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LAWRENCE S. S. KLAS

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NAME OF SUPERVISOR/NOM DU DIRECTEUR DE THÈSE

Hymie Anisman

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Stress and Coping Factors Influence Tumor Growth

Lawrence S. Sklar

Dissertation presented to
the Faculty of Graduate Studies
of Carleton University
in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Psychology

The undersigned recommend to the Faculty
of Graduate Studies acceptance of the thesis
"Stress and Coping Factors Influence Tumor Growth"
submitted by
Lawrence S. Sklar
in partial fulfillment of the requirements
for the degree of
Doctor of Philosophy

.....
Thesis Supervisor

.....
Chairman, Department of Psychology

Carleton University

August 1979

Abstract

Growth of syngeneic P815 Mastocytoma in DBA/2J male mice was evaluated following various social and physical stress regimens. Social housing conditions were found to influence tumor development. That is, social isolation following tumor cell transplantation exacerbated tumor growth. However, the exacerbation of tumorigenicity appeared, to a large degree, to be due to abrupt changes in social conditions (i.e. from grouped to individual housing) rather than to the isolation treatment per se. Enhanced tumor growth was also evident among mice transferred from the isolated to grouped condition, but this effect was reduced among mice that engaged in fighting.

Exposure to footshock was found to influence tumorigenicity, but such an effect was dependent upon social conditions, the chronicity of the stress regimen, the organism's ability to cope with stress, and its prior stress experience. Acute uncontrollable footshock 24 hours after tumor cell transplantation was found to enhance tumor growth among group housed mice, but to have an inhibitory effect among mice housed in isolation. The effects of shock among group housed animals varied as a function of the animal's control over shock offset. Although exposure to acute controllable footshock following tumor cell transplantation did not influence tumor development, similar amounts of inescapable footshock, in a yoked paradigm, resulted in earlier tumor appearance and enhanced tumor sizes relative to nonshocked and escapably shocked mice. The fact that the tumor enhancing effects of acute shock were not observed when animals could control shock offset suggests that

it was the inability to cope with stress behaviorally, rather than the physical stress per se which was responsible for the tumor promotion.

The enhancement of tumor growth ordinarily produced by acute uncontrollable shock was not evident if mice had been exposed to either 4 or 9 successive shock sessions prior to tumor cell transplantation. These results indicated that the processes underlying the effects of acute shock on tumorigenicity are subject to adaptation. Likewise, administration of shock over 4 successive days following tumor cell transplantation eliminated the enhancement of tumor growth produced by a single shock session. Moreover, application of uncontrollable shock over 10 successive days following tumor cell transplantation had an inhibitory effect on tumor development. Inasmuch as a single session of shock applied 1, 3, or 5 days after tumor cell transplantation augmented tumor growth, the inhibitory effects of chronic shock could not be attributed to differential effects of shock at different stages of tumor development. It was suggested that chronic shock results in transient physiological changes which actively inhibit tumor growth.

In contrast to the effects of shock following transplantation of a large number of tumor cells (6.25×10^4), enhanced tumorigenicity was not observed among mice that received 40, 60, or 100 tumor cells. The absence of enhanced tumorigenicity under the latter conditions could not be readily deduced.

In light of the various factors that contribute to stress effects on tumor growth, it was suggested that many of the inconsistent and contradictory published reports concerning the tumorigenic effects of stress might be a consequence of the social conditions and stress parameters employed. It was provisionally hypothesized that some of the neurochemical, hormonal and

immunological changes produced by stress might subserve the alterations of tumorigenicity. Finally, implications for this work to human neoplastic disease were discussed.

For Celia

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A handwritten signature in dark ink, appearing to read "L. Shlos", is written over a horizontal line.

Glossary

Angiogenesis: The development of (blood) vessels.¹

Antibody: An immunoglobulin molecule that has a specific amino acid sequence by virtue of which it interacts only with the antigen (or a similar one) that induced its synthesis in lymphoid tissue.¹

Antigen: Any substance which is capable of inducing the formation of antibody and of reacting specifically in some detectable manner with the antibodies so induced.¹

Burkitt's Lymphoma: A form of undifferentiated malignant lymphoma (neoplastic disorder of the lymphoid tissue).¹

Capillary: Any one of the minute vessels that connect the arterioles and venules. Their walls act as semipermeable membranes for the interchange of various substances.¹

Cell Contact Inhibition: Inhibition of cell mitosis by physical contact with other cells.

Dopamine-β-hydroxylase: The enzyme responsible for the conversion of dopamine to norepinephrine.

Epstein-Barr virus: A herpesvirus originally isolated from Burkitt lymphoma and believed to be the etiologic agent of infectious mononucleosis.¹

Herpes Simplex virus: An acute viral disease marked by groups of vesicles on the skin, often on the borders of lips and nares, or on the genitals. Often accompanied by fever, sunburn, skin abrasions, and emotional disturbances.¹

Herpesvirus: Any of a large group of DNA viruses. The viruses mature in the nucleus of the infected cell.

Laparotomy: Surgical incision through the flank. ¹

Lymphocyte: A mononuclear leukocyte 7 μ - 20 μ in diameter. It is chiefly a product of lymphoid tissue and participates in humoral and cell-mediated immunity. ¹

B-lymphocyte: "bursa equivalent" lymphocytes. Lymphocytes that are thymus independent, migrating to the tissues without passing through, or being influenced by, the thymus. B-lymphocytes mature into plasma cells that synthesize humoral antibody. ¹

T-lymphocytes (T-cells): Thymus dependent lymphocytes, that either pass through the thymus or are influenced by it. They are involved in cell mediated immunity and can kill tumor cells. ¹

Macrophage: Any of the large, highly phagocytic cells. Involved in the inflammation and immune response. ¹

Metastasis (plural: metastases): The transfer of disease from one organ or part to another not directly connected with it. ¹

Natural Killer Cells: Cytotoxic cells which do not need to be sensitized by exposure to antigen and are fairly specific to abnormal entities such as tumor cells. They are believed to be immature lymphocytes.

Neoplastic Disease (cancer, tumor): The progressive multiplication of cells under conditions that would not elicit, or would cause cessation of, multiplication of normal cells. Cancers by definition are metastatic; Tumors may not be necessarily so. ¹

Positioning Regulators: Those factors which keep tissue cells immobile and in their appropriate place.

Radiations: Electromagnetic waves or particulate rays which emanate from a source.¹

Corpuscular radiation: Radiations other than x-rays and gamma rays, such as alpha-, beta-, proton-, neutron-, positron-, and deuteron-rays. (particulate)¹

Ionizing radiation: High-energy radiations (x-rays and gamma-rays) which interacts to produce ion pairs in matter.¹

Ultraviolet radiation: Rays of radiation between violet rays and roentgen rays. They have powerful actinic and chemical properties.¹

Tyrosine-hydroxylase: The enzyme which converts tyrosine to L-DOPA.

¹Dorlands Illustrated Medical Dictionary. 25th Edition. Philadelphia: Saunders, 1974.

Figure Captions

- Figure 1. Mean ($\pm$ S.E.M.) day of tumor appearance as a function of cell dose and housing condition.
- Figure 2. Mean ($\pm$ S.E.M.) tumor area over days as a function of cell dose and housing condition.
- Figure 3. Mean ($\pm$ S.E.M.) day of mortality as a function of cell dose and housing condition.
- Figure 4. Mean ($\pm$ S.E.M.) tumor area over days, as well as mean ($\pm$ S.E.M.) tumor weight on day 11 (inset), as a function of housing condition.
- Figure 5. Mean ($\pm$ S.E.M.) day of tumor appearance among mice that were raised in communal cages and then transferred to isolation (G - I), raised in isolation and then transferred to communal cages (I - G), or housed either in isolation (I - I) or in communal cages (G - G) throughout the experiment.
- Figure 6. Mean ($\pm$ S.E.M.) tumor area over days among mice that were raised in communal cages and then transferred to isolation (G - I), raised in isolation and then transferred to communal cages (I - G), or housed either in isolation (I - I) or in communal cages (G - G) throughout the experiment. The inset shows the mean ($\pm$ S.E.M.) tumor area of mice of group I - G categorized with respect to whether they exhibited persistent fighting after transfer to communal cages.

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Figure 13. Mean ($\pm$ S.E.M.) day of tumor appearance among mice that were exposed to 1 session of inescapable shock, either 1, 3, or 5 days following tumor cell transplantation or no shock.

- Figure 14. Mean ($\pm$ S.E.M.) tumor area over days, as well as mean ($\pm$ S.E.M.) day of mortality (inset), among mice that were exposed to 1 session of inescapable shock either 1, 3, or 5 days following tumor cell transplantation or no shock.
- Figure 15. Mean ($\pm$ S.E.M.) day of tumor appearance as a function of adaptation treatment. Mice received either no shock pre-exposure (NO ADAPT), 4 successive days of shock pre-exposure (4 ADAPT.), or 9 successive days of shock pre-exposure (9 ADAPT.). Tumors were transplanted immediately after the last adaptation session, and mice received one final session of inescapable shock 24 hours later. A fourth group served as a no shock control.
- Figure 16. Mean ($\pm$ S.E.M.) tumor area over days, as well as mean ($\pm$ S.E.M.) day of mortality (inset), as a function of adaptation treatment. Mice received either no adaptation (0), 4 successive days of adaptation exposure (4), or 9 successive days of adaptation exposure (9). An additional group served as a no shock control (NS).
- Figure 17. Mean ($\pm$ S.E.M.) day of tumor appearance among mice that received escapable shock (ES), yoked inescapable shock (YIS), or no shock (NS).
- Figure 18. Mean ($\pm$ S.E.M.) tumor area over days, as well as mean ($\pm$ S.E.M.) day of mortality (inset), among mice that received escapable shock (ES), yoked inescapable shock (YIS), or no shock (NS).

I. Introduction

Exposure to aversive stimulation will typically result in behavioral and physiological changes in order to meet environmental demands (Anisman, 1978; Appley & Trumbull, 1967; Barry & Buckley, 1966; Selye, 1956; Yuwiler, 1976). For example, behaviorally, animals may attempt flight responses or aggressive postures in order to diminish the potential impact of the stress¹. Physiologically, stressors elicit alterations in neurochemical (Anisman, 1978; Stone, 1975), hormonal (Yuwiler, 1976), and immunological (Amkraut & Solomon, 1975) functioning. In light of the varied physiological consequences of aversive stimulation, it is not surprising that stress has been implicated as a precipitating factor of a number of disease entities. For example, the role of stress in several psychological and physical pathologies, such as depression (Akiskal & McKinney, 1973, 1975), gastric ulceration (Weiss, 1968, 1970, 1971a,b,c), and hypertension (Galosy & Gebelein, 1977) has been well documented. In addition, there is evidence suggesting that physical and social stressors may be involved in carcinogenesis; however, inconsistent and often contradictory results have been reported in this respect (Fox,

¹Although the term stress has been used extensively in the psychological literature for several decades, a precise definition of the term has proven to be elusive (see discussion in Ursin, Baade, & Levine, 1978; Yuwiler, 1976). Stress in the present investigation will be thought of as any aversive stimulus whose impact results in physiological or behavioral changes with apparent adaptive value. It is recognized that some nonaversive stimuli will produce behavioral or physiological changes with adaptive significance, and some apparently aversive stimuli will not produce such changes or will have delayed effects. Unfortunately, a more precise definition of stress is not available.

1978; LaBarba, 1970). Whereas some investigators have reported stress-induced exacerbation of tumorigenicity, other investigators have found stress to retard tumor growth (LaBarba, 1970). Interpretation of these divergent results is complicated by the fact that researchers have tended to use different animal species, tumor systems and stressors, as well as different methods of measuring tumor development.

The physiological response to stress will be described in the ensuing section in order to assess the relationship between stress and carcinogenesis. The neurochemical, hormonal and immunological consequences of stress will be reviewed first. These mechanisms are possibly involved in the mediation of stress-induced alterations in tumorigenicity. Thus, through examination of the general characteristics of stress effects on these systems, some order may be forthcoming in the apparently inconsistent effects of stress on carcinogenesis. Following the review of the physiological consequences of stress, the various phases of neoplastic disease will be discussed briefly, in order to acquaint the reader with the carcinogenic process, and to supply a different framework into which stress-tumor interactions might fall in an orderly manner. Finally, a review of the literature implicating the involvement of stress in carcinogenesis will be presented, indicating what is known about the relationship between stress and cancer, what is suggested, and what cannot be determined on the basis of the presently available data.

II. Physiological Consequences of Stress

Prior to examining the effects of stress on carcinogenesis it is necessary to evaluate the neurochemical, hormonal and immunological consequences of stress. This is necessary since a stress effect on carcinogenesis may be mediated by one or by a combination of these mechanisms, and an understanding of them will be useful when attempting to evaluate stress-tumor interactions. Moreover, relatively little research has been conducted which directly assesses the effects of stress on tumorigenicity, and an examination of the possible interaction of stress-related physiological mechanisms with cancer development may lead to relevant hypotheses concerning the role of stress in cancer growth. Finally, and most importantly, a determination of the general characteristics of stress effects on physiological systems may contribute to both the design of an experimental strategy, and to the understanding of stress-tumor interactions.

II A. Central Nervous System

Aversive insults result in a multiplicity of neurochemical changes. Some of these alterations are transient in nature, while others are fairly long lasting. A wide variety of factors have been shown to modify stress-induced alterations of central nervous system function (cf. Anisman, 1978; Stone, 1975). Among other things, the organisms ability to cope with stress, its previous stress history, social conditions, and genetic factors all determine the nature and extent of the observed neurochemical changes. Although a variety of stressors have been shown to produce similar neurochemical consequences, only the central effects of the three most

widely employed stressors in cancer research (cold, restraint and footshock) will be examined in detail. In addition the neurochemical sequelae of isolation, which is sometimes considered to be a stressor itself, and is a potent modifier of stress-induced neurochemical alterations, will be considered.

II A.1 Stress and Catecholamines: Acute effects.

Exposure to acute, moderate, hypothermic stress among rats, mice and pigeons has been found to increase utilization of dopamine (DA) (Ishii, Homma, & Yoshikawa, 1975; Kobayashi, Palkovits, Kizer, Jacobowitz, & Kopin, 1976) and norepinephrine (NE) (Beley, Beley, Rochette, & Bralet, 1977; Goldstein & Nakajima, 1966; Gordon, Spector, Sjoerdsma, & Udenfriend, 1966; Reid, Volicer, Smookler, Bearen, & Brodie, 1968; Saarela, Hissa, Hohtola, & Jeronen, 1977; Simmonds, 1969, 1971). The effects of cold stress on brain NE were much more extensive than on brain DA. Increased utilization of NE was observed in whole brain (Goldstein & Nakajima, 1966; Gordon, et al., 1966; Reid, et al., 1968; Saarela, et al., 1977) as well as in hypothalamus, hippocampus and brainstem (Beley, et al., 1977; Simmonds, 1969; 1971; see review in Anisman, 1978). In contrast, increased utilization of DA has not been observed in whole brain or in structures such as the hypothalamus (Corrodi, Fuxe & Hokfelt, 1967; Reid, et al., 1968). More discrete analyses have, however, revealed DA depletion in the arcuate nucleus of the hypothalamus (Kobayashi, et al., 1976). Not unexpectedly, the increased utilization of NE following hypothermic stress was accompanied by increased synthesis of the amine (Beley, et al., 1977; Goldstein & Nakajima, 1966; Gordon, et al., 1966; Reid, et al., 1968; Saarela, et al., 1977; Simmonds, 1969, 1971). If core temperature was reduced quickly, either by shaving the animals prior to

cold exposure, or by immersing them in cold water, the utilization of DA and NE exceeded their rate of synthesis, and resulted in a net depletion of these amines in the hypothalamus and telencephalon (Barchas & Freedman, 1963; Ritter & Pelzer, 1978; Ritter, Pelzer, & Ritter, 1978; Ritter & Ritter, 1977), as well as in the arcuate nucleus (Kobayashi, et al., 1976).

Exposure to acute (0.5 - 4.0 hr) restraint stress also produced increased utilization and synthesis of DA and NE (Bliss & Ailion, 1971; Carr & Moore, 1968; Corrodi, et al., 1968; Hustzi & Kenessey, 1976; Kiem & Sigg, 1976; Lindbrink, Corrodi, Fuxe, & Olson, 1972; Welch & Welch, 1968a,b, 1970). Again the effect of stress on NE was more extensive than on DA. Depletions of NE levels following restraint stress were observed in the whole brain (Carr & Moore, 1968; Welch & Welch, 1968a,b), brainstem, cerebellum, cortex (Bliss & Zwanziger, 1966) and the hypothalamus (Bliss & Zwanziger, 1966; Kiem & Sigg, 1976), as well as in several areas of the brain ventricular system (Mitro, Palkovits, & Kvetnansky, 1976). Furthermore, within the hypothalamus, a depletion of NE was observed in the supraoptic, ventromedial, and arcuate nuclei (Kobayashi, et al., 1976; Kvetnansky, Palkovits, Mitro, Torda, & Mikulaj, 1977). Depletion of DA levels after restraint stress, on the other hand, were only observed in the arcuate nucleus (Kobayashi, et al., 1976; Kvetnansky, Mitro, Palkovits, Vigas, Albrecht, Torda, & Mikulaj, 1975; Kvetnansky, et al., 1977). In fact, increased DA synthesis induced by restraint was more than sufficient to compensate for the increase in utilization in less discrete brain areas (Bliss & Ailion, 1971), as indicated by the increased levels of DA observed in the whole brain and hypothalamus (Carr & Moore, 1968; Kiem & Sigg, 1976; Lindbrink, et al., 1972; Welch & Welch, 1968b, 1970).

Following exposure to uncontrollable electric shock, the neurochemical changes observed are similar to those seen after cold exposure or restraint. Stress-induced increased utilization and synthesis of DA and NE have been reported (Bliss & Ailion, 1971; Bliss, Ailion, & Zwanziger, 1968; Brown, Snider, & Carlsson, 1974b; Korf, Aghajanian, & Roth, 1973; Ladisich & Baumann, 1971; Otto & Paalzow, 1975; Thierry, Blanc, & Glowinski, 1971; Thierry, Javoy, Glowinski, & Kety, 1968; Thierry, Tassin, Blanc, & Glowinski, 1976; Weiss, Glazer, & Pohorecky, 1976). After protracted and more severe stress, depletions of these amines have been reported in whole brain, cortex, hypothalamus, cerebellum, and brainstem (Bliss & Ailion, 1969; Bliss, et al., 1968; Bliss & Zwanziger, 1966; Gordon, et al., 1966; Maynert & Levi, 1964; Moore & Lariviere, 1964; Ordy, Samorajski & Schroeder, 1966; Pare & Livingston, 1970; Paulsen & Hess, 1963; Ritter, et al., 1978; Stone, 1971, 1973; Thierry, et al., 1968; Zigmond & Harvey, 1970). The shock-induced DA changes may have been due to stress specifically activating the mesolimbic DA system (Thierry, et al., 1976), while some of the NE changes may have been due to activation of the dorsal NE bundle (Korf, et al., 1973; Korf, 1976).

II A.2 Stress and Catecholamines: Chronic effects.

While acute stress increases utilization and synthesis of catecholamines, the reductions of available DA and NE presumably occur because utilization exceeds synthesis. Not unexpectedly, chronic exposure to stress also results in increased utilization and synthesis of catecholamines; however, reductions in levels of DA and NE are not apparent.

It has been shown that during a regimen of chronic cold exposure NE utilization remains greatly increased (Bhagat, 1969; Reid, et al., 1968). The rate of NE synthesis, however, was even further increased, and

surpassed the rate of utilization, so that increased levels of brain NE were found (Bhagat, 1969; Ingenito, 1968; Ingenito & Bonneycastle, 1967). The increased synthesis seemed to be due to increased tyrosine hydroxylase activity following chronic cold exposure (Thonen, 1970). As in the case of cold exposure, one session of protracted immobilization, or repeated immobilizations of shorter duration, did not result in the depletions of NE that were ordinarily induced by acute stress (Keim & Sigg, 1976; Kvetnansky, et al., 1975, 1977). In fact, increased NE levels were found in several discrete hypothalamic nuclei (Kvetnansky, et al., 1975, 1977). Like NE, the reduction of DA in the arcuate nucleus which occurred after acute immobilization was no longer apparent following repeated restraint stress (Kvetnansky, et al., 1977). Since increased tyrosine hydroxylase activity in the arcuate and ventromedial nuclei of the hypothalamus (Kobayashi, et al., 1976), as well as increased dopamine- β -hydroxylase activity in the dorsomedial nucleus (Kvetnansky, et al., 1977), were observed following chronic immobilization stress, it is likely that a further increase in the synthesis of the amines was responsible for this effect. In a similar fashion, chronic shock exposure also increased brain DA and NE levels (Huttenen, 1971; Neilson & Fleming, 1968; Pare & Livingston, 1970; Thierry, et al., 1968; Weiss, Glazer, Pohorecky, Brick, & Miller, 1975), or at least ameliorated the depletion provoked by acute stress (Zigmond & Harvey, 1970). Again, increased tyrosine hydroxylase activity was noted following chronic shock exposure (Weiss, et al., 1975) indicating that increases in synthesis likely mediated this effect (Thierry, et al., 1968).

Summarizing, it appears that neurochemical adaptation occurs during chronic stress exposure. While utilization of catecholamines remains at a constant

increased level, continual exacerbation of synthesis takes place so that amine availability is equal to, or exceeds, requirements.

II A.3. Stress and Other Neurochemical Systems.

While an extensive amount of research has been conducted concerning the catecholaminergic consequences of stress exposure, relatively little research has been conducted examining the effects of stress on other neural mechanisms. By far, most of the remaining information deals with stress effects on serotonin (5-HT) function, with a few studies examining the acetylcholine (ACh) and gamma-aminobutyric acid (GABA) changes induced by stress.

Several reports have indicated that acute hypothermic stress has no effect on 5-HT activity in the whole brain (Ingenito, 1967; Maynert & Levi, 1964). However, others have reported a slight reduction in 5-HT whole brain levels (Saito, Morita, Myazaki, & Tagaki, 1976), and a more extensive depletion of 5-HT in the hypothalamus (Telegdy & Vermes, 1976). Similarly, acute restraint stress produced a reduction of 5-HT levels in the median eminence, lateral amygdaloid nucleus, hippocampus, cingulate cortex and the dorsal raphe nucleus (Palkovits, Brownstein, Kizer, Saavedra, & Kopin, 1976).

The apparent restraint-produced increase in both synthesis and utilization of 5-HT in the whole brain (Bliss, Thatcher, & Ailion, 1972; Corrodi, et al., 1968; Curzon & Green, 1969; Curzon, Joseph, & Knott, 1972; Thierry, Fekete, & Glowinski, 1968b) suggests that synthesis of 5-HT could not keep pace with demand in the more discrete brain regions. Confusing the picture somewhat are the findings of increased whole brain levels of 5-HT following restraint stress (De Schaepdauver, Preziosi, & Scapagnini, 1969; Welch & Welch, 1968a,b),

however differences in parameters such as housing (Modigh, 1973, 1974, 1976; Thoa, Tizabi, & Jacobowitz, 1976; Welch & Welch, 1968a,b) and length of interval between stress offset and decapitation (Telegdy & Vermes, 1976) could conceivably account for the discrepant findings. The changes in 5-HT activity induced by shock stress were similar to those produced by cold and restraint. Utilization and synthesis of 5-HT were increased (Bliss, et al., 1972; Thierry, et al., 1968a,b; Thierry, 1973) in direct proportion to stress severity (Thierry, et al., 1968a,b). In discrete brain areas, such as the hypothalamus, utilization appeared to exceed synthesis after severe stress, and a depletion of 5-HT levels was observed (Telegdy & Vermes, 1976). It should be noted, however, that much more severe stress was necessary to elicit these changes in 5-HT than is normally necessary to produce the NE alterations (Thierry, et al., 1968a,b).

Increased brain levels of ACh following hypothermic (Zajackowska, 1975; Saito, et al., 1975) and footshock stress (Aprison & Hingtgen, 1966, 1969, 1970; Aprison, Hingtgen, & McBride, 1975; Aprison, Kariya, Hingtgen, & Toru, 1968; Karczmar, Scudder, & Richardson, 1973) have also been reported. Similarly, restraint (Chattopadhyay & Uniyal, 1975) and footshock stress (Chattopadhyay & Uniyal, 1975; McBride, Hingtgen, & Aprison, 1976) appeared to increase GABA levels as well. Whether these increased levels represented decreased utilization, increased synthesis, or both, remains unclear at present. Since the ACh changes occur with a somewhat longer latency than the DA and NE alterations, it is conceivable that the ACh changes are a function of the stress-induced amine changes.

II A.4 Factors Influencing the Central Consequences of Stress.

(1) Social Conditions

Since isolation can be considered a stressor in its own right, as well as a condition which modifies the effects of other stressors (Welch & Welch, 1968a,b, 1970), the neurochemical consequences of isolation alone will be discussed first, followed by an examination of its interaction with other stressors. Unlike the stressors described previously, the neurochemical consequences of isolation seem to vary a great deal between species (Brain, 1975). Among mice, isolation produced a decrease in utilization of DA and NE (Welch & Welch, 1968a; Modigh, 1974), as well as a corresponding decline in synthesis (Modigh, 1973). Endogenous levels of NE have been reported to be both increased (Welch & Welch, 1968a) and decreased (Welch & Welch, 1968b). With respect to 5-HT, there are conflicting reports as to whether this amine is affected by isolation among mice (Modigh, 1974, 1976; Welch & Welch, 1967, 1968a,b,c, 1970).

Among rats, effects opposite to those seen in mice have been reported. That is, isolation appeared to increase synthesis and utilization of NE and 5-HT in the brainstem and telencephalon (Stolk, Conner, & Barchas, 1974a), as well as increase the level of NE in the whole brain (Geller, Yuwiler, & Zolman, 1965; Nishikawa, Kajiwara, Kono, Sano, Nagasaki, Tanaka, & Norda, 1974). However, some of the variations among animal species might be an artifact of the assaying of relatively large tissue samples. When more discrete brain regions are examined, both increases and decreases of DA and NE concentrations have been found, and decreased amine turnover has been noted among rats (Thoa, Tizabi, & Jacobowitz, 1977).

As previously mentioned, housing conditions could potentially influence stress-induced neurochemical alterations (Modigh, 1973, 1974, 1976; Thoa, et al., 1976; Weiss, et al., 1976; Welch & Welch, 1968a,b). For example, Welch and Welch (1968b) found that among mice raised in isolation, restraint increased the utilization of DA and NE, whereas this stress decreased the utilization of these amines among group housed mice. Similarly, Weiss, et al. (1976) have reported that shock stress reduced NE levels only among group housed rats. This protective effect of isolation was mitigated, however, when different shock parameters were employed (see Weiss, et al., 1975).

(2) Behavioral Coping

The ability to cope behaviorally with stress can modify the neurochemical consequences of stress as well. Specifically, only inescapable/unavoidable shock produced depletions of central NE (Weiss, Stone & Harrell, 1970; Weiss, et al., 1976). Equivalent amounts of escapable shock had either no effect, or produced increased NE levels in various brain areas (Weiss, et al., 1970, 1976). Similarly, allowing rats to fight during shock stress prevented the alterations of NE levels that were otherwise observed (Stolk, Conner, Levine, & Barchas, 1974b). Since fighting is a species specific defense response, it has been suggested that coping with stress, as reported by Weiss, et al. (1970, 1976), may have been responsible for the prevention of the neurochemical changes otherwise observed. Thus, it appears that when animals are placed in a stressful situation, increases of both the utilization and synthesis of catecholamines occur. If the organism finds a method with which to cope behaviorally with stress, utilization declines somewhat (Weiss, et al., 1976), resulting in either no change, or increases in net amine availability. However, if coping responses are not available, utilization of catecholamines will remain at high levels, or continue to increase,

eventually exceeding synthesis and thus producing a reduction of available amines. Summarizing, stress per se does not appear to be the critical factor necessary to produce NE depletion. Rather, the organism's inability to cope behaviorally with stress seems to be responsible for the neurochemical change.

The role of coping in producing neurochemical alterations may not be restricted to NE. Indeed, Karczmar, et al. (1973) found that although inescapable shock produced increased brain ACh levels, escapable shock had no such effect. Unfortunately, since the inescapable shock and escapable shock groups received different amounts of shock in this study, conclusions pertaining to the role of controllability of stress must be made cautiously.

(3) Chronicity

As pointed out in the preceding sections, the chronicity of stress exposure determines the nature and extent of the neurochemical changes. With the exception of isolation, it was apparent that acute severe stress increased utilization of catecholamines and increased synthesis to a somewhat lesser degree, so that a net reduction of available amines was observed (e.g. Barchas & Freedman, 1963; Beley, et al., 1977; Bliss & Ailion, 1971; Brown, et al., 1974b; Carr & Moore, 1968; Goldstein & Nakajima, 1966; Hustzi & Kenessey, 1976; Kiem & Sigg, 1976; Kobayashi, et al., 1976; Kvetnansky, et al., 1975, 1977; Pare & Livingston, 1970; Ritter, et al., 1978; Thierry, et al., 1968a,b, 1971, 1976; Zigmond & Harvey, 1970). However, following chronic stress exposure, synthesis was further enhanced, so that either increases, or no change, in catecholamine levels were noted (e.g. Bhagat, 1969; Ingenito, 1968; Kiem & Sigg, 1976; Kvetnansky, et al.,

1975, 1977; Reid, et al., 1968; Thierry, et al., 1968a; Weiss, et al., 1975; Zigmond & Harvey, 1970). Thus, following acute stress exposure there is a reduction of amine availability, and following chronic stress there is enhanced amine availability.

(4) Previous Stress History

Previous stress history also appears to modify stress-induced alterations of neurochemical activity. Specifically, a small number of footshocks could elicit hypothalamic NE depletion among mice provided that the animals were previously exposed to severe footshock stress (Anisman & Sklar, 1979). Since the small number of footshocks were not sufficient to elicit this neurochemical change in naive mice, these results suggested that neurochemical activity was subject to either sensitization or conditioning processes. Indeed, a CS paired with footshock came to elicit increased neuronal firing in brainstem cells which previously increased their rate of firing in response to stress (Vertes & Miller, 1976). Similarly, stress-induced cholinergic changes have been reported to come under stimulus control (Hingtgen, Smith, Shea, Aprison, & Gaff, 1976). Furthermore, it has been shown that the extent of NE depletion is exaggerated over successive stress sessions, although levels of the amine return to basal values within 24 hours of a given session (Kiem & Sigg, 1976). Thus, it seems that relatively mild stressors, or stimuli with no inherent aversive properties, may come to elicit neurochemical alterations that are similar to those produced by stress of a more severe nature. Of course, these alterations are entirely dependent upon the organism's previous stress experience.

II B. Hormonal Mechanisms

The distinction between transmitters and hormones is that the former are thought to act on tissue receptors over a short distance with a short time course, whereas the latter are linked to long distance communication via the blood stream, with a somewhat longer time course (Kebabian, 1978). For this reason, peripheral secretion of substances which can be thought of as transmitters, (e.g. norepinephrine), will be considered in conjunction with other hormones.

Stress results in the release of corticotropin releasing factor (CRF) from the neurosecretory cells in the supraoptic and periventricular nuclei of the hypothalamus. Corticotropin releasing factor is released from the terminals of these cell bodies present in the median eminence, and stimulates the release of adrenocorticotrophic hormone (ACTH) from the pituitary (Soderburg, 1967; Vernikos-Danellis, 1964; Yuwiler, 1976). Release of ACTH in turn, stimulates the synthesis and release of adrenal corticoids from the adrenal cortex (Yuwiler, 1976). This system appears to be under negative feedback control, in that circulating adrenal corticoids may inhibit the synthesis and release of CRF, and thus the release of ACTH as well (Fortier, 1959; Mason, 1968; Sayers & Sayers, 1947; Schapiro, Marmorston, & Sobel, 1958; Yates, Leeman, Glenister, & Dallman, 1961). Stress-induced release of other pituitary hormones has also been documented; these include thyrotropin (TSH) (Del Conte, Rovello, & Stux, 1955; Ducommun, Vale, Sakiz, & Guillemin, 1967; McCann, Ajika, Fawcett, Hefco, Illner, Negro-Villar, Orias, Watson, & Krulich, 1973; Pumtriano & Meites, 1951), prolactin (PRL) (Ajika, Kalra, Fawcett, Krulich, & McCann, 1972; Grosvenor, McCann, & Naller,

1965; Neill, 1970), growth hormone (GH) (Brown & Reichlin, 1972; Brown, Schlach, & Reichlin, 1971a,b; Mason, Maher, Hartley, Mougey, Perlow, & Jones, 1976; McCann, et al., 1973) and leuteinizing hormone (LH) (McCann, et al., 1973). In addition to these, stress also resulted in enhanced synthesis and release of NE (Bassett & Cairncross, 1976a,b,c; Goldstein & Nakajima, 1966; Gordon, et al., 1966; Leduc, 1961; McCarty, Chiueh, & Kopin, 1978; Oliverio & Starjne, 1965; Rubensen, 1969; Saarela, et al., 1977; Snider, Brown, & Carlson, 1974; Weil-Fugazza & Godefray, 1976), and epinephrine (E) (Bassett & Cairncross, 1976a; Klem & Sigg, 1976; Kvetnansky & Mikulaj, 1970) from a variety of peripheral organs. The stress-induced release of pituitary hormones appeared to be biphasic, commencing with an initial increase of secretion followed thereafter by inhibition of release (Badrack, Brimblecombe, Reiss, & Reiss, 1954; Brush & Levine, 1966; Levine & Brush, 1967; McCann, et al., 1973).

II B.1 Stress and Hormones: Acute Effects.

Acute exposure to hypothermic stress resulted in enhanced secretion of ACTH from the pituitary (Knigge, 1960) and increased synthesis and release of adrenal corticosteroids (Boulourd, 1966; Jonac, 1964; Knigge, 1960) in rats and mice. Abrupt changes in core temperature (as measured by rectal temperature) were more conducive to these hormonal alterations than gradual cooling (Bernhard, 1956). A short-lived increased secretion of TSH and thyroid hormones has also been observed (Bondy & Hagewood, 1953; Cottle & Carlson, 1956; Martin & Reichlin, 1970; Onaya & Hashizume, 1976; Tache, Ruisseau, Ducharme, & Collu, 1978). In addition, cold stress appeared to have profound effects on peripheral NE activity. Specifically, in both

rats and mice, exposure to hypothermic stress has been found to increase utilization of NE in the heart (Bhagat & Friedman, 1969; Corrodi, et al., 1967; Corrodi, Fuxe, Hamberger, & Ljungdahl, 1970; Draskoczy, Pulley, & Burnock, 1966; Goldstein & Nakajima, 1966; Gordon, et al., 1966; Olivario & Starjne, 1965; Rubensen, 1969; Saarela, et al., 1977), brown fat (Draskoczy, et al., 1966) and skin (Rubensen, 1969). Synthesis of peripheral NE was also enhanced by cold stress in these species (Corrodi, et al., 1967, 1970; Goldstein & Nakajima, 1966; Gordon, et al., 1966; Olivario & Starjne, 1965). In man, an increased release of NE, as well as increased DBH activity has been noted in plasma (Winer & Carter, 1977; Wooten & Cardon, 1973).

Like cold exposure, acute restraint stress also resulted in an increase of plasma and adrenal corticosteroids (Brown, et al., 1971a; Burstein, Bhavani, & Kimball, 1964; Carr & Moore, 1968; DeSchaepe-dryver, Preziosi, & Scapagnini, 1969; Feldman & Brown, 1975, 1976; Keim & Sigg, 1976, 1977; Kvetnansky, et al., 1975, 1976; Levine & Treiman, 1964; Mason, et al., 1976; Mikulaj, Mitro, Murgas, & Dobrakovova, 1973; Zimmerman & Critchlow, 1967). Moreover, acute restraint stress appeared to induce increased secretion of prolactin (Van Vugt, Bruni, & Meites, 1978) and renin (Sigg, Kiem, & Sigg, 1978), as well as TSH and GH (Baldrick, et al., 1954; Brown, et al., 1971a; Mason, et al., 1976); however, the effect on the latter two hormones was of fairly short duration, lasting for only 2 hours. Immobilization stress also increased the synthesis and release of NE (Kiem & Sigg, 1976; Kvetnansky & Mikulaj, 1970; Rubensen, 1969; Weil-Fugazza & Godefray, 1976) and E (Kiem & Sigg, 1976; Kvetnansky & Mikulaj, 1970) in the adrenals and heart.

Consistent with these findings, acute electric shock resulted in

increased ACTH secretion from the pituitary, as well as increased release and synthesis of adrenal corticosteroids (Bassett & Cairncross, 1975; Coover, Ursin, & Levine, 1973; Friedman, Ader, Grotta, & Larson, 1967; Levine, Madden, Conner, Moskal, & Anderson, 1973). Similarly, acute shock increased synthesis and release of NE and E peripherally (Bassett & Cairncross, 1976a,b,c; McCarty, et al., 1978; Ord, et al., 1966; Rubensen, 1969), as well as inducing an increase in the synthesis of DA in the adrenals (Snider, et al., 1974).

II B.2 Factors Influencing the Hormonal Consequences of Stress.

(1) Chronicity

As in the case of the neurochemical alterations produced by stress, the stress-induced hormonal changes appear to undergo adaptation following chronic stress. Following chronic exposure to cold, restraint, or shock stress the ACTH and adrenocorticoid release induced by acute stress was greatly reduced (Feldman & Brown, 1975, 1976; Kiem & Sigg, 1976; Kvetnansky, et al., 1975, 1976; Levine, et al., 1973; Mason, et al., 1976; Mikulaj, et al., 1973; Mikulaj, Kvetnansky, Murgas, Parizkova, & Vencel, 1976; Tache, et al., 1978; Weiss, et al., 1975), as was the restraint-induced GH release (Mason, et al., 1976) and the cold-induced TSH release (Martin, 1974). Adaptation also occurs with respect to peripheral NE and E; however, unlike the previously discussed hormones, adaptation appeared to result from a further increase in synthesis induced by chronic stress rather than a reduction in the amount released (Bassett & Cairncross, 1976a,b; Kiem & Sigg, 1976; Leduc, 1961; Mikulaj, et al., 1976).

(2) Behavioral Coping

Coping factors may influence stress-induced hormonal activation. Inescapable

shock increased levels of plasma corticosterone to a much larger degree than did shock stress which could be controlled behaviorally (Weiss, 1971a,c). In these studies a yoked paradigm was employed, such that the animals received identical amounts of shock, but differed with respect to their ability to control shock offset. Thus, it appears that the ability to cope behaviorally with stress reduced adrenal activity. Contradictory data have been reported (Bassett & Cairncross, 1975); however, in this particular study the animals in the controllable and uncontrollable groups did not receive identical amounts of shock. In fact, if animals received identical amounts of shock, the ability to predict shock onset was found to mitigate the stress-induced enhanced corticosterone levels as well (Weiss, 1970). In support of the notion that coping processes modify stress-induced corticosteroid secretion are the findings that corticosterone levels were maximally elevated early in avoidance training, but then declined when the response became well established (Coover, et al., 1973).

II C. Stress and Immunological Functioning

Immunological functioning is mediated via various biological substrates including antibodies, T- and B-lymphocytes, natural killer cells, and phages (Alexander, 1977; Herberman, 1978; Herberman & Holden, 1978; Shin, Johnson, Pasternack, & Economou, 1978). While the possibility exists that stress, and other environmental factors, affect some of these functions (cf. Amkraut & Solomon, 1975; Herberman, 1978), only sparse evidence has been provided. The available data provisionally suggest that acute exposure to stress results in immunosuppression, whereas chronic stress seems to produce immunofacilitation. Specifically, acute footshock and restraint stress increased susceptibility to herpes simplex virus among mice (Rasmussen, Spencer, & Marsh, 1957). Similarly, acute footshock also

increased susceptibility to Coxsackie B virus in normally resistant mice (Friedman, Ader, & Glasgow, 1965; Johnson, Lavender, Hultin, & Rasmussen, 1963). Using somewhat more refined measures of immune functioning, Gisler Bussard, Mazie and Hess (1971) reported immunosuppression in the form of decreased immune reactivity of peritoneal and spleen cells induced by acute acceleration or ether stress. Likewise, acute noise and/or water deprivation stress as well as surgical stress induced immunosuppression with respect to both antibody and T-cell functioning (Folch & Waksman, 1974; Greer & Felsenfeld, 1967). In humans, surgical stress and bereavement have been reported to produce immunosuppression as well (Bartrop, Lazarus, Luckhurst, Kiloh, & Penny, 1977; Pees, 1977). Interestingly, the effects of stress upon the immune system appear to undergo adaptation similar to the neurochemical and hormonal consequences of stress. That is, the direction of the stress effect appears to be dependent upon the chronicity of stress exposure. Monjan and Collector (1977) have demonstrated that acute noise stress results in both specific and nonspecific immunosuppression in the T and B cell systems in mice. Chronic exposure to exactly the same stressor, on the other hand, was shown to enhance immunological functions.

The acute-chronic dichotomy does not appear to hold for all stressors. For example, chronic handling, isolation, and predator stress have been reported to suppress rather than to enhance immunological functioning (Brayton & Brain, 1974; Friedman, Glasgow, & Ader, 1964; Hamilton, 1974; Solomon, Levine, & Kraft, 1968). Whether the lack of consistency between the effects of sound stress and these social stressors is due to procedural variations between the studies, or to the nature of the stressors employed, is undetermined. However, it is noteworthy that in the case of chronic predator stress adrenocortical adaptation was also not observed (Hamilton, 1974).

Since coping factors have been found to be more important in determining the neurochemical and hormonal consequences of stress than the stress per se, it would be interesting to examine the effects of effective coping on the stress-induced immunological alterations. Unfortunately, no studies directly examining the effects of coping processes on stress-induced immunological alterations have been reported to date.

II D. Neurochemical, Hormonal and Immunological Interactions

In the preceding sections I have discussed the consequences of stress on neurochemical, hormonal and immunological functioning independently. However, the changes produced by stress in these physiological systems are probably not mutually exclusive. The discussion will now turn to the ways in which these systems interact with one another.

An extensive amount of data has been reported indicating neurochemical involvement in hormonal regulation. The tuberoinfundibular neurons of the hypothalamus contain the peptide releasing factors which act on the anterior pituitary via median eminence capillaries to produce synthesis and secretion of ACTH, TSH, PRL, LH and GH (Guilleman, 1978; Terry & Martin, 1978). The secretion of releasing factors appears to be under the neural control of DA, NE, 5-HT, histamine, ACh and GABA (Terry & Martin, 1978). Although it is possible that additional neural systems might be involved in the control of hormone secretion under conditions of stress (Seggie & Brown, 1976; Seggie, Shaw, Uhler, & Brown, 1974b; Seggie, Uhler, & Brown, 1974a), the fact that the normal secretion of releasing factors is under the control of the same neural systems that are affected by stress exposure, suggests that the stress-induced hormonal alterations may be, at least in part, a function of stress-induced neurochemical changes.

Release of CRF, and thus ACTH, was stimulated by both ACh and 5-HT in vitro (Bennett & Edwardson, 1975; Bradbury, Burden, Hillhouse, & Jones,

1974; Edwardson & Bennett, 1974; Edwardson, Bennett, & Bradford, 1972; Jones, Hillhouse, & Burden, 1976) and in vivo (Ganong, 1976; McCann & Ojeda, 1976; Meyer, Buckholtz, & Boggan, 1978). Moreover, CRF and ACTH release were inhibited by NE and DA in vitro (Bennett & Edwardson, 1975; Edwardson & Bennett, 1974) and tonically inhibited by NE in vivo (Ganong, 1976; Ganong, Kramer, Reid, Boryczka, & Shackelford, 1976; Scapagnini, Annunziato, & Preziosi, 1973; Van Loon, 1976). Thus, when NE and/or DA availability is reduced in the hypothalamus, CRF release is increased and hence synthesis and release of ACTH is promoted. Similar changes will also occur when brain concentrations of ACh and/or 5-HT are increased. These findings raise the possibility that the stress-induced release of ACTH is, at least in part, a function of the stress-induced reductions of DA and/or NE in the hypothalamus (e.g. Kobayashi, et al., 1976; Kvetnansky, et al. 1975, 1977) and stress-induced increases in ACh availability (Aprison & Hingtgen, 1966, 1969, 1970; Aprison, et al., 1968, 1975; Karczmar, et al., 1973; Zajackowska, 1975).

Prolactin release appears to be tonically inhibited by DA and stimulated by 5-HT and histamine (Terry & Martin, 1978). Administration of the catecholamine precursor, L-DOPA (Malarkey, Jacobs, & Daughaday, 1971), the DA receptor agonist, apomorphine (Lal, de la Vega, Sourkes, & Friesen, 1972; Martin, Lal, Tolis, & Friesen, 1974; Vijayan & McCann, 1978), or DA itself (Vijayan & McCann, 1978) inhibited prolactin release in vivo. Similarly, DA inhibited prolactin release in vitro by direct action on pituitary receptors (Macleod, 1976). Conversely, inhibition of dopamine synthesis, or DA receptor blockade, resulted in a marked increase in serum

prolactin levels (Login & Macleod, 1977; Martin, Durand, Gurd, Faille, Audet, & Brazeau, 1978; Meites & Clemens, 1972). Since tuberoinfundibular DA inhibits prolactin secretion, these data suggest that the stress-induced increased prolactin release is secondary to DA alterations. Thus, when DA is reduced in the arcuate nucleus by stress (Kobayashi, et al., 1976; Kvetnansky, et al., 1975, 1977), the secretion of prolactin from the pituitary is probably disinhibited. It is noteworthy that restraint stress-induced increased prolactin secretion was attenuated by histamine receptor blockade as well (McCann, Krulich, Ojeda, & Vijayan, 1978), suggesting that stress-induced alterations in histamine activity (Mazurkiewicz-Kwilecki & Taub, 1978) might also be responsible for the increased prolactin secretion.

The secretion of growth hormone releasing factor, and thus growth hormone, appears to be stimulated by DA, NE, 5-HT, and ACh. Stimulation of DA receptors by L-DOPA (Boyd, Lebovitz, & Pfeiffer, 1970; Jacoby, Greenstein, Sassin, & Weitzman, 1974), or apomorphine (Brown, Krieger, Van Woert, & Ambani, 1974; Lal, et al., 1972; Lal, Guyda, & Bikadoroff, 1977), NE receptor stimulation through clonidine (Chambers & Brown, 1976; Durand, Martin, & Brazeau, 1977; Eden, 1978; Lal, Tolis, Martin, Brown, & Guyda, 1975), 5-HT loading by administration of 5-hydroxytryptophan (Chambers & Brown, 1976; Smythe & Lazarus, 1973; Takahashi, Kondo, Yoshimure, & Ochi, 1974) and cholinergic stimulation via pilocarpine or the acetylcholinesterase inhibitor physostigmine (Bruni & Meites, 1978) all enhanced plasma growth hormone levels. Depletion of catecholamines via alpha-methyl-p-tyrosine administration, on the other hand, and alpha-adrenergic receptor blockade induced by phenoxybenzamine (Durand, et al., 1977, 1978) inhibited growth hormone secretion.

The fact that hypothalamic DA and NE appear to stimulate growth hormone release might explain the transient enhancement of secretion induced by stress (Brown, et al., 1971a; Mason, et al., 1976). That is, upon stress inception the release of DA and NE is increased (see previous section), whereas during protracted stress amine release exceeds synthesis, resulting in a net reduction of catecholamine levels in the arcuate nucleus. Thus, the short-lived increased secretion of growth hormone during stress may be due to the initial increased release of catecholamines, and the subsequent inhibition of growth hormone release due to the eventual depletions of DA and NE. It should be born in mind, however, that the eventual stress-induced increases in ACh concentration should act to prolong growth hormone release after DA and NE are depleted. Since it is not clear that this is the case, an assessment of the stress-neurochemical-growth hormone interaction must be held in abeyance.

Both NE (Grimm & Reichlin, 1973) and DA (Bennett, Edwardson, Holland, Jeffcoate, & White, 1975) have been found to stimulate thyrotropin release in vitro. Paradoxically, depletion of DA and NE by alpha-methyl-p-tyrosine did not inhibit thyrotropin release in vivo (Kardon, Marcus, Winokur, & Utiger, 1977). In fact, if anything, DA and NE may tonically inhibit in vivo thyrotropin release (Martin, Reichlin, & Brown, 1977). Any speculations as to how stress might alter TSH release via neurochemical mechanisms must await the clarification of the differential in vivo and in vitro results observed.

In addition to the effects of neurochemical activity on hormonal processes, it should be considered that both neurochemical activity and hormonal activity may in turn promote the stress-induced immunological

alterations. Specifically, hypothalamic lesions have been found to reduce antibody production and hence levels of circulating and tissue fixed antibodies (Filipp & Szentivanyi, 1958; Janakovic & Isakovic, 1973; Korneva & Khai, 1964; Konovalov, Korneva, & Khai, 1971; see also the review in Stein, Schiavi, & Camerino, 1976). Anterior hypothalamic lesions reduced cell-mediated immune activity as well (Janakovic & Isakovic, 1973; Stein, et al., 1976). It seems conceivable, therefore, that these lesions resulted in reductions of hypothalamic DA and NE, as does stress, and that these neurochemical changes, or the ensuing hormonal alterations, were in turn responsible for the observed immunosuppression. In support of such a contention are the findings that reserpine, which depletes storage pool DA and NE, produced immunosuppression (Dukor, Salvin, Dietrich, Gelzer, Hess, & Loustalot, 1966). Conversely, drugs that enhanced immune functioning also augmented the activity of DA stimulated adenylate cyclase (Cotzias & Tang, 1977; Tang & Cotzias, 1974; Tang, Cotzias, & Dunn, 1974) and the behavioral response to L-DOPA administration (Cotzias & Tang, 1977). Finally, it has been well established that corticosteroids can produce immunosuppression (Balow & Rosenthal, 1973; Dougherty & White, 1944; Selye, 1936, 1956). Indeed, corticosteroid administration is frequently employed clinically to inhibit immunological functioning (cf. Johnson, 1979). Thus, stress may produce its effects on the immune system via the mediation of neurochemical and hormonal mechanisms.

II E. Summary

It appears that stress has consistent and predictable effects upon neurochemical, hormonal and immunological functioning. Furthermore, these systems may interact with one another in order to determine the eventual physiological outcome. The stress-induced alterations of these systems seem to be influenced in a similar fashion. The chronicity of the stress

regimen determines the physiological consequences in each of these three mechanisms. Acute stress results in depletions of catecholamines and increases in ACh, increased synthesis and secretion of hormones, and immunosuppression. With chronic stress, adaptation in these biological mechanisms is observed, and normal levels of functioning, or alterations opposite to those induced by acute stress are apparent. The ability to cope behaviorally with stress also appears to determine the physiological consequences of stress. Inability to cope with stress, rather than the stress per se, seems to be the critical variable responsible for the catecholamine reductions and ACh increases, and possibly for the hormonal alterations as well. The role of this variable in the immunological alterations induced by stress, however, has not been evaluated. Finally, social conditions and previous stress history also appear to modify stress-induced neuronal and hormonal functioning.

III. Neoplastic Disease

Prior to examining the effects of stress on tumor development, a brief review of the carcinogenic process will be presented. The defining characteristics of tumor cells are their abilities to proliferate uncontrollably, to invade normal tissues, and to metastasize to distant sites (Poste, 1977). Following carcinogenic transformation, tumor cells develop in a progressive manner (Foulds, 1954, 1964, 1969) until they are no longer restrained by cell contact inhibition (Ponten, 1975; Rapin & Burger, 1974; Stoker & Rubin, 1967), hormones (Foulds, 1956a,b), or other mitosis inhibitors (Houck & Attallah, 1975), and thus proliferate freely. This autonomy from the normal mitosis inhibiting factors is believed to be due to, at least in part, alterations in the cell surface characteristics of tumor cells (Poste, 1977). Furthermore, altered cell surface properties are believed to be responsible for the capacity of tumor cells to escape from positioning regulators (Gail & Boone, 1971; Lipton, Klinger, Paul, & Holley, 1971; Trinkaus, 1976), and hence increase the probability of metastases formation. Endogenous secretion of proliferation and locomotion stimulating factors by tumor cells may also be responsible for these actions (Burk, 1973; LoBue & Potmesil, 1975). There are many conceivable ways in which to divide the several stages of tumor development. While a complete review of the carcinogenic process is beyond the scope of this paper, a brief review will be presented, outlining the basic phases of the carcinogenic process and how stress may influence each phase. It should be noted, however, that each discussed phase can be broken down into many more discrete stages.

III A. Phases of Tumor Development

III A.1 Phase 1: Tumor Induction

The first stage of neoplastic disease is the appearance or induction of a tumor cell. There are many possible causes of this initial stage, and it is correct to think of it as a multi-step process (Berenblum, 1975; Weinstein, 1977). Although cancer can be conceptualized as a spontaneous condition due to either spontaneous cell mutation (Neel, 1972; Ohno, 1969), genetic inheritance (Heston, 1975), or both, it is clear that many types of cancer in humans are caused by environmental factors (Doll, 1977; Higginson & Muir, 1973; Wynder & Mabuchi, 1972). In fact, various chemical compounds (Bartsch & Montesano, 1975; Fishbein, 1976; Jerina, Lehr, Schaefer-Rider, Yagi, Karle, Thaker, Wood, Lu, Ryan, West, Levine, & Conney, 1978; Kada & Murakami, 1975; Kramers, 1975; Magee & Barnes, 1967; Nago, Sugimura, & Matsushima, 1978; Tazima, Kada, & Murakami, 1975), ultraviolet, ionizing, and corpuscular radiations (Cronkite, Malony, & Bond, 1960; Fruth & Lorenz, 1954; Jablon & Kato, 1970; Storer, 1975; Upton, 1967, 1975; Urbach, 1975), as well as viruses (Bittner, 1942; Gross, 1951, 1953; Hanafusa, 1975; Harvey, 1964; Ito, 1975; Khoury & Salzman, 1975; Little, 1933; Melnick, 1962; Moore, 1975; Rous, 1911; Shope, 1932, 1933; Stewart, Eddy, & Borgese, 1958; Theilen, 1975; Tretin, Yabe, & Taylor, 1962) produce cancer in a wide variety of animal species. While no conclusive evidence exists of virus-induced cancer in humans, with the exception of the common wart (Hewitt, 1978), there are data suggestive of herpes-simplex virus 2 being involved in the etiology of cervical cancer, and of epstein-barr virus (herpes-simplex 4) being involved in the etiology of Burkitts lymphoma

(Roizman & Kieff, 1975). The evidence pertaining to the notion that cancer in man can and is produced by chemical compounds and radiations is much stronger (see reviews in Doll, 1977; Nago, et al., 1978; Storer, 1975; Upton, 1967, 1975).

Tumor-active stimuli, whether chemical or physical, can be divided into two basic classes with three sub-divisions in each. In the first category, carcinogens, there are direct-acting carcinogens, procarcinogens and cocarcinogens (Hecker, 1976; Weisburger & Williams, 1975). Direct-acting carcinogens are those which directly produce a neoplastic transformation in normal cells without the necessity of some change in their structure induced by interaction with the host. Procarcinogens, are stimuli which are active in producing neoplastic changes only after some interaction with host mechanisms. That is, some resultant of the stimulus-host interaction is the direct-acting carcinogen. Cocarcinogens, are stimuli which by themselves cannot initiate tumors, but potentiate or promote the effects of direct-acting and procarcinogens. The other category of tumor-active stimuli are the anticarcinogens (Falk, 1971). An anticarcinogen is a stimulus which interferes with the carcinogen-induced transformation of cells, and thus leads to an inhibition of tumor induction. Conceivably, anticarcinogens can be either direct-acting, pro, or co anticarcinogens.

The mechanism of action of carcinogens in producing cellular changes, or of anticarcinogens in inhibiting them, is not well understood. Carcinogens may produce their effect by disrupting cellular processes or structures (Svoboda & Reddy, 1975; Poste, 1977), by interacting with and changing DNA and RNA (Kanazir, 1969; Malling & Deserres, 1969; Sarma, Rajalakshmi, &

Farber, 1975), or by debilitating those mechanisms necessary for DNA repair (Epstein, Fukuyama & Epstein, 1971; Fox & Lajtha, 1973; Urbach, 1975; Zajdela & Latarjet, 1978). Anticarcinogens may inhibit any of these actions. Whatever the mechanisms, it is clear that a large number of stimuli can produce or enhance neoplastic transformation (Heckler, 1976; Nago, et al., 1978; Storer, 1975; Upton, 1975; Urbach, 1975; Weisburger & Williams, 1975), and a smaller number of stimuli can inhibit these alterations (Falk, 1971).

Conceivably, stress and/or the physiological consequences of stress might act as either a carcinogen or anticarcinogen. On the basis of the available data, there is no reason to believe that stress is a direct-acting carcinogen. Rather, stress may act as a promoter or enhancer of direct-acting carcinogens and anticarcinogens. The possible involvement of stress and/or stress related physiological variables in tumor induction will be discussed in the following section.

III A.2 Phase 2: Growth

Once tumor induction has taken place (i.e. a neoplastic cell is present) various stimuli and host reactions can influence mitosis, and thus the rate of growth and eventual size of the tumor. The immune systems have been thought to play a central role as a natural defense against neoplasia at this phase of tumor development through immune surveillance (Burnet, 1957, 1961, 1970, 1971). According to the current form of this hypothesis, some aspect of the immune response, possibly sensitized T-cells and antibodies, but more likely nonsensitized macrophages (Alexander, 1977; Hibbs, 1973) and lymphocytes (Pross & Baines, 1977; Herberman & Holden, 1978;

Oehler, Lindsay, Nunn, Holden & Herberman, 1978; Oehler, Lindsay, Nunn, & Herberman, 1978; Oehler & Herberman, 1978) can identify tumor cells and destroy them during early development when the population of tumor cells is not very large. The sensitized T-cell system which was originally believed to play a major role in immune surveillance against primary tumors (Herberman & Holden, 1978), is more likely involved in defense against metastases (Alexander, 1977), although B-lymphocytes may be more important in this regard (Yuhas, 1977). Although the role of immune mechanisms in tumor development has been questioned (Hewitt, 1978; Hewitt, Blake, & Walder, 1976), their possible involvement cannot be dismissed at present (Herberman & Holden, 1978). Since stress and/or its physiological consequences can affect immune functioning, it is conceivable that stress may have an effect on this phase of tumor development via these mechanisms.

In addition to immunological mechanisms, hormones may also play a role in this phase of tumor development. While only specific types of tumors are hormone dependent at this point of growth (Huggins, 1967), it is hard to imagine of tissue cells which will not show some minimal response to endocrine stimulation (Higgins & Gehring, 1978). Moreover, hormonal changes might influence the growth of "hormone independent" tumors indirectly, through effects on immune systems (Riley, Spackman, Fitzmaurice, Santisteban, McClanahan, Louthan, Dennis, & Bloom, 1976; Spackman & Riley, 1976) or other, as yet unspecified, physiological mechanisms (Fiedler & Lieber, 1972; Peters & Kelly, 1977; Zeidman, 1962). Thus, since stress affects hormonal functioning, it is possible that stress may directly influence the growth of hormone dependent tumors at this stage of development. Stress may also, via hormonal changes, effect the growth of tumors which appear to be hormone independent, although this might be an indirect effect.

Angiogenesis, the process of acquiring vascularization by a solid tumor, may contribute to the regulation of tumor development. During the initial stages of tumor growth, after one or more tumor cells have been induced, the tumor tends to grow extremely slowly, or not at all, yet the cells remain viable (Folkman, 1974a,b, 1975; Folkman & Tyler, 1977). However, after vascularization has occurred, rapid growth is exhibited (Folkman, 1975; Folkman & Tyler, 1977). Thus, the vascularization of a tumor seems to be a control point in its growth (Folkman, 1975). Vascularization appears to be an active induction of blood supply by the tumor cells (Folkman, 1974a; Gimbrone, Cotran, & Folkman, 1974; Gimbrone, Leapman, Cotran, & Folkman, 1973; Greenblatt & Shubik, 1968) possibly owing to the release of a stimulating factor (Folkman, 1974b; Folkman & Tyler, 1977; Folkman, Merler, Abernathy, & Williams, 1971; Klagsbrun, Knighton, & Folkman, 1976; Langer & Folkman, 1976). Normal tissues, on the other hand, do not seem capable of inducing vascularization (Auspruck, Knighton, & Folkman, 1975; Folkman & Tyler, 1977). Since vascularization appears to play such a large role in determining the growth of the tumor, the possibility should be entertained that stress has its effect by altering the natural progression of tumor angiogenesis.

III A.3 Phase 3: Metastasis

The last phase of tumor development, and perhaps that which is the largest problem in the medical treatment of human cancer, is metastasis. Metastases refers to the invasion of tumor cells, and the development of secondary neoplasms, in areas of the body not directly adjacent to the primary tumor (Dorland, 1965; Fidler, 1978; Fidler, Gersten & Riggs, 1977; Nicolson, 1977). Metastasis appears to occur through various mechanisms including cell transportation via the blood stream and lymphatic system

(del Regato, 1977; Fidler, 1978; Nicolson, 1977). It should be noted, however, that the presence of tumor cells in these systems does not invariably result in the development of secondary tumors (Fidler, 1975; Salsbury, 1975; Weiss, 1977), as most tumor cells cannot remain viable in circulation (Clifton & Agostino, 1962; Fidler, 1970; 1975; Salsbury, 1975). Furthermore, factors such as size of the tumor cell colony and capillary deformability, as well as other specific properties of the tumor cells themselves are extremely important in determining whether or not secondary growths will develop (Fidler, 1978; Nicolson, 1977). The importance of the specific properties of the tumor cells themselves has been demonstrated by the findings that cells which have the ability to metastasize could be selected from a tumor cell population (Fidler, 1973). If stress has an effect on the metastatic process, it is likely that it will have this effect via alterations in circulation, selection factors, or hormonal and immunological mechanisms which may be active in inhibition of secondary tumor spread.

Taken together, it appears possible that stress and/or its physiological consequences may affect tumor development at each phase. The following sections will now examine the data indicating a role for stress in tumor development at each of these phases. At the same time, the effects of stress-related physiological manipulations will also be considered as they may lead to the elucidation of testable hypotheses concerning the role of stress.

IV. Stress and Cancer

The notion that psychological factors may be involved in the neoplastic disease process is an ancient one. It has extended from Galen in the second century through medical practitioners in the eighteenth and nineteenth centuries to the medical researchers and clinicians of today (LeShan, 1959; LaBarba, 1970; Fox, 1978). Galen is believed to have thought that melancholic women were more likely to develop cancer than those who were more confident and vital (Hueper, 1942). Several eighteenth and nineteenth century physicians strongly stated that there was a real and possibly causal relationship between emotional trauma and the development of cancer. In fact, this concept was not considered a radical one, but was an accepted fact by most writers of the time (LeShan, 1959). In his review of this historical literature, LeShan (1959) points out that these writers were not quacks or charlatons, but highly respected cancer specialists who based their notions on clinical observations. In the following section, the possible role of stress, coping with stress, and other psychological variables in the development of cancer in humans will be examined. While some of the studies purport to have examined life-stress events that occurred prior to cancer diagnosis, it cannot be determined if these events took place prior to the actual beginning of the disease. Since the clinical manifestation of cancer may occur at least six years following neoplastic change, the possibility exists that the disease was present prior to and during the reported events (Fox, 1978). As such, it is impossible to determine if psychological variables interact with tumor induction, growth or metastases in these human studies. Therefore, specific

reference to these phases will have to wait for the discussion of the studies involving infrahuman organisms.

IV A. Human Studies

From the first quarter of the twentieth century to the present, there have been numerous research studies published concerning the effects of stress and psychological variables on cancer development and growth. These studies can generally be classified as retrospective, prospective, or prognostically oriented.

By far, the majority of retrospective studies have indicated a strong relationship between life-stress events, coping style, other psychological factors, and neoplastic disease. Cancer has been found to be particularly prevalent among individuals who had previously lost an important emotional relationship (Bahnson & Bahnson, 1964a,b, 1966; Bloom, Asher & White, 1978; Evans, 1926; Greene, 1966; LeShan, 1966; Lombard & Potter, 1950; Murphy, 1952; Peller, 1940, 1952; Schmale & Iker, 1964, 1966). That is, cancer wards in hospitals tended to have a higher proportion of widowed (Evans, 1926; Greene, 1966; Murphy, 1952) and divorced (Murphy, 1952) patients. Similarly, those people in the general population who were widowed, divorced, or separated had significantly higher incidences of cancer than the rest of the population (Bloom, et al., 1978; LeShan, 1966; Lombard & Potter, 1950; Peller, 1940, 1952) even when controlled for age (Lombard & Potter, 1950; Peller, 1940, 1952). Moreover, it appeared that the occurrence of cancer was correlated with an inability to cope with the separation, and a sense of loss and hopelessness (Evans, 1926; Greene, 1966; LeShan, 1966). In fact, reliable prediction of cancer development

has been based solely on response to life-stress events (Schmale & Iker, 1964, 1966). These predictions were made on essentially healthy and asymptomatic women who were predisposed to cervical cancer (class III Papanicolaou cells). The prediction of cancer development was made if women had been unable to cope with stress and had responded with feelings of helplessness (Schmale & Iker, 1964, 1966).

Other psychological variables such as poor emotional outlet (Kissen, 1963, 1964, 1965, 1966a,b,c), reduced aggressive expression (Bacon, Rennecrier, & Cutler, 1952; Bahnson & Bahnson, 1969; LeShan, 1966; Stavrak, Buck, Lott, & Wanklin, 1968), diminished introspection and self-awareness (Abse, Wilkins, Kirschner, Weston, Brown, & Buxton, 1972; Abse, Wilkins, Vandecastle, Buxton, Demars, Brown, & Kirschner, 1974) and masochistic personality (Bacon, et al., 1952) have all been reported to be significantly correlated with cancer. However, the independence of these variables and stress-coping variables is by no means clear.

On the whole, the retrospective research seems to indicate a correlation between psychological variables and neoplastic disease. More importantly, it suggests that stress and the inability to cope with stress might be influential in cancer development and growth. However, there are several rather severe problems with all of these retrospective studies (Fox, 1978). Problems, in fact, which render them at the best merely suggestive, rather than seemingly conclusive.

One of the problems with many of these studies is that the cancer patient is being asked to remember the important life-events that he had encountered. It is conceivable, and even likely, that the knowledge of

having cancer may cause the individual to become more reflective about his past history, and may colour the individual's perception or interpretation of previous events. Thus, cancer patients may remember more and interpret differently previous life-stress events than do controls, simply as a function of knowing that they have the disease. The only retrospective studies which do not encounter this difficulty are those of Schmale & Iker (1964, 1966), where all subjects have a pre-neoplastic condition and so their recollection of stress-events should be equally influenced. It is interesting that under these conditions, the researchers were still able to predict cancer development on the basis of coping responses.

A second and more serious problem in the retrospective evaluation of the effects of psychological variables on cancer development is the fact that cancer can have physiological consequences which may produce profound effects upon the mental and behavioral functioning of the patient (Fox, 1978).

Thus, one is confronted with the problem of which came first, the psychological and behavioral change (i.e. inability to cope) or the cancer. Specifically, cancer can effect the brain and behavior through its physical sequelae (Bunn, Scheir, Bankes, & DeVita, 1976; Lister, Whithouse, Beard, Paxton, Brearly, Brown, Wrigly, & Crowther, 1977; Mitchell, 1967; Newman & Hansen, 1974). Direct effects such as brain metastases has been noted with broncogenic (Newman & Hansen, 1974), lymphomic (Bunn, et al., 1976) and leukemic (Lister, et al., 1977) carcinoma. In all of these studies, a large proportion of the metastases were not noted prior to treatment, and thus any retrospective study done on similar patients could have been confounded by this direct effect. Similarly, behavioral and psychological functioning may be influenced

by more indirect effects of cancer on metabolic, endocrine and hematological functioning (Mitchell, 1967) before cancer is clinically evident. Thus, even in the studies which attempted to assess the relationship of life stress and cancer prior to complete neoplastic transformation (Schmale & Iker, 1964, 1966), the central nervous system, and thus psychological functioning, may have been altered due to undetected metastases or hormonal changes.

Prospective studies are not open to these criticisms and, interestingly, they have also indicated a relationship between psychological factors and cancer development (Greer & Morris, 1975; Hagnell, 1966; Harrower, Thomas, & Altman, 1975; Keehn, Goldberg, & Beebe, 1974; Thomas, 1976; Thomas & Duszynski, 1974; Thomas & Greenstreet, 1973). "Substable" personality (not well defined) in women has been found to be indicative of subsequent tumor development (Hagnell, 1966), whereas psychoneurosis has not proven to be a reliable predictor (Keehn, et al., 1974). Moreover, measures such as the Closeness To Parents Scale, the Draw A Person Test, and amount of insomnia, all differentiated people that subsequently developed tumors, from people who subsequently developed hypertension and heart disease and from those who remained healthy (Harrower, Thomas, & Altman, 1975; Thomas, 1976; Thomas & Duszynski, 1974; Thomas & Greenstreet, 1973). It is noteworthy that the people who subsequently developed tumors in these studies responded in a similar fashion to those who later committed suicide or developed mental illness. If suicide and mental illness are reflective of an underlying inability to cope with stress, as suggested by several researchers (e.g. Akiskal & McKinney, 1973, 1975; Levi, Fales, Stein, & Sharp, 1966), then the fact that the prospective suicides and mentally ill subjects responded in a similar manner to the

prospective cancer patients might be indicative of a similar inability to cope with stress in the cancer patients. This speculation is, in fact, reinforced by the finding that coping inappropriately with anger is also predictive of the subsequent development of cancer (Graer & Morris, 1975).

A limited number of prognostic studies have also been reported. The previously mentioned studies of Schmale and Iker (1964, 1966) used coping profiles to predict successfully (36 out of 51) subsequent development of cancer from cells in pre-neoplastic condition. Furthermore, women who tended to express high levels of anger toward their disease and their doctor (possibly a way of coping) survived significantly longer than those who did not (Derogatis & Abelloff, 1977). Psychological tests, particularly those involved with imagery of defense reactions against cancer, have been found to be more predictive of length of survival than blood chemistry tests in patients with metastasized cancer (Achterberg & Lawlis, 1978; Achteberg, Simonton, & Mathews-Simonton, 1976). Apparently, those patients who imagined strong bodily attacks on the metastasizing cancer lived the longest. These prognostic studies again suggest that psychological variables can influence the development of cancer and the subsequent survival of cancer patients. Furthermore, although not tested directly, the results raise the possibility that appropriately coping with stress may be a major psychological component involved in determining the effects of life-stress on cancer development.

In summary, the retrospective and prognostic studies are plagued by poor design, inadequate controls, and a plethora of potentially confounding variables, whereas the prospective studies do not encounter these difficulties. Nonetheless, the findings of the retrospective and prognostic studies are consistent with those of the prospective studies, and all provisionally suggest that

certain psychological variables, including inability to cope with stress, are associated with higher cancer incidence and length of survival. It would be clearly falacious, however, to infer causation and/or modification of cancer development from these human studies. Moreover, it is entirely possible that this correlation is a spurious one, derived from some other variable(s) which affects both cancer development and coping style or other psychological attributes. For example, physical and chemical stimuli, viruses, chronic infection, genetic predisposition, hormonal stimuli, and aging are all variables which may induce cancer. These variables can also have immediate and direct effects on psychological functioning (cf. Fox, 1978); thus bringing about the high correlations observed. Yet the two variables, cancer and psychological functioning, may really be independent of one another. Furthermore, the apparent correlation between psychological variables and cancer may be inflated by the influence of the psychological profile of the patient. That is, the patient's profile may in some way bias his behavior so that he increases his exposure to carcinogens (see Fox, 1978). In conclusion then, there appears to be a correlation between tumor growth and psychological factors in humans. However, the interdependence of these two variables has in no way been demonstrated.

IV B. Animal Studies

The effects of stress on animal tumor systems has not been intensively studied, and appear to be inconsistent and contradictory upon first blush. It is practically impossible to draw generalities across studies because various researchers use different species of animals, different tumor systems and stressors, and different methods of tumor growth measurement. Furthermore, the possible conclusions derived from any given study are limited by a lack of attention to the parameters of the stressors employed, and in some instances by a lack of information about these parameters. Nonetheless, stress does appear to affect tumorigenicity in animals; the nature of the stress effect being possibly dependent upon such factors as the type of stress employed, the stage of the neoplastic disease process when stress was applied, housing conditions, and the duration and chronicity of stress exposure. Conceivably, the stress-induced alterations of tumorigenicity may be subserved by the neurochemical, hormonal, and immunological mechanisms discussed earlier. Thus, it might be expected that the variables which influence stress-induced neurochemical, hormonal and immunological changes will have predictable consequences on tumorigenicity. The following sections will examine the effects of stress on tumor induction, growth, and metastasis among infrahuman animals.

IV B.1 Effects of Stress on Tumor Induction

While studies have not been carried out to examine the effects of acute stress on tumor induction, several studies have reported the inhibition of tumor induction following protracted chronic stress exposure (Newberry, Frankie, Beatty, Maloney, & Gilchrist, 1972; Newberry, Gildow, Wogan, &

Reese, 1976; Pradhan & Ray, 1974; Ray & Pradhan, 1974). Specifically, chronic restraint (Newberry, et al., 1976), footshock (Newberry, et al., 1972; Pradhan & Ray, 1974; Ray & Pradhan, 1974), electro-convulsive shock and sound stress (Pradhan & Ray, 1974) all reduced the incidence of 7,12,dimethylbenz(a)anthracene (DMBA)-induced mammary tumors in rats.

Chronic stress does not invariably inhibit tumor induction, however, and may in fact exacerbate the induction of tumors as well (Andervont, 1944; Henry, Stephens, & Watson, 1975; Riley, 1975). The nature of the stressor employed may be an important determinant of the direction of the chronic stress effect. Specifically, chronic isolation (Andervont, 1944) and chronic exposure to moderate and intermittent background stressors such as human presence (Riley, 1975) in C3H/He mice, as well as chronic social disruption in CBA/USC mice (Henry, et al., 1975) all increased the incidence of spontaneous mammary tumor development. The fact that these stressors appear to be less "severe" than footshock or restraint stress may account for the inconsistent results. However, this possibility is only a speculative one in light of the fact that inhibition of tumor induction was noted with carcinogen-induced tumors, and exacerbation was observed in the case of spontaneous tumors.

Aside from stress severity, another factor which determines the stress effect on tumor incidence is the stage of the neoplastic process when stress is applied. Chronic restraint, either prior to, or during, DMBA administration did not inhibit mammary tumor incidence. Only chronic restraint during the period following DMBA administration had an inhibitory effect on tumor induction (Newberry, 1978).

The effects of predictability on stress-induced alterations of tumor incidence have not been directly evaluated. It has been reported that slightly less inhibition of DMBA-induced tumors occurs following signalled footshock as compared with unsignalled footshock; however, this difference was not statistically significant (Newberry, et al., 1972). In another series of studies it was found that chronic signalled footshock increased the incidence of spontaneous tumors in C3H/A mice and DMBA-induced tumors in rats (Kavetsky, Turkevich, & Balitsky, 1966), a finding diametrically opposite that of the other studies employing chronic footshock stress (Newberry, et al., 1972; Pradhan & Ray, 1974; Ray & Pradhan, 1974). However, owing to a lack of procedural information in the Kavetsky, et al. (1966) investigation, as well as inadequate controls (i.e. no unsignalled shock group), one can neither be certain of the chronicity and density of the shock regimen, nor of the importance of signals. Thus any valid conclusions concerning the effects of shock predictability cannot be made.

Since DMBA-induced mammary tumors and spontaneous mammary tumors in C3H/He mice are hormone dependent, or at the very least, hormone responsive (Dao, Bock, & Greiner, 1960; Huggins, 1967; Huggins, Brizziarelli, & Sutton, 1959; Huggins, Grand, & Brillantes, 1961; Weisburger, Weisburger, Griswold, & Casey, 1968; Welsch & Clemens, 1973; Welsch, Clemens, & Meites, 1968; Welsch & Gribler, 1973; Welsch, Gribler, & Clemens, 1974; Welsch & Meites, 1969; Yanai & Nagasawa, 1972; see also the review in Furth, 1975) any effect of stress on mammary tumor induction might be limited to hormone dependent tumors. Prolactin and ovarian hormones are those which are most closely related to mammary carcinogenesis (see reviews in Furth,

1975; Welsch & Nagasawa, 1977), but they seem to have opposite effects on carcinogen-induced and spontaneously arising tumors. For example, prolactin levels were positively correlated with spontaneous tumor development. Increased levels of prolactin secretion were associated with increased incidence of spontaneous mammary tumors (Yanai & Nagasawa, 1972), and decreased prolactin secretion was associated with decreased incidence of spontaneous mammary tumors in mice (Welsch & Clemens, 1973; Welsch & Gribler, 1973; Welsch, et al., 1974). On the other hand, prolactin secretion was negatively correlated with carcinogen-induced mammary tumor incidence, with increased secretion inhibiting DMBA-induced tumors (Dao, et al., 1960; Klezdick, Bradley, & Meites, 1974; Welsch, et al., 1968). Thus, chronic exposure to a stress such as isolation, which reduces turnover of DA and NE, might result in chronic increased prolactin secretion and hence enhance spontaneous mammary tumor induction. However, chronic shock or restraint would probably not result in enhanced prolactin secretion, owing to adaptation in DA neurons (e.g. Kvetnansky, et al., 1975, 1977), and would thus not inhibit DMBA-induced mammary tumor incidence via this mechanism. Accordingly, the inhibition of tumor incidence among DMBA treated animals following chronic stress may not be limited to hormone dependent tumors but might be a more generalized effect. In fact, it appears that stress-induced inhibition of DMBA-induced tumors may act independently of ovarian hormones, as evidenced by the finding that chronic restraint stress did not affect the proportion of tumors regressing after ovariectomy (Newberry, 1978).

It should be noted that even if the stress-induced inhibition of tumor induction is found to occur only in hormone dependent tumors, it would still

be a relevant and important finding. Indeed, among humans, carcinoma of the breast, prostate, thyroid, kidney, endometrium and seminal vesicle, as well as leukemia, are all hormonally dependent (Huggins, 1967).

IV B.2 Effects of Stress on Tumor Growth

Stress appears to have an effect on tumor development after the induction of tumor cells has occurred. Acute severe stress application exacerbated the growth of virus-induced (Amkraut & Solomon, 1972) and transplanted tumors (Jamasbi & Nettesheim, 1977; Peters, 1975; Peters & Kelly, 1977). Specifically, acute uncontrollable shock decreased the latency, and increased the size of molony murine sarcoma virus-induced tumors in mice. Similarly, acute surgical stress (laparotomy), and acute whole body X-irradiation dramatically reduced the number of cells necessary for 50% successful transplantation takes (TD_{50}) among two different transplantable tumor systems in syngeneic mice (Jamasbi & Nettesheim, 1977; Peters, 1975; Peters & Kelly, 1977). The effects of surgical and X-irradiation stress did not appear to be due to suppressive effects on the classical immunological mechanisms. For example, T-cell deprived mice did not show an increase in susceptibility to identical tumor cell transplantation. (Peters, 1975). Furthermore, immunological reconstitution with syngeneic spleen cells and thymic implants immediately following irradiation and immediately prior to tumor cell transplantation did not have any effect on the irradiation induced TD_{50} reduction (Jamasbi & Nettesheim, 1977). Moreover, if 6 weeks, rather than 48 hours, were allowed between irradiation and tumor transplantation, the stress effect was no longer apparent in irradiated thymectomized mice even though immunological functioning (as measured by the haemagglutin and

homograft rejection response) showed no signs of recovery (Jamabbi & Nettesheim, 1977). These findings, when coupled with those indicating that these two tumors were non-immunogenic with respect to T-cell functions in syngeneic mice (Jamabbi & Nettesheim, 1977; Peters & Kelly, 1977), suggest that the stress-induced exacerbation of tumorigenicity was not due to inhibition of T-cell function. However, these findings do not negate the possibility that the stressors had their effect via other immune mechanisms, such as spontaneous cell mediated cytotoxicity and cytotoxic macrophages. Likewise, while hormonal mediation of the acute stress-induced exacerbation of tumorigenicity is a possibility, it should be noted that total adrenalectomy did not have any effect on susceptibility to transplanted tumors following irradiation or surgical stress (Peters & Kelly, 1977).

Exposure to chronic stress did not have the same effects as acute stress on tumor growth, just as it did not have the same effects as acute stress on neurochemical, hormonal and immunological functioning. In fact, chronic exposure to severe stress appeared to inhibit rather than to exacerbate tumor growth (Burchfield, Woods, & Elich, 1978; Gershben, Benuck, & Shurrager, 1974; Marsh, Miller, & Lamson, 1959; Molomut, Lazare, & Smith, 1963; Newberry, et al., 1972, 1976; Pradhan & Ray, 1974; Rashkis, 1952; Ray & Pradhan, 1974). The inhibition of tumor growth has been noted in many transplanted tumor systems (Burchfield, et al., 1978; Gershben, et al., 1974; Marsh, et al., 1959; Pradhan & Ray, 1974; Rashkis, 1952; Ray & Pradhan, 1974), as well as in tumors induced by DMBA (Newberry, et al., 1972, 1976; Pradhan & Ray, 1974; Ray & Pradhan, 1974) and 20-methylcholanthrene (Molomut, et al., 1963). Specifically, repeated exposure to footshock stress, ranging anywhere

from 15-85 days, inhibited the growth of DMBA-induced mammary tumors and transplanted 256 Walker carcinosarcoma, 4M-mammary carcinoma, and Erlich carcinoma in rats and mice (Marsh, et al., 1959; Newberry, et al., 1972; Pradhan & Ray, 1974). Similarly, chronic (29-54 daily sessions) footshock punishment of a food reinforced bar press response following daily non-punished responding (Ray & Pradhan, 1974) significantly inhibited the growth of both transplanted (4M-mammary carcinoma) and DMBA-induced tumors among rats. Daily repeated immobilization stress (15-85 days) also inhibited the growth of DMBA-induced and transplanted tumors (Marsh, et al., 1959; Newberry, et al., 1976; Pradhan & Ray, 1974) as did repeated electroconvulsive shock (Pradhan & Ray, 1974), sound (Molomot, et al., 1963; Pradhan & Ray, 1974), swim stress (Gershben, et al., 1974; Rashkis, 1952) and cold stress (Burchfield, et al., 1978).

While it appears that acute stress exacerbates tumor growth and chronic stress inhibits tumor growth, the distinction between acute and chronic stress employed in these studies is not clearcut. For example, although the application of surgical and irradiation stress were acute, the possibility exists that the physical and sensory consequences of these stressors lasted for a protracted period of time. This is the case in humans (Fox, 1978) and there does not appear to be any a priori reason to doubt it occurs among infrahuman animals as well. However, even if these effects were to last for a week, this would still be a much shorter duration than the chronic stress exposure employed in most of these studies. Nonetheless, the different stressors employed, rather than chronicity, might be the source of the divergent results.

Factors other than the chronicity of the stress may also modify the effects on tumor growth. For example, early experience with various seemingly milder stressors, such as handling and intermittent maternal separation have been found both to inhibit (Ader & Friedman, 1965; LaBarba & White, 1971; Newton, Bly, & McCrary, 1962) and exacerbate (Ader & Friedman, 1965; Levine & Cohen, 1959) transplanted tumor growth. It is not clear whether the differences between these studies were due to the stressors employed or to the different developmental periods during which stress exposure occurred. In fact, the possibility exists that both of these factors play a role in determining the effect of stress on tumorigenicity. That is, chronic isolation of adult animals exacerbated, rather than inhibited, transplanted tumor growth (Dechambre & Gosse, 1973) as was the case when stress such as footshock or restraint was employed. Unfortunately, no conclusive studies examining the effects of age have been reported.

The stage of tumor development during which stress occurs appears to be important in determining the stress effect. Specifically, acute uncontrollable shock stress following malony murine sarcoma virus injections exacerbated tumor growth, whereas exactly the same stress applied prior to tumor virus inoculation inhibited tumor growth (Amkraut & Solomon, 1972). Likewise, chronic cold stress prior to tumor cell transplantation inhibited subsequent tumor growth, while chronic cold stress following cell transplantation had no effect (Burchfield, et al., 1978).

While both chronic uncontrollable shock (Newberry, et al., 1972; Pradhan & Ray, 1974) and chronic avoidable shock (Marsh, et al., 1959) inhibited tumor growth, an analysis of the role of coping factors is not

possible on the basis of these studies. More explicitly, comparisons between experiments are hampered by the fact that mice were employed as the experimental subjects in the Marsh, et al. (1959) study, whereas rats were used in all of the others. Furthermore, tumor systems, as well as shock parameters, vary from study to study, and there is no assurance that the animals which had control over shock received the same amount of physical stress as those that did not have control. Moreover, the utilization of different housing conditions between studies (even within a single paper in the case of Marsh, et al., 1959) makes it impossible to dissociate the relative contribution of this variable from the possible contribution of the coping variable. Since each of these factors can drastically modify the neurochemical alterations induced by stress, any attempt to determine the effects of coping would be futile.

Although a role for adrenal corticosteroids and T-cells in the acute stress-induced exacerbation of tumor growth is questionable in specific instances (Jamasbi & Nettesheim, 1977; Peters, 1975; Peters & Kelly, 1977), the possible mediation of the stress-induced altered tumor growth by these mechanisms cannot be ruled out. Similarly, the neurochemical alterations induced by stress may also mediate both the exaggerated and inhibited tumor growth, and catecholamine changes may be the first step in a neurochemical, hormonal, immunological interaction. A role for central catecholamines in the mediation of the stress-induced alterations of tumor growth is based on the fact that DA and NE changes produced by stress might predict drastic acute-chronic differences. In fact, administration of reserpine, a drug that reduces amine availability, exacerbated tumor growth in

rats (Lapin, 1978; Welsch & Meites, 1970) and mice (Lacassagne & Duplan, 1959). Moreover, administration of the catecholamine precursor, L-DOPA (Wick, 1977, 1978a), the catecholamine stimulant, d-amphetamine (Driscoll, Melnick, Quinn, Lomax, Davignon, Ing, Abbott, Congleton, & Dudeck, 1978), as well as DA or NE themselves (Boulos, Dajuvone, & Azarnoff, 1976; Driscoll, et al., 1978; Wick, 1978b; Yamafugi, Murakami, & Shinozuka, 1970) inhibited the growth of many different transplantable tumor systems in mice (these include B-16 melanoma, L1210 lymphocytic leukemia, and P388 lymphocytic leukemia). Interestingly, administration of the catecholamine receptor blocker chlorpromazine (Belkin & Hardy, 1957; Cohen, 1972, 1975; Gottlieb, Hazel, Braitman, & Zamcheck, 1960; Pollack & Levi, 1972; Van Woert & Palmer, 1969) and the more specific DA receptor blocker haloperidol (Driscoll, et al., 1978; Kanzawa, Hoshi, & Kuretsani, 1970) also inhibited tumor growth. It could be argued that the receptor blockers increased synthesis of catecholamines, thereby increasing amine availability and hence mitigating tumor growth. However, it is hard to imagine where the amines could have acted if their receptors were occupied.

Although catecholamines are implicated in the mediation of the stress effect on tumor growth, it is difficult to discern on the basis of the available data whether the effects of these pharmacological treatments were due to peripheral or central actions. Nonetheless, a role for central involvement is suggested by the finding that L-DOPA, when given in conjunction with the peripheral decarboxylase inhibitor, MK-486, inhibited tumor growth to a larger extent than did L-DOPA alone (Wick, 1977).

IV B.3 Effects of Stress on Metastasis

There are only a few studies examining the effects of stress on metastasizing tumors. Nevertheless, there is some indication that acute stress may exacerbate the development of metastases. The TD_{50} measure can be considered to be a limited model of metastases. That is, metastases usually occurs when tumor cells detach from the primary tumor, enter the blood stream or lymphatic system, and subsequently lodge in a new area. Thus, injection of a small number of cells into syngeneic animals is analagous to the final stage of the metastatic process. As has been previously mentioned, acute surgical stress and whole body X-irradiation stress markedly reduced the TD_{50} in syngeneic mice (Jamazbi & Nettesheim, 1977; Peters, 1975; Peters & Kelly, 1977), suggesting that stress permits smaller colonies of tumor cells to successfully establish themselves. In support of such a contention are the findings that whole body irradiation produced a 7-fold increase in the number of tumor takes from transplantation of one lymphosarcoma cell in syngeneic mice (Maruyama & Johnson, 1969). Using a potentially more appropriate model of metastases, it was found that intravenous injection of tumor cells resulted in significantly more liver (Fisher & Fisher, 1959) and pulmonary (Saba & Antikatzides, 1976; Van Den Brenk, Stone, Kelly, & Sharpington, 1976) tumors if animals had been exposed to surgical (Fisher & Fisher, 1959; Saba & Antikatzides, 1976), irradiation, tumbling or restraint (Van Den Brenk, et al., 1976) stress. Consistent with these results, surgical stress was found to increase metastases formation in a spontaneous metastatic tumor system (Lundy, Lovett, Wolinsky, & Conran, 1979).

Taken together, the aforementioned studies raise the possibility that acute stress may exacerbate metastases. Moreover, it appears that chronic shock stress inhibited metastases formation and growth (Zimel, Zimel, Petresco,

Ghinea, & Tasca, 1977), paralleling the effects of chronic stress on primary tumor induction and growth.

IV C. Summary

In general, examination of all of the available data provisionally suggests that factors such as duration and chronicity of stress exposure, the type of stressor employed, and the timing of stress application (with respect to both the developmental stage of the host and the tumor), may all be important in determining the effect of stress on tumor development. Acute stress appeared to exacerbate tumor growth (Amkraut & Solomon, 1972; Jamasbi & Nettesheim, 1977; Peters, 1975; Peters & Kelly, 1977) and possibly metastasis (Fisher & Fisher, 1959; Jamasbi & Nettesheim, 1977; Lundy, et al., 1979; Maruyama & Johnson, 1969; Peters, 1975; Peters & Kelly, 1977; Saba & Antikatzides, 1976; Van Den Brank, et al., 1976), whereas chronic stress seemed to inhibit tumor induction (Newberry, 1978; Newberry, et al., 1972, 1976; Pradhan & Ray, 1974; Ray & Pradhan, 1974), tumor growth (Burchfield, et al., 1978; Carshben, et al., 1974; Marsh, et al., 1959; Molomut, et al., 1963; Newberry, et al., 1972, 1976; Pradhan & Ray, 1974; Rashkis, 1952; Ray & Pradhan, 1974), and metastasis (Zimel, et al., 1977). This acute-chronic dichotomy is not without problems, however, owing to the tendency of researchers to utilize different stressors, and owing to the fact that this conclusion is based totally on a between-experiment analysis. Specifically, two of the stressors that exacerbated tumor growth and metastasis (surgery and whole body irradiation) have protracted physical and sensory aftereffects, and so it is difficult to determine if the enhanced tumorigenicity is attributable to the acute application of the stressors or to the protracted aftereffects. However, the fact that acute footshock, tumbling and restraint exacerbated tumor growth (Amkraut & Solomon, 1972) and metastasis

(Van Den Brenk, et al., 1976) in conjunction with the findings that chronic footshock and restraint inhibited tumor induction and growth (Newberry, 1978; Newberry, et al., 1972, 1976; Pradhan & Ray, 1974; Ray & Pradhan, 1974), suggest that the former rather than the latter was responsible for the effect. Confusing the situation further are the findings that chronic exposure to isolation and handling stress exacerbated tumor induction and growth (Ader & Friedman, 1965; Andervont, 1944; Dechambre & Gosse, 1973; Levine & Cohen, 1959), rather than inhibiting tumorigenicity as was the case of chronic footshock, restraint, cold, and sound stress. These divergent findings with respect to chronic stress exposure might be due to the differences in the time of stress application. It is equally conceivable, however, that the apparent differences in the effects of acute and chronic stress are due solely to the differences in the nature of the stressors and tumor systems utilized. Accordingly, it is possible that an acute-chronic dichotomy does not exist after all.

The fact that coping processes might influence the alterations in tumorigenicity produced by stress complicates matters further. While the ability to cope with stress was suggested earlier (p. 38) to be an important factor in the possible stress-induced enhancement of carcinogenesis in humans, and has been demonstrated to be an important factor modifying stress-induced neurochemical and hormonal alterations (Coover, et al., 1973; Karczmar, et al., 1973; Stolk, et al., 1974; Weiss, 1970, 1971a,c; Weiss, et al., 1970, 1976), no attention has been paid to the role of coping processes in the animal cancer studies. In fact, it is difficult to determine to what extent coping responses may have been available to the animals in some of these studies.

The purpose of the present investigation was as follows: to determine

whether (1) housing conditions influence tumor growth, (2) housing conditions modify the effects of another stressor on tumor growth, (3) stress type or severity are important factors in determining the effect on tumor growth, (4) acute and chronic stress exposure differentially influence tumor growth, (5) adaptation to acute stress effects on tumor growth would be observed, and (6) coping processes are important determinants of the stress effect on tumor growth.

Experiment 1

It has been observed that social conditions such as isolation (Andervont, 1944; Dechambre & Gosse, 1973), community order breakdown (Henry, et al., 1975), and intermittent maternal separation (LaBarba & White, 1971) can influence tumor induction and growth. The effects of isolation appear to be quite consistent in this regard. Specifically, social isolation increased the incidence of spontaneous tumors (Andervont, 1944) and exacerbated the growth of transplanted tumors (Dechambre & Gosse, 1973) among mice.

The purpose of the first experiment was to determine the number of tumor cells necessary to observe the isolation-induced exacerbation of tumor growth when another tumor system (P815 Mastocytoma) was employed.

Method

Subjects:

A total of 96 inbred DBA/2J male mice were obtained from the Jackson Laboratories, Bar Harbor, Maine, at 40 - 45 days of age. Mice were acclimatized to the laboratory for 14 days before being employed in the experiment. During this time they were housed in groups of 5 in standard opaque polypropylene cages and permitted ad lib access to food and water.

Tumor System:

Syngeneic P815 Mastocytoma (Dunn & Potter, 1957) was obtained from Dr. R. S. Kerbel (Queens University) and maintained in DBA/2J male mice by weekly transfer of 1×10^5 ascites cells. For the purposes of this and all ensuing experiments, the P815 cells were acquired from a donor mouse bearing an ascites tumor, and after extraction were washed twice in

RPMI-1640 (GIBCO). Cell viability was assessed by the Trypan Blue exclusion test. Experimental animals always received a subcutaneous injection of P815 cells suspended in RPMI-1640 in the left anterior flank region. Regardless of dosage, a constant volume of 0.25 ml of cell suspension was injected in all instances (see Appendix A for details of cell extraction, counting, and viability assessment).

Procedure:

Following the 14 days of laboratory acclimatization mice were divided into 6 groups of 16 mice each. The animals in each group received a subcutaneous injection in the left anterior flank region of either 1×10^6 , 0.5×10^6 , 0.25×10^6 , 0.125×10^6 , 0.0625×10^6 , or 0.03125×10^6 viable syngeneic P815 cells respectively. Each of these six groups of mice were further subdivided into 2 groups of 8 mice each, so that half the mice were housed individually in opaque polypropylene cages and the other half of the mice at each dose level were group housed (5/cage) in identical cages. Additional non-injected animals were employed in order that five animals were present in all of the cages. All animals were tailmarked with non-washable ink.

Tumor size was measured horizontally and vertically with vernier calipers each day of the 14 day period following cell transplantation. Since tumors grew in somewhat irregular shapes, the largest dimensions perpendicular to one another were chosen in all instances. An approximation of the area of each tumor was obtained by multiplying the two measurements for each animal. This measure was found to be a valid indicant of tumor size, in that the correlation between tumor area obtained by this technique

and tumor weight among 54 additional animals was highly significant ($r = 0.85$, $p < .001$). Moreover, both within and between rater reliability were found to exceed 0.80. Although measurements ceased on the fourteenth day, animals were handled and monitored daily until death occurred.

Results and Discussion

Figure 1 shows the mean day of tumor appearance (defined as 3 mm^2) as a function of the Dose and Housing conditions. Analysis of variance of the day of tumor appearance yielded only a significant main effect of Dose, $F(5,84) = 42.27$, $p < .001$. Newman-Keuls multiple comparisons ($\alpha = .05$) between the dose levels revealed that as the number of cells transplanted increased, the latency of tumor appearance decreased. Moreover, the mean day of tumor appearance among mice of each dose group significantly differed from that of every other dose group, with the exception of the two lowest doses which did not differ from one another in this respect.

In contrast to the day of tumor appearance data, analysis of variance of the tumor areas revealed a significant Dose x Housing Condition x Days interaction, $F(65, 992) = 1.43$, $p = .016$. As seen in Figure 2 and confirmed by Newman-Keuls multiple comparisons ($\alpha = .05$) of the simple main effects involved in this interaction, dose dependent differences of tumor size were apparent between 10 to 14 days following tumor cell transplantation among both the aggregated and isolated mice. That is to say, tumor size varied monotonically as a function of the number of cells injected on days 10 - 14 in most cases. There were two exceptions to this general finding. Specifically,

Figure 1. Mean ($\pm$ S.E.M.) day of tumor appearance as a function of cell dose and housing condition.

Figure 4. Mean ($\pm$ S.E.M.) tumor area over days, as well as mean ($\pm$ S.E.M.) tumor weight on day 11 (inset), as a function of housing condition.

tumor sizes among group housed mice that received the two highest cell doses did not differ from one another. Similarly, among isolated mice, transplantation of 0.0625×10^6 cells resulted in larger tumors than did 0.125×10^6 cells on day 14.

Consistent with earlier reports (Andervont, 1944; Dechambre & Cosse, 1973), Newman-Keuls multiple comparisons ($\alpha = .05$) between the isolated and aggregated mice on each day at each dose level indicated that social housing influenced tumor development. With the exception of the 0.125×10^6 dose group, mice that were housed in isolation immediately following tumor cell transplantation exhibited larger tumors than did their group housed counterparts, although the specific days on which such an effect was apparent varied as a function of dose. Among mice that received the largest number of tumor cells (1×10^6), social isolation significantly enhanced tumor area on days 10 - 14. Isolated mice exhibited larger tumors than aggregated mice on days 13 and 14 in the 0.5×10^6 cell condition, on days 10 and 14 in the 0.25×10^6 cell condition, on days 12, 13 and 14 in the 0.0625×10^6 cell condition, and on day 14 in the 0.03125×10^6 cell condition.

With respect to survival time, analysis of variance of the day of mortality indicated that longevity following tumor cell transplantation varied both as a function of the Dose of cells injected, $F(5,84) = 2.96$, $p = .016$, as well as the Housing Condition, $F(1,84) = 13.26$, $p < .001$. As can be seen in Figure 3, and confirmed by Scheffe multiple comparisons ($\alpha = .05$), mice injected with the three largest doses of tumor cells succumbed significantly earlier than did mice injected with the three lowest doses. Moreover, as indicated by the main effect of Housing Condition, mice housed in isolation died earlier

Figure 3. Mean ($\pm$ S.E.M.) day of mortality as a function of cell dose and housing condition.

than did the aggregated animals irrespective of tumor cell dose. It should be noted that none of the pairwise comparisons between dose levels was significant, and only when groups were considered in combination did the effect of dose on survival time become apparent. As such, it appears that the day of mortality was not as sensitive a measure as the day of tumor appearance or tumor area.

Taken together, the results of this experiment indicate that both the number of cells transplanted and the housing condition of the host influence subsequent tumor development. The day of tumor appearance, tumor area, and survival time following tumor cell transplantation appeared to vary in a dose-related manner. In addition, housing mice in isolation immediately following tumor cell transplantation appeared to exacerbate tumorigenicity, as evidenced by the fact that this treatment resulted in enhanced tumor areas and shortened survival time. These latter results are consistent with earlier reports of isolation-induced exacerbation of spontaneous (Andervont, 1944) and transplanted (Dechambre & Gosse, 1973) tumor development. The inconsistent results obtained with the 0.125×10^6 cell dose with respect to both the dose-response and the effects of social isolation are puzzling. These inconsistencies may have been due to such factors as sampling bias or error in cell dose preparation. This notwithstanding, the fact that isolation consistently resulted in exaggerated tumor areas and reduced survival time in each of the remaining dose groups supports the contention that social isolation immediately following tumor cell transplantation exacerbates the development of transplanted tumors.

Experiment 2

Experiment 2 represented a partial replication of the first experiment. Since the measurement of tumor area in Experiment 1 had a subjective component to it, despite its reliability, the primary purpose of Experiment 2 was to determine whether the isolation effect would be apparent when tumor weight was employed as the measure of tumor size.

Method

Subjects and Tumor:

Thirty DBA/2J male mice were employed as the subjects in this experiment. All subject and tumor specifications were the same as those described in Experiment 1.

Procedure:

All mice were subcutaneously injected with 6.25×10^4 viable syngeneic P815 Mastocytoma cells in the anterior left flank region. Following cell transplantation, 15 of these animals were isolated, while the remaining 15 mice were housed in groups of 5. All animals were then tailmarked with indelible ink. Caliper measurements of tumor size were taken for the ensuing 11 days in a manner identical to that described in Experiment 1. On day 11, all mice were sacrificed, and their tumors extracted and weighed.

Results and Discussion

Although tumor appearance occurred somewhat sooner among isolated animals ($\bar{x} = 6.0 \pm 0.47$ days) than among group housed mice ($\bar{x} = 7.0 \pm 0.46$

days), this difference did not reach an acceptable level of statistical significance, $F(1,28) = 2.33$, $p = .138$. In accordance with the results of the previous experiment, and in agreement with other reports (Andervont, 1944; Dechambre & Gosse, 1973), analysis of variance of the mean tumor areas revealed a significant Housing Condition $\times$ Days interaction, $F(10,280) = 8.17$, $p < .001$. Newman-Keuls multiple comparisons ($\alpha = .05$) of the simple main effects involved in this interaction (see Figure 4) indicated that isolated mice exhibited significantly larger tumors than did group housed mice on days 8 - 11, but not on the preceding days.

Consistent with the caliper measure of tumor size, tumor weight determined on day 11 indicated that isolated mice had significantly heavier tumors than did the group housed mice, $F(1,28) = 5.93$, $p = .022$ (see inset of Figure 4). Moreover, the caliper measure of tumor size and tumor weight on day 11 proved to be highly correlated, $r(28) = 0.83$, $p < .001$.

The results of this experiment thus confirm the findings of Experiment 1 which suggested that social isolation immediately following tumor cell transplantation enhanced tumor development. Moreover, consistent with preliminary observations, the high correlation between caliper measure of tumor area on day 11 and tumor weight suggests that tumor area as estimated by the caliper procedure is a valid measure of tumor size.

Experiment 3

Although Experiments 1 and 2 indicated that social isolation enhanced tumorigenicity, such an effect may have simply been due to the change in housing conditions rather than isolation per se (Dechambre & Gosse, 1973).

Figure 4. Mean ($\pm$ S.E.M.) tumor area over days, as well as mean ($\pm$ S.E.M.) tumor weight on day 11 (inset), as a function of housing condition.

That is, the larger tumors found among isolated mice may have resulted from the fact that these animals experienced a change in housing conditions (from grouped to isolated), whereas the housing condition of the grouped mice remained constant throughout. The third experiment was designed to assess this possibility.

Method

Subjects and Tumor:

For the purposes of this experiment 40 DBA/2J male mice were bred in our laboratory from breeders obtained from the Jackson Laboratories. These mice were weaned at 25 days of age. All other breeder and tumor specifications were the same as those described in Experiment 1.

Procedure:

The experiment consisted of a 2 x 2 factorial design. Immediately post-weaning, half the mice were isolated while the remaining mice were housed in groups of 5. The animals remained in these housing conditions for the ensuing 50 days. Following this 50 day period all mice received subcutaneous injections of 6.25×10^4 viable syngeneic P815 Mastocytoma cells in the left anterior flank area. Immediately following cell transplantation, mice in each group were subdivided such that 10 of the originally group housed mice were now isolated (group G - I), while the other 10 mice remained housed in groups of 5 (group G - G). Similarly, 10 of the originally isolated mice were housed 5 per cage (group I - G), while the other 10 mice remained isolated (group I - I). All animals were tailmarked with indelible ink immediately after the change of housing conditions. Caliper measurements

of tumor size were taken on each day for the ensuing 16 days in a manner identical to that described in Experiment 1. Although measurements ceased on day 16, all animals were handled and monitored daily until they died. One animal was eliminated from group I - G owing to extensive injuries sustained from fighting.

Results and Discussion

Analysis of variance of the day of tumor appearance (see Figure 5) revealed that neither the Initial Housing Condition, the Transfer of Housing, nor their interaction approached statistical significance, $p > .30$ in all cases. In contrast, analysis of variance of the tumor areas revealed an Initial Housing x Transfer of Housing x Days interaction, $F(15,525) = 8.47$, $p < .001$. Consistent with the first two experiments, Newman-Keuls multiple comparisons ($\alpha = .05$) of the simple main effects involved in this interaction (see Figure 6) revealed that animals transferred from the grouped to the isolated condition (G - I) displayed larger tumors on days 10 - 16 than did animals that were group housed throughout (G - G). Moreover, animals transferred from group housing to isolation (G - I) displayed larger tumors during this period of time than did the animals that remained isolated throughout (I - I). Indeed, the size of the tumors among the I - I mice did not differ from those among the G - G animals. These data suggest that the change of social conditions was more important in the enhancement of tumor development than was the isolation per se. This position is supported to a limited extent by the finding that mice transferred from isolation to group housing (I - G) displayed significantly larger tumors on days 13 and 16 than did mice that had been isolated throughout the experiment (I - I).

The finding that mice of group I - G had smaller tumors than did mice

Figure 5. Mean ($\pm$ S.E.M.) day of tumor appearance among mice that were raised in communal cages and then transferred to isolation (G - I), raised in isolation and then transferred to communal cages (I - G), or housed either in isolation (I - I) or in communal cages (G - G) throughout the experiment.

MEAN DAY OF APPEARANCE

Figure 6. Mean ($\pm$ S.E.M.) tumor area over days among mice that were raised in communal cages and then transferred to isolation (G - I), raised in isolation and then transferred to communal cages (I - G), or housed either in isolation (I - I) or in communal cages (G - G) throughout the experiment. The inset shows the mean ($\pm$ S.E.M.) tumor area of mice of group I - G categorized with respect to whether they exhibited persistent fighting after transfer to communal cages.

of group G - I on days 11 - 16, even though both these groups experienced transfer stress, is at first blush not entirely consistent with the hypothesis that the change of social conditions, rather than isolation per se, was responsible for the enhanced tumorigenicity. However, the smaller tumor enhancing effects of transfer from isolation to group housing might have been due to the behavioral response of the animals upon the shift to communal living. In fact, on the basis of their behavioral response, mice of group I - G could be categorized into two further groups; those mice that engaged in persistent fighting ($n = 4$), and those mice that remained relatively passive ($n = 5$). Analysis of variance of the tumor areas of these animals yielded a significant Fighting x Days interaction, $F(15,105) = 3.54$, $p < .001$. Newman-Keuls multiple comparisons ($\alpha = .05$) between fighting and nonfighting animals on each day revealed that fighters had significantly smaller tumors than non-fighters on days 11 - 14 (see inset of Figure 6). Indeed, tumor sizes among the non-fighters were roughly comparable, although by no means identical, to those of the mice in group G - I. Taken together, these data suggest that social changes may promote the growth of transplanted tumors; however, this effect seems to be dependent on the behavior of the animals upon change of housing condition. The apparent importance of the behavior of the mice following social change might lie in the possibility that fighting is a coping response which is employed in the face of social stress. Indeed, fighting has previously been shown to prevent some of the neurochemical changes induced by stress (Stolk, et al., 1974b) in a manner similar to that observed when animals were able to escape stress (Weiss, et al., 1970, 1976). Moreover, fighting has also been found to ameliorate the ulcerogenic effects

of shock stress (Weiss, Pohorecky, Salman, & Gruenthal, 1976). Since fighting appeared to function as a coping response in these situations, it raises the possibility that coping with social stress in this manner was responsible for the amelioration of the enhanced tumorigenicity otherwise observed.

Parenthetically, it should be noted that since the mice in the present experiment were bred in our laboratory rather than purchased, they did not experience the stress of shipment from the breeder to our laboratory. Nevertheless, the effect of isolation following cell transplantation on tumor area among previously group housed mice was almost identical to that of the previous experiments. Moreover, the group housed mice in this experiment (G - G) exhibited tumor sizes comparable to those of the group housed controls of Experiments 1 and 2. While these data suggest that shipment stress did not greatly influence the effect of social isolation on tumor growth, this conclusion remains a provisional one. Specifically, this notion is based solely on between-experiment comparisons, and the possibility that shipment stress interacted with the experimental manipulations cannot be ruled out. For example, the absence of shipment stress may have interacted with the chronic isolation of group I - I to result in the inhibition of the normal isolation effect.

The mean day of mortality for each group is shown in Table 1. In contrast to the tumor area data, analysis of variance yielded only a significant main effect of Transfer of Housing Condition, $F(1,35) = 5.24$, $p = .028$. That is to say, animals isolated after tumor transplantation died significantly earlier than mice group housed after cell transplantation

Table 1

Mean ($\pm$ S.E.M.) Day of Mortality as a Function of the Initial
Housing Condition and the Transfer of Housing Condition

		Initial Housing Condition	
		Isolated	Grouped
Post-Transfer	Isolated	20.60 $\pm$ 0.52	19.30 $\pm$ 0.56
Housing Condition	Grouped	21.56 $\pm$ 0.84	21.70 $\pm$ 0.94

irrespective of their prior social history. Although not statistically significant, inspection of Table 1 suggests that transfer from group housing to isolation reduced survival time to a greater degree than did chronic isolation. Moreover, the survival time of the mice transferred from isolation to group housing did not appreciably differ from those mice group housed throughout the experiment. The lack of congruency between the mortality measure and that of tumor area is not particularly surprising. Experiment 1 indicated that the mortality measure was not as sensitive a measure as tumor area, at least with respect to dose differences. Moreover, death appears to be the result of peritoneal invasion and subsequent internal hemorrhage. While there is no doubt a relationship between tumor size and peritoneal invasion, the degree of correspondence between these processes may be limited. In fact, there are data available which suggest that tumor invasion is mediated in part by mechanisms independent of those involved in cell proliferation (Burk, 1973; Fidler, 1978; Gail & Boone, 1971; Lipton, et al., 1971; LoBue & Potmesil, 1975; Trinkhaus, 1976). Such mechanisms, as indicated earlier, may include endogenous secretion of locomotion stimulating factors by tumor cells (Burk, 1973; LoBue & Potmesil, 1975), certain cell surface alterations (Gail & Boone, 1971; Lipton, et al., 1971; Trinkhaus, 1976), or the selection of certain cell types within the host environment (Fidler, 1978). Although these mechanisms have been elucidated in attempts to analyse the metastatic process, it seems conceivable that they might be involved in the more local phenomenon of invasion as well. Since the mechanisms operative in cell proliferation and cell invasion may be distinct from one another to some extent, the possibility exists that these mechanisms were differentially

affected by stress, and hence resulted in the incongruency between tumor size and mortality.

Although the tumor area data of Experiment 3 suggest that social change may promote tumor growth, and that this promotion may be modifiable by the behavior of the organism following social change, an alternative interpretation is available. It is possible that isolation, as a stressor, was responsible for the increased tumor size and more rapid death. The diminution of the isolation effect on tumor size, and to a lesser extent on mortality following chronic pre-isolation may have reflected an adaptation process. That is to say, with chronic pre-isolation animals may have adapted to the stress, thus precluding the effects that might otherwise have been observed. Since changes in brain NE activity have been found to be sensitive to stress adaptation (e.g. Thierry, et al., 1968; Thonen, 1970; Weiss, et al., 1975), a subsidiary experiment was conducted to evaluate isolation effects on turnover of brain NE among DBA mice (see Appendix B). Consistent with other reports (e.g. Modigh, 1973, 1974), the results of this experiment indicated that 7 days of isolation reduced turnover of whole brain NE, and that adaptation to this effect did not occur, even with as much as 57 days of isolation. While these data militate against an explanation of the chronic pre-isolation effect on tumorigenicity based on adaptation, the possibility should still be considered that adaptation might have occurred following chronic pre-isolation in chemical systems other than brain NE.

2

Experiment 4

The results described thus far indicate that social isolation following tumor cell transplantation will exacerbate tumor growth. However, this effect is only observed among animals that had been group housed since weaning. If mice had been isolated immediately post-weaning, continued isolation had a smaller effect on survival time and no apparent effect on tumor growth. Furthermore, it appeared as if a change in housing conditions, rather than the isolation per se, was at least partially responsible for the enhancement of tumorigenicity.

It will be recalled that as well as directly influencing neuronal activity housing conditions also modified the alterations of neurochemical activity induced by other stressors (e.g. Welch & Welch, 1968a, b). Based upon these findings, it was suggested that differences in housing conditions might be responsible for some of the inconsistent effects of stress on tumor growth reported in the literature. Since the first 3 experiments demonstrated that housing conditions influence tumor development, Experiment 4 attempted to determine whether housing conditions would also modify the effects of another stressor (uncontrollable footshock) on tumor growth.

Method

Subjects and Tumor:

One hundred DBA/2J male mice served as subjects. All subject and tumor specifications were identical to those described in experiment 1.

Apparatus:

Uncontrollable footshock was administered in 6 identical rectangular black Plexiglas chambers that measured 30 x 14 x 15 cm. The lids of each box consisted of red translucent Plexiglas thus providing limited illumination. The floors of the chambers were made up of 0.32 cm stainless steel rods spaced 1.0 cm apart (center to center). The rods were connected in series by neon bulbs, thereby preventing animals from escaping shock by selecting a particular combination of rods. Footshock was delivered through a 3000 volt source.

Procedure:

Experiment 4 involved a 2 x 2 factorial design. All mice were subcutaneously injected with 6.25×10^4 viable syngeneic P815 Mastocytoma cells in the anterior left flank region. Immediately following cell transplantation all mice were tailmarked with indelible ink. Half of the mice were housed in isolation while the remaining half continued to be housed in groups of 5. Twenty-four hours following cell transplantation these two groups were further subdivided. Half the mice in each of the housing conditions ($n=25/\text{group}$) were individually placed in the shock boxes and exposed to 60 inescapable/uncontrollable shocks (150 μ A, AC) of 6 seconds duration, at intervals of 60 seconds between shocks. The remaining mice in both of the housing conditions ($n=25/\text{group}$) were placed in the boxes for an equivalent 1.1 hour shock-free period. Caliper measurements of tumor size were taken for the 11 days following cell transplantation in a manner identical to that described in experiment 1. On day 11, all mice were sacrificed, and their tumors excised and weighed. It should be noted that throughout the study the experimenter was blind as to the shock treatment mice had received.

Results and Discussion

In contrast to the previous experiments, analysis of variance of the day of tumor appearance yielded a significant main effect of Housing, $F(1,96) = 6.35$, $p = .013$. Although the Housing $\times$ Shock interaction did not reach an acceptable level of statistical significance, $F(1,96) = 2.75$, $p = .10$, Newman-Keuls multiple comparisons ($\alpha = .05$) were carried out on the simple main effects involved in this interaction (see Figure 7) as an a priori prediction had been made on the basis of preliminary data and on the basis of the tumor size measure (see also Experiments 5 - 9). As seen in Figure 7 and confirmed by the multiple comparisons, footshock stress accelerated the appearance of tumors among group housed animals. Among isolated mice, however, tumor appearance did not differ as a function of the shock treatment. Moreover, consistent with the trend noted in the second experiment, in the absence of shock tumors appeared significantly earlier among isolated than among group housed mice. The more robust effect of housing condition in this experiment might have been due to the reduced variance associated with increased sample size.

Tumor area for each group over days is displayed in Figure 8. Analysis of variance revealed that tumor area varied as a function of the Housing $\times$ Shock $\times$ Days interaction, $F(10,960) = 5.39$, $p < .001$. Consistent with Experiments 1 - 3, Newman-Keuls multiple comparisons ($\alpha = .05$) indicated that in the absence of shock larger tumors were noted throughout days 8 - 11 among the isolated animals. In accordance with the day of tumor appearance data, and consistent with reports indicating stress-induced exacerbation of tumor development (Amkraut & Solomon, 1972; Jamasbi & Nettesheim, 1977; Peters, 1975;

Figure 7. Mean ($\pm$ S.E.M.) day of tumor appearance as a function of housing condition and shock treatment. I/NS = isolated - no shock condition, I/S = isolated - shock condition, G/NS = group housed - no shock condition, G/S = group housed - shock condition.

MEAN DAY OF APPEARANCE

Figure 8. Mean ($\pm$ S.E.M.) tumor area over days, as well as mean ($\pm$ S.E.M.) tumor weight on day 11 (inset), as a function of housing condition and shock treatment. I/N = isolated - no shock condition, I/S = isolated - shock condition, G/N = group housed - no shock condition, G/S = group housed - shock condition.

Peters & Kelly, 1977), shock treatment enhanced tumor area on days 9 - 11 among group housed mice. Interestingly, this was not the case among isolated animals. In fact, consistent with reports of stress-induced inhibition of tumor development (Gershben, et al., 1974; Molomut, et al., 1963; Newberry, et al., 1972, 1976; Pradhan & Ray, 1974; Rashkis, 1952; Ray & Pradhan, 1974), the shock treatment resulted in smaller tumors on days 10 and 11 among socially isolated mice.

With respect to the mean tumor weight on day 11 (see inset of Figure 8), analysis of variance yielded a significant Housing Condition x Shock Treatment interaction, $F(1,96) = 6.25$, $p = .014$. As in the case of tumor area, Newman-Keuls multiple comparisons ($\alpha = .05$) of the simple main effects involved in this interaction revealed that in the absence of shock isolated mice had heavier tumors than did group housed mice. Shock produced a significant increase of tumor weight among group housed animals, but resulted in a non-significant reduction of tumor weight among the isolated animals. The correlation between tumor area and tumor weight was once again found to be highly significant, $r(98) = 0.79$, $p < .001$.

The results of this experiment indicate that inescapable shock may influence tumor size, but that such an effect is dependent on the housing condition of the host. Accordingly, it is conceivable that some of the inconsistent effects of stress on tumor growth reported in the literature might be due to differences in housing conditions between the various experiments. Moreover, it is clear that the effects of stress on tumorigenicity cannot be considered in a unitary fashion. The results of the present experiment indicate that it is important not only to evaluate the contributions of sudden

traumatic stress, but also to consider the background environment onto which the stressor is imposed.

Experiment 5

Although housing condition appeared to influence the tumorigenic effects of footshock, other factors should also be considered as important determinants for the effects of stress on tumor development. For example, stress severity, which is an important determinant of the neurochemical and hormonal alterations produced by stress, might also be among the various factors influencing or modifying stress-induced alterations in tumorigenicity. Experiment 5, therefore, was designed to evaluate the possibility that stress severity is a critical factor in determining the direction of the stress effect on tumor growth.

Method

Subjects, Tumor and Apparatus:

A total of 90 DBA/2J male mice served as subjects. All specifications concerning subjects, tumor system, and apparatus were the same as those described in Experiments 1 and 4.

Procedure:

As in the previous experiments, all mice were subcutaneously injected with 6.25×10^4 viable syngeneic P815 Mastocytoma cells in the left anterior flank region. Unlike the procedure of the previous experiments, however, all mice remained group housed (5/cage) throughout. Experiment 5 was comprised of a 3×3 factorial design ($n = 10/\text{group}$). Independent groups of mice

were tailmarked and received either 1.1, 2.2, or 3.3 hours of apparatus exposure 24 hours after tumor cell transplantation. These groups were further subdivided such that an equal number of animals in each of these 3 groups were individually exposed to shock of 75 μ A, 150 μ A, or no shock. Shock presentations of 6 seconds duration were delivered at 1 minute intervals as described in Experiment 4. Caliper measurements of tumor size were taken each day for the 14 days following cell transplantation as described in experiment 1. Although measurements ceased on day 14, animals were handled and monitored daily until death.

Results and Discussion

As observed in Experiment 4 among group housed animals, the day of tumor appearance was significantly influenced by shock stress, $F(2,81) = 5.47$, $p = .006$. The duration of apparatus exposure, and hence the number of shocks delivered, did not appear to be important in this respect, as neither the main effect of Duration of Apparatus Exposure nor the Duration $\times$ Shock Intensity interaction achieved statistical significance (p 's $> .30$ in both instances). As seen in Figure 9, and confirmed by Newman-Keuls multiple comparisons ($\alpha = .05$), tumors appeared significantly earlier among mice that received uncontrollable shock of either 75 or 150 μ A intensity than among nonshocked mice. The mice of the 75 and 150 μ A groups did not differ from one another in this respect.

In accordance with these results, tumor area varied as a function of shock over days, $F(26,1053) = 4.78$, $p < .001$. Again, the duration of apparatus exposure (and hence the number of shocks delivered) did not appear

Figure 9. Mean ($\pm$ S.E.M.) day of tumor appearance as a function of shock intensity. NS = no shock, 75 = 75 μ A, 150 = 150 μ A.

to be an important determinant of tumor growth, as evidenced by the fact that neither the main effect of Duration, the Duration x Shock Intensity interaction, nor the Duration x Shock Intensity x Days interaction approached statistical significance (F 's < 1 in all cases). The mean tumor areas as a function of shock intensity (0, 75, and 150 μ A) collapsed across duration of apparatus exposure are shown in Figure 10. Newman-Keuls multiple comparisons ($\alpha = .05$) revealed that both shock groups (75 and 150 μ A) displayed larger tumors than control animals throughout days 9 - 14. The size of the tumors among mice exposed to uncontrollable shock of 75 μ A did not differ from the tumor areas exhibited by the mice exposed to uncontrollable shock of 150 μ A.

The mean day of mortality (see inset of Figure 10) varied with shock treatment, $F(2,81) = 12.61$, $p < .001$, while the main effect of the Duration of Apparatus Exposure and the Duration x Shock Intensity interaction did not approach statistical significance (F 's < 1). Newman-Keuls multiple comparisons ($\alpha = .05$) indicated that mice of both the 75 and 150 μ A groups died significantly earlier than did the nonshocked controls. Consistent with the day of appearance and tumor area data, the mice of the 75 and 150 μ A groups did not differ from one another with respect to survival time.

Summarizing, the results of experiment 5 suggest that the severity of the stress is not a critical factor in determining the ultimate effects of stress on transplanted tumor growth. Of course, this conclusion is valid only with respect to the parameters of shock intensity and amount of shock examined in the present investigation. It is entirely possible that stress severity would be an important factor in modifying tumor growth using other shock intensities or durations.

Figure 10. Mean ($\pm$ S.E.M.) tumor area over days, as well as mean ($\pm$ S.E.M.) day of mortality (inset), as a function of shock intensity. NS = no shock, 75 = 75 μ A, 150 = 150 μ A.

Experiment 6

As discussed earlier, one possible factor influencing the direction of stress-induced alterations of tumor growth may be the chronicity of stress exposure. Indeed, chronicity is an important variable determining some of the neurochemical, hormonal, and immunological changes induced by stress (e.g. Kiem & Sigg, 1976; Kvetnansky, et al., 1975, 1977; Monjan & Collector, 1977; Weiss, et al., 1975). With respect to tumor development, however, no firm conclusions concerning the role of stress chronicity can be drawn on the basis of the currently available data. Experiment 6, therefore, was conducted in order to determine whether acute and chronic exposure to uncontrollable shock would differentially influence tumor growth.

Method

Subjects, Tumor and Apparatus:

Forty male DBA/2J mice were utilized as subjects in this experiment. All specifications concerning subjects, tumor system, and apparatus were the same as those described in Experiments 1 and 4.

Procedure:

All mice were subcutaneously injected with 6.25×10^4 viable syngeneic P815 Mastocytoma cells in the left anterior flank region, and remained housed in groups of five throughout the experiment. Commencing 24 hours after cell transplantation the animals were tailmarked with indelible ink and assigned to 4 independent groups of 10 mice each. Mice of one group were individually placed in the shock boxes and exposed to 60 inescapable/unavoidable shocks of 6 seconds duration (150 μ A, AC) at 7 minute intervals between shocks.

Mice of the second group received 5 such shock sessions on consecutive days, while the animals of the third group received 10 such shock sessions on consecutive days. Finally, mice in the fourth group received no shock, but were individually placed into the shock boxes for a 1.1 hour shock-free period on 10 consecutive days. After each session, the mice were returned to their home cages. Caliper measurements of tumor size were taken each day for the 14 days following cell transplantation as described in Experiment 1. As in the previous experiments, mice were handled and monitored daily until death.

Results and Discussion

The mean day of tumor appearance in Experiment 6 (see Figure 11) was somewhat retarded relative to the previous experiments. Nevertheless, the day of tumor appearance varied as a function of the uncontrollable shock treatment, $F(3,36) = 20.96$, $p < .001$. Consistent with Experiments 4 and 5, Newman-Keuls multiple comparisons ($\alpha = .05$) revealed that mice exposed to only 1 inescapable shock session exhibited tumors significantly earlier than did the mice of the remaining groups. Likewise, tumors among mice that received 5 sessions of inescapable shock appeared significantly earlier than did those of mice that received either 10 shock sessions or no shock. The difference between the latter two groups approached, but did not reach, an acceptable level of statistical significance.

The mean tumor size over days followed from these initial differences, in that the mean tumor area varied over days as a function of the shock treatment, $F(39,468) = 8.95$, $p < .001$. As seen in Figure 12 and confirmed

Figure 11. Mean ($\pm$ S.E.M.) day of tumor appearance among mice that received no shock (0), 1 session of inescapable shock (1), 5 sessions of inescapable shock (5), or 10 sessions of inescapable shock (10), following tumor cell transplantation.

MEAN DAY OF APPEARANCE

DAYS OF SHOCK

Figure. 12 Mean ($\pm$ S.E.M.) tumor area over days, as well as mean ($\pm$ S.E.M.) day of mortality (inset), among mice that received no shock (0), 1 session of inescapable shock (1), 5 sessions of inescapable shock (5), or 10 sessions of inescapable shock (10), following tumor cell transplantation.

by Newman-Keuls multiple comparisons ($\alpha = .05$), mice that received a single shock session had significantly larger tumors than did the remaining groups throughout days 9 - 14. The nonshocked control animals and mice that received 5 shock sessions did not differ from one another on any days, but had significantly larger tumors than did the mice of the 10 shock session group on days 12 - 14.

Finally, analysis of the day of death (see inset of Figure 12), revealed that the shock treatment influenced survival time, $F(3,36) = 7.02$, $p < .001$. Newman-Keuls multiple comparisons ($\alpha = .05$) revealed that a single session of shock decreased survival time relative to nonshocked controls. Five shock treatments likewise reduced survival time, but this effect was absent in the 10 shock session group. It will be noted that the growth and mortality measures, although roughly comparable, were not entirely congruent.

Summarizing, it appears that uncontrollable shock may influence the growth of transplanted tumors; however, such an effect is dependent upon the chronicity of the stress regimen. Acute uncontrollable shock appeared to exacerbate tumorigenicity, whereas exposure to chronic uncontrollable shock appeared to inhibit tumor growth.

Experiment 7

At first blush it seems paradoxical that tumor exacerbation was not apparent after repeated shock, although this finding is in agreement with other reports (Burchfield, et al., 1978; Gershben, et al., 1974; Marsh, et al., 1959; Pradhan & Ray, 1974; Newberry, et al., 1972, 1976; Rashkis, 1952; Ray & Pradhan, 1974). That is, since tumors began to appear approximately

48 -72 hours after a single shock session, tumors in the groups that received 5 or 10 shock sessions should have appeared well before the conclusion of the stress regimen. One possible explanation for the delayed tumor appearance is that certain physiological after-effects of uncontrollable shock are responsible for the tumor promotion, but these physiological states are precluded with repeated shock at 24 hour intervals.

While such a notion could partially account for the fact that chronic shock antagonized the effects of an acute shock session on tumor development, it cannot account for the fact that chronic shock also exerted an inhibitory effect on tumor growth. Such an inhibitory action, however, may be attributable to factors other than the chronic regimen of stress exposure. Specifically, it has been demonstrated that the stage of tumor development at which stress is introduced may influence the subsequent effects (Amkraut & Solomon, 1972; Burchfield, et al., 1978; Newberry, 1978). In fact, tumor growth characteristics are very different immediately following transplantation than they are after angiogenesis has taken place (Folkman, 1975; Folkman & Tyler, 1977). Thus it is conceivable that even if the first session of inescapable shock exerted a tumor enhancing effect, the subsequent stress sessions might have masked this effect owing to inhibitory effects of stress during this later developmental period of the transplanted tumors. Experiment 7 was designed to determine whether stress administered at different times after tumor cell transplantation would differentially influence tumor growth.

Method

Subjects, Tumor and Apparatus:

A total of 40 DBA/2J male mice were used as the subjects in this experiment.

All subject, tumor and apparatus specifications were identical to those described in Experiments 1 and 4.

Procedure:

All mice were injected subcutaneously with 6.25×10^4 viable syngeneic P815 Mastocytoma cells in the left anterior flank region. Mice remained group housed (5/cage) throughout the entire experiment. The animals were tailmarked with indelible ink and assigned to 4 groups ($n = 10/\text{group}$). Twenty-four hours following tumor cell transplantation mice of one group were individually placed in the shock boxes and exposed to 60 inescapable/unavoidable shocks (150 μA , AC) of 6 seconds duration with 1 minute intervals between shocks. Mice of a second group were exposed to exactly the same shock parameters 3 days after tumor cell transplantation, while mice of a third group received shock 5 days following cell transplantation. Finally, no shock controls were individually placed in the shock boxes for a 1.1 hour shock-free period on the fifth day following cell transplantation. As in the previous experiments, caliper measurements of tumor size on the 13 days following tumor cell transplantation were carried out, and all animals continued to be handled and monitored daily until death.

Results and Discussion

The day of tumor appearance varied as a function of the shock treatment, $F(3,36) = 3.59$, $p = .023$. Newman-Keuls multiple comparisons ($\alpha = .05$) indicated that mice that were exposed to one session of inescapable shock either 1 or 3 days following tumor cell transplantation exhibited tumors significantly earlier than did the nonshocked control mice.

Predictably, the mean day of tumor appearance among the mice that received inescapable shock on the fifth day following tumor cell transplantation did not differ from that of the nonshocked control mice (see Figure 13). The latter finding is not surprising in view of the fact that approximately half the mice in both these groups exhibited tumors before stress exposure. In all probability, tumors among the remaining mice had already formed but were not as yet detectable.

Analysis of variance of the tumor areas (see Figure 14) yielded a significant Shock Treatment x Days interaction, $F(36,432) = 2.00$, $p < .001$. Newman-Keuls multiple comparisons ($\alpha = .05$) of the simple main effects involved in this interaction indicated that mice exposed to uncontrollable shock at any of the times following cell transplantation had significantly larger tumors than did the nonshocked mice throughout days 9 - 13. The three shock groups did not differ from one another in this respect on any of the days.

The mean day of mortality for each of the groups is shown in the inset of Figure 14. Although it appeared as if the mice that were exposed to inescapable shock succumbed earlier than the nonshocked mice, this effect approached, but did not reach, statistical significance, $F(3,36) = 2.15$, $p = .111$. In light of the results of the previous experiments, the lack of a congruency between survival time and the other measures was not unexpected.

The results of the present experiment confirm and extend the findings of Experiments 4, 5, and 6. One session of uncontrollable shock 24 hours after tumor cell transplantation enhanced the development of transplanted tumors. Similar effects were noted when mice were exposed to one session

Figure 13. Mean ($\pm$ S.E.M.) day of tumor appearance among mice that were exposed to 1 session of inescapable shock either 1, 3, or 5 days following tumor cell transplantation or no shock.

Figure 14. Mean ($\pm$ S.E.M.) tumor area over days, as well as mean ($\pm$ S.E.M.) day of mortality (inset), among mice that were exposed to 1 session of inescapable shock either 1, 3, or 5 days following tumor cell transplantation or no shock.

of inescapable shock either 3 or 5 days following cell transplantation. As such, it does not appear that the antagonism of the acute stress effect, or the tumor inhibition, produced by 5 or 10 consecutive days of shock exposure was due to the later stress sessions occurring during a different developmental period of the tumor (i.e., after vascularization). If the antagonism of the acute shock-induced exaggeration of tumor growth in Experiment 6 was due to a later shock session producing an inhibitory effect, then this inhibitory effect should have been apparent among the mice that were exposed to stress on the fifth day after tumor cell transplantation. To the contrary, inescapable shock administered at this time enhanced, rather than inhibited, tumorigenicity.

Experiment 8

The finding that footshock applied 1, 3, or 5 days after tumor cell transplantation enhanced tumor development indicates that the mitigation of tumor growth following chronic stress is probably not a consequence of the stress being applied several days after cell transplantation. Two related hypotheses are available to account for the antagonistic, although not the inhibitory effects of chronic stress. First, as discussed earlier, it is possible that the after-effects of shock are responsible for the promotion of tumor development. By repeatedly shocking mice at 24 hour intervals expression of the after-effects are precluded. Second, it must be considered that some degree of adaptation to stress occurs within the first few shock sessions, thereby preventing the tumorigenic effects of the last shock session. It follows from the latter alternative that some inhibition of the acute stress effect should be observed even if the chronic stress was applied prior

to tumor cell transplantation. Experiment 8, therefore, attempted to determine whether chronic shock pre-exposure would mitigate the tumor enhancing effects of acute shock.

Method

Subjects, Tumor and Apparatus:

Forty male DBA/2J mice served as subjects. Apparatus, tumor system and subject specifications were identical to those described in Experiments 1 and 4.

Procedure:

Mice, housed 5 per cage throughout the experiment, were assigned to one of four treatment conditions and tailmarked with indelible ink. Animals of one group were individually placed in the shock boxes and exposed to 60 uncontrollable shocks (150 μ A, 6 seconds duration) at 1 minute intervals over each of 10 consecutive days. Immediately following the ninth shock session, these mice were subcutaneously injected with 6.25×10^4 viable syngeneic P815 Mastocytoma cells in the left anterior flank region. Mice received their last shock session 24 hours after cell transplantation. Similarly, mice of a second group were individually exposed to uncontrollable footshock; however, these mice received shock on only 5 consecutive days. Cell transplantation took place immediately after the fourth shock session, followed 24 hours later by the fifth and final shock session. Animals in the third group were individually exposed to only one session of uncontrollable shock 24 hours after cell transplantation. Finally, mice of the fourth group received no shock, but were placed in the shock boxes for a 1.1 hour

shock-free period on 10 consecutive days, with tumor transplantation occurring on the ninth day. The dose of tumor cells and site of transplantation were identical for all groups. Moreover, the study was conducted such that all animals received the tumor transplant on the same day. Commencing 24 hours after tumor cell transplantation, caliper measurements of tumor size were taken on each day for the ensuing 14 days. Animals were handled and monitored daily until they died.

Results and Discussion

Figure 15 shows the mean day of tumor appearance for each group. Analysis of variance of the day of tumor appearance yielded a significant main effect of Shock Treatment, $F(3,36) = 3.16$, $p = .036$. Consistent with the earlier experiments, Newman-Keuls multiple comparisons ($\alpha = .05$) indicated that the tumors of mice exposed to a single shock session 24 hours after cell transplantation appeared significantly earlier than did those of the nonshocked mice. Chronic pre-exposure to either 4 or 9 consecutive daily shock sessions partially antagonized the acute stress-induced acceleration of tumor appearance. The mean day of tumor appearance among these animals fell between and did not significantly differ from that of the nonshocked and acutely shocked mice. Although 9 days of shock pre-exposure appeared to antagonize the tumorigenic effect of acute shock to a larger degree than did 4 days of shock (see Figure 15), the mean day of tumor appearance of the two chronic shock groups did not statistically differ from one another.

The mean tumor area for each of the treatment groups over days are shown in Figure 16. Analysis of variance of the tumor areas yielded a significant Shock Treatment x Days interaction, $F(39,468) = 2.38$, $p < .001$. Newman-Keuls multiple comparisons ($\alpha = .05$) between the groups on each day

Figure 15. Mean ($\pm$ S.E.M.) day of tumor appearance as a function of adaptation treatment. Mice received either no shock pre-exposure (NO ADAPT.), 4 successive days of shock pre-exposure (4 ADAPT.), or 9 successive days of shock pre-exposure (9 ADAPT.). Tumors were transplanted immediately after the last adaptation session, and mice received one final session of inescapable shock 24 hours later. A fourth group served as a no shock control.

Figure 16. Mean ($\pm$ S.E.M.) tumor area over days, as well as mean ($\pm$ S.E.M.) day of mortality (inset), as a function of adaptation treatment. Mice received either no adaptation (0), 4 successive days of adaption exposure (4), or 9 successive days of adaptation exposure (9). An additional group served as a no shock control (NS).

revealed that mice that received one session of inescapable shock 24 hours after tumor cell transplantation had significantly larger tumors than did the mice of the remaining three groups on days 11 - 14. Moreover, the tumor areas of the mice that received 4 or 9 shock pre-exposure sessions did not differ from one another or from the nonshocked mice throughout the entire experiment. Thus, it appears that with 4 or 9 days of pre-exposure to shock the tumor enhancing effects of uncontrollable shock administered 24 hours after tumor cell transplantation are antagonized.

The inset of Figure 16 shows the mean day of mortality of the four groups. Although shock slightly reduced survival time, the main effect of shock did not approach statistical significance, $F(3,36) = 0.88$, $p = .461$. The inconsistency between this experiment and the previous one is probably due to the variability of the death measure previously discussed.

Consistent with the results of Experiment 3, this experiment again illustrates the importance of prior stress history. Moreover, the results suggest that the mechanisms which subserve the tumor promoting properties of acute shock are subject to adaptation processes. Specifically, the tumor enhancing effects of acute stress were not evident if mice received chronic shock exposure prior to cell transplantation. As such, it could be argued that the elimination of the acute stress effects which were observed in Experiment 6, might have been due, in part, to stress adaptation as well. According to this formulation, by repeatedly shocking animals at 24 hour intervals after tumor cell transplantation, the after-effects of stress, which may be responsible for the tumor enhancement, were precluded. In addition, the physiological after-effects of the last shock session were not manifested in the form of increased tumor growth, because by this time, stress adaptation had occurred.

While such an hypothesis might account for the fact that chronic shock following tumor cell transplantation eliminated the effects of acute shock on

tumor growth, it is clear that the actual inhibition of tumor growth relative to nonshocked mice that was observed in Experiment 6 cannot be adequately accounted for by these formulations. That is to say, the fact that tumor growth was retarded relative to nonshocked mice indicates effects other than, or in addition to, the elimination of the acute shock effect. Moreover, the fact that similar inhibition of tumor growth was not observed with chronic shock exposure prior to tumor cell transplantation in the present experiment, raises the possibility that chronic shock may result in relatively transient physiological changes which actively inhibit tumor growth.

Experiment 9

The results thus far indicate that housing conditions, stress chronicity, and previous stress history all influence the ultimate effect of stress exposure on tumor growth. Moreover, these data suggest that all of these factors may have been responsible for some of the inconsistent stress effects that have been reported in the literature. In addition to these factors, it was suggested earlier that the availability of coping responses may also contribute to the effects of stress on tumor growth. This possibility is suggested by the data of Experiment 3, which indicated that fighting might alter the course of tumor growth. Furthermore, the importance of the coping variable is emphasized by studies indicating that the inability to cope with stress, rather than the stress per se, is the major determinant of stress-induced neurochemical and hormonal alterations (Karczmar, et al., 1973; Stolk, et al., 1974b; Weiss, 1970, 1971a,c; Weiss, et al., 1970, 1976), gastric ulceration (Weiss, 1968; 1970, 1971a,b,c), and possibly myocardial injury as well (Miller, Grossman, Richardson, Wistow, & Thomas, 1978). Experiment 9 evaluated the possibility that coping processes might modify the effects of acute stress on tumor growth.

Method

Subjects and Tumor:

Thirty DBA/2J male mice were employed as the subjects in this experiment. All subject and tumor specifications were identical to those described in Experiment 1.

Apparatus:

Shock was delivered in 3 identical black Plexiglas shuttle boxes which measured 29.2 x 8.9 x 16.5 cm. The grid floor, composed of 0.32 cm stainless steel rods spaced 1.0 cm apart (center to center), was connected through neon bulbs. The shock source was the same as that described in Experiment 1. Each shuttle box was divided into two compartments by a black Plexiglas wall, partially made up of a solenoid-controlled horizontally moveable gate. In the open gate position a 1.27 cm hurdle separated the two compartments and a 5.2 x 6.1 cm space allowed the animal access to the adjacent compartment. Thin stainless steel plates, which lined the hurdles and protruded slightly above them, were connected in series with the grid floor and in this way mice were prevented from avoiding shock by sitting on the hurdle. Similarly, the end walls of each box were lined with stainless steel plates which were connected in series to the grid floor. Therefore, mice were not able to avoid shock by leaning against these walls. On each side of the hurdle (1.1 cm) there were two infrared photocells and these were 1.27 and 2.54 cm, respectively, above the grid floor. The cells were wired so that they would not trigger if the beams on both sides of the hurdle were crossed simultaneously as would happen if the mouse was halfway through the gate. The cells were triggered when a mouse crossed the beam on the non-shock side only, and the latency was recorded. Another set of photocells were

situated 2.54 cm from the end walls. These cells were triggered if an animal failed to trigger the first photocells by jumping over them. All shuttle boxes were housed in sound attenuated chambers.

Procedure:

Mice were injected subcutaneously with 6.25×10^4 viable syngeneic P815 Mastocytoma cells in the left anterior flank region as described in Experiment 1. Immediately following cell transplantation mice were assigned to one of three treatment groups ($n = 10/\text{group}$) and tailmarked with indelible ink. Animals were housed in groups of five throughout the experiment.

Twenty-four hours following cell transplantation the animals were exposed to footshock stress. Mice of the escape group (ES) were individually placed in the shuttle boxes and exposed to 60 escape trials using shock of 150 μA . Each trial consisted of shock being presented for 5 seconds during which the gate separating the compartments was closed, thereby preventing escape. The gate was then opened and the mouse permitted to enter the adjacent non-shock compartment. Since preliminary results indicated that DBA/2J mice escaped within approximately 1 second, this delay procedure was employed to assure that the duration of shock mice received approximated the 6 seconds employed in Experiments 4 - 8. Mice received 60 such trials at intervals of 1 minute between trials. Mice of a second yoked inescapable shock group (YIS) were individually placed in the shuttle boxes and exposed to 60 inescapable shocks. Since the inescapable shock boxes were connected in series with the escape boxes, mice in this group received shock on the same schedule as their partners in the escapable condition. Thus, the shock delivered was the same in both these conditions, but only mice in the escape

group could control shock offset. The animals of the third group, the no shock controls (NS), were placed in the shuttle boxes for an equivalent shock-free period. Caliper measurements of tumor size were taken each day for 14 consecutive days, commencing 24 hours following tumor cell transplantation. Although measurements ceased on day 14, animals continued to be handled and monitored daily until death.

Results and Discussion

The mean escape latency, and therefore the mean shock duration for both the escapable and inescapable shocked animals was 6.29 seconds per trial. The mean day of tumor appearance as a function of the shock treatment is shown in Figure 17. Analysis of variance indicated that tumor appearance varied as a function of Shock Treatment, $F(2,27) = 4.0$, $p = .030$. Newman-Keuls' multiple comparisons ($\alpha = .05$) revealed that tumors among mice that received yoked inescapable shock appeared significantly earlier than those of either the no shock controls or the mice that received escapable shock. The latter two groups did not differ significantly from one another in this regard.

As seen in Figure 18, daily group differences in tumor size corresponded with the day of appearance data. That is, tumor size varied as a function of the shock treatment over days, $F(26,351) = 3.66$, $p < .001$. Newman-Keuls multiple comparisons ($\alpha = .05$) between the groups on each of the days indicated that the yoked inescapably shocked mice exhibited significantly larger tumors than did the other two groups throughout days 10 - 14. Animals that received escapable shock did not differ from the no shock mice, with the

Figure 17. Mean ($\pm$ S.E.M.) day of tumor appearance among mice that received escapable shock (ES), yoked inescapable shock (YIS), or no shock (NS).

MEAN DAY OF APPEARANCE

Figure 18.

Mean ($\pm$ S.E.M.) tumor area over days, as well as mean ($\pm$ S.E.M.) day of mortality (inset), among mice that received escapable shock (ES), yoked inescapable shock (YIS), or no shock (NS).

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exception of day 13, when larger tumors were seen among the escapable animals.

The inset of Figure 18 displays the mean day of mortality for each of the three groups. While the effect of shock treatment only approached statistical significance, $F(2,27) = 2.59$, $p = .093$, visual inspection of the data suggested that only yoked inescapable shock reduced survival time, as the mean days of mortality of the escapably shocked and no shock mice were almost identical.

The absence of a significant mortality effect notwithstanding, the results of Experiment 9 strongly suggest that acute footshock stress will only exacerbate tumor growth if control over the stress is not available. These data, together with those of Experiment 3, indicate that the inability to behaviorally cope with stress, rather than the physical stress per se, was responsible for the effects of shock on tumor growth. Thus, the inconsistent effects of stress on tumorigenicity reported in the literature might have also been due to differential availability of coping responses in those studies.

Experiment 10

One of the most serious problems in the control of cancer among humans is the development of metastases. In almost all cases patients do not die from the primary tumor, but succumb to undetected or inoperable metastases (Fidler, 1978; Nicolson, 1977; Poste, 1977). Although the data of the previous experiments indicate that social conditions and stress influence tumor growth, they do not address themselves to the question of metastases.

While the tumor system utilized in present study does not lend itself to a comprehensive investigation of metastases, some tentative and preliminary observations concerning this problem can be derived through examination of the TD_{50} . As previously discussed, the TD_{50} measure can be considered to be a limited model of metastases, analagous only to the portion of the metastatic process which occurs after a cell aggregate has escaped the blood or lymphatic vessels and has imbedded itself into host tissue. Experiment 10, therefore, was conducted in order to assess the effects of stress, and the ability to cope behaviorally with stress, on the effectiveness of a small number of cells to produce tumors.

Method

Subjects, Tumor and Apparatus:

A total of 360 male DBA/2J mice served as subjects in this experiment. Apparatus, tumor system and subject specifications were identical to those described in Experiments 1 and 9.

Procedure:

Experiment 10 consisted of a 3 x 3 factorial design. Mice were divided into 3 groups of 120 mice each and subcutaneously injected in the left anterior flank region with either 40, 60, or 100 viable syngeneic P815 Mastocytoma cells respectively. Preliminary studies had revealed that 40 - 60 cells produced tumors in approximately 50% of the mice. Twenty-four hours later mice were tailmarked with indelible ink and the animals among each dose group were subdivided such that 40 mice at each dose level were exposed to either escapable shock, yoked inescapable shock, or no shock.

The shock parameters, escape training, and yoking procedures were identical to those described in Experiment 9. It should be noted that animals were group housed throughout the experiment. Mice were handled and monitored daily, and the day of tumor appearance was noted. If mice did not develop a tumor within 90 days, they were considered to be tumor free.

Results and Discussion

The mean escape latencies, and thus the mean shock duration for both the escapable and inescapable shock animals were 6.36, 6.21, and 6.43 seconds per trial for the mice in the 40, 60, and 100 cell conditions, respectively. Table 2 shows the proportion of mice in which tumors developed as a function of the dosage and shock treatment. Chi square analysis at each level of dose revealed that there were no significant differences in the proportion of yoked inescapably shocked, escapably shocked and no shock mice that developed tumors, $\chi^2(2)$'s = 0.068, 1.83, and 2.39 for the 40, 60, and 100 cell conditions, respectively. Even when the groups were collapsed across dose level, the differences in the proportion of tumor takes among mice exposed to yoked inescapable shock, escapable shock, and no shock did not approach statistical significance, $\chi^2(2) = 1.28$, $p > .90$. The absence of a difference in tumor takes was not due to a ceiling effect precluding such differences since subcutaneous injection of 40 cells produced tumors in approximately 50% of the animals, whereas injections of 60 or 100 cells resulted in substantially higher proportions of tumor takes (approximately 77% and 90% respectively).

Table 2

Proportion of Mice in which Tumors Developed as
a Function of Dosage and Shock Treatment

Dosage	Shock Treatment		
	Yoked Inescapable Shock	Escapable Shock	No Shock
40 cells	22/40	23/40	23/40
60 cells	34/40	28/40	31/40
100 cells	39/40	36/40	34/40

The results of Experiment 10 are inconsistent with earlier studies which indicated that stress exposure (in the form of whole body irradiation or surgery) either 24 or 48 hours following cell transplantation would drastically reduce the number of cells necessary for a TD_{50} (Jamasbi & Nettesheim, 1977; Peters, 1975; Peters & Kelly, 1977). However, the differences in the nature of the stressors employed in the present investigation and in those earlier studies may account for this inconsistency. Both X-irradiation and surgery are severe stressors and have after-effects which persist for at least several days. In contrast, the physiological effects of footshock, at least when relatively low intensities are employed, are fairly transient (Anisman & Sklar, 1979). Thus it may be the case that more severe stress, or several days of less intense stress, was necessary in order to reduce the TD_{50} in the present study. Indeed, we have observed that when social isolation (a more chronic form of stress) was employed, almost twice as many isolated than aggregated mice developed tumors following subcutaneous transplantation of 100 CaD_2 mammary adenocarcinoma cells (unpublished observations). However, this finding may be due to the different tumor system employed, rather than to the relative chronicity of the stress conditions. Alternatively, it is possible that stress exposure several days after cell transplantation is the critical factor necessary to observe effects on the TD_{50} . This hypothesis is not inconsistent with the previously reported studies, since the after-effects of surgery and irradiation are presumed to last for at least several days. Thus, it may have been necessary to shock the animals 72 or 144 hours following cell transplantation in order to substantially alter the proportion of animals that developed tumors after low dose implants.

It is not clear, therefore, whether footshock stress might not have had an effect on the TD_{50} had appropriate stress parameters been employed.

V. General Discussion

Consistent with earlier reports (e.g. Burchfield, et al., 1978; Dechambre & Gosse, 1973; Fisher & Fisher, 1959; Gershben, et al., 1974; Jamasbi & Nettesheim, 1977; Marsh, et al., 1959; Maruyama & Johnson, 1969; Newberry, et al., 1972, 1976; Peters, 1975; Peters & Kelly, 1977; Pradhan & Ray, 1974; Rashkis, 1952; Ray & Pradhan, 1974; Saba & Antikatzides, 1976; Van Den Brenk, et al., 1976), the results of the present investigation indicated that social and physical stressors influenced the development of transplanted tumors. However, an analysis of the effects of stress on tumorigenicity requires consideration of several experiential and organismic variables. Indeed, the present experiments indicated that factors, such as the availability of coping responses, stress chronicity and stress type, as well as the social housing conditions and premorbid stress history of the host, all contribute to the consequences of stress on tumor development and growth.

One of the striking features of the present investigation was that even apparently subtle manipulations could have dramatic effects on tumor development. Thus, while social isolation influenced tumor growth (see also Andervont, 1944; Dechambre & Gosse, 1973), it is likely that change in social conditions played a major role in this respect. That is, the tumor enhancing properties of social isolation were only evident among mice that had been reared in communal cages prior to tumor cell transplantation. If mice had been raised in isolation, continued isolation had a much smaller and inconsistent tumorigenic effect. The position that social change could

enhance tumor growth was further supported by the findings that transfer from isolation to communal housing also promoted tumor development. Interestingly, however, the tumor promoting effects of social change were not evident among mice that engaged in fighting. Inasmuch as fighting has been implicated as a coping response employed in the face of physical stress (Stolk, et al., 1974; Weiss, Pohorecky, Salman & Gruenthal, 1976), the distinct possibility exists that factors related to coping behaviors were instrumental in the antagonism of the tumorigenic effects of social change. Of course, it should be borne in mind that the apparent relationship between fighting and tumor size might not have been a causal one, but rather one derived from some other variable which produced both the fighting and the smaller tumors.

Like social change, acute exposure to physical stress in the form of footshock was found to enhance the growth of transplanted tumors (see also Amkraut & Solomon, 1972). Within the limits of the shock parameters used in the present investigation, neither the shock intensity, nor the shock duration within a session, appeared to influence the magnitude of the stress effects. The importance of coping factors in determining changes in tumor growth were evident from the differential effects of escapable and inescapable shock. Whereas acute exposure to escapable shock 24 hours after tumor cell transplantation had little, if any, effect on tumor growth, acute exposure to yoked inescapable shock resulted in earlier tumor appearance and enhanced tumor sizes relative to nonshocked mice. The fact that the tumor promoting effects of shock were not observed when animals could control shock offset suggests that it was the inability to cope with stress behaviorally, rather

than the physical stress per se, which was responsible for the tumor promotion. As such, these results point to the importance of the psychological factors associated with stress in determining the tumorigenic consequences.

Inasmuch as psychological factors such as controllability and predictability have been shown to be important determinants of the neurochemical and hormonal consequences of stress (Weiss, 1970, 1971a,c; Weiss, et al., 1970, 1976), it was not entirely unexpected to find that coping factors could influence the tumorigenic consequences of footshock as well. Whether the neurochemical or hormonal consequences of stress were responsible for the promotion of tumor growth is not certain. ~~As~~ possibility, however, will be discussed at length in a later section. Suffice it at this point, that any number of endogenous chemical changes that occur following uncontrollable shock might be involved in the stress-induced enhancement of tumorigenicity.

In addition to behavioral coping, several other factors were found to influence the tumorigenic effects of stress. Although acute uncontrollable shock reliably enhanced tumor development, such an effect was dependent upon the organism's social condition. The tumor enhancing effects of acute uncontrollable shock were only apparent among mice that were communally housed. If mice were socially isolated, exposure to the same shock regimen appeared to inhibit, rather than to exacerbate, tumor development. These results further highlight the importance of social conditions in the growth of transplanted tumors. Moreover, the fact that differential housing conditions could so drastically alter the tumorigenic consequences of stress, indicates that the effects of stress on tumor development and

growth cannot be considered in a unitary fashion.

As mentioned earlier, social housing conditions have been reported to have a wide variety of endogenous chemical consequences in the mouse (Modigh, 1973, 1974, 1976; Welch & Welch, 1967, 1968a,b,c, 1970; also see the review in Brain, 1975). Moreover, social housing conditions have been found to modify the neurochemical alterations induced by exposure to various stressors in mice and rats (Modigh, 1973, 1974, 1976; Thoa, et al., 1976; Weiss, et al., 1976; Welch & Welch, 1968a,b). Thus, the possibility exists that the biochemical consequences of shock interacted in some way with those of social housing conditions to determine the ultimate effects on tumor growth. The various physiological mechanisms which might be involved in such an interaction will be discussed in greater detail in a later section.

The notion that the effects of stress on tumor growth cannot be considered in a unitary fashion is reinforced by the findings that the premorbid shock experience of the mice also altered the tumor promoting effects of acute uncontrollable shock. Exposure to uncontrollable shock over four or nine successive days prior to tumor cell transplantation mitigated the exacerbation of tumorigenicity otherwise produced by acute stress. These data clearly indicate that previous stress history is an important determinant of the effects of stress on tumor development. Moreover, these findings suggest that the mechanisms which subserve the tumor promoting properties of acute footshock stress are subject to adaptation processes.

In accordance with earlier reports of inhibition of tumor induction and growth when chronic physical stress was applied after the initiation of the carcinogenic process (i.e. after carcinogen administration or tumor

transplantation) (Gershben, et al., 1974; Marsh, et al., 1959; Molomut, et al., 1963; Newberry, 1978; Newberry, et al., 1972, 1976; Pradhan & Ray, 1974; Rashkis, 1952; Ray & Pradhan, 1974), it was found that 10 successive shock sessions following tumor cell transplantation inhibited tumor growth relative to nonshocked controls. The inhibitory effects of chronic shock exposure following tumor cell transplantation could not be attributed to antitumor effects exerted by a shock session applied several days after cell transplantation. That is, it could have been argued that shock exposure during a later developmental stage of the tumor (e.g. after the tumor cells have had the opportunity to adhere and vascularize over a number of days) had effects which differed from that of stress applied soon after cell transplantation. However, it appeared unlikely that this could account for the inhibition of tumor growth by chronic stress exposure, as a single shock session administered either 3 or 5 days after tumor cell transplantation enhanced, rather than inhibited, tumor growth.

An hypothesis based on adaptation to stress could not account for the inhibited tumor growth seen among mice that received tumor cell transplantation prior to any shock exposure. After all, the initial shock session should have produced accelerated tumor appearance and enhanced tumor growth regardless of any adaptation that might have developed subsequently. Moreover, the very fact that the successive shock treatments after tumor cell transplantation inhibited tumor growth relative to non-shocked animals points to effects other than, or in addition to, the elimination of the acute shock effect (e.g. adaptation). As such, these data suggest that chronic shock may result in physiological changes which actively inhibit tumor growth. Moreover,

the fact that the inhibition of tumor growth was only observed when the repeated shock was administered in the presence of the tumor (i.e. after cell transplantation), and not when it was administered prior to tumor transplantation, indicates that the physiological consequences of shock responsible for the inhibition do not persist for a protracted period of time following the last shock session. It is of interest to note that some of the neurochemical alterations induced by chronic shock exposure also do not persist for a protracted period of time after the last stress session (Thierry, et al., 1968a).

In discussing the effects of chronic stress on tumor promotion and inhibition, it is important to consider the nature of the stressor employed. As discussed earlier, although both isolation-transfer stress and footshock stress exacerbated tumorigenicity under certain conditions, several differences in the tumorigenic effects of the two stressors were evident. Specifically, while acute exposure to uncontrollable footshock almost always enhanced tumor appearance, this was not the case with isolation-transfer stress. In fact, among socially isolated mice accelerated tumor appearance was only observed when large sample sizes were employed. Moreover, whereas chronic footshock following tumor cell transplantation resulted in a small inhibition of tumor growth, maintaining mice in isolation continuously following cell transplantation resulted in tumor promotion. These differences may reflect the different physiological consequences that accompany these forms of stress.

Summarizing briefly, the results of the present investigation indicated that stress may either exacerbate or inhibit tumor development; however, the

effect manifested was dependent upon the availability of coping responses, premorbid stress history, stress type, stress chronicity, and social conditions. In light of these findings, it is possible that the conflicting reports of stress-induced exacerbation of tumorigenicity from some laboratories (Ader & Friedman, 1965; Amkraut & Solomon, 1972; Andervont, 1944; Dechambre & Gosse, 1973; Fisher & Fisher, 1959; Henry, et al., 1975; Jamasbi & Nettesheim, 1977; Kavetsky, et al., 1966; Levine & Cohen, 1959; Lundy, et al., 1979; Maruyama & Johnson, 1969; Peters, 1975; Peters & Kelly, 1977; Riley, 1975; Saba & Antikatzides, 1976; Van Den Brenk, et al., 1976) and stress-induced retardation of tumor development from others (Ader & Friedman, 1965; Burchfield, et al., 1978; Gershben, et al., 1974; Labarba & White, 1971; Marsh, et al., 1959; Molomut, et al., 1963; Newberry, 1978; Newberry, et al., 1972, 1976; Newton, et al., 1962; Pradhan & Ray, 1974; Rashkis, 1952; Ray & Pradhan, 1974; Zimel, et al., 1977) may have been due to procedural variations that are common across studies. In fact, most of these contradictory findings can be readily accounted for in terms of the experiential variables and stress parameters employed in these earlier investigations. In particular, as observed in the present report, stress-induced exacerbation of tumorigenicity was observed, for the most part, in studies that either employed acute exposure to uncontrollable physical stress shortly after tumor cell transplantation (Amkraut & Solomon, 1972; Fisher & Fisher, 1959; Jamasbi & Nettesheim, 1977; Lundy, et al., 1979; Maruyama & Johnson, 1969; Peters, 1975; Peters & Kelly, 1977; Saba & Antikatzides, 1976; Van Den Brenk, et al., 1976) or utilized protracted exposure to social stressors such as isolation (Andervont, 1944; Dechambre &

Gosse, 1973), community order breakdown (Henry, et al., 1975), or housing conditions in which animals were exposed to phermones, external noise (Riley, 1975) and human presence (Ader & Friedman, 1965; Levine & Cohen, 1959; Riley, 1975). Indeed, the only study which reported stress-induced exacerbation of tumor growth that does not seem to be easily accounted for on the basis of the variables described in the present investigation, is one in which chronic signalled footshock was apparently employed (Kavetsky, et al., 1966). However, as discussed earlier (p. 42), the ~~lack~~ of procedural information pertaining to the shock-regimen employed, makes this study difficult to evaluate.

The use of chronic uncontrollable physical stressors after the initiation of the carcinogenic process might have been responsible for many of the reports of stress-induced inhibition of tumorigenicity (Gershben, et al., 1974; Molomut, et al., 1963; Newberry, 1978; Newberry, et al., 1972, 1976; Pradhan & Ray, 1974; Rashkis, 1952; Ray & Pradhan, 1974; Zimel, et al., 1977). There are a few studies, however, which are difficult to reconcile within this framework. Specifically, the findings that chronic handling (Newton, et al., 1962) and chronic intermittent maternal separation (Labarba & White, 1971) inhibited tumor growth are at odds with the interpretation presented in the present report and with studies which indicated that protracted social stress would exacerbate tumorigenicity (Ader & Friedman, 1965; Andervont, 1944; Dechambre & Gosse, 1973; Henry, et al., 1975; Riley, 1975). However, since the social stress in these two studies was initiated early in life, these seemingly paradoxical findings might have been due to the influence of developmental factors (Ader & Friedman, Levine & Cohen, 1959).

In fact, Labarba and White (1971) have themselves suggested that developmental processes played an important role in determining the effects of intermittent maternal separation on tumor growth.

Although both chronic cold stress (Burchfield, et al., 1978) and chronic exposure to avoidable shock (Marsh, et al., 1959) have also been reported to inhibit tumor growth, other aspects of these studies are inconsistent with the data of the present investigation. Specifically, Burchfield, et al. (1978) reported that cold stress would only inhibit tumor growth if it was chronically applied prior to tumor cell transplantation. There are no apparent causes for this contradictory finding, although the utilization of an extremely low dose of tumor cells (TD_{25}) in one experiment, as well as the statistical analysis employed, might have been contributing factors. The fact that chronic avoidable shock was found to inhibit tumor growth (Marsh, et al., 1959) also seems to be inconsistent with the present results. While it is possible that controllability is not a critical factor when a chronic stress regimen is employed, latency data were not reported by Marsh et al. (1959) and the actual amount of shock mice received cannot be determined. Moreover, the mice were individually housed in this study, and thus, housing conditions might have influenced the findings as well. As such, it is not possible to accurately determine what factors were responsible for the observed inhibition of tumor growth.

It is clear from the preceding discussion that the findings of many of the previous reports concerning the effects of stress on tumorigenicity are consistent with the results of the present investigation when factors such as the availability of coping responses, stress chronicity, stress type, premorbid stress history, and social conditions are considered. At the same

time given the number of variables found to influence stress effects on tumor growth, it is difficult to imagine a source for inconsistent findings could not be found when employing a post hoc analysis. Clearly, additional research that considers these variables in a systematic fashion when other stressors are employed is required before a firm conclusion can be arrived at.

V A. Neurochemical, hormonal and immunological mechanisms in relation to stress: A provisional model.

The divergent consequences of stress on tumor growth that have been reported in various laboratories, and the various factors found to influence tumor growth in the current investigation, present considerable difficulty when attempting to provide a unified analysis. Indeed, there is no a priori reason to believe that a single mechanism, or set of mechanisms, account for all of the effects of stress on tumor growth. Furthermore, hypothesizing a single set of mechanisms to account for the effects of stress is subject to double jeopardy. That is, because of the inconsistent results reported one would imagine that only a very limited number of explanations could adequately account for the available data. At the same time, the unsystematic approach previously taken to the analysis of stress effects on carcinoma, together with the limited knowledge of the neoplastic process, leads to the possibility that any number of models could be made to fit the data eventually. These caveats notwithstanding, a highly provisional explanation of the stress effects on tumorigenesis can be gained on the basis of the neurochemical, hormonal, and immunological consequences of stress (see pp. 1 - 26).

There appears to be a remarkable parallel between the neurochemical and tumorigenic alterations produced by stress. For example, acute inescapable shock, and not escapable shock, resulted in NE depletions in several brain

areas (Weiss, et al., 1970; 1976). Likewise, only acute inescapable shock resulted in the enhancement of tumor development in the present study. Similarly, adaptation to the neurochemical consequences of acute shock stress was observed following chronic shock exposure (Thierry, et al., 1968a; Weiss, et al., 1975, 1976; Zigmond & Harvey, 1970), and analagous adaptation to the tumorigenic effects of uncontrollable footshock was noted as well. In contrast to shock stress, the neurochemical alterations induced by social isolation did not undergo adaptation (Modigh, 1973, 1974, 1976; see also Appendix B). Likewise, the reduction of the tumor enhancing properties of isolation among mice that were chronically housed in this condition did not appear to be a consequence of adaptation (see also Andervont, 1944). Finally, the parallel between the neurochemical and tumorigenic effects of stress is illustrated by the fact that social housing conditions modified the turnover of catecholamines produced by stress exposure (Modigh, 1973, 1974, 1976; Thoa, et al., 1976; Weiss, et al., 1976; Welch & Welch, 1968a,b), just as housing conditions appeared to modify the effect of footshock on transplanted tumor development in the present study.

The congruency between the neurochemical and tumorigenic alterations induced by stress provisionally suggests that the tumorigenic changes might be subserved, at least in part, by the stress-induced neurochemical alterations. It is important to bear in mind that this hypothesis does not exclude a role for other mechanisms (e.g. hormonal, immunological, hematological; see review in Amkraut & Solomon, 1975). Indeed, if they are involved, the neurochemical alterations induced by stress would probably only represent a step in a series of physiological changes which culminate in the observed variations of transplanted tumor development and growth. Inasmuch as exposure to acute uncontrollable stress has been shown to reduce levels of central NE (Bliss & Ailion, 1969; Bliss, et

al., 1968; Gordon, et al., 1966; Kiem & Sigg, 1976; Kobayashi, et al., 1976; Ritter, et al., 1978; Stone, 1971, 1973; Weiss, et al., 1970, 1976), and in some cases DA (Kobayashi, et al., 1976; Kvetnansky, et al., 1975, 1977; Moore & Lariviere, 1964), and social isolation among mice has been shown to reduce turnover of DA and NE (Welch & Welch, 1968b; Modigh, 1973, 1974, 1976; see also Appendix B), it seems plausible that the exacerbation of tumorigenicity produced by these stressors might have been a consequence of the stress-induced reductions of central catecholamine activity. Moreover, the absence of the tumor promoting effects of social change when mice engaged in fighting, and the absence of the tumor promoting effects of footshock when animals could control shock offset, might have been a consequence of the prevention of the stress-induced reduction of catecholamine activity by these coping behaviors. (Modigh, 1973, 1974, Stolk, et al., 1974b; Weiss, et al., 1970, 1976).

17 The antagonism of the tumor enhancing properties of acute shock among mice exposed to chronic shock prior to tumor cell transplantation might have been due to the fact that the catecholamine reductions ordinarily produced by acute stress did not occur after long-term stress exposure (e.g. Bhagat, 1969; Ingenito, 1968; Kiem & Sigg, 1976; Kvetnansky, et al., 1975, 1977; Nielson & Fleming, 1968; Thierry, et al., 1968a; Weiss, et al., 1975, 1976; Zigmond & Harvey, 1970). Moreover, the finding that a small reduction of tumor growth was induced by long-term shock treatment after tumor cell transplantation, but not by similar premorbid experience, could have resulted from the increased catecholamine activity induced by long-term shock exposure (Stone, Freed & Margano, 1978; Thierry, et al., 1968a; Weiss, et al., 1975, 1976) being present during the growth phase of the tumor. That is, chronic premorbid shock would only have

prevented the catecholamine depletion ordinarily induced by exposure to acute shock 24 hours after cell transplantation. Chronic shock following tumor cell transplantation, however, would have resulted in increased amine activity at a time when the tumor was present, thereby retarding tumor growth. Accordingly, it seems possible that the retardation of tumor development in some of the present experiments might have been a consequence of increased central catecholamine activity.

The differences between the tumorigenic effects of shock and isolation-transfer stress also seem to be amenable to an interpretation within this framework. Specifically, the differential effects of the two treatments on tumor appearance might have been due to the rapidity with which the neurochemical changes occur. Whereas, the reductions of central amine activity by social isolation are slow to develop, taking at least several days (Anisman & Sklar, Note 1), the reductions of catecholamine activity induced by acute footshock are almost immediate. Moreover, the fact that increased tyrosine hydroxylase activity occurs after chronic shock (Stone, et al., 1978; Thierry, et al., 1968a; Weiss, et al., 1976), but not after chronic isolation (Modigh, 1973, 1974; Welch & Welch, 1968b), might account for the differential effects of these two stressors when chronically applied after tumor cell transplantation.

Indirect support for the hypothesis that the alterations of tumorigenicity were a consequence of the stress-induced changes in catecholamine activity is derived from studies which showed modification of tumor development following administration of pharmacological compounds with known central catecholamine effects (Belkin & Hardy, 1957; Boulos, et al., 1976; Driscoll,

et al., 1978; Gottlieb, et al., 1960; Kanzawa, et al., 1970; Lacassagne & Duplan, 1959; Lapin, 1978; Quadri, Clark & Meites, 1973; Quadri, Kledzik & Meites, 1973; Welsch & Meites, 1970; Wick, 1977, 1978a,b). Consistent with the effects of stress, administration of reserpine, a drug that reduces central catecholamine levels, was found to exacerbate tumor growth (Lacassagne & Duplan, 1959; Lapin, 1978; Welsch & Meites, 1970). Likewise, we have found that reduction of catecholamine levels by alpha-methyl-para-tyrosine administered 21 hours following P815 cell transplantation exacerbated tumor development (see Appendix C). Conversely, increasing brain amine activity through administration of L-DOPA, in conjunction with a peripheral decarboxylase inhibitor, or by administration of d-amphetamine was found to inhibit tumor growth (Driscoll, et al., 1978; Quadri, Kledzik & Meites, 1973; Wick, 1977, 1978a). Although all of these pharmacological compounds have peripheral as well as central effects, it seems that the central actions of the drugs might have been responsible for the observed consequences on tumor growth, since L-DOPA plus a peripheral decarboxylase inhibitor (which increases central DA and NE concentrations), had a much greater antitumor effect than did L-DOPA administered alone (Wick, 1977, 1978a).

While the data presented thus far suggest that reduced catecholamine activity might produce tumor exacerbation, and increased central catecholamine activity might result in tumor inhibition, there exist several findings which are, at first blush, difficult to reconcile within this framework. Specifically, it has been reported that administration of the catecholamine receptor blocker, chlorpromazine (Belkin & Hardy, 1957; Gottlieb, et al., 1960; Van Woert & Palmer, 1969), and the more specific DA receptor blocker, haloperidol (Driscoll,

et al., 1978; Kanzawa, et al., 1970) inhibited, rather than exacerbated, tumor growth. However, it is likely that these paradoxical findings were not due to the catecholamine receptor blocking properties of these compounds. It appeared that the effects of chlorpromazine could largely be attributed to nonspecific toxic actions (Belkin & Hardy, 1957; Gottlieb, et al., 1960; Driscoll, et al., 1978). Indeed, at the doses employed in these studies (Belkin & Hardy, 1957; Driscoll, et al., 1978; Gottlieb, et al., 1960) drug mortality rates of 70 - 80 % were reported (Belkin & Hardy, 1957). With acute administration of lower non-toxic doses, antitumor actions were not evident in both identical and different tumor systems (Cranston, 1958; Driscoll, et al., 1978). While long-term administration of non-toxic doses of chlorpromazine were reported to inhibit tumor growth (Van Woert & Palmer, 1969), it was not clear whether this effect was due to catecholamine receptor blockade, or to the resulting increase of catecholamine synthesis (Anden, Butcher, Corrodi, Fuxe, & Ungerstedt, 1970; Bunney, Walters, Roth, & Aghajanian, 1973; Aghajanian & Bunney, 1973, 1974; Rebec & Groves, 1975) producing stimulation at receptors insensitive to chlorpromazine (Cools, 1978; Cools & Van Rossum, 1976). Furthermore, since the drug was administered over a 30 day period, receptor supersensitivity may have developed, thus producing the antitumor effect (e.g. Dunstan & Jackson, 1979; Yarbrough, 1975).

The reported antitumor effects of haloperidol (Kanzawa, et al., 1970) were probably not due to this compound's affinity for DA receptors. Although non-toxic doses of haloperidol have been reported to inhibit tumor growth in an allogeneic tumor system (i.e. where the subject and the tumor are not histocompatible) (Kanzawa, et al., 1970), similar doses had no antitumor effects

in three different syngeneic tumor systems (Driscoll, et al., 1978). As such, the antitumor effects exhibited by this compound in the Kanzawa, et al. (1970) study were probably due to an interaction between the drug and the host allograft rejection response, thus invalidating any possible conclusions as to the specific tumorigenic effects of the drug (for a complete discussion of this issue see the review in Hewitt, 1978). Moreover, consistent with the notion that reduction of catecholamine activity promotes tumor growth, it was found that haloperidol markedly enhanced the growth of DMBA-induced tumors (Quadri, Clark & Meites, 1973). While this latter result might only be valid for this particular tumor system, since DMBA-induced tumors are hormone-dependent, this appears to be unlikely, since L-DOPA administration has been found to influence both DMBA-induced tumors (Quadri, Klezdik, & Meites, 1973) and "hormone-independent" transplantable tumors (Wick, 1977, 1978a) in a consistent fashion.

A problem for the hypothesis of catecholamine involvement in the stress-induced tumor alterations is presented by some of the findings of the present investigation. Specifically, raising mice in isolation resulted in reduced NE activity, but did not enhance tumor growth. It is possible, however, that such a prolonged period of reduced catecholamine activity resulted in compensation in other transmitter systems, thus eliminating the effect of isolation on tumor growth. Indeed, it is hard to imagine of catecholamine neurons functioning independent of other transmitters. Furthermore, the possibility exists that the developmental period (i.e. immediately after weaning) contributed to the altered tumorigenic consequences of social isolation since other stressors have been found to result in tumorigenic effects that are peculiar to this developmental period (Labarba & White, 1971). Of course, empirical data must be forthcoming in order for such arguments to be maintained. A second

difficulty for the neurochemical hypothesis arises from the finding that acute footshock had differential effects on tumorigenicity among socially isolated and group housed mice. We have found that footshock stress reduced hypothalamic NE levels to a greater extent among isolated than aggregated Swiss-Webster mice (Anisman & Sklar, Note 1). As such, exacerbation of tumor growth should have been observed among both socially isolated and group housed mice. It might even have been expected that a more pronounced tumor enhancement would be observed among isolated animals. To the contrary, however, acute exposure to uncontrollable shock resulted in tumor retardation among socially isolated mice. Owing to the diverse strain differences in neurochemical synthesis, utilization, and enzyme activity (see review in Anisman, 1978), any firm conclusions concerning the role of central amines in mediating the tumorigenic effects of stress must be held in abeyance pending completion of pharmacological and biochemical studies which directly assess this notion.

As mentioned earlier, even if brain amines are involved in the mediation of the tumorigenic changes induced by stress, they probably do not act alone. The final physiological processes through which the stress-induced alterations of tumor growth are manifested are probably local alterations of the micro-environment surrounding the tumor. Inasmuch as acute uncontrollable shock has been shown to elicit the release of corticosterone to a much greater degree than either acute controllable shock (Weiss, 1971a,c) or chronic uncontrollable shock (Weiss, et al., 1975), a role for adrenal corticosteroids in subserving the tumorigenic effects of stress is suggested. While reports vary as to the effect of social isolation on corticosteroid secretion (see review in Brain, 1975), the possible involvement of these hormones in the tumorigenic effects of social change cannot be ruled out. Moreover, acute stress has been found to elicit the release of several other pituitary

and glandular hormones (e.g. Baldrick, et al., 1954; Brown, et al., 1971a; Knigge, 1960; Martin & Reichlin, 1970; Mason, et al., 1976; Sigg, et al., 1978; Tache, et al., 1978; Van Vugt, et al., 1978; for a fuller review see p. 14 - 18), as well as to increase sympathetic activity (Bassett & Cairncross, 1976a,b,c; Corrodi, et al., 1967, 1970; Goldstein & Nakajima, 1966; Gordon, et al., 1966; Kiem & Sigg, 1976; Kvetnansky & Mikulaj, 1970; McCarty, et al., 1978; Olivario & Starjne, 1965; Ordy, et al., 1966; Rubensen, 1969; Winer & Carter, 1977; Wooten & Cardon, 1973) and to produce immunosuppression (Bussard, et al., 1971; Folch & Waksman, 1974; Lundy, et al., 1979; Monjan & Collector, 1977; Pees, 1977). In contrast, chronic stress was found to antagonize these acute hormonal and sympathetic effects (Bassett & Cairncross, 1976a,b; Feldman & Brown, 1975, 1976; Kiem & Sigg, 1976; Kvetnansky, et al., 1975, 1976; Levine, et al., 1973; Martin, 1974; Mason, et al., 1976; Mikulaj, et al., 1973, 1976; Tache, et al., 1978), and to produce immunofacilitation, as well (Monjan & Collector, 1977). Accordingly, these data raise the possibility that these hormones and peripheral transmitters, as well as immunological mechanisms, might also be involved in the mediation of the tumorigenic effects of stress. As discussed earlier (p. 20 - 25), the hormonal changes are probably secondary to the central alterations induced by stress, and further, may themselves influence immune functioning. Thus, the secondary hormonal and immunological changes induced by stress might interact with the neurochemical alterations, as well as with other, as yet unspecified physiological processes, to produce the internal environmental alterations and hence the variations of tumor development.

Although data which question the possible role of hormonal and

immunological mechanisms in the mediation of stress-induced altered tumorigenicity have recently been reported (Jamashi & Nettesheim, 1977; Peters, 1975; Peters & Kelly, 1977), a role for these mechanisms cannot be entirely ruled out (Lundy, et al., 1979; Riley, et al., 1976; Spackman & Riley, 1976; Zimel, et al., 1977). Support for the notion that hormonal processes subserved the stress-induced alterations of tumor growth is derived from the findings that systemic administration of either cortisol, ACTH, or adrenaline enhanced tumorigenicity among mice and rats that received tumor cell transplants (Peters & Kelly, 1977; Riley, et al., 1976; Zimel, et al., 1977). However, total adrenalectomy, which itself had been reported to inhibit metastases formation (Zimel, et al., 1977), did not abrogate the enhancement of tumorigenicity induced by surgical or whole body irradiation stress (Peters & Kelly, 1977). While the latter data are suggestive of a lack of hormonal involvement in the stress-induced alterations of tumorigenicity, they are by no means conclusive. The possibility exists that other sites of ACTH action, other pituitary hormones, and perhaps sympathetic amine release may all be involved in mediating the tumorigenic effects of stress.

The possible role of immunological mechanisms in subserving the tumorigenic effects of stress is similarly clouded. Specifically, it has been shown that surgical and irradiation stress produce immunosuppression via inhibition of cell mediated (Jamashi & Nettesheim, 1977; Lundy, et al., 1979; Peters, 1975; Peters & Kelly, 1977; Stratton Byfield, Byfield, Benfield, Small, & Pilch, 1975; Vose & Moudgil, 1975) and humoral immune responses (Jamashi & Nettesheim, 1977). Moreover, administration of thiabendazole, an immunorestorative drug, has been reported to antagonize both the suppression of cell-mediated

immunity and the enhanced tumor metastases induced by surgical stress (Lundy, et al., 1979). Taken together, these data suggest that immunosuppression produced by stress might subserve the enhancement of tumorigenicity. However, data are also available that indicate that the T- and B-cell immune systems do not subserve the stress-induced tumor enhancement. For example, although surgical and whole body irradiation stress exacerbated tumorigenicity, inhibition of T-cell function did not have this effect under otherwise identical conditions (Peters, 1975). Moreover, immunological reconstitution by administration of syngeneic spleen cells and thymic implants did not antagonize the tumorigenic effects of irradiation stress (Jamasbi & Nettesheim, 1977). Finally, the time course of the inhibition of immune functioning and that of the tumor enhancing effects of irradiation stress did not parallel one another. Although the immunosuppression was evident six weeks following irradiation stress, the tumor enhancing properties of this treatment were absent at this time (Jamasbi & Nettesheim, 1977). While these data suggest that the T- and B-cell immune mechanisms are not important in the stress-induced tumorigenic alterations, the possibility that other immune mechanisms such as nonsensitized thymus independent lymphocytes (Herberman & Holden, 1978; Oehler, et al., 1978a,b; Oehler & Herberman, 1978) and macrophages (Alexander, 1977; Hibbs, 1973) are involved still exists. The possible contribution of these latter immunological mechanisms in subserving the tumorigenic effects of stress has not been evaluated to date.

V B. Implications for human neoplastic disease.

Regardless of the mechanisms mediating the changes in tumor development and growth, it is clear that physical or psychological insults can alter transplanted tumor development among mice in a predictable fashion. As such, these data lend credence to the human experimentation which provisionally suggests a role for stress and coping processes in the development of carcinoma (see pp. 34 - 39, and the review in Fox, 1978). It should be emphasized, however, that such a notion is speculative and that caution must be taken when generalizing from the results of studies on animal tumor models to neoplastic disease among humans. This is of particular importance, since the human research to date has by and large been of a retrospective nature, has not fully evaluated the psychological factors associated with stress, and has not considered the importance of stress chronicity, stress type, and social conditions (see pp. 34 - 39; and the review in Fox, 1978).

In contrast to the effects of stress on the growth and development of transplanted tumors, only limited information is available concerning the effects of stress on carcinogen-induced tumors. In the case of chronic stress, the effects described in the present report on transplanted tumors are paralleled by studies involving carcinogens. In fact, chronic uncontrollable footshock, or chronic restraint, have both been found to inhibit the induction of tumors by DMBA (Newberry, 1978; Newberry, et al., 1972, 1976). Unfortunately, data are not available concerning the effects of acute stress on the induction and growth of carcinogen-induced tumors. Thus, while the present data would implicate an effect of stress on the cancer process, it is premature to ascribe

a role for acute stress in the initiation and development of carcinogen-induced tumors. However, given that cancer development is quite variable among individuals exposed to similar amounts of carcinogen (see reviews in Doll, 1977; Nago, et al., 1978; Storer, 1975; Upton, 1967, 1975), it is tempting to speculate that experiential and organismic factors might contribute to the induction of tumors following carcinogen exposure.

The effects of stress during the later stages of neoplastic disease has received considerably more attention. The data of the present investigation, and those of other researchers (Jamasbi & Nettesheim, 1977; Lundy, et al., 1979; Maruyama & Johnson, 1969; Peters, 1975; Peters & Kelly, 1977; Saba & Antikatzides, 1976; Van Den Brenk, et al., 1976) suggest that stressful treatments such as surgery, irradiation, and chemotherapy, will exacerbate tumor growth and metastases among mice. Although stress did not seem to influence metastases in the present investigation, this was probably due to both the type of stress, and the model (TD₅₀) of metastases, employed (see Experiment 10, pp. 88-92). Nevertheless, stress clearly affected tumor growth in the present experiments, and appeared to enhance metastases in various models of the metastatic process (Fisher & Fisher, 1959; Jamasbi & Nettesheim, 1977; Lundy, et al., 1979; Peters, 1975; Peters & Kelly, 1977; Saba & Antikatzides, 1976; Van Den Brenk, et al., 1976). In accord with the results derived from the animal studies, enhanced tumor growth and metastases are sometimes observed clinically after either, surgery, radiation therapy, or chemotherapy (e.g. Arseneau, Sponzo, Levin, Schnipper, Bonner, Young, Cannello, Johnson, & Devita, 1972; Carter, 1978; Lundy, et al., 1979; Mathe, 1978; Schmahl, 1977; Stjernsward, 1974). Moreover, it appears that

there are two time courses for this effect (Arseneau, et al., 1972; Carter, 1978; Miller, Nichols, & Meadows, 1978; Lundy, et al., 1979; Pees, 1977; Peters, 1975; Schmahl, 1977; Stjernsward, 1974; Van Den Brenk, 1976). That is, enhanced tumor growth and metastases are sometimes observed shortly after therapy (i.e. 1 - 12 months; predominantly in the case of surgery), and are also seen at longer intervals after treatment (i.e. 5 - 30 years).

The arguments invoked to account for the development of secondary tumors which appear at longer intervals following treatment have typically not included the stress associated with treatment as an important factor. Rather, the secondary tumor appearance has variously been ascribed to (1) the direct carcinogenic properties of these "ameliorative" treatments (Miller, et al., 1978; Russ, Scanlon, & Sener, 1978; Schmahl, 1977; Urano, Koike, & Ohora, 1979), (2) the survival of a group of patients who, owing to some genetic or metabolic quirk, are highly susceptible to cancer (see reviews in Fox, 1978; Heston, 1975; Miller, et al., 1978), (3) the existence during treatment of undetected, or therapy insensitive metastases, and in the specific case of surgery, the release of tumor cells into circulation (Fisher & Fisher, 1959; Peters, 1975; Van Den Brenk, et al., 1976), and (4) the immunosuppressive effects of these treatments (Amkraut & Solomon, 1975; Arseneau, et al., 1972; Carter, 1978; Lundy, et al., 1979; Mathe, 1978). It is interesting that of these arguments only the latter two can potentially account for the "explosions" of tumor growth and metastases sometimes seen very shortly after surgery (Lundy, et al., 1979; Peters, 1975; Saba & Antikatzides, 1976; Van Den Brenk, et al., 1976). Moreover, data reported by Lundy, et al. (1979) suggest that the argument dealing with undetected metastases or the release of cells by

surgical treatment, does not necessarily apply in all cases. Indeed, among mice, in which the possibility of undetected metastases was precluded, it was found that amputation of a limb contralateral to the one with the transplanted tumor resulted in a massive enhancement of metastases. As such, the release of tumor cells could not be the sole causative factor for the metastases sometimes observed shortly after surgery (Lundy, et al., 1979), although it clearly cannot be ruled out in clinical cases.

It seems conceivable that the "explosions" of tumor growth and metastases infrequently observed shortly after treatment might be a consequence of the stress associated with therapy. Such a notion is not independent of the position which attributes this phenomenon to direct immunosuppression induced by the treatment (Arseneau, et al., 1972, Carter, 1978; Lundy, et al., 1979; Mathe, 1978). Indeed, as discussed earlier, the immune systems may be one of the physiological mechanisms through which stress exerts its tumorigenic effects. In addition, the stress of surgery might enhance metastases formation in the clinical cases where cells are released into circulation, as it did in the animal studies (Fisher & Fisher, 1959; Saba & Antikatzides, 1976; Van Den Brenk, et al., 1976). Hence, this explanation of the "metastatic explosion" is also not independent of the stress hypothesis.

It might be considered that a major limitation of the hypothesis is the relatively small population of patients that exhibit the explosive tumor growth and metastases, as well as the anecdotal way in which these data are reported (Lundy, et al., 1979; Miller, 1977; Peters, 1975). Yet, given that the therapies are usually of a chronic nature, some degree of adaptation to the physiological consequences of stress would be expected. Accordingly, only those

patients who received acute treatment and who had difficulties in coping with stress, might be expected to exhibit "explosions" of malignancy shortly after therapy.

One further comment appears to be in order with respect to the possible implications of the present investigation for traditional cancer treatment methods. In view of the fact that chronic exposure to uncontrollable stress initiated after the onset of the carcinogenic process inhibited tumor growth (Gershben, et al., 1974; Molomut, et al., 1963; Newberry, et al., 1972, 1976; Pradhan & Ray, 1974; Rashkis, 1952; Ray & Pradhan, 1974), it seems possible that some of the beneficial effects of long-term irradiation and chemotherapy might be attributable to the stress associated with them. Of course, the degree to which stress contributes to the cytotoxic actions of these treatments cannot presently be determined.

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Appendix A

Cell Extraction, Counting and Viability Assessment

In all experiments cells were extracted from a donor mouse bearing an ascites tumor. The donor mouse was killed by cervical dislocation and then the abdominal skin sectioned so that the intact peritoneal membrane and cavity was exposed. Five ml of cold RPMI-1640 was then injected into the peritoneal cavity and the peritoneal membrane was palpitated for several seconds. Approximately 6 ml of peritoneal fluid was subsequently withdrawn. The fluid was centrifuged at a slow speed (setting # 2 on an I.E.C. tabletop centrifuge) for 10 minutes. The supernatant was removed, approximately 5 more ml of RPMI-1640 added, and the cells resuspended. This centrifuging procedure was repeated twice more in order to cleanse the cells of all extraneous matter.

Cell viability assessment and cell counting were undertaken after the washing procedure. The cell suspension (0.1 ml) was added to 0.9 ml of 5% acetic acid in order to lyse any red blood cells that remained. The resulting suspension was placed on the hemacytometer and counted with a phase-contrast microscope. Cell viability was assessed by the trypan blue exclusion test. Trypan blue (0.4% in normal saline) was diluted 1:2 with 4.25% saline. A drop of stain was added to a drop of the cell suspension on a microscope slide. The proportion of cells which were non-viable and took up stain were assessed on a phase-contrast microscope. A sampling procedure was employed with 10 samples of the slide being examined. The mean proportion of viable cells was deemed to represent cell viability. In all cases viability exceeded 95%. Following these procedures, the cell suspension was diluted with RPMI-1640, so that the desired number of viable cells were suspended in 0.25 ml of this medium.

Appendix B

Effects of Isolation on Whole Brain NE Turnover In DBA/2J Mice

In Experiment 3 it was observed that mice which had been housed in isolation for 50 days following weaning, and then maintained in this social condition after tumor cell transplantation, did not exhibit the enhanced tumor growth ordinarily induced by this housing condition. It was suggested that following chronic pre-isolation animals might have adapted to the social stress, thus precluding the effects on tumor size otherwise observed. Since changes in brain NE activity have been found to be sensitive to stress adaptation (e.g. Thierry, et al., 1968; Thonen, 1970; Weiss, et al., 1975), this subsidiary experiment was conducted to evaluate isolation effects on turnover of brain NE in DBA mice. It should be noted that adaptation to the neurochemical consequences of social isolation did not occur in other studies employing different strains of mice (e.g. Modigh, 1973, 1974).

Method

Subjects:

Sixty DBA/2J male mice served as subjects. All subject and breeder specifications were identical to those described in Experiment 3.

Procedure:

Mice were reared under three housing conditions ($n = 20/\text{group}$) and were decapitated and brains removed at 82 days of age. Mice of one group were raised in communal cages until time of decapitation. Mice of a second group were raised in communal cages as well, however these animals were transferred to social isolation 7 days prior to decapitation (the number of

days before all of the animals in the G - I group of Experiment 3 exhibited tumors). Mice of the last group were housed in isolation immediately post-weaning for the entire 57 day period prior to decapitation. Three hours before decapitation half the mice in each of the housing conditions received intraperitoneal injection of the tyrosine hydroxylase inhibitor alpha-methyl-para-tyrosine methyl ester (α -MpT; 125 mg/kg), while the remaining mice received equivalent volumes (10ml/kg) of the saline vehicle. After decapitation, brains were quickly removed and placed in liquid nitrogen until fluorimetric assay by a modification of the hydroxyindole method (Lavery & Taylor, 1968; Maickel, Cox, Saillant, & Miller, 1968). One animal died during the long-term isolation, and hence, the 57 days isolated - saline group was comprised of only 9 mice.

Results and Discussion

Table 3 shows the mean whole brain norepinephrine levels as a function of Housing Conditions and Drug Treatment. Analysis of variance of whole brain NE yielded a Housing Condition x Drug Treatment interaction which approached statistical significance, $F(2,53) = 3.11$, $p = .053$. The failure to achieve a level of significance less than .05 was probably due to the unequal sample sizes (Winer, 1971). Newman-Keuls multiple comparisons ($\alpha = .05$) of the simple main effects involved in this interaction revealed that NE levels did not differ as a function of housing condition in the saline treated mice. As expected, administration of α -MpT reduced NE levels among mice in each of the three housing conditions. Although NE levels appeared to differ as a function of housing condition among the α -MpT treated mice, this effect just failed to

Table 3

Mean ($\pm$ S.E.M.) whole brain NE levels (g/g of tissue)
as a function of Housing Condition and Drug Treatment.

	<u>Grouped</u>	<u>Isolated 7 Days</u>	<u>Isolated 57 Days</u>
Saline	220.879 $\pm$ 23.97	206.263 $\pm$ 20.31	215.292 $\pm$ 19.21 ^o
α -MPT	124.842 $\pm$ 26.07	140.529 $\pm$ 14.172	140.991 $\pm$ 9.01

achieve statistical significance ($p = .055$). Nevertheless, as can be seen in Table 3, α -MPT was more effective in reducing NE levels among group housed mice than among mice isolated for either 7 or 57 days. Moreover, the NE levels of these latter two groups were identical.

The fact that α -MPT resulted in a greater depletion of NE among group housed than isolated mice suggests that the turnover of NE was lower among the isolated animals. In addition, since α -MPT had virtually identical effects on brain NE levels of mice housed in isolation for either 7 or 57 days, these data indicate that adaptation to the isolation-induced reduction of NE turnover did not occur with as much as 57 days of isolation.

Appendix C

Effect of Catecholamine Depletions on
Growth of P815 Mastocytoma

As indicated in the general discussion, there appeared to be a remarkable congruency between the tumorigenic and neurochemical consequences of stress. Indeed, it appeared as if the catecholamine reductions induced by acute exposure to uncontrollable stress (Weiss, et al., 1970, 1976), might have partially subserved the alterations of tumorigenicity. This experiment was conducted in a preliminary attempt to assess this hypothesis.

Method

Subjects and Tumor:

Thirty DBA/2J male mice were employed as the subjects in this experiment. Mice were group housed (5/cage) throughout the experiment. All subject and tumor specifications were the same as those described in Experiment 1.

Procedure:

All mice were subcutaneously injected with 6.25×10^4 viable syngeneic P815 Mastocytoma cells in the anterior left flank region. Twenty-one hours following cell transplantation animals were tailmarked with indelible ink and 10 of the mice received intraperitoneal (ip) injection of α -MpT (125 mg/kg), 10 mice received ip injection of α -MpT (62.5 mg/kg), and the remaining 10 mice received ip injection of an equivalent volume (10 ml/kg) of the saline vehicle. These doses were selected on the basis of earlier work which indicated that 125 mg/kg of α -MpT would reduce DA and NE levels by approximately 50% (see Appendix B). Caliper measures of tumor size were taken for the ensuing

15 days in a manner identical to that described in Experiment 1.

Results and Discussion

Analysis of variance of the day of tumor appearance yielded a significant main effect of α -MpT, $F(2,27) = 3.81$, $p = .035$. Newman-Keuls multiple comparisons ($\alpha = .05$) revealed that the mice that received the highest dose of α -MpT exhibited tumors ($\bar{x} = 5.0 \pm 0.42$ days) significantly sooner than did the saline treated mice ($\bar{x} = 6.9 \pm 0.57$ days). The lower dose of α -MpT (62.5 mg/kg) had an intermediate effect on tumor appearance as the mice in this group exhibited tumors ($\bar{x} = 5.8 \pm 0.47$ days) at a time between that of the 125 mg/kg and saline groups, and did not differ significantly from either of them.

In accordance with the day of appearance data, analysis of variance of tumor size yielded a significant Drug Treatment x Days interaction, $F(28,378) = 2.47$, $p < .001$. Newman-Keuls multiple comparisons ($\alpha = .05$) between the groups on each day (see Table 4), revealed that mice that received 125 mg/kg of α -MpT had significantly larger tumors than saline treated mice on days 11 - 15. Mice that received 62.5 mg/kg of α -MpT had larger tumors than saline treated mice on days 14 and 15, and the size of their tumors did not differ from those of the mice treated with 125 mg/kg of α -MpT on these latter two days. On days 11, 12, and 13, however, mice of the 125 mg/kg group had larger tumors than mice among the 62.5 mg/kg group.

Although α -MpT appeared to reduce survival time in a dose-dependent fashion ($\bar{x}$'s = 26.3 ± 1.12 , 27.7 ± 0.70 , and 28.6 ± 1.07 days, for the 125 mg/kg, 62.5 mg/kg, and saline groups respectively), this effect did not achieve an acceptable

Table 4

Mean ($\pm$ S.E.M.) Tumor Areas as a Function of Drug Treatment
and Days (square mm.).

Days	Drug Treatment		
	α -MpT (125 mg/kg)	α -MpT (62.5 mg/kg)	Saline
1	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0
2	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0
3	2.4 $\pm$ 1.6	0.9 $\pm$ 0.9	0.0 $\pm$ 0.0
4	3.9 $\pm$ 2.2	2.7 $\pm$ 1.9	0.7 $\pm$ 0.7
5	8.5 $\pm$ 2.5	4.2 $\pm$ 2.3	2.5 $\pm$ 1.7
6	19.3 $\pm$ 3.5	9.0 $\pm$ 2.8	6.7 $\pm$ 2.8
7	28.6 $\pm$ 3.9	18.9 $\pm$ 2.9	15.5 $\pm$ 4.4
8	42.2 $\pm$ 5.1	33.8 $\pm$ 6.0	25.3 $\pm$ 7.2
9	75.9 $\pm$ 9.4	60.3 $\pm$ 8.2	46.6 $\pm$ 8.7
10	120.7 $\pm$ 17.5	109.8 $\pm$ 10.6	81.6 $\pm$ 11.1
11	174.5 $\pm$ 19.1 ^{*b}	134.7 $\pm$ 8.5	110.4 $\pm$ 12.0
12	228.3 $\pm$ 26.2 ^{*b}	183.2 $\pm$ 16.7	150.8 $\pm$ 12.6
13	270.7 $\pm$ 28.6 ^{*b}	231.2 $\pm$ 23.6	193.4 $\pm$ 8.1
14	301.2 $\pm$ 28.5 [*]	268.9 $\pm$ 23.7 [*]	224.7 $\pm$ 12.1
15	351.9 $\pm$ 33.5 [*]	328.0 $\pm$ 35.1 [*]	261.4 $\pm$ 13.3

* $p < .05$ compared to saline treated mice

^b $p < .05$ compared to α -MpT (62.5 mg/kg)

level of statistical significance, $F(2,27) = 1.40$, $p = .263$. The lack of significance of the mortality measure is probably due to its poor sensitivity, and the sample sizes employed (see discussion of Experiment 3).

The results of this preliminary experiment indicate that α -MPT induced catecholamine depletion would enhance tumor growth under the same conditions that inescapable shock did. As such, it is suggested that the enhancement of tumor growth and development by acute uncontrollable shock might be due to the depletions of central catecholamines engendered by this treatment. However, since α -MPT has peripheral, as well as central effects, this notion is clearly a provisional one, and a detailed pharmacological and biochemical investigation is required in order to determine its viability.

Appendix D

Analysis of Variance Summary Tables

Table 1d
Analysis of Variance of the Day of Tumor Appearance
(Experiment 1)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Dose	5	124.50	24.9	42.47	$p < .001$
Housing Condition	1	1.50	1.5	2.56	$p = .113$
Dose x H.C.	5	5.25	1.05	1.79	$p = .124$
Within Cells	84	49.25	0.5863		

Table 2d
Analysis of Variance of Tumor Area
(Experiment 1)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Dose (D)	5	1467900	293590	40.90	p < .001
Housing Condition (HC)	1	77665	77665	10.82	p < .001
D x HC	5	31206	6241.2	0.87	p = .505
Ss within groups	84	602990	7178.5		
Days	13	13740000	1056900	832.37	p < .001
D x Days	65	1317000	20262	15.96	p < .001
HC x Days	13	150470	11575	9.12	p < .001
D x HC x Days	65	118300	1820.0	1.43	p = .016
Days x Ss within groups	992	1386600	1269.8		

Table 3d
Analysis of Variance of the Day of Mortality
(Experiment 1)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Dose (D)	5	268.71	53.742	2.96	p = .016
Housing Condition (HC)	1	240.67	240.67	13.26	p < .001
D x HC	5	35.204	7.0417	0.39	p = .856
within cells	84	1524.8	18.152		

Table 4d
Analysis of Variance of the Day of Tumor Appearance
(Experiment 2)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Housing Condition	1	7.50	7.50	2.33	$p = .138$
within cells	28	90.00	3.2143		

Table 5d
Analysis of Variance of Tumor Area
(Experiment 2)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Housing Condition (HC)	1	25947	25947	9.73	$p = .004$
Ss within groups	28	74633	2665.5		
Days (D)	10	523490	52349	115.88	$p < .001$
HC x Days	10	36918	3691.8	8.17	$p < .001$
Days x Ss within groups	280	126490	451.75		

Table 6d
Analysis of Variance of Tumor Weight
(Experiment 2)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Housing Conditions	1	0.16089	0.16089	5.93	p = .022
within cells	28	0.76013	0.027147		

Table 7d

Analysis of Variance of the Day of Tumor Appearance

(Experiment 3)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Initial Housing Condition (IHC)	1	2.7191	2.7191	1.07	p = .309
Transfer Housing Condition (THC)	1	1.2368	1.2368	0.49	p = .491
IHC x THC	1	0.013235	0.013235	0.01	p = .943
within cells	34	86.675	2.5493		

Table 8d

Analysis of Variance of Tumor Area

(Experiment 3)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Initial Housing Condition (IHC)	1	38399	38399	5.90	p = .020
Transfer of Housing Condition (THC)	1	23917	23917	3.67	p = .063
IHC x THC	1	74936	74936	11.51	p = .002
Ss within groups	35	227790	6508.4		
Days	15	5182500	345500	427.08	p < .001
IHC x Days	15	54586	3639.1	4.50	p < .001
THC x Days	15	22203	1480.2	1.83	p = .028
IHC x THC x Days	15	102780	6852.0	8.47	p < .001
Days x Ss within groups	525	424710	808.98		

Table 9d

Analysis of Variance of Tumor Area among Mice of
Group I - G as a Function of Fighting
(Experiment 3)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Fighting	1	10561	10561	3.28	$p = .113$
Ss within groups	7	2254	322		
Days	15	43027	2868.5	147.69	$p < .001$
Fighting x Days	15	10303	686.89	3.54	$p < .001$
Days x Ss within groups	105	20394	194.22		

Table 10d
Analysis of Variance of the Day of Mortality
(Experiment 3)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Initial Housing Condition (IHC)	1	3.248	3.248	0.62	p = .436
Transfer Housing Condition (THC)	1	27.389	27.389	5.24	p = .028
IHC X THC	1	5.0751	5.0751	0.97	p = .331
within cells	35	182.82	5.2235		

Table 11d
Analysis of Variance of the Day of Tumor Appearance
(Experiment 4)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Housing Condition (HC) 1	1	16.81	16.81	6.35	p = .013
Shock	1	6.25	6.25	2.36	p = .128
HC x Shock	1	7.29	7.29	2.75	p = .100
within cells	96	254.24	2.6483		

Table 12d
Analysis of Variance of Tumor Area
(Experiment 4)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Housing Condition (HC)	1	23991	23991	10.42	p = .002
Shock	1	580.04	580.04	0.25	p = .617
HC x Shock	1	17190	17190	7.47	p = .007
Ss within groups	96	220960	2301.6		
Days	10	1977900	197790	491.10	p < .001
HC x Days	10	24405	2440.5	6.06	p < .001
Shock x Days	10	909.05	90.905	0.23	p = .994
HC x Shock x Days	10	21714	2171.4	5.39	p < .001
Days x Ss within groups	960	386640	402.75		

Table 13d
Analysis of Variance of Tumor Weight on Day 11
(Experiment 4)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Housing Condition (HC)	1	53.13	53.13	1.98	p = .163
Shock	1	8.6304	8.6304	0.32	p = .572
HC x Shock	1	167.69	167.69	6.25	p = .014

Table 14d

Analysis of Variance of the Day of Tumor Appearance
(Experiment 5)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Shock Intensity (SI)	2	25.089	12.544	5.47	p = .006
Duration of Apparatus Exposure (DURAT)	2	1.3556	0.6778	0.30	p = .745
SI x DURAT	4	11.311	2.828	1.23	p = .304
within cells	81	185.90	2.295		

Table 15d
Analysis of Variance of Tumor Area
(Experiment 5)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Shock Intensity (SI)	2	131590	65793	8.11	p < .001
Duration of Apparatus Exposure (DURAT)	2	4487.6	2443.8	0.30	p = .741
SI x DURAT	4	19146	4786.4	0.59	p = .671
Ss within groups	81	657460	8116.8		
Days	13	9320000	716920	683.67	p < .001
SI x Days	26	130390	5015	4.78	p < .001
DURAT x Days	26	9792.2	376.62	0.36	p = .999
SI x DURAT x Days	52	26903	517.36	0.49	p = .999
Days x Ss within groups	1053	1104200	1048.6		

Table 16d
Analysis of Variance of the Day of Mortality
(Experiment 5)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Shock Intensity (SI)	2	493.42	246.71	12.61	p < .001
Duration of Apparatus Exposure (DURAT)	2	24.822	12.411	0.63	p = .533
SI x DURAT	4	4.9111	1.2278	0.06	p = .993
within cells	81	1585.3	19.572		

Table 17d
Analysis of Variance of the Day of Tumor Appearance
(Experiment 6)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Shock	3	79,475	26.492	20.96	$p < .001$
within cells	36	45.5	1.2639		

Table 18d
Analysis of Variance of Tumor Area
(Experiment 6)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Shock Treatment	3	86316	28772	23.46	p < .001
Ss within groups	36	44154	1226.5		
Days	13	1108000	85234	316.62	p < .001
Shock Treatment x Days	39	93992	2410	8.95	p < .001
Days x Ss within groups	468	125980	269.20		

Table 19^a

Analysis of Variance of the Day of Mortality

(Experiment 6)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Shock Treatment	3	220.88	73.625	7.02	p < .001
within cells	36	377.50	10.486		

Table 20d
Analysis of Variance of the Day of Tumor Appearance
(Experiment 7)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Shock Treatment	3	11.3	3.7667	3.59	p = .023
within cells	36	37.8	1.0500		

Table 21d
Analysis of Variance of the Tumor Area
(Experiment 7)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Shock Treatment	3	85924	28641	2.78	$p = .055$
Ss within groups	36	370380	10288		
Days	12	4084000	340340	254.92	$p < .001$
Shock Treatment x Days	36	96246	26735.5	2.00	$p < .001$
Days x Ss within groups	432	576760	1335.1		

Table 22d
Analysis of Variance of the Day of Mortality
(Experiment 7)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Shock Treatment	3	269.3	89.767	2.15	p = .111
within cells	36	1502.6	41.739		

Table 23d

Analysis of Variance of the Day of Tumor Appearance

(Experiment 8)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Shock Treatment	3	16.475	5.4917	3.16	p = .036
within cells	36	62.500	1.7361		

Table 24d
Analysis of Variance of the Tumor Area
(Experiment 8)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Shock Treatment	3	113560	37852	3.47	$p = .026$
Ss within groups	36	392230	10895		
Days	13	3844600	295740	240.75	$p < .001$
Shock Treatment x Days	39	113920	2921.1	2.38	$p < .001$
Days x Ss within groups	468	574880	1228.4		

Table 25d
Analysis of Variance of the Day of Mortality
(Experiment 8)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Shock Treatment	3	80.400	26.800	0.88	$p = .461$
within cells	36	1098.0	30.500		

Table 26d
Analysis of Variance of the Day of Tumor Appearance
(Experiment 9)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Shock Treatment	2	20.067	10.033	4.00	p = .030
within cells	27	67.800	2.5111		

Table 27d
Analysis of Variance of the Tumor Area
(Experiment 9)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Shock Treatment	2	91826	45913	5.70	$p = .009$
Ss within groups	27	217580	8058.5		
Days	13	2708000	208310	203.08	$p < .001$
Days x Shock Treatment	26	97727	3758,7	3.66	$p < .001$
Days x Ss within groups	351	360030	1025.7		

Table 28d
Analysis of Variance of the Day of Mortality
(Experiment 9)

<u>Source</u>	<u>df</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>SIG</u>
Shock Treatment	2	50.867	25.433	2.59	p = .093
within cells	27 .	265.000	9.8148		

END

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FIN