several parasitic infestations. For example, Wharton (618) reports on the occurrence and relations of hemoglobin in several worms in the turtle. He shows that certain parasites living free in the blood stream, such as Cruzia testudinis and Falcaustra affinis, lack hemoglobin, while others which merely have contact with the blood stream, such as Allassostoma magnum, Camallanus trispinosus and Telorchis robustus, have Hb, which has a greater affinity for oxygen than that of the host. If eosinophils have a function in furnishing peroxidase, the granules may function in catalyzing peroxidatic reactions of the parasite, as well as of the host; for example, H_2O_2 produced by diamino acid oxidase may be used in the presence of peroxidase to oxidize a substrate of the parasite.

Eosinophilia in infiltration by Ascaris and other parasites has been attributed to a hypersensitive response to keratin, which causes hypersensitivity in the host (88), because they are retained in the body after antibodies form. Keratin is a fibrous protein characterized by its high content of lysine, arginine, and histidine

(435). Differences in response of eosinophils to various groups of amino acids are indicated in the report of Harris and Lange (244) who found that only the dicarboxylic amino acids decrease eosinophils in normal animals.

X Irradiation

Results of using several types of the so-called protective measures against X irradiation suggest that granulocytes may be an important factor in postirradiation recovery (112). Bone marrow, blood, spleen, and other tissues which have protective or ameliorating effects against irradiation sickness are the tissues in which eosinophils, neutrophils, and platelets are formed or stored.

The peroxidase-containing cells appear to be important in recovery from exposure to irradiation. Peroxidase has been reported to be absent in the marrow of leg bones of dogs and rabbits at, or near, death resulting from neutron radiation (631), whereas catalase activity in the rabbits was not affected, but was decreased in the irradiated dogs. That heterophils are important in postirradiation recovery was fairly conclusively demonstrated by experiments in which lethally irradiated rats were joined in parabiosis with nonirradiated rats. This series of experiments showed that depleting the heterophil leukocytes in the nonirradiated partner, by intravenous injection with myleran (20 mg/kg), resulted in all the irradiated partners (700 r) dying, whereas 60 per cent of the lethally irradiated parabionts which were joined to nonirradiated partners survived (509). Jacobson (278) summarized the facts indicating that humoral factors are active in the protective measures, such as spleen-shielding, intraperitoneal implantation of splenic tissue and suspensions of embryos, or intraperitoneal or intravenous injection of homologous bone marrow suspensions, and related techniques.

Ting and Zirkle, 1940, hold that leukocytes are radioresistant in contrast to mature lymphoid cells which are very radiosensitive (287). Cells in the erythrocytic series are also considered by Bloom and Bloom, 1947, to be more sensitive to irradiation than those in the leukocytic series (46). The presence of peroxidase may account for the greater resistance of granulocytes to irradiation. Mature granulocytes are quite resistant and are not directly affected by irradiation in any except excessive doses (433).

Many conditions, such as dosage and extent of X irradiation, time after irradiation, and presence or absence of infection, alter the number of neutrophils and eosinophils in the blood. It is not possible, therefore, to determine definitely the significance of peroxidase granules in relation to H_2O_2 production. George and Irvine (204) consider that the reaction of peroxidase, catalase, and other hemoproteins with peroxides suggests interesting connections with problems in ionizing radiation. Other investigators hold that the protective mechanism may involve removal of free radicals and inhibition of enzyme activity (12), which Dale, 1940,

has attributed to radiation products of water (32). However, Woodward (631) observed that peroxide was not present in the bone marrow of animals which were near death or died following neutron irradiation, and that peroxidase was much greater in the bone marrow of normal animals.

Peroxidase in the cytoplasm of the neutrophils and eosinophils in the bone marrow, spleen, and blood may have a beneficial effect in catalyzing oxidations utilizing H_2O_2 formed following irradiation. It has been suggested that formation of H_2O_2 is the most important of the primary reactions of X irradiation (67), and it is held to be an important factor in X ray toxicity (67, 185). Philpot, 1956, points out that organic peroxides as well as hydrogen peroxide are produced in cells by irradiation (22, 566); however, Horgan and Philpot (267) state that Dubouloz, Dumas, and Vigne, 1950, and Dubouloz and Dumas, 1952, are the only investigators who have found organic peroxides in irradiated animals. Barron (32) apparently holds that the H_2O_2 produced in animals by X irradiation results from its ionic effects on oxygen-saturated tissue water, for he found that X irradiation in the absence of O_2 failed to produce any H_2O_2 under controlled conditions. Radiation-produced H_2O_2 is a most effective agent in inhibiting tissue metabolism (32), and production of free hyperperoxide radicals HO_2 results in excessive oxidations not due solely to H_2O_2 (566).

X irradiation has been considered to cause formation of H_2O_2 directly and indirectly. Allen, 1948, proposed that X irradiation of water resulted in formation of hydrogen and hydrogen peroxide molecules and also in formation of hydrogen and hydroxyl radicals, which could convert the H_2 and H_2O_2 molecules back to water (126). Bonet-Maury and Lefort, 1950, reported that the amount of oxygen dissolved in water, in addition to the amount of X irradiation, temperature, pH, and electrolytes, determines the amount of hydrogen peroxide formed by irradiation (32). Formation of H_2O_2 was considered to have little effect on biological systems because addition of electrolytes, protein or Fe^{++} ions significantly decreased the amount of H_2O_2 formed by X irradiation of water (34). However, Dainton (126) states that the presence of highly reactive solutes, such as Fe^{++} in high concentrations, is not likely to cause great reduction in the yield of H_2 and H_2O_2.

Many of the methods of protection against irradiation are directed against decreasing H_2O_2 or its detrimental effects. Jolly, 1924, showed that ischemia reduced the effect of irradiation (46). Formation of peroxide after irradiation has been considered a harmless means of dissipating energy absorbed from radiation (310). Irradiation at low oxygen tension inhibited the reduction in number of cells and of DNA synthesis in bone marrow (456) and thus had a protective property in the rat. Absence of oxygen in irradiated water has been shown by Patt and Brues, 1954, to prevent formation of H_2O_2 (32, 265). Anoxia has also been

reported to protect mice against some of the injurious effects of radiation (205) and against death of cells as indicated by pycnosis of small lymphocytes (124). The protective effects of p-aminopropiophenone (PAPP), which reduces the mortality rate in irradiated mice and rats, is attributed to hypoxia resulting from methemoglobinemia formed by preirradiation administration of PAPP (124). The protective effects of preirradiation injections of serotonin into rats receiving total body X irradiation has also been attributed to temporary tissue anoxia (228). Attempts to decrease cellular oxidations by action of thiouracil on the thyroid and thereby inhibit effects of irradiation were unsuccessful (67).

Shielding

The mechanism by which shielding hematopoietic tissue or injecting hematopoietic tissue affords protection for animals receiving lethal dosage of irradiation has not been determined. Peroxidase occurs in neutrophils, eosinophils and their stem cells, and in blood platelets. Imprints of bone marrow, blood, spleen, liver, lymph nodes, pancreas, kidney, adrenal, and testis of normal, adult hamsters were stained by Graham's oxidase method. The only tissues in which significant quantities of peroxidase occurred were the bone marrow and spleen. The localization of peroxidase in these tissues occurred in leukocytes and platelets and to a very small extent in cytoplasm of the megakaryocytes. Furthermore, the sparse peroxidase granules detected in other tissues occurred in the leukocytes. The amount of peroxidase in the spleen of adult hamsters was increased under the conditions of extramedullary hematopoiesis induced by implanted tumors or by pregnancy (301, 302, 305).

The protective effect of shielding the spleen of irradiated mice has been attributed to preservation of its hematopoietic function (463). A single intraperitoneal injection of a spleen-homogenate, representing the equivalent of 1 to 2 spleens, administered 1 to 45 hours after irradiation decreased mortality of adult mice exposed to total body X irradiation of 650, 700, and 800 r. The protective factor was more abundant in the spleen of mice 1 to 3 weeks old than of adult mice (110). One group of investigators reported that implantation of fresh spleen increased survival in mice after 1,025 r of X irradiation (281); other investigators reported that they obtained negative results by implantation of fresh spleen (67); still another group found that postirradiation injection of spleen homogenate (1–45 hours) as a single, intraperitoneal dose decreased loss in weight of mice (110).

The greater number of eosinophils and neutrophils in the spleen than in the thymus and lymph nodes may explain the greater radioresistance of the spleen reported by Warren and Dunlap, 1942 (495). In addition, part of the beneficial effect of spleen shielding may be due to increasing resistance against infection, for it was noted that resistance to experimental infection with Pseudomonas was

related to leukocyte count in irradiated mice and that the association "depends upon granulocyte count with no measurable lymphocyte contribution" (544) Thus, either granulocytes or specific constituents of the recovery more closely linked with granulocytic than with lymphocytic recovery were held to be responsible for the observed association. This indicated that the recovery factor was linked to granulocytic recovery rather than to lymphocytic (544). Other investigators, using low dosage (25–100 r) of X irradiation of dogs, support this idea by suggesting that under conditions of their experiments total body irradiation leads to maturation of white cells in the bone marrow with subsequent release of "band neutrophils into the peripheral blood stream" (455). It has been suggested that megakaryocytes play an important part in recovery since injection of lethally irradiated mice with rat bone marrow is followed by the appearance and persistence of rat platelets in the peripheral blood of the mice (543) Campbell and Ross (89) injected lymphocytes into irradiated rats and concluded that the protection afforded by Jacobson's method of shielding the spleen "is probably due to a substance related to another cell", or, possibly, it may be that the transfused lymphocytes, though motile for some time, were fatally injured or that those obtained from the mesenteric ducts differ from splenic lymphocytes.

Injection of bone marrow from mice into inbred and hybrid mice and into guinea pigs induced an immediate protective effect on these animals, and the homologous bone marrow grew luxuriantly in the omentum following intraperitoneal or intravenous injection (355). It was suggested that the mode of protection afforded by injection of the heterologous bone marrow was humoral, or non-cellular, while the superior protection produced by the homologous marrow was the result of summated humoral and a cellular factor (355), but these investigators did not suggest how these factors hastened recovery. Lorenz and Congdon (354) obtained comparable results by transplanting cleaned, marrow-free bone of rats and mice intraperitoneally into mice. The homologous bone transplants produced marrow but the heterologous grafts did not; however, both types of bone transplantation protected mice from lethal X irradiation.

Shielding ectopically induced marrow has been shown to increase survival from exposure to total body X irradiation of 650 r, but shielding the in situ fatty marrow did not increase survival (560). However, Simmons, et al. (532) noted that daily injections of yellow bone marrow (Armour's preparation) into non-irradiated rabbits increased the initial rise in leucocyte, heterophil, and lymphocyte count up to 16 days, after which the count fell to below that of normal, non-irradiated control animals. In other work with rabbits, daily injection of yellow bone marrow up to 6 days prior to 600 r exposure and during 14 days postirradiation did not deter the postirradiation fall in heterophil count (532). Other investigators apparently (543) attribute the beneficial results of injecting rat bone

marrow into lethally irradiated mice to the appearance of rat blood platelets and their persistence in the peripheral blood of the mice.

The effect of bone marrow transplant differs in several species of mammals. Reckers, et al., 1949, 1950, reported that transplants of bone marrow do not alter recovery in dogs; and Talbot and Pinson, 1951, in rats (433). However, if rats have a small area of the intestine shielded by applying a lead belt $\frac{1}{8}$ inch wide or shielding the exteriorized intestine with sheet lead and are then intravenously injected with 30 mg of bone marrow per 100 gm of body weight, their tolerance is trebled over the effect of shielding intestine alone (572). Intravenous or intraperitoneal administration of bone marrow into guinea pigs and mice has a protective effect, as Lorenz, et al., 1951, 1952, have shown (433). Intravenous injections of bone marrow emulsion or of its supernatant fraction into rabbits 3 days after exposure to total body X irradiation of 1200 r increased 30-day survival from 20 to 60 per cent (259). Mice are protected from effects of irradiation by implants of rat bone marrow, but do not form bone marrow (354). Isologous bone marrow cells after being incubated at 25 C for 24 days also prevented death in a lethally irradiated strain of mice (54).

Protection or injection of bone marrow apparently has some beneficial effect on lymphoid tissue because shielding red bone marrow or intravenously injecting "normal isologous marrow cells" strikingly inhibits production of lymphoid tumors in mice (296). The factor in bone marrow which is responsible for thymic regeneration apparently is strain-specific in action, for shielding the thigh of several strains of mice during total irradiation or injection of isologous bone marrow consistently increased regeneration of the thymus, whereas heterologous or homologous marrow was ineffective (261). In evaluating effects on the thymus, it is necessary to recognize whether the gonads are functioning or have been permanently damaged. The thymus of hamsters that survived 18 to 30 days after 995 r was considerably larger than that of normal hamsters of the same age and sex. The absence of spermatogenesis in the testis would be expected to cause hypertrophy of the thymus in view of the function of the thymus being a DNA-histone storage organ until the gonads function. The greater increase in lymphocytopoiesis and of nucleoprotein synthesis and storage in the thymus of irradiated animals which had non-functioning gonads might be related to development of lymphoid leukemia (305).

X irradiation affects the number of leukocytes in the blood. It is necessary to recognize that initial effects of irradiation are not the same as later effects and that the stimuli which evoke a transient (prolonged and extensive) leukocytosis can also cause depletion of bone marrow. Various changes in leukocytes have been reported after irradiation. Lawrence and co-workers found an increase in eosinophils for part of the first 48 hours after 300 r total-body X irradiation of

dogs (123). Aubertin and Beaujard, 1908, also reported an increase in eosinophils after irradiation (279). Leukocytosis following exposure of rabbits to 500 r or more of X irradiation is due entirely to increased numbers of heterophils (280).

An initial leukocytosis followed by leukopenia has been reported in man (280, 516), in rats (163) and other animals after total body X irradiation over 100 r. Patt and Brues (433) state that the heterophils or granulocytes are the only circulating cells which were initially increased numerically and that eosinophils, as well as the lymphocytes, monocytes, reticulocytes, and platelets, were invariably reduced after acute X irradiation. Relation of various types of irradiation dosage and of acute and accumulative chronic poisonings of several mammals has been thoroughly summarized (10). Neutropenia, as well as decreases in other bone marrow derivatives, is due to the destruction of bone marrow that follows various forms of irradiation (163, 497).

Several explanations for the beneficial effects of protecting and promoting resumption of hematopoiesis after irradiation are given. The beneficial effect of spleen and bone marrow cells injected into irradiated mice and hamsters has been attributed to the promotion of early recovery of the granulocytes (368), while the beneficial effect of parabiosis in irradiated leucopenic rats with a nonirradiated parabiont has been attributed to the passage of blood cells from the nonirradiated partner across capillary anastomoses (391). Granulocytes transfused into irradiated dogs having aplastic bone marrow migrated to infection sites (73). Some of the beneficial effects of sulfhydryl compounds have been attributed to protection of blood granulocytes and their precursors in the bone marrow (124). Protection obtained by injecting chemicals is attributed to the protection "afforded the bone marrow count" as shown by the rapid recovery of the bone marrow counts in mice exposed to as much as 900 r of X irradiation (598).

The blood eosinophilia following irradiation may also be a response to increased protein catabolism produced by lysis of small lymphocytes. As early as 1907, Edsall and Pemberton considered the toxic reaction of lysis of tissue as a cause of clinical radiation sickness (433). Lymphocytes, which are considered one of the most, if not *the* most, sensitive cells to irradiation (65, 123, 280, 433, 582, 627) disintegrate very rapidly. Barrow and Tullis (35) reported fragmentation and lysis of lymphoid cells one hour after irradiation and Cramer, Drew, and Mottram (121) state that the first change after exposure to X rays was a decrease in the circulating leukocytes. Released histamine and other substances or formation of products from cytolyzed lymphocytes might be a cause for the initial eosinophilia. X irradiation does not cause extensive lysis of plasmacytes as it does of lymphocytes. Part of the difference may be due to the greater amount of RNA in the cytoplasm of these cells, and to a protective effect on the inhibitor or a deterrent effect of RNAase because H_2O_2 and oxidized glutathione have been

reported to inhibit activity of RNAase (338). Campbell and Ross (89) injected lymphocytes of rats made lymphopenic by X rays and found that there were fewer neutrophils in the lymph-injected group. If some of these lymphocytes and the protein in the injected lymph underwent lysis, the amount of extracellular H_2O_2 would be increased, and if this provoked release of peroxidase granules from neutrophils, neutropenia would be an expected result rather than a seeming discrepancy.

Stimulation of hematopoiesis by several methods has beneficial effects on irradiation sickness. Pentnucleotide in 5.0 ml doses administered after irradiation caused higher leukocyte counts on the third day in rabbits, but daily injection of 5.0 ml during 14 days preceding exposure to 600 r had no beneficial effect although lymphocytes were increased 5 to 9 days after irradiation (532). Preirradiation stimulation of hematopoiesis with estrogens increased recovery of granulocytopenia in irradiated mice (433). The beneficial effects of glutathione has been considered to be due to protection of the control mechanism for hematopoiesis (124); however, stimulation of erythropoiesis by feeding a cobalt supplemental diet has not been found beneficial and has been considered detrimental to recovery when given in polycythenic doses (113). Apparently stimulation of erythropoiesis by cobalt may not be due directly to cobalt ions, but to stimulation of the formation of erythropoietin and does not increase leukopoiesis (218). There are several possible "delayed" causes of irradiation sickness that pertain to formation of peroxides. Autoxidation of unsaturated fatty acid chains after X irradiation causes formation of H_2O_2, which develops more rapidly after irradiation because of the destruction of antioxidants (243). The ameliorating effects of azide and cyanide has been attributed to inhibition of catalase which may form a catalase-inhibitor complex that is more stable to effects of radiation than uncomplexed catalase (184). Resistance of bacteria to irradiation is increased by catalase, which, however, loses its effect in the presence of formate (103).

Various explanations of the mechanism for the beneficial effects of compounds containing SH groups have been given. However, most of these means counteract effects of oxidative changes. Reactivation of enzymes containing SH groups in the protein moiety has been considered the mechanism for the beneficial effect of glutathione administered after small or moderate amounts of X ray dosage (33). Preradiation treatment with glutathione has also been reported to increase survival time (196). Barron (32) strongly supports these findings by stating that addition of glutathione gives "complete protection of the enzyme". Preirradiation injections of mice with cysteamine or cystamine mitigated the lethal effects of 1100 r total-body X irradiation, and this protective effect was increased in mice rendered hypoxic before and during the irradiation (135). Other investigators (432) found that addition of cysteine to a suspension of rabbit thymocytes de-

creased the sensitivity of these cells to X rays over a wide range of dosage. When the thymocytes were packed in vitro, cysteine failed to protect them, and this failure is suggested as being a consequence of hypoxia resulting from competition with the cell substrate for oxygen. Later, it was found that cysteinamine is 5 times as effective as cysteine when equimolar amounts are administered intravenously prior to X irradiation (561). Formation of a temporary disulfide linkage, which is more resistant to ionizing radiation than the "unprotected" sulfhydral group, can be restored by normal processes and is considered to be the protective mechanism of cystamine (352). A single intravenous injection of cysteins (950 mg/kg) 5 minutes prior to total body X irradiation (88 r) decreased the effects on the hematopoietic system and hastened recovery in rats (434), as well as decreasing other lethal effects (541). Preirradiation addition of cysteine in vitro also inhibited the expected decrease in viscosity of alkaline solutions of nucleoproteins subjected to X radiation (191).

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