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TITLE: Design, Sythesis, and Testing of Breast Cancer  
Angiogenesis Inhibitors

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<b>13. ABSTRACT (Maximum 200 Words)</b>  Thymidine phosphorylase (TP) catalyzes the phosphorolysis of thymidine and other pyrimidine 2'-deoxyribonucleosides. In addition, TP has been shown to possess angiogenic activity in a number of <i>in vitro</i> and <i>in vivo</i> assays, and its angiogenic activity has been linked to its catalytic activity. Several 5- and 6-substituted uracil derivatives were synthesized and evaluated for their ability to inhibit TP activity. In the past year we have identified a 6-amino-substituted uracil analog, 6-(2-aminoethyl)amino-5-chlorouracil (AEAC) to be one of the most active compounds. AEAC was found to be a competitive inhibitor of TP with a $K_i$ of 165 nM. Human recombinant TP induced human umbilical vein endothelial cell (HUVEC) migration in a modified Boyden chamber assay <i>in vitro</i> , and this action could be abrogated by the AEAC. This was specific for TP, as the inhibitor had no effect on the chemotactic actions of vascular endothelial growth factor (VEGF). HUVEC migration was also induced when TP-transfected human breast carcinoma cells were used in a co-culture assay in place of the purified angiogenic factors, and a TP inhibitor nearly completely blocked the tumor cell-mediated migration. These studies suggest that inhibitors of TP may be useful in breast cancers which are dependent upon TP-driven angiogenesis.			
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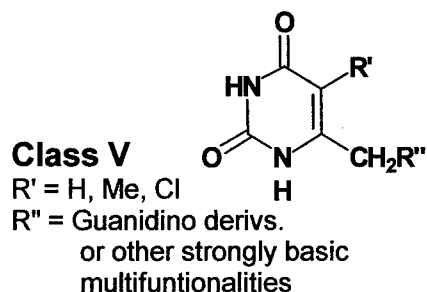
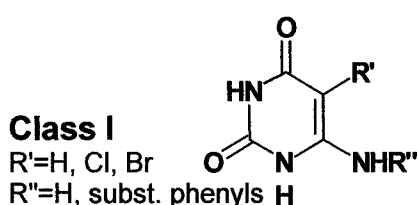
**Introduction.** There is a need for alternative approaches to treat metastatic breast cancer. One rapidly developing area of investigation is the study of tumor angiogenesis, the process by which a growing tumor mass recruits the new blood vessels required for its continued growth, and through which the tumor can spread to distant sites. Indeed the neovascularization process is thought to be one of the rate limiting steps for the growth of primary and metastatic tumors (1-2). Most studies have demonstrated the importance of angiogenesis in the progression of human breast malignancies and found the extent of vascularization to be correlated with tumor size and an indicator of node metastasis (3-8). Several polypeptides and growth factors that are produced by breast cancer epithelial and stromal cells have been identified as having endothelial cell mitogenicity and angiogenic activity (1,9). Our studies are focusing on the angiogenic factor PD-ECGF, based on evidence demonstrating its role in experimental and human cancer, and the finding that PD-ECGF is identical to human thymidine phosphorylase (TP), an enzyme that catalyzes the reversible conversion of thymidine to thymine and 2'-deoxyribose-1-phosphate (10-12). When transfected into NIH 3T3 cells, TP was found to increase the vascularization of tumors growing in nude mice after sc inoculation (13). Similarly, overexpressing TP in MCF7 breast carcinoma cells markedly increased tumor growth *in vivo*, although it had no effect on the growth of the cells *in vitro* (14). Western blot analysis of primary human breast tissue showed that TP expression was elevated in the tumors compared to the normal tissue, a finding which provides clinical relevance to the transfection experiments. Studies suggest that the angiogenic and endothelial cell chemotactic activities of PD-ECGF are dependent upon its enzymatic activity, and this has been confirmed with site-directed mutagenesis studies (14,15-17). Of the angiogenic factors identified to date, TP is the only one in which an enzymatic activity of the factor is required for angiogenic activity. These observations serve as the basis for our hypothesis that inhibition of the catalytic activity of TP will also block its angiogenic properties. By synthesizing inhibitors of TP, we will be able to test this hypothesis and provide a basis for the development of a novel class of antitumor agents.

**Technical objective 1: Synthesis of inhibitors of TP.**

Our original proposal suggested the synthesis of four structural classes of pyrimidine and pyrimidine nucleosides for evaluation as potential TP inhibitors. Recent developments in the area of TP inhibitors as potential antiangiogenic agents which had taken place in the last 2-3 years led us to incorporate a fifth class of analogs in last year's report.

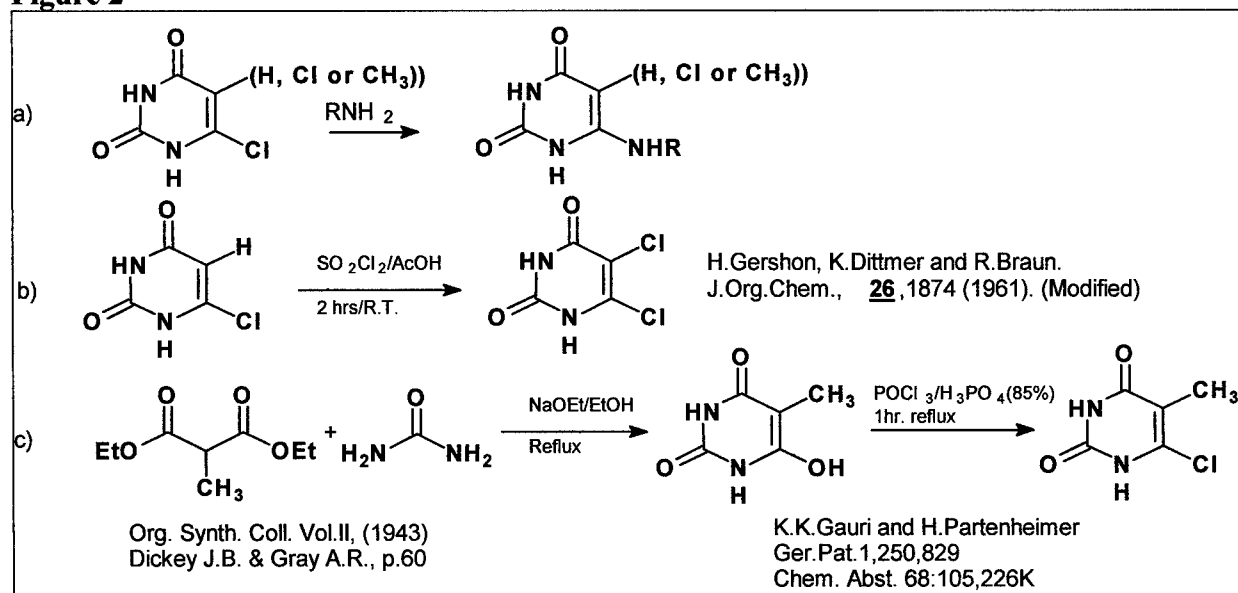
In the previous year, we have concentrated our synthetic efforts on the preparation of derivatives of class I and V (see below) since these two series had demonstrated the highest activities found as yet and seemed to hold the best promise for the generation of new potent analogs. Efforts were also expended on the resynthesis, at larger scales, of compounds previously synthesized for more extensive biological evaluation.

**Figure 1**



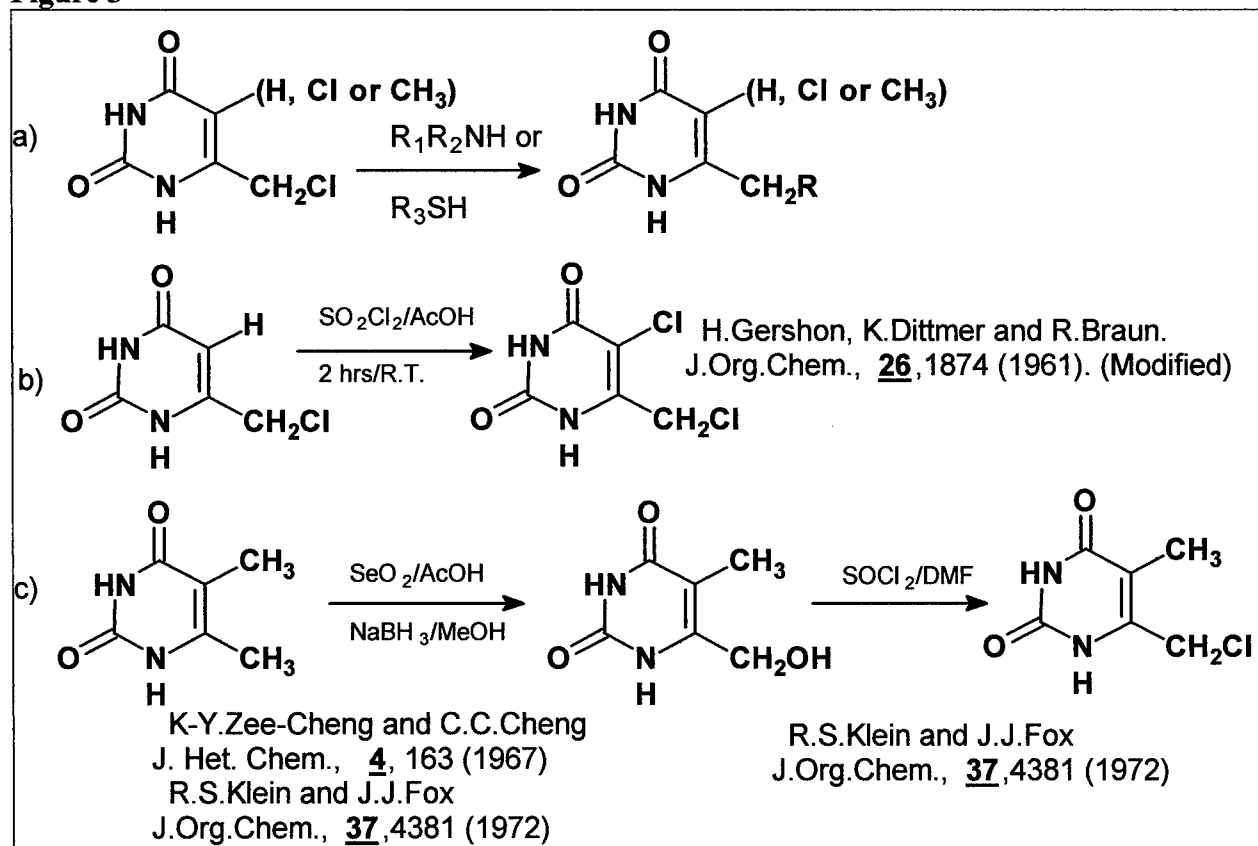
The most active members of these two classes of analogs discovered to date have been compiled in table 1. (See below). Compounds 2 – 12 (all derivatives of class I) were prepared as shown in Fig. 2 (a) by substitution of the 6-chloro group of a variety of uracil derivatives by appropriate primary amines of commercial sources of readily available through procedures reported in the chemical literature. The 6-chloro substituted pyrimidine precursors were themselves obtained by adaptations (or modifications) of published procedures.

Figure 2



The precursor 5,6-dichlorouracil was obtained by the chlorination of commercially available 6-chlorouracil with sulfuryl chloride in acetic acid (Fig.2 (b)). The 5-methyl substituted derivative was obtained by substitution of the 6-OH group of 5-methylbarbituric with Cl using phosphorous oxychloride in 85% phosphoric acid (Fig.2 (c)).

Figure 3

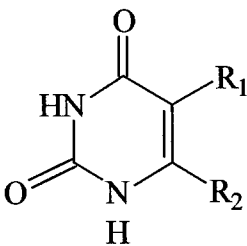
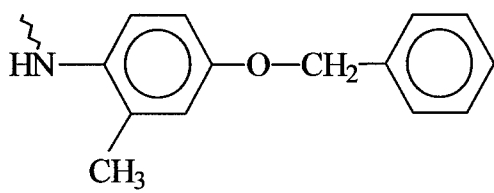
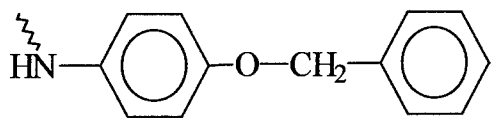
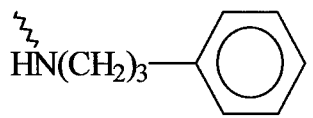




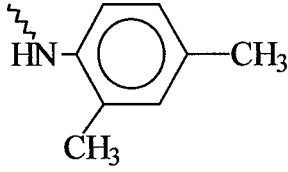
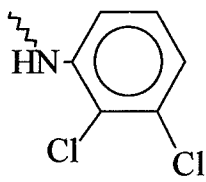
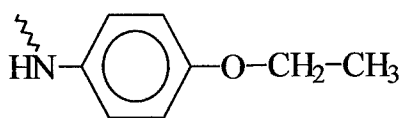
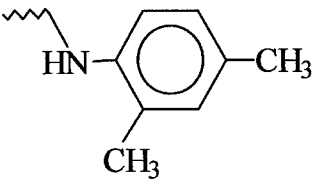
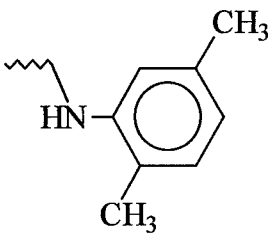
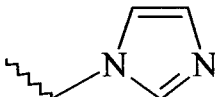
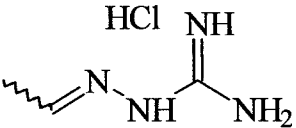
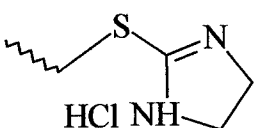
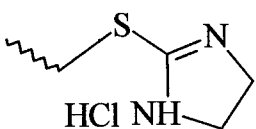
Compounds 13-20 (all derivatives of class II) were prepared as shown in Fig. 3 (a) by substituting the Cl group of variously 5-substituted 6-chloromethyluracils with the appropriate amine or thiono- derivative. Precursor 5-chloro-6-chloromethyluracil was obtained by direct chlorination of the 5-position of 6-chloromethyluracil (commercially available) with sulfuryl chloride in acetic acid (Fig.3 (b)). The 5-methyl-6-chloromethyluracil precursor was obtained from readily available 5,6-dimethyluracil by oxygenation to the 6-aldehyde derivative, reduction to the 6-hydroxymethyl intermediate and chlorination with thionyl chloride and dimethylformamide (Fig.3 (c)).

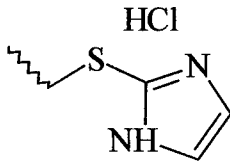
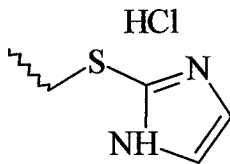
**Technical objective 2: Evaluation of target compounds as TP inhibitors.**

Table 1: Inhibition of TP activity by 5-, 6-substituted uracil analogs.

			
Compound	R <sub>1</sub>	R <sub>2</sub>	IC <sub>50</sub>
1	Br	-NH <sub>2</sub>	17 μM
2	Cl	-NHCH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub> HCl	0.25 μM
3	CH <sub>3</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub> HCl	1.7 μM
4	Cl	-NHCH <sub>2</sub> CH <sub>2</sub> OH	100 μM
5	CH <sub>3</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> OH	> 1000 μM
6	Cl	-NHCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	650 μM
7	H		30 μM
8	H		114 μM
9	H		122 μM

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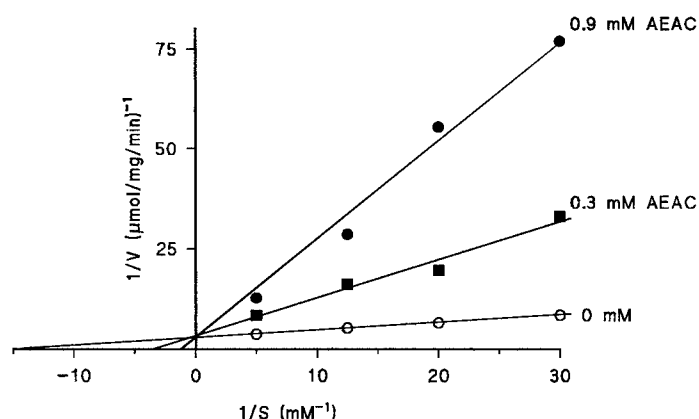
10	H		160 $\mu\text{M}$
11	H		220 $\mu\text{M}$
12	H		275 $\mu\text{M}$
13	H		>300 $\mu\text{M}$
14	H		10 $\mu\text{M}$
15	Cl		0.30 $\mu\text{M}$
16	Cl		500 $\mu\text{M}$
17	CH <sub>3</sub>		200 $\mu\text{M}$
18	Cl		15 $\mu\text{M}$

19	H		> 300 $\mu\text{M}$
20	Cl		300 $\mu\text{M}$

TP activity was measured in assays which contained 0.2 M  $\text{KH}_2\text{PO}_4$  (pH 7.8), 0.2 mM  $[5\text{-}^3\text{H}]$  thymidine (1  $\mu\text{Ci}$ ), human TP (5 ng), and several different concentrations of the inhibitor being tested. Reactions were stopped after 30 min at 37 by the addition of ice-cold TCA containing activated charcoal. After centrifugation, an aliquot of the supernatant was counted in a liquid scintillation counter.  $\text{IC}_{50}$  values for each compound shown in Table 1 were calculated from data from at least 3 determinations.

We next further the mechanism of inhibition of compound 2, 6-aminoethylamino-5-chlorouracil (AEAC) on TP inhibition by varying both the concentration of inhibitor, and that of the substrate thymidine.

**FIG. 4: Double reciprocal analysis of TP inhibition by AEAC.**



Assays of TP activity were carried out as described in Table 1 except that the concentration of substrate thymidine was varied between 33 and 200  $\mu\text{M}$ . AEAC was used at concentrations of 0 mM (○), 0.3 mM (■), and 0.9 mM (●). Data are means of two experiments.

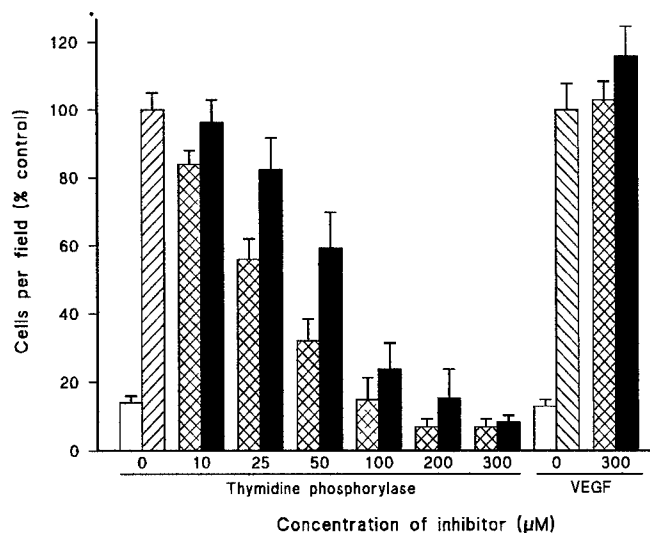
Conclusion: Compound 2 (AEAC) is a competitive inhibitor of TP.

We next examined the effect of AEAC and a second potent TP inhibitor, 5-chloro-6(1-imidazolyl-methyl) uracil (CIMU; compound 15) on TP-mediated endothelial cell migration.

Human umbilical vein endothelial cells (HUVEC) were isolated from umbilical cords obtained less than 5 hours after delivery. After rinsing, veins were incubated with collagenase (100 U/ml) in Medium 199 with Earles salts for 10 min. Primary cultures were seeded into flasks precoated with 0.02% (w/v) gelatin in PBS. Culture medium consisted of M199 containing 20% newborn calf serum, 5% pooled human serum, 2 mM L-glutamine, 5 U/ml penicillin and 5  $\mu$ g/ml streptomycin. Cells were incubated at 37° in a humidified incubator with 5% CO<sub>2</sub> with a medium change after 24 hours and every 2 days thereafter until confluent. Primary cultures of HUVEC were harvested by incubation with 0.05% trypsin/0.02% EDTA, and the cells collected and cell number determined using a Coulter counter.

**Modified Boyden chamber migration assay.** HUVEC (passages 1-4) were harvested using cell dissociation solution (Sigma) and pelleted by centrifugation. Cells (10<sup>5</sup>) were placed into transwell inserts (Becton Dickinson; 8  $\mu$ m pore) precoated with fibronectin (10  $\mu$ g/ml). Inserts containing cells were placed into a 24 well plate containing 0.7 ml M199 with 1% serum and incubated (37°) for 1 hour. A chemotactic stimulus, recombinant human TP (200 ng/ml) or human VEGF (10 ng/ml; R&D Systems) was added to the lower wells in the presence and absence of various concentrations of inhibitors, and the cells incubated for 5 hours at 37°. At the end of the incubation period, the surface of the upper membrane was swabbed with a cotton-tipped applicator to remove non-migrating endothelial cells. Wells and inserts were washed 3 times with PBS and stained for 30 min. in medium with 10  $\mu$ M Cell Tracker Green (Molecular Probes). The cluster plate was washed 3X with PBS, cells fixed in 3.7% formaldehyde for 10 min. and mounted on microscope slides. For quantitation, five random fields were photographed (100x total magnification) and the number of HUVEC in each field counted.

**FIG. 5: Effect of TP inhibitors on endothelial cell migration.**



Human endothelial cells, isolated as described above, were used in a modified Boyden chamber assay. Cells (10<sup>5</sup>) were placed into fibronectin-coated transwell inserts, which were then placed into 24 well plates in which the lower wells contained 0.7 ml M199 with 1% serum. After 1 hour, recombinant human TP (200 ng/ml) or human VEGF (10

ng/ml) were added to the lower wells, as indicated (single hatched bars). Control wells (open bars) had no added angiogenic factor. Wells also contained the indicated concentrations (0 to 300  $\mu$ M) of either CIMU (double hatched bars) or AEAC (solid bars). Cells were incubated for 5 hours at 37 $^{\circ}$ , at which time non-migrating endothelial cells were removed from the upper surface of the membrane. Cells were stained with Cell Tracker Green, washed with PBS, fixed in formaldehyde, and mounted on microscope slides. Migration was quantitated by counting five random photographed (100x total magnification) fields, and the number of HUVEC in each field counted.

**Technical objective 3: *In vivo* assays.** We have had difficulty in establishing *in vivo* assays for assessing the activity of our TP inhibitors. While we can observe angiogenesis using a Matrigel plug in mice, the assay is not reproducible and is highly subjective, making it unlikely to be useful for the quantitative assessment of the activity of the inhibitors. We have also not been able to establish tumors in nude mice from a MCF7 xenograft, despite attempting a number of different modifications to the protocol.

As an alternative to these approaches, we have adapted the Boyden chamber assay with HUVECs to incorporate human mammary tumor cells in a co-culture assay. These assays utilized tumor cells in place of the purified angiogenic factors; no other angiogenic stimulus was added to the incubation. Wild type MCF7 breast carcinoma cells and cells which had been stably transfected with a human TP cDNA (MCF7/TPneo) were used.  $10^5$  cells were added to the lower wells and were allowed to attach for 24 hours. The medium was then replaced with M199 medium with and without 0.3 mM of the inhibitor CIMU (see above), combined with HUVEC-containing transwells, and migration over a 5 hour period was analyzed as described above.

**TABLE 2: Inhibition of HUVEC migration by a TP inhibitor in a co-culture assay.**

<u>Tumor Cells</u>	<u>CIMU</u>	<u>HUVEC cells per field</u>	<u>Inhibition</u>
None	-	11 $\pm$ 1.7	
MCF7/TPneo	-	115 $\pm$ 9.0	
MCF7/TPneo	+	28 $\pm$ 2.6	84%

Data are means  $\pm$  SEM.

Conclusion: Breast cancer cell-mediated angiogenesis can be blocked by a TP inhibitor.

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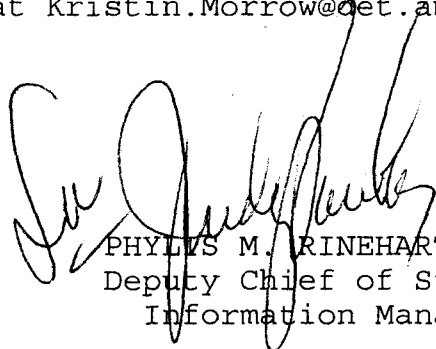
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1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for this Command. Request the limited distribution statement for the enclosed accession numbers be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Kristin Morrow at DSN 343-7327 or by e-mail at Kristin.Morrow@det.amedd.army.mil.

FOR THE COMMANDER:

Encl

  
PHYLLIS M. RINEHART  
Deputy Chief of Staff for  
Information Management



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