[CANCER RESEARCH 38, 4257–4262, November 1978]
0008-5472/78/0038-0000$02.00

Discrepancies between *in Vivo* and *in Vitro* Effects of Glucocorticoids in Myelomonocytic Leukemic Cells with Steroid Receptors[1]

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Abstract

Leukocytes from peripheral blood and bone marrow of an 8-month-old infant with acute myelomonocytic leukemia were studied for the presence of steroid receptors and hormone responsiveness *in vitro*, as well as for clinical response to glucocorticoid therapy. With the use of a competitive protein-binding assay on cytoplasmic extracts, it was possible to demonstrate saturable binding of radiolabeled glucocorticoid. Scatchard analysis of the binding was consistent with a single class of receptor sites with a dissociation constant of 3.5×10^{-9} M and 2.4×10^{-9} M for peripheral blood and bone marrow, respectively. The concentration of receptor sites was 187 fmol per mg protein (peripheral blood) and 122 fmol per mg protein (bone marrow) corresponding to approximately 2400 and 1500 sites/cell. Sucrose density gradient revealed the presence of macromolecules sedimenting between 6s and 8s (low ionic strength) and at 3.6s (in gradients containing 0.4 M KCl). Significant competition for radioactive triamcinolone acetonide was observed with natural and synthetic glucocorticoids, but not with other steroids. Under *in vitro* incubation, macromolecular synthesis was inhibited by glucocorticoid concentrations which saturated the receptor sites. Administration of either dexamethasone or prednisolone produced a sharp increase in the absolute number of circulating leukocytes, which was accompanied by an increase in the percentage of more-immature cells. A temporal relationship was also observed between the withdrawal of the drug and the drop in the leukocyte count. These results indicate that cells which contain glucocorticoid receptors and are responsive to steroids *in vitro* seem to be sensitive to a stimulatory effect *in vivo*. Moreover, the results suggest that a factor(s) other than steroid binding and responsiveness *in vitro* is important in determining the *in vivo* effects of glucocorticoids.

Introduction

Controversies exist in the literature about the therapeutic value of glucocorticoids in AMML[3] and in acute myelogenous leukemia. In some cases the drugs were found to aggravate these leukemic disorders and accelerate their course, while in others they either have no effect or induce transient remission (5, 7). At present, no clear explanations are given for the variability of the glucocorticoid effects in these conditions. Recently, evidence has been presented concerning the presence of specific cytoplasmic glucocorticoid receptors in the lymphoblasts of some patients with acute lymphoblastic leukemia (1, 2). It has also been shown that the presence or absence of these receptors correlates closely with steroid response both *in vivo* and *in vitro* (1, 2).

We recently had the opportunity to study a case of AMML for the presence of glucocorticoid receptors. The leukemic cells, which were found to contain specific receptors, showed *in vitro* inhibition of DNA, RNA, and protein synthesis, whereas they appeared to be sensitive to a stimulatory effect of the same hormone *in vivo*. Critical implications can be derived from the above observations, since they offer a unique example of discrepancy between the *in vivo* and *in vitro* effects of glucocorticoids and suggest that these hormones may not exert their action directly on the leukemic cells, but through a still-unknown mechanism.

Materials and Methods

Case Report. An 8-month-old male infant was admitted to the hospital with a diagnosis of AMML. Physical examination revealed moderate hepatosplenomegaly (spleen 4 cm below the costal margin) and slight cervical and inguinal lymphadenopathy. The initial hematological investigations revealed: hemoglobin, 8%; WBC, 120,000 cells/cu mm (blast cells, 60%; promonocytes and monocytes, 25%; neutrophils, 4%; lymphocytes, 11%); and platelets, 100,000 cells/cu mm. Many of the primitive cells were difficult to differentiate from myeloblasts, but the majority possessed the characteristics of monoblasts. Bone marrow also showed the features of AMML. Myeloperoxidase was positive. Surface marker analysis revealed: E-rosettes (9%) and Ehrlich ascites carcinoma (87%). Fluorescent studies revealed that only 1 to 2% of the cells had surface immunoglobulins. Chromosome analysis was performed on "direct" bone marrow preparation. The modal number was 46, but many metaphases were pseudodiploid.

Reagents and Chemicals. [^{3}H]TA (28 Ci/mmol) was obtained from the Radiochemical Centre, Amersham, England, as were L-[^{14}C]leucine (348 mCi/mmol) and [^{3}H]thymidine (3.1 Ci/mmol). [5-^{3}H]Uridine (30 Ci/mmol) was purchased from New England Nuclear Corp., Boston, Mass. Dexamethasone was a gift of Merck, Darmstadt, Germany. 17,21-Dimethyl-19-nor-4,9-pregnadiene-3,20-dione (R5020) was provided by Dr. J. P. Raynaud from Roussel-Uclaf Labs, Romainville, France. All other steroids were obtained from Steraloids, Pawling, N. Y. Eagle's modified Dulbecco medium, penicillin, and streptomycin

[1] Presented at the John E. Fogarty International Center Conference on Hormones and Cancer, March 29 to 31, 1978, Bethesda, Md. Supported in part by Progetto Finalizzato C. N. R. Biologia della Riproduzione.

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[3] The abbreviations used are: AMML, acute myelomonocytic leukemia; [^{3}H]TA, 1,2,4-[^{3}H]triamcinolone acetonide; DCC, dextran-coated charcoal.

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were obtained from Grand Island Biological Co., Bio-Cult Ltd., Paisley, Scotland. Multiwell dishes were obtained from Sterlin Ltd., Teddington, Middlesex, England. Dextran was purchased from Pharmacia, Uppsala, Sweden. Norit A (acid-washed) and Trizma base were from Sigma Chemical Co., St. Louis, Mo. Lumagel was obtained from Lumac System AG, Aeschngraben, Basel, Switzerland. All other chemicals were reagent grade.

Glucocorticoid Receptor Analysis. Leukocytes were separated from peripheral blood and bone marrow by spontaneous sedimentation in dextran mixture (9). Viability was greater than 90%, as determined by nigrosine exclusion.

Cell pellets (3 to 5 × 10^8 cells) were suspended in ice-cold 10 mM Tris-HCl:1.5 mM EDTA:10% glycerol buffer (pH 7.5) and were disrupted by a sonifier (Branson, Heusenstamm, Germany). Cytosol was prepared by centrifugation of the disrupted cells at 145,000 × *g* for 60 min at 2°. Aliquots (0.25 ml) of the cytosol were incubated for 16 to 18 hr at 0° with [^{3}H]TA (0.5 to 33 × 10^{-9} M) in the presence or absence of 3 × 10^{-5} M unlabeled TA. Following incubation, 0.02 ml of DCC suspension (5% Norit A and 0.05% dextran in 10 mM Tris-HCl:1.5 mM EDTA buffer, pH 7.4) was added and incubated for an additional 15 min at 0°. Following centrifugation at 3,000 rpm for 5 min, 0.15 ml liquid was removed and counted in 6 ml of Lumagel.

Sucrose Gradient Analysis. Cell extracts prepared as above were incubated for 5 hr at 0° with 1 × 10^{-8} M [^{3}H]TA alone or in the presence of 1 × 10^{-6} M unlabeled TA. Following incubation, 0.2-ml aliquots were transferred to plastic tubes containing a DCC pellet previously prepared by centrifuging 0.5 ml of DCC suspension containing 0.5% Norit A and 0.05% dextran in 10 mM Tris-HCl:1.5 mM EDTA buffer (pH 7.4) and removing the buffer by aspiration. The tubes were then incubated for 15 min at 0°. After centrifugation, 0.15 ml of supernatant was layered over linear gradients of 5 to 20% sucrose in 10 mM Tris-HCl:1.5 mM EDTA (pH 7.5) or 10 mM Tris-HCl:1.5 mM EDTA:0.4 KCl (pH 7.5) buffers. These gradients were then centrifuged with the use of a Spinco SW 50.1 rotor (0°). Fractions of 5 drops were collected from the top of the tube by pumping concentrated sucrose from the bottom of the gradient; fractions were counted in 6 ml of Lumagel.

Nuclear and Cytoplasmic Receptor-bound Hormone. Aliquots (0.8 ml) of cell suspension (8 × 10^7 cells/ml) were incubated with [^{3}H]TA 2 × 10^{-8} M alone or in the presence of 2 × 10^{-5} M unlabeled TA in an atmosphere of 95% O_2:5% CO_2 for 120 min at 0°. Following incubation, one-half of the cell suspension was heated at 25° for 10 min and then quickly cooled; the rest of the suspension was maintained at 0°. Cells were then sedimented, washed, and assayed for nuclear and cytoplasmic bound hormone as previously reported (4).

***In Vitro* Sensitivity to Glucocorticoids.** Cells were suspended in Eagle's modified Dulbecco medium supplemented with penicillin and streptomycin. Cells were plated in replicate in multiwell sterile plastic dishes at a density of 2 × 10^6 cells/ml. Dexamethasone was added from a stock ethanol solution to achieve the final concentrations of 10^{-9} to 10^{-5} M. The same concentration of ethanol (0.05%) was added to control wells. After 20 hr at 37° in a humidified 5% CO_2 incubator, radioactive precursors (final concentrations: 0.1 × 10^{-6} M [^{3}H]thymidine, 3.7 × 10^{-8} M [^{3}H]uridine, and 2.8 × 10^{-6} M [^{14}C]leucine), were added. One hr later, the cultures were terminated by centrifugation at 600 × *g* for 5 min at 4°. Cell pellets were then extracted with successive washes of 10% (w/v) trichloroacetic acid (twice), 80% (v/v) ethanol, and absolute ethanol:ethyl ether (v/v, 1:1). The dried residue was dissolved in 0.3 ml of formic acid and assayed for radioactivity with the use of 10 ml of Lumagel.

Measurement of [^{3}H]Thymidine Incorporation by Whole-Blood Incubations. Two ml of blood were collected by venipuncture and immediately transferred to a plastic culture tube containing preservative-free sodium heparin to give a final concentration of 10 IU/ml. After cell counting, a whole-blood cell suspension was prepared by adding prewarmed Eagle's modified Dulbecco medium containing penicillin and streptomycin to provide various dilutions of whole blood containing approximately 0.4, 0.8, 1.6, 3.2, or 6.4 × 10^{-6} leukocytes/ml. Aliquots (1 ml) of the dilutions were transferred into plastic tubes containing [^{3}H]thymidine (final concentration, 0.1 × 10^{-6} M) and incubated for 1 hr at 37°. At the end of the incubation period, 3 ml of 3% acetic acid were added to each tube to lyse the erythrocytes, and the leukocytes were sedimented by centrifugation at 450 × *g* for 6 min. Cell pellets were then extracted with trichloroacetic acid, washed with ethanol and ethanol:ethyl ether, and dissolved in formic acid for counting, as described in the previous paragraph.

Clinical Trials. Informed of the poor prognosis of the disease, the parents refused the conventional treatment. However, they accepted a trial with corticosteroids because of the theoretical possibility of a response *in vivo*, as already observed *in vitro* with these drugs (see "Results"). The first corticosteroid tried was dexamethasone at a dosage of 0.3 mg per kg per day for 11 days. After an interval of 15 days with no therapy, another trial was made with prednisolone at a dosage of 2 mg per kg per day for 8 days and then at 10 mg per kg per day for another 10 days.

Calculations. Samples were counted in a Packard model 3255 scintillation spectrometer; counting efficiency was 38% for ^{3}H and 65% for ^{14}C. Binding capacity was expressed as fmol (10^{-15} mol) [^{3}H]TA bound either on a per-milligram cytosol protein or per-cell basis. Conversion of radioactivity (dpm) to number of binding sites/cell was accomplished by determining the amount of [^{3}H]TA bound per reaction containing cytosol deriving from a known number of cells and by then applying Avogadro's number.

Results

Glucocorticoid Receptor Studies. The data in Chart 1 demonstrate that cytosols prepared from myelomonocyte leukemic cells derived from either peripheral blood or bone marrow contain high-affinity, limited-capacity glucocorticoid receptors. Scatchard analysis (8) of binding data (Chart 1*B*) indicates that in both types of cells, triamcinolone acetonide is bound to a single class of receptor sites of uniform affinity (K_d = 3.5 × 10^{-9} M for peripheral blood, K_d = 2.4 × 10^{-9} M for bone marrow). The x intercept allows an estimation of the total number of receptor sites of 187 fmol per mg of cytosol protein (peripheral blood) and 122 fmol per mg of cytosol protein (bone marrow). These

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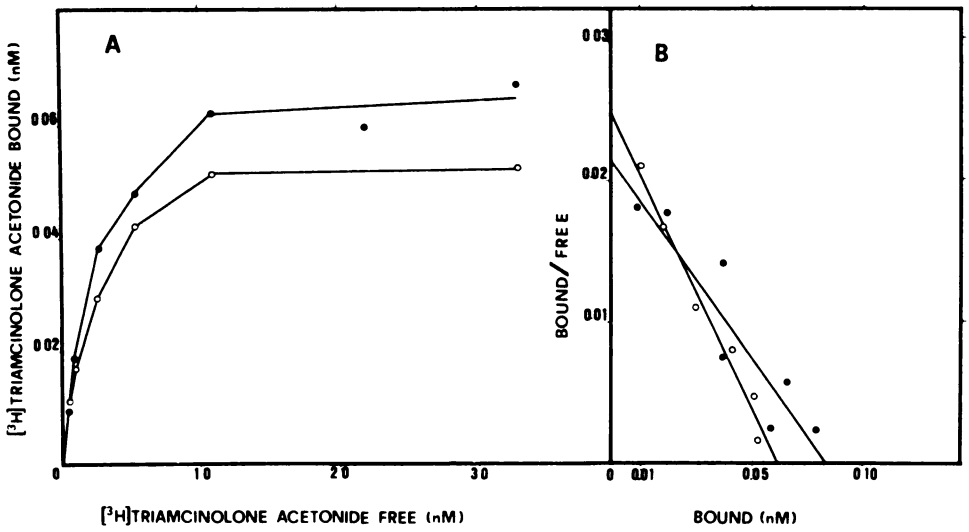

Chart 1. *A*, titration of glucocorticoid binding sites in peripheral blood (●) and bone marrow (○) cell cytosols. A constant volume of cytosol was incubated with varying concentrations of [³H]TA in the presence or absence of 3×10^{-6} M unlabeled TA. The *curves* show the specific binding taken as difference between total binding ([³H]TA alone) and nonspecific binding ([³H]TA plus unlabeled TA). *B*, binding data shown in *A* are replotted with the use of the Scatchard equation.

values, when corrected for the original cell number, gave about 2400 and 1500 receptor sites/cell for peripheral blood and bone marrow, respectively.

To characterize further the glucocorticoid binding components, cell cytosols from peripheral blood were examined on sucrose gradients following the formation of TA:receptor complexes, as illustrated in Chart 2. Cytosol, incubated at 0° and centrifuged through low-salt gradients, exhibited a peak of radioactivity in the 6 to 8*s* region of the gradient. Cytosol, incubated similarly but also containing unlabeled TA, reduced the amount of [³H]TA to near background levels, demonstrating the specific nature of the binding in the peak. When cytosols, prepared in low-salt buffer, were separated on sucrose gradients containing 0.4 M KCl, a 3.6*s* form of the hormone:receptor complex was observed. Finally, cytosol incubated at 0° and heated for 5 min at 37° prior to centrifugation on low-salt gradients exhibited a steroid:receptor complex sedimenting at 4*s*.

The ability of various unlabeled steroids to compete with [³H]TA for glucocorticoid binding sites was examined next (Table 1). Synthetic steroids, triamcinolone acetonide, dexamethasone, betamethasone, prednisolone, and natural cortisol readily compete for receptor sites. Testosterone acetate and 17β-estradiol compete very slightly at large excess. The synthetic progestin 17,21-dimethyl-19-nor-4,9-pregnadiene-3,20-dione showed an appreciable competition with [³H]triamcinolone acetonide.

The biological activity of the receptor involves the nuclear translocation of an activated ligand:receptor complex (6). As illustrated in Chart 3, incubation of the cells for 120 min at 0° with saturating concentrations of [³H]TA (2×10^{-8} M), followed by heating at 25° for 10 min, resulted in greater than an 80% hormone uptake by the nuclei. However, when the incubation was continuously maintained at 0°, the specific binding was restricted to the cytosol, and no localization of bound steroid was observed above the low level of background. Thus the [³H]TA:receptor complex was readily transferred into the nucleus through a temperature-dependent process.

Steroid Responsiveness in Culture. Having observed the presence of a "complete" receptor system in myelomonocytic leukemic cells, we throught it was appropriate to

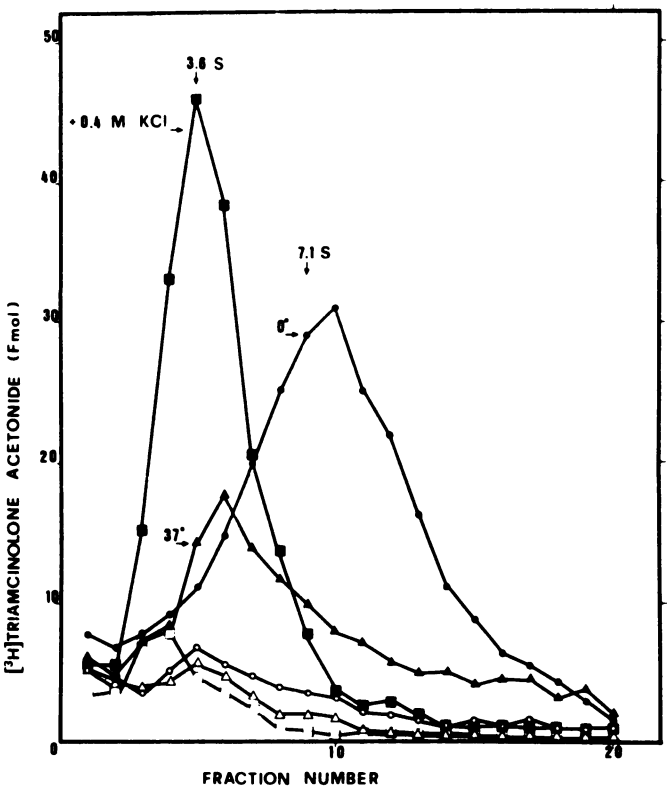

Chart 2. Sedimentation profiles of the glucocorticoid receptors separated on sucrose gradients. Cytosols prepared from peripheral blood leukocytes were applied to 5 to 20% sucrose gradients as described in "Materials and Methods" after incubation with tritiated steroid in the presence (○, □, △) or absence (●, ▲, ■) of unlabeled steroid. Shown are the sedimentation profiles of the receptors centrifuged through low-salt gradients (●), on gradients containing 0.4 M KCl (■), and those observed after heating the cytosol at 37° for 5 min prior to centrifugation through low-salt gradient (▲).

examine the effects of glucocorticoids on cells in culture. This was prompted by the fact that some human and animal cell lines in tissue culture fail to respond to steroid, despite the fact that they appear to have a normal complement of receptors (3). Effects of varying concentrations of dexamethasone on thymidine, uridine, and leucine incorporation are shown in Chart 4. Significant inhibition of thymidine and uridine incorporation is seen after exposure of the

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Table 1
Steroid specificity of [³H]TA binding in AMML

Competitive steroid	Molar ratio	% inhibition[a]
Triamcinolone acetonide	10^{-1}	33.8
	10	45.7
	10^{2}	67.9
Dexamethasone	10^{-1}	22.3
	10	50.8
	10^{2}	62.7
Prednisolone acetate	10^{-1}	4.2
	10	31.4
	10^{2}	55.2
Betamethasone	10^{-1}	3.6
	10	48.0
	10^{2}	55.9
	10^{3}	64.0
Cortisol	10^{-1}	12.3
	10	14.7
	10^{2}	46.8
	10^{3}	60.0
17β-estradiol	10^{2}	1.2
	10^{3}	6.5
Testosterone acetate	10^{2}	0.11
	10^{3}	10.8
17,21-dimethyl-19-nor-4,9-pregnadiene-3,20-dione	10^{2}	41.2
	10^{3}	57.4

[a] Results are expressed as percentage of inhibition of [³H]TA bound in the presence of unlabeled steroid relative to control (no steroid added). The binding capacity of control incubation (assigned as 100% of binding) was 3.850 cpm/mg protein.

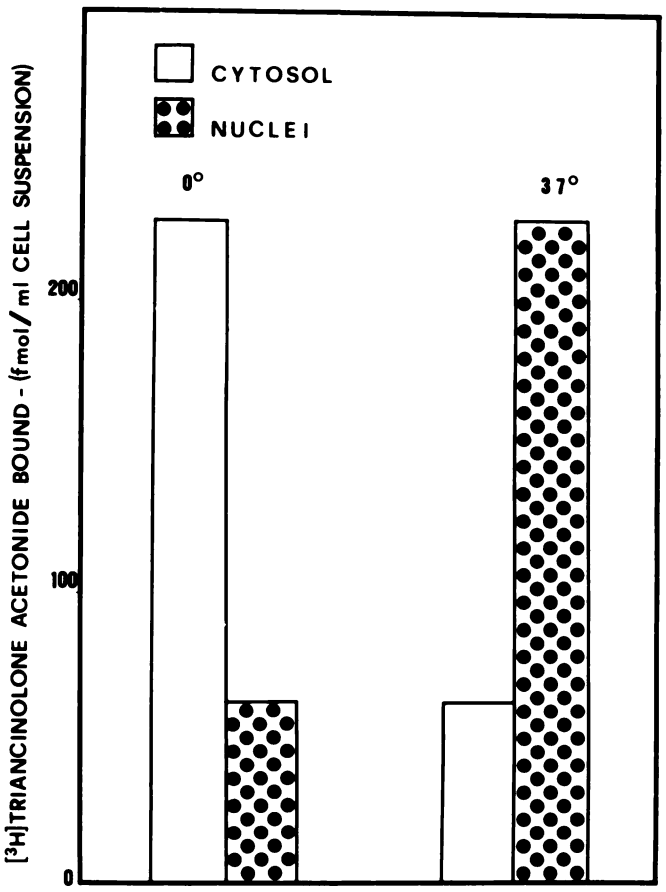

Chart 3. Distribution of receptor-bound [³H]TA between supernatant and nuclei from disrupted cells. Cell suspensions were incubated at 0° for 120 min with tritiated steroid alone or in the presence of unlabeled TA (2×10^{-6} M). At the end of the incubation period, one-half of the cell suspension was heated at 25° for 10 min. Cytoplasmic and nuclear-bound radioactivities at 0 and 25° were determined as described in "Materials and Methods."

cells to as little as 1×10^{-9} M dexamethasone/20 hr. At a steroid concentration of 1×10^{-8} M, the inhibition reached a maximum not modified by higher steroid concentrations up to 1×10^{-5} M. Similarly, the rate of leucine incorporation was also sensitive to dexamethasone. Thus, DNA and RNA protein syntheses in the cells were responsive to concentrations of dexamethasone required to saturate glucocorticoid receptor sites.

Effects of Glucocorticoid Therapy. The effects of glucocorticoid therapy on the peripheral WBC are shown in Chart 5. Due to the difficulties inherent in the morphological appearance, a certain number of cells classified as "monocytes" may well be late monoblasts. The first corticosteroid used was dexamethasone. The child showed, soon after the beginning of the therapy, a sharp increase in the leukocyte count with a high percentage of the more immature cells. Granulocytes and platelets remained at very low levels. A temporal relationship was also evident between the withdrawal of the drug and the drop in the leukocyte count. The other steroid used was prednisolone. At the dosage of 2 mg per kg per day, a slight increase in leukocyte count was observed. A second trial with prednisolone at a much larger dosage (10 mg per kg per day) was then made with the rationale that perhaps a higher concentration of the drug at the cellular level would have a cytocidal effect on leukemic cells. Again, the leukocytes (particularly the more immature) tended to increase rapidly, and at the same time liver and spleen appeared to be enlarging and scattered small s.c. nodules were evident on the scalp and in the orbital regions.

Measurement of [³H]thymidine incorporation in short-term incubations of whole blood showed a higher level of DNA synthesis in cells collected at the time of high WBC under steroid therapy as compared to cells collected 2 days after discontinuation of the therapy (Chart 6).

Discussion

The results of this study indicate that leukemic cells of the myelomonocytic variety contain complete glucocorticoid receptor systems and are inhibited *in vitro* by concentrations of steroid which saturate glucocorticoid receptor sites. Despite these facts, *in vivo* administration of glucocorticoid produced a rapid increase in WBC with a marked increase in the percentage of the more-immature cells. This phenomenon appears to be due to proliferative changes rather than to a shift of the cells from the bone marrow reserve and/or from the marginal pool into the circulation for two reasons. First, a clear temporal relationship between the beginning of therapy and the onset of a significant increase in WBC associated with clinical deterioration were observed. Secondly, and probably most important, the differences in *in vitro* incorporation of thymidine by

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peripheral leukocytes collected during steroid therapy and upon discontinuation of the drug were observed.

The discrepancy between the *in vivo* and *in vitro* effects of glucocorticoids suggests that the mechanism of action of these hormones is probably mediated by a factor(s) present *in vivo*. While the nature of this factor(s) remains to be elucidated, it should be pointed out that the presence of glucocorticoid receptors, as well as the *in vitro* sensitivity to hormone, do not specify the kind of response to therapy. Finally, the foregoing observations may have potential relevance to clinical situations. It is well known that a pool of out-of-cycle leukemic cells (G_0) relatively insensitive to chemotherapeutic drugs represents a major kinetic obstacle to cellular destruction in the management of patients with leukemia. Thus, an important clinical implication would be the possibility of using glucocorticoid hormones in selected

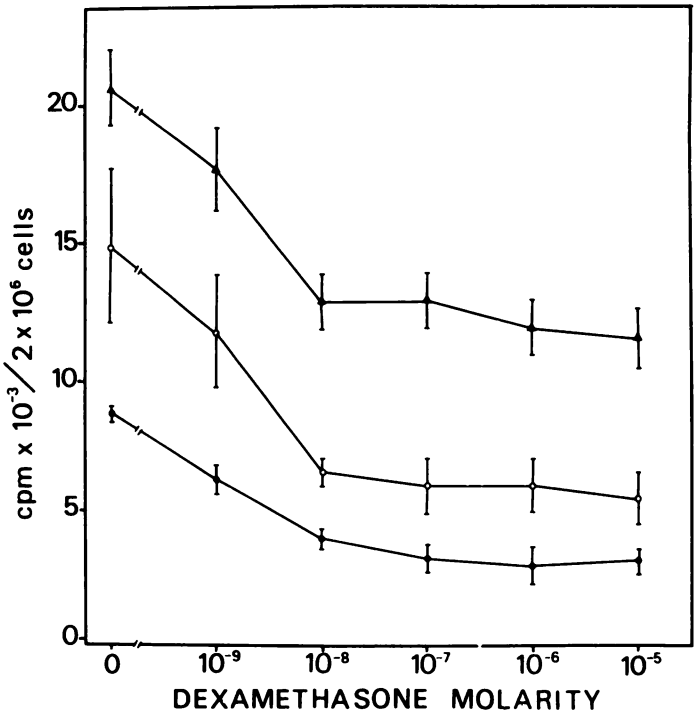

Chart 4. Effects of dexamethasone on [^{3}H]thymidine (●), [^{3}H]uridine (○), and [^{14}C]leucine (▲) incorporation. Cells were cultured for 20 hr with varying concentrations of steroid. At the end of the incubation period, radioactive precursors were added to different series of triplicate cultures. One hr later, the cells were harvested, and acid-insoluble residues were extracted and counted as described in "Materials and Methods." Each *point* represents the mean ± S.D. of 3 determinations.

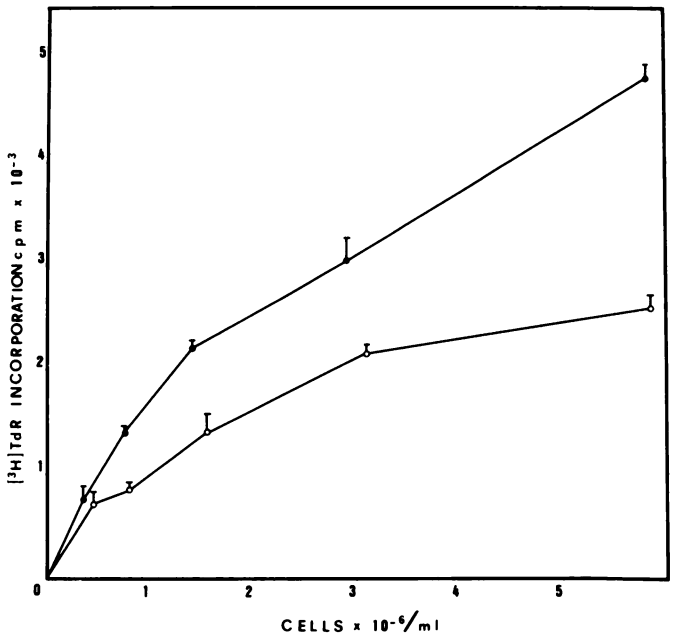

Chart 6. *In vitro* incorporation of [^{3}H]thymidine (*[^{3}H]dThd*) by peripheral leukocytes collected during prednisolone therapy (●) or 48 hr after discontinuation of therapy (○). Serial dilutions of whole blood were incubated with radioactive precursor and acid-precipitable radioactivity in the leukocytes was measured as described in "Materials and Methods."

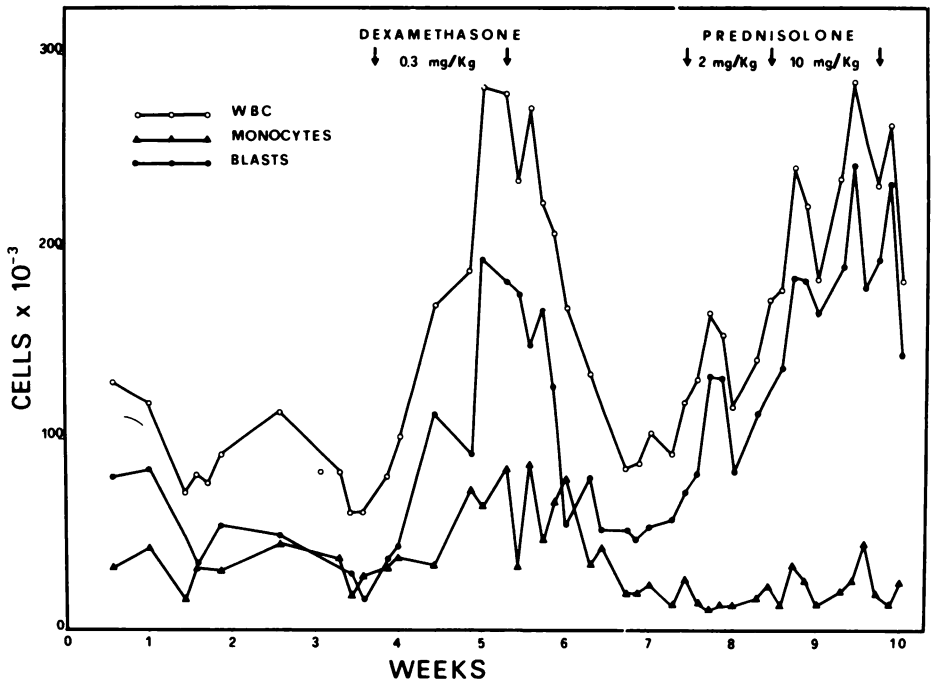

Chart 5. Effects of glucocorticoid therapy on time-course of WBC, monocytes, and blasts.

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cases of AMML for the recruitment of these leukemic cells which are otherwise insensitive to cycle-specific chemotherapeutic drugs.

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Cancer Res 1978;38:4257-4262.

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