Alteration of Prostaglandin Biosynthesis in Rat Chloroleukemic Tumor

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SUMMARY

Data from our present studies demonstrate the capability of a 105,000 × g pellet from rat normal bone marrow, turpentine-induced hyperplastic bone marrow, and chloroma tumor to transform precursor arachidonic acid into prostaglandins. The activity of the prostaglandin synthetase systems in these tissues is inhibited by the known nonsteroid antiinflammatory drug indomethacin and by two unsaturated fatty acids previously demonstrated in other tissues. Although the overall biosynthesis of prostaglandin E₂ (PGE₂) was higher in the hyperplastic bone marrow than in the chloroma tumor, the PGF₂α:PGE₂ ratio was markedly higher (8-fold) in the chloroma tissue. This latter increase was probably due to the increased transformation of PGE₂ into PGF₂α by the NADPH-dependent PGE₂-9-ketoreductase (an enzyme that catalyzes the transformation of PGE₂ and PGF₂α). These results indicate the greater capability of the malignant chloroma tissue to form PGF₂α than of nonmalignant hyperplastic bone marrow. Although the role of PGF₂α in the malignant myelogenous leukemic tumor is presently unclear, its increased formation in this tissue suggests that this substance may play a role in the hyperproliferative process.

INTRODUCTION

In recent years the study of prostaglandins has added another dimension to the physiology of tumors. They have been implicated in various aspects of tumor growth including cell replication. In several instances symptoms associated with tumors are thought to be due to an overproduction of prostaglandins. In 1968 William et al. (20) reported elevated levels of prostaglandins in tumor tissues and in plasma patients with medullary carcinoma of the thyroid. Since then, several investigators (2–4, 8, 9, 14, 27) have either confirmed or shown the presence of large amounts of prostaglandins in a variety of other human and animal carcinomas. Furthermore, experiments with mouse fibrosarcoma and Walker carcinoma have contributed significantly to understanding of the role of prostaglandins in the hypercalcemia of neoplastic disease (10, 16, 17). Results from these studies have important clinical implications. Despite these observations the role of prostaglandins in cellular differentiation and neoplasia is still unclear. Nonetheless, it seems that alterations in the biosynthesis and metabolism of prostaglandins could be a function of increased proliferative activity per se or a property associated with the neoplastic process. To examine these possibilities we have used, as an experimental model, rat chloroma, a transplantable tumor composed of immature granulocytes. As an actively proliferating control tissue, we used granuloid hyperplastic rat bone marrow, which is also composed of immature granulocytes, predominantly myeloblasts, promyelocytes, and myelocytes. This report describes the in vitro biosynthesis of PGE₂* and PGF₂α from arachidonic acid by 105,000 × g preparations from these tissues.

MATERIALS AND METHODS

Materials. [1-14C]Arachidonic acid (58.0 mCi/mmole) and [3H]PGE₂ (125 Ci/mmole) were purchased from New England Nuclear, Boston, Mass. Radiopurity for arachidonic acid was ascertained after a portion of this material was methylated with diazomethane, and the methyl ester was chromatographed on a thin-layer (TLC) plate coated with AgNO₃-impregnated Silica Gel G. Approximately 95% of the chromatographed ¹⁴C was found to have the retention time of methyl arachidonate. Radiopurity for PGE₂ was ascertained by TLC in the solvent system chloroform:methanol:acetic acid:water (90:8.5:1:0.65). Seventy to 80% of the chromatographed ³H was found to have similar chromatographic mobility as authentic PGE₂. Authentic PGE₂ and PGF₂α were gifts from Dr. Udo Axen of The Upjohn Co., Kalamazoo, Mich. The fatty acids (99%) were obtained from Lipid Organic Research, Elysian, Minn. Indomethacin was a gift from Merck Sharp and Dohme Research Laboratories, Rahway, N. J. Turpentine was U.S.P. grade. NADPH was purchased from Sigma Chemical Co., St. Louis, Mo. Sephadex (G-25; coarse) was purchased from Pharmacia Fine Chemicals, Inc., Piscataway, N. J. Reagents were of analytical grade, and solvents were redistilled before use.

Methods. The chloroleukemic tumors used in these stud-

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4 The abbreviations used are: PGE₂, prostaglandin E₂; PGF₂α, prostaglandin F₂α; TLC, thin-layer chromatography; PGB₂, prostaglandin B₂; PGE₁, prostaglandin D₁.
ies were produced in newborn Sprague-Dawley rats by the injection of chloroma cells (1 × 10⁶ cells/rat s.c.) maintained in culture (Mia C51) as described by Yunis et al. (21). The tumors used in these experiments were fresh 1-cm tumors with no evidence of necrotic areas. This type of tumor has been studied and characterized by Yunis and Gentry (22).

Intense bone marrow granuloid hyperplasia was induced in Sprague-Dawley rats by the s.c. injection of 2 ml of turpentine in the dorsolumbar region as reported by Murray and Connell (12). The rats were sacrificed, and their marrow was harvested 48 to 72 hr after injection.

Preparation and Incubation of 105,000 × g Fractions from Normal and Hyperplastic Bone Marrows and Chloroma Tissue. Fresh bone marrow and chlora tumor specimens were homogenized in 4 volumes of ice-cooled 0.1 M potassium phosphate, pH 7.4, in an ice bath with a motor-driven glass homogenizer. The low-speed pellet and cellular debris were removed by centrifugation of the homogenate at 800 × g for 15 min. The supernatant fluid was first centrifuged at 12,000 × g for 15 min to give the intermediate pellet fraction, and the resultant supernatant fluid was centrifuged at 105,000 × g for 60 min to give the crude 105,000 × g particulate fraction. This final high-speed pellet was rinsed with buffer, resuspended in the same buffer, and stored in ice for incubations. The protein contents of 105,000 × g pellets from hyperplastic bone marrow and chlora tumor tissues were determined by the method of Lowry et al. (11) with bovine serum albumin as standard.

The procedure for the study of PGE₂ biosynthesis in human skin reported previously (23) was used. [1-¹⁴C]Arachidonic acid (0.2 μCi; 5 pmoles) was dissolved in benzene first and then was added to the incubation flask. The solvent was then evaporated to dryness by a stream of nitrogen. To the flask was added hydroquinone (0.55 mM) in buffer, and the flask was shaken in a vortex mixer as described previously (23). The reaction was initiated by the addition of 2 ml of the suspension of the 105,000 × g pellet in 0.1 M phosphate buffer, pH 7.4, to the incubation medium. In preliminary experiments the mixture was incubated aerobically with shaking at 37°C for 5, 15, 30, and 60 min, respectively. Since maximal transformation of arachidonic acid into prostaglandins was attained at 15 min, all subsequent incubations were carried out for this time period. Control experiments were incubated with 2 ml of a suspension of the 105,000 × g pellet, which had been boiled for 15 min. The incubations were stopped by the addition of 5 ml of chloroform:methanol (2:1, v/v) to each flask. This procedure has been shown in previous prostaglandin biosynthetic studies in our laboratory (23) to stop the enzymatic transformation of arachidonic acid into prostaglandins. The suspension was transferred into a separator flask and extracted twice with 25 ml of the same solvent mixture. The combined extracts were evaporated to dryness in a rotary evaporator. The residue was dissolved in a small volume of chloroform:methanol (1:1, v/v) and subjected to TLC on Silica Gel G thin-layer plates.

TLC and Determination of Prostaglandins. TLC on Silica Gel G was performed according to Nuyten and Hazenhof (13). Thin layers of Silica Gel G were prepared on glass plates and activated at 110°C for 30 min before use. The ¹⁴C extract was applied to the activated plate. Small amounts of reference PGE₂ and PGF₂α were applied to another activated plate. Both plates were developed simultaneously in the solvent system diethyl ether:methanol:acetic acid (90:1:2). The plate containing authentic reference standards of PGE₂ and PGF₂α was placed in a tank of iodine vapor to visualize these prostaglandins. This plate was placed beside the plate containing the ¹⁴C extract, the silica gel that corresponded with the reference PGE₂ and PGF₂α was scraped into a sintered glass funnel, and the ¹⁴C was eluted with chloroform:methanol (1:1). Aliquots of the eluates were assayed for radioactivity with a Packard Tri-Carb Model 2002 liquid scintillation counter as reported previously (23). The remaining portions of the eluent were evaporated to dryness under a stream of nitrogen for further identification. The above TLC system is effective for the separation of ¹⁴C primary prostaglandins from [1-¹⁴C]arachidonic acid and other radioactive polar and neutral lipid products.

For further identification of PGE₂ and more efficient separation from PGF₂α, reference PGE₂ and PGF₂α were treated with 3 ml of 0.5 N NaOH in 50% aqueous ethanol at room temperature for 30 min as reported previously (23). Under these conditions, prostaglandin E's form products containing the Δ⁹(11)-5-keto chromophore by elimination of the 11-hydroxy group and isomerization of the resulting double bond. The sample was diluted with H₂O and then acidified with 6 N HCl to pH 2 to 3. The acidified extract was extracted 3 times with 10 ml of dichloromethane, and the combined extracts were evaporated to dryness under nitrogen. The sample was dissolved in a minimum amount of chloroform:methanol (1:1) and applied to activated Silica Gel G plates. The plates were then developed in the solvent system ether:acetic acid (100:2). After the PGB₂ and PGF₂α were visualized in iodine vapor, the areas of silica gel corresponding to each of the 2 prostaglandins were scraped at 0.5-cm portions into scintillation vials. The radioactivity was determined in toluene containing 0.4% PPO with a Packard Tri-Carb Model 2002 liquid scintillation counter.

Estimation of Prostaglandins E and F by Gas-Liquid Chromatography with Electron Capture Detection. Specimens from normal bone marrow, hyperplastic bone marrow, and chloroma tumor were removed rapidly and dropped immediately into vials containing chloroform:methanol (2:1) (25) to stop enzymatic release of precursor fatty acid and synthesis of prostaglandins. The tissues were homogenized in chloroform:methanol with a motor-driven glass homogenizer at 4°C. An aliquot of the homogenate was dried under N₂. The residue was dissolved in 1 N NaOH, and the solution was used for protein assay according to the method of Lowry et al. (11) with bovine serum as standard. The remaining extract was filtered and rinsed on a sintered glass funnel to remove tissue debris. The filtrate was evaporated to dryness in a rotary evaporator. The residue containing total lipids was dissolved in a small volume of chloroform:methanol (1:1) and subjected to TLC on Silica Gel G in the solvent system diethyl ether:methanol:acetic acid (90:1:2). In this system, prostaglandins E and F effectively separate from the other lipids.
Authentic samples of prostaglandins E and F were carried through the entire procedure. Recovery of prostaglandins was greater than 95%.

Methyl esters of PGE\textsubscript{2} and PGF\textsubscript{2\alpha} were prepared by treatment of both fractions with ethereal diazomethane solution at room temperature for 30 min. The O-methoxime derivatives were produced by reacting the methyl esters with 100 \(\mu\)l of pyridine containing methoxime hydrochloride overnight at room temperature according to Green (7). The O-methoxime methyl esters were dissolved in bis(trimethylsilyl)acetamide for 3 hr to form the methoxime trimethylsilyl derivatives of methyl esters of prostaglandins E and F. Reference PGE\textsubscript{2} and PGF\textsubscript{2\alpha} were treated similarly as described above for identification and quantitative comparison. Standard curve of the reference prostaglandin derivatives was obtained and used to estimate the amounts in the tissue samples. Aliquots of the samples were injected into a Hewlett-Packard 5730A gas chromatograph equipped with a \(^{63}\)Ni ED detector and connected to a HP 3380A integrator. The column used in these experiments was a coiled glass column [6 ft long x 0.25 inch (internal diameter)] packed with 1\% SE 30 on 100 to 120 mesh Supelcoport. The carrier gas was nitrogen. Column temperature and chromatographic runs were as reported by Green (7). Quantitation was by comparison of integrated peak areas of tissue samples with authentic prostaglandin standards.

**Conversion of PGE\textsubscript{2} into PGF\textsubscript{2\alpha} by 105,000 \(\times\) g Supernatant Fraction from Hyperplastic Bone Marrow and Chloroleukemic Tumor.** For localization of the activity of the PGE\textsubscript{2} 9-ketoreductase, the above specimens were homogenized with a Polytron PT-20 homogenizer (Kinematica, Lucerne, Switzerland) in 5 volumes of ice-cold 0.1 mM dithiothreitol. Preparation of the 105,000 \(\times\) g supernatant fraction by differential centrifugation was as described previously (24). For removal of endogenous pyridine nucleotides and other small-molecular-weight substances, the 105,000 \(\times\) g supernatant fraction was partially purified and concentrated by filtering through Sephadex G-25 (coarse). The protein in the concentrated 105,000 \(\times\) g supernatant fraction was determined by the method of Lowry et al. (11) with bovine albumin used as standard.

**Enzyme Assay.** The enzymatic reduction of PGE\textsubscript{2} was measured, unless otherwise stated, in a final volume of 1 ml of 0.1 M phosphate buffer (pH 7.4) containing MgCl\textsubscript{2} (4 mM), NADPH (2.0 mM), dithiothreitol (0.1 mM), 105,000 \(\times\) g supernatant fraction (6 mg protein), and [\textsuperscript{3}H]PGE\textsubscript{2} (0.1 \(\mu\)Ci; 1 pmole) as reported previously (24). The mixture was incubated aerobically with shaking in a Dubnoff incubator at 37° for 15 min. Details of incubation conditions and the TLC system, polar lipids (phospholipids) remain near the origin, whereas the neutral lipids are near the solvent front ahead of the 3 primary prostaglandins. For further purification and identification of the radioactive products, the \(^{14}\)C corresponding to authentic reference PGE\textsubscript{2} and PGF\textsubscript{2\alpha} was eluted and treated with ethanolic KOH as described under "Methods." Final separation of radioactive PGE\textsubscript{2} (PGE\textsubscript{2}) from PGF\textsubscript{2\alpha} was achieved after thin-layer chromatography with authentic PGF\textsubscript{2\alpha} as a percentage of the total radioactivity recovered.

**RESULTS**

Histological evaluations of normal bone marrow, turpentine-induced hyperplastic bone marrow, and chloroma tumor specimens are shown in Fig. 1. Normal rat marrow (Fig. 1A) is characterized by a mixture of granuloid (largely mature granulocytes), erythroid, and lymphoid cells, whereas the turpentine-induced hyperplastic bone marrow (Fig. 1B) and the chloroma tumor (Fig. 1C) are characterized by a predominance of immature granulocytes. The hyperplastic bone marrow (nonmalignant) tissue serves as a control for the chloroma (malignant) tissue.

**Biosynthesis of \([^{14}\text{C}]\text{PGE}_2\) and \([^{14}\text{C}]\text{PGF}_{2\alpha}\) from \([^{14}\text{C}]\text{Arachidonic Acid.}\)** Incubation of [1-\(^{14}\text{C}\)]arachidonic acid (0.2 \(\mu\)Ci; 5 pmoles), respectively, with 105,000 \(\times\) g pellets from normal bone marrow, hyperplastic bone marrow, and chloroma tumor for 15 min resulted in the formation of radioactive products with chromatographic mobilities similar to PGE\textsubscript{2} and PGF\textsubscript{2\alpha}. A typical chromatogram of radioactive products formed after incubation of \([^{14}\text{C}]\text{arachidonic acid and 105,000 } \times\) g pellet from hyperplastic bone marrow is shown in Chart 1. Several radioactive peaks including chromatographic mobilities similar to authentic PGE\textsubscript{2}, PGF\textsubscript{2\alpha}, and PGD\textsubscript{2} are shown. In this TLC system, polar lipids (phospholipids) remain near the origin, whereas the neutral lipids are near the solvent front ahead of the 3 primary prostaglandins. For further purification and identification of the radioactive products, the \(^{14}\)C corresponding to authentic reference PGE\textsubscript{2} and PGF\textsubscript{2\alpha} was eluted and treated with ethanolic KOH as described under "Methods." Final separation of radioactive PGE\textsubscript{2} (PGE\textsubscript{2}) from PGF\textsubscript{2\alpha} was achieved after thin-layer chromatography with authentic PGF\textsubscript{2\alpha} as a percentage of the total radioactivity recovered.
The transformation of arachidonic acid into \([^{14}C]PGE_2\) and \([^{14}C]PGF_{2\alpha}\) by 105,000 \(\times\) \(g\) pellet preparations from normal bone marrow, turpentine-induced hyperplastic bone marrow, and chloroma pellet preparations are shown in Table 1. The results indicate that 105,000 \(\times\) \(g\) preparations from both bone marrow specimens and from chloroma tumor are capable of transforming arachidonic acid into \(PGE_2\) and \(PGF_{2\alpha}\), although transformation is low in normal bone marrow. The normal bone marrow cells are, however, different from those of the proliferating hyperplastic bone marrow and chloroma tissue (Fig. 1) and therefore are not suitable for comparison with 2 proliferating specimens. Nonetheless, these results are consistent with the 2 proliferating reports that have demonstrated that the 105,000 \(\times\) \(g\) pellet fraction from various tissues is the site of prostaglandin biosynthesis (5, 6, 15, 23). These results also indicate that the 105,000 \(\times\) \(g\) particulate preparations from turpentine-induced hyperplastic bone marrow specimens are most active in the transformation of precursor arachidonic acid into prostaglandins \(E\) and \(F\). Furthermore, prostaglandin biosynthesis by 105,000 \(\times\) \(g\) pellet preparations from chloroma tumor was lower than that by 105,000 \(\times\) \(g\) pellet preparation from hyperplastic nonmalignant bone marrow.

**Time Course of \(^{14}C\) Incorporation from \([1-^{14}C]\)Arachidonic Acid into \(PGE_2\) and \(PGF_{2\alpha}\) by 105,000 \(\times\) \(g\) Pellet Preparations from Hyperplastic Bone Marrow.** Since the turpentine-induced hyperplastic bone marrow represents our control for the studies with the chloroleukemic tumor, because cells from both tissues were predominantly myeloblasts, promyelocytes, and myelocytes (Fig. 1), the time course of the transformation of \([1-^{14}C]\)arachidonic acid into \(^{14}C\)-prostaglandins by 105,000 \(\times\) \(g\) pellet from the hyperplastic bone marrow was tested. The results shown in Chart 2 indicate that the transformation of the precursor fatty acid by the bone marrow 105,000 \(\times\) \(g\) pellet preparation into prostaglandins \(E\) and \(F\) was maximal in approximately 15 min. A similar maximal condition was observed for incubations with the chloroma 105,000 \(\times\) \(g\) pellet preparation.

**Inhibition of Prostaglandin Biosynthesis by Indomethacin and Fatty Acids.** The effects of known inhibitors of prostaglandin biosynthesis in other tissues were tested on the transformation of arachidonic acid into prostaglandins by 105,000 \(\times\) \(g\) pellets prepared from hyperplastic bone marrow and chloroma tissue. Inhibition of the biosynthesis of \(PGE_2\) and \(PGF_{2\alpha}\) by the 3 substances are shown in Table 2. Thus, the prostaglandin synthetase enzymes in the bone marrow and the chloroma tissue are also responsive to the inhibitory action of these substances.

**Prostaglandin Levels in Normal Bone Marrow, Hyperplastic Bone Marrow, and Chloroleukemic Tumor.** Prostaglandin levels in normal bone marrow, hyperplastic bone marrow, and chloroleukemic tumor specimens were determined by gas-liquid chromatography as described under Methods. Quantitation of tissue samples was derived from a standard curve obtained with authentic \(PGE_2\) and \(PGF_{2\alpha}\). The results are shown in Table 3. Endogenous levels of \(PGE_2\) and \(PGF_{2\alpha}\) were elevated in both turpentine-induced hyperplastic bone marrow and chloroma tumor compared to normal bone marrow. Of interest is the endogenous level of \(PGF_{2\alpha}\) in the chloroma tumor, which is approximately 5-fold greater than that in the hyperplastic bone marrow. The \(PGF_{2\alpha}:PGE_2\) ratio was also markedly greater in the chloroma tissue than it was in the hyperplastic bone marrow specimens. These data suggest the possible formation of \(PGF_{2\alpha}\) from a source other than directly from the cyclic endoperoxides.

**Activity of the \(PGE_2\) 9-Ketoreductase Activity in 105,000 \(\times\) \(g\) Supernatant Fractions from Hyperplastic Bone Marrow and Chloroleukemic Tumor.** Incubations of \([^{3}H]PGE_2\) with the above supernatant fractions and NADPH resulted in the formation of radioactive \(PGF_{2\alpha}\). The data in Chart 3 show an approximately 4-fold increase in the activity of the NADPH-dependent \(PGE_2\) 9-ketoreductase in the chloroma tissue compared to that in the hyperplastic bone marrow.
Effects of nonsteroid antiinflammatory drug and unsaturated fatty acids on the biosynthesis of prostaglandins by hyperplastic bone marrow and chloroma tissue

Pellet fractions (105,000 × g; 10 mg protein) from turpentine-induced hyperplastic bone marrow and chloroma tissue were incubated with [1-14C]arachidonic acid (0.2 μCi), respectively. Details of the procedure and identification of the radioactive products are described under "Methods". The data are the means ± S.E. from 3 experiments.

<table>
<thead>
<tr>
<th>Hyperplastic bone marrow</th>
<th>Chloroma tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Concentration (μM)</strong></td>
<td><strong>% 14C/mg protein</strong></td>
</tr>
<tr>
<td>None</td>
<td>3.8 ± 0.42</td>
</tr>
<tr>
<td>5,8,11,14-Elcosatetraenoic acid</td>
<td>20 0.8 ± 0.09 79</td>
</tr>
<tr>
<td>5,8,11,14-Eicosatrienoic acid</td>
<td>20 2.3 ± 0.26 39</td>
</tr>
</tbody>
</table>

Table 3

Endogenous levels of prostaglandins in normal bone marrow, hyperplastic bone marrow, and chloroma tumor

Gas-liquid chromatographic analysis was done of O-methoxime silyl derivatives of prostaglandins E and F. Details of the analysis are described in the text. Tissues were rapidly homogenized in chloroform:methanol (2:1) to stop the enzymatic production of prostaglandins during the extraction procedure; however, the values reported could also reflect in part slight contributions of prostaglandins formed by the tissues after trauma. Each value represents the mean ± S.E. from 4 specimens.

<table>
<thead>
<tr>
<th></th>
<th>PGE2 (pg/mg protein)</th>
<th>PGF2α (pg/mg protein)</th>
<th>PGF2α:PGE2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal bone marrow</td>
<td>210.4 ± 25.6</td>
<td>114.2 ± 19.2</td>
<td>0.54</td>
</tr>
<tr>
<td>Hyperplastic bone marrow</td>
<td>620.8 ± 58.9</td>
<td>789.1 ± 129.6</td>
<td>1.27</td>
</tr>
<tr>
<td>Chloroma tumor</td>
<td>430.1 ± 44.2</td>
<td>3986.9 ± 420.3</td>
<td>9.2</td>
</tr>
</tbody>
</table>

The activity of the NADH-dependent PGE2 9-ketoreductase in the 105,000 x g pellets of the above specimens were also assayed, but they were found to be too low for comparison.

DISCUSSION

The present studies have demonstrated that 105,000 × g particulate preparations from normal rat bone marrow, turpentine-induced hyperplastic bone marrow, and chloroma tumor contain the enzyme systems for the transformation of arachidonic acid into prostaglandins. The activity of the prostaglandin synthetase systems in the 105,000 × g preparations is inhibited by the nonsteroid antiinflammatory drug indomethacin and the unsaturated fatty acids eicosatetraenoic acid (acytylenic analog of arachidonic acid) and eicosatrienoic acid (Table 2). These substances have been shown to inhibit the activity of the prostaglandin synthetase in other tissues (1, 5, 6, 18, 23, 26). Thus, the properties of the prostaglandin synthetase in rat bone marrow and in chloroma tumor are similar in at least this respect to those reported in other tissues.

Although the 105,000 × g particulate preparations from turpentine-induced hyperplastic bone marrow transformed more [14C]arachidonic acid into PGE2 than did preparations from chloroma tumor, the PGF2α:PGE2 ratio differed markedly in these 2 proliferative tissues. For instance, the PGF2α:PGE2 ratio in the hyperplastic bone marrow is approximately 0.4 as determined from the biosynthetic activity of the 105,000 × g particulate fraction, whereas that in the chloroma tumor is 1.10 (Table 1). In another assay system by gas-liquid chromatography of the endogenous prostaglandins in both tissues, the PGF2α:PGE2 ratio in the hyperplastic bone marrow is approximately 1.3, whereas the ratio of the chloroma tissue is 9.2 (Table 3). A further test
to explain the increased elevation of PGF$_{2\alpha}$ in the chloroma tissue revealed a 4-fold increase in the activity of the PGE$_2$ 9-ketoreductase in this tissue (Chart 3) over the hyperplastic tissue revealed a 4-fold increase in the activity of the PGE$_2$ 9-ketoreductase in this tissue (Chart 3) over the hyperplastic tissue. Although the role of PGF$_{2\alpha}$ in the malignant myelogenous leukemic tumor is presently unclear, its increased formation suggests that this substance may at least in part play a role in the hyperproliferative process.

REFERENCES

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