MINIREVIEW

The Actions of Exogenous Dehydroepiandrosterone in Experimental Animals and Humans (44285)

FRANK SVEC[1] AND JOHNNY R. PORTER

Obesity Research Program, Section of Endocrinology, Departments of Medicine and Physiology, Louisiana State University Medical School at New Orleans, New Orleans, Louisiana 70112

Abstract. **Dehydroepiandrosterone (DHEA) is the major adrenal steroid of young adults; however, its physiologic functions, if any, are not known. The purpose of this review is to evaluate the current literature in which DHEA was administered to either humans or experimental animals to discern what these functions might be. Reports are divided into five areas: neurologic, immunologic, cardiovascular, oncologic, and metabolic. Particular attention is paid to the dosage and route of administration. This type of analysis shows that at the lowest doses, DHEA has effects on neurologic and immunologic tissues, suggesting that these two sites may be physiologic targets. DHEA also affects cardiologic and metabolic functions as well as tumor growth, but such actions require higher doses and may reflect 'pharmacologic' activities. It is proposed that DHEA's pattern of activity represents a new class of steroid hormones, the "Regnantoids." Further progress in the endocrinology of this family of steroids may only come when synthetic, long-acting analogs of DHEA are available for *in vitro* studies to allow correlations between hormone action and receptor binding.**

[P.S.E.B.M. 1998, Vol 218]

DHEA (dehydroepiandrosterone) in its free, sulfated, and lipoidal forms is the most abundant steroid secreted by the adult human adrenal. Whether it is a member of a distinct class of steroid hormones that exerts unique physiologic actions is still debated. DHEA is most often referred to as an adrenal androgen because it can be converted in the periphery to testosterone. However, DHEA itself does not interact with androgen receptors, and separate DHEA-specific receptors have been identified.

This paper examines the results of trials in which DHEA was administered to test subjects to evaluate whether this steroid has a definite and unique spectrum of actions. If so, these actions define a new category of steroid hormones.

Classically, endocrinologists use two approaches to delineate the actions of hormones: 1) Serum levels are correlated with physiologic and/or pathologic findings; and 2) the effects of exogenous hormone given to experimental animals and humans are monitored.

Results of experiments using the first approach suggest that DHEA influences a variety of systems (1). For example, DHEA may be cardioprotective in men (2–6) but a cardiac risk factor in women (7). Likewise, a significant body of evidence suggests that DHEA may protect against certain cancers (8–9). Some reports suggest that DHEA levels are related to obesity (10) and immune function (11).

[1] To whom requests for reprints should be addressed at Department of Medicine, LSU Medical School in New Orleans, 1542 Tulane Ave., New Orleans, LA 70112. E-mail: fsvec@lsumc.edu

Received September 9, 1997. [P.S.E.B.M. 1998, Vol 218]
Accepted January 26, 1998.

0037-9727/98/2183-0174$10.50/0

Publications using the second approach, monitoring the results of DHEA administered to test subjects, provide the basis for this report. Ideally trials would involve giving DHEA to subjects who have adrenal insufficiency and who are cortisol replete. Such studies are currently under way (12), but at this point not widely employed. Some studies however, report using other experimental groups that are pertinent. For example, some studies have evaluated the effects of DHEA given to older individuals who, because of the age-related decline in DHEA-secretion, have very low levels of DHEA. Distinct effects were noted. DHEA has also been given to a number of younger individuals who were not DHEA deficient, and in some cases the findings were surprising. Finally, DHEA has been administered to a variety of experimental animals, and here the results are very promising. The purpose of this review is to summarize the results of these studies with a goal of determining whether, taken as a whole, these reports reveal that DHEA exerts the physiologic and/or pharmacologic actions of a distinct class of hormones. If so, exploitation of these properties may prove useful in clinical medicine.

A computerized search of the English language literature was used to identify articles published in the 1990s in which DHEA was administered to intact organisms. These were supplemented with key articles published before 1990 retrieved from the authors' files. Experiments involving *in vitro* additions to cell, tissue, or organ cultures were excluded. All articles retrieved are not included. To make the report more manageable, articles that simply extended a group's previous observations were not included unless they brought out some new important aspect of the observation (the effect of a different route of administration or the effect of a new dosage range).

Once identified, articles were summarized by species involved, dose, route of DHEA administration, and biologic effect of the hormone. These summaries were listed, in general, according to dosage administered. Attempts were made to include articles that involved all routes of DHEA administration and representative articles of all aspects of DHEA biology, both beneficial and detrimental to the test subject. Articles that report negative results refuting the positive claims of others are included. Nearly all articles involving administration to humans are included.

The articles were placed into five categories based upon the reviewers' understanding of the main conclusions of the work: N = having to do with the nervous system, I = having to do with the immune system, CV = having to do with cardiovascular disease, C = having to do with cancers, and M = having to do with metabolic changes.

In many cases, DHEA was administered as an injection or as a defined oral dose. These articles allowed the precise tabulation of the amount of hormone administered. However, in many articles, especially those involving rodents, DHEA was administered over a prolonged period as a food supplement [usually ranging from 0.2%–0.8% (wt of hormone/weight of food)]. In many of these articles, the authors did not report how much hormone or food was consumed. Hence, the amount of DHEA administered could not be determined with certainty. To estimate how much DHEA was consumed in these trials, the following intakes were assumed: mice, rats, and rabbits consume 4, 20 and 100 g of laboratory chow/day respectively. Next, in order to compare the results between different experiments and different species, the amount of DHEA administered was expressed as mg of hormone/kg body weight. Again, the weights of subjects were not always supplied. In those cases, the following assumptions were made: humans, rabbits, rats, and mice weigh 70, 4, 0.25, and 0.02 kg each respectively.

Tabulation of Reports

Table I lists the articles included. Those that involve administration of DHEA to humans are shown in boldface type. The first column identifies the general category under which the observation falls (neurologic, immune, cardiovascular, cancer, or metabolic), and the second column briefly summarizes the major findings. Articles are presented, in general, in ascending order by dose of hormone administered (fourth column) expressed as mg/kg.

The first thing that can be gleaned from Table I is that most studies have been conducted using rodents. However, there are a significant number of observations in dogs, rabbits, monkeys, pigs, and humans. Twenty one articles are listed that involve the administration of DHEA to humans. An additional article is included that involves the administration of etiocholanedione, a metabolite of DHEA to humans.

Dosage Considerations. The second observation that is immediately apparent from reviewing Table I is that a 10,000-fold range of doses has been investigated. In mice, doses below 0.1 mg/kg have been found to be active as well as doses calculated to be 1200 mg/kg. The range evaluated in humans is much narrower. On the low side is a report of the actions of 0.1 mg/kg (7.5 mg at one time) (16), whereas the upper range is about 40 mg/kg/day (67). Most of the recent studies with humans use doses of 1–5 mg/kg/day.

Figure 1 presents the dosage information in graphical form. The data are divided into the five areas of action attributed to DHEA: neurologic, immunologic, cardiovascular, cancer, and metabolic. Again, it is readily apparent that a wide range of doses has been used to demonstrate effects in each area, but, in general, neurologic actions have been demonstrated with the lowest doses of DHEA whereas metabolic actions generally require some of the highest doses.

Since such large doses of DHEA have been used to demonstrate effects, many observers discount the physiologic relevance of DHEA. However, examination of the information in Table I shows that in most of these experiments the oral route was used in rodents and as will be discussed in the next paragraph, this may not be an effective route of administration. When administered by either subcutaneous or intraperitoneal injection, much smaller doses

Table I. Articles Reviewed. The Articles Reviewed are Listed in Approximate Order of the Dose of DHEA Administered

Category	Action	Species	Dose	Route of administration and comments	Reference
N	Enhances memory in mice trained by foot shock	Mice	<0.1 mg/kg	Administered by intracerebroventricular injection	(13)
N	Enhances memory and alleviates amnesia	Mice	<0.1 mg/kg	Administered by intracerebroventricular injection	(14)
N	Decreases sound stress	Rats	<0.1 mg/kg	Administered by intracerebroventricular injection; neither estrogens, androgens, nor progesterone had similar effects; DHEA effect blocked by glucocorticoid agonist	(15)
I	**Enhances immune response to influenza vaccination**	**Older humans**	**0.1 mg/kg**	**7.5 mg administered as subcutaneous injection at same time as vaccination**	(16)
N	Decreases food intake	Obese Zucker rats	0.2 mg/kg	Administered by intracerebroventricular injection	(17)
I	Improves immunosen-escence	C3H/HeN MTV-, C57BL/6 mice 85–105 weeks old	0.5 mg/kg	Administered once as topical preparation at site of immunization or in vaccine	(18)
N	Anxiolytic in plus maze	Mice	0.005–1.0 mg/kg	Intraperitoneal injection; both DHEA and DHEA-S worked	(19)
N	**Treats depression**	**Humans**	**0.4–1.3 mg/kg/day**	**Oral—tried in an open label study for 4 weeks in six depressed men and women with low DHEA levels**	(20)
I	**Decreases CD4+ cells and increases T-helper cells**	**Post-menopausal women**	**0.7 mg/kg/day for 3 weeks**	**Morning administration in a micronized pill—placebo-controlled, randomized, double-blinded, crossover study**	(21)
M	**Increases insulin binding and degradation in lymphocytes**	**Post-menopausal women**	**0.7 mg/kg/day for 3 weeks**	**Morning administration of micronized pill**	(22)
N	**No effect on cognitive function and perception of well-being**	**Elderly men and women**	**0.7 mg/kg/day for 2 weeks**	**Placebo-controlled; oral administration at night; 2-week study on active agent and placebo; a trend toward improvement was seen in women**	(23)
N	**Increases perception of well-being**	**Humans**	**0.7 mg/kg/day**	**Oral, 3-month trial**	(24)
I	**Enhances the immune response of elderly humans to influenza vaccine**	**Elderly humans**	**0.7 mg/kg**	**Oral, administered along with vaccine**	(25),(26)

Table I. Continued

Category	Action	Species	Dose	Route of administration and comments	Reference
I	**No effect on immune response of humans to influenza vaccination**	**Elderly humans**	**0.7 mg/kg**	**Oral, administered for 4 days beginning 2 days before vaccination**	(27)
I	**Activates immune system and raises IGF-I levels**	**Older men with low DHEA-S levels**	**0.7 mg/kg/day**	**Oral, daily 50-mg dose for 20 weeks**	(28)
M	**Increases levels of serum amyloid P in older women**	**Post-menopausal women**	**0.9 mg/kg/day**	**Oral, daily administration of 60-mg dose of 3 weeks**	(29)
N	Potentiates neuronal response to NMDA in hippocampus	Rats	0.1–2 mg/kg	Administered by intravenous route, utilized sigma receptors	(30)
CV	Reduces dermal ischemia by thermal injury	Mice	1.0 mg/kg/day	Subcutaneous administration within 96 hr of burn; dihydrotestosterone did not have same effect	(31)
N	Diminishes despair in animals with mixed despair and anxiety	Rats	1.0 mg/kg	Intraperitoneal injections	(32)
CV	**Reduces plasminogen activator inhibitor type 1**	**Humans**	**2 mg/kg/day**	**50-mg tablet given 3 times a day in placebo-controlled trial to men for 12 days**	(33)
N	Decreases aggression in castrated male mice toward lactating females	Mice	2 mg/kg/day	Given by intraperitoneal injections for 4 weeks; dose did not have effect on sex organs; doubt DHEA acted as androgen	(34)
I	**Improves lupus erythematosus**	**Humans**	**3 mg/kg/day**	**Oral, treated for 3–6 months in an open study with improvement**	(35)
M	**Raises serum level of estradiol**	**Panhypopituitary humans**	**3 mg/kg/day**	**Oral, 200 mg/day for 1 month; also evaluated 50 mg/day**	
M	**Decreases insulin resistance**	**Human**	**4 mg/kg/day**	**Single case report; oral DHEA given along with dexamethasone**	(36)
CV	Improves microcirculation hemodynamics in muscle after ischemia	Rats	4 mg/kg	Administered by subcutaneous injection	(37)
I	Increases levels of cytokines	Mice	4 mg/kg/day	In food or injection of DHEA-S	(38)
I	Lack of effect on septic symptoms after administration of lipopolysaccharide (LPS)	Pigs	4 mg/kg/day	Doses up to 20 mg/kg were not effective; LPS administration lowered DHEA levels	(39)
I	Improves immune function of burned mice	Mice	5 mg/kg	Administered subcutaneously within 1 hr of burn; DHEA showed antiglucocorticoid effect	(40)

Table I. Continued

Category	Action	Species	Dose	Route of administration and comments	Reference
I	Fails to improve immune function of burned mice	Mice	5 mg/kg	Administered subcutaneously 1 hr after burn; isolated splenocytes assayed	(41)
I	Alters Interleukin 2 synthesis	Mice	5 mg/kg	Administered as intraperitoneal injection; DHEA-S also had effect	(42)
I	Reverses immune suppression induced by high-dose antigen	Mice Balb/c	5 mg/kg	Administered subcutaneously after being made immune tolerant by injection of sheep red cells	(43)
I	Reverses age-associated decline in immune function	CB-17 mice	5 mg/kg	One subcutaneous injection of DHEA-S before immunization with Pnu-immune vaccine	(44)
I	Preserves immune function after burn	CF-1 and BALB/c mice	5 mg/kg	Subcutaneous injections; improves immune function and acts as more than antiglucocorticoid	(45)
M	Antagonizes effect of dexamethasone on induction of hepatic enzymes	Zucker rats	5 mg/kg	Intraperitoneal injections	(46)
N	Increases prolactin mRNA in pituitary	Rat	6 mg/kg/day	Two days of subcutaneous administration	(47)
N	**Increases rapid eye movement**	**Humans**	**7 mg/kg**	**Oral, administered before sleep**	(48)
C	Diminishes DNA synthesis in response to tumor promoter	Mice	2–15 mg/kg	Single intraperitoneal dose	(49)
M	Prevents dexamethasone induced hypertension	Rats	3–15 mg/kg/every other day	Administered by subcutaneous administration along with 6 mg/kg of dexamethasone every other day	(50)
CV	**Inhibits platelet aggregation**	**Humans**	**13 mg/kg/day**	**Oral, 300 mg 3 times/day to men for 14 days**	(51)
I	Reduces mortality when inoculated with virus and exposed to cold stress	ICR female mice	10–20 mg/kg	Intraperitoneal DHEA prevented involution of lymphoid organs; suggesting immune modulation	(52)
I	Improves survival of mice after thermal injury	Mice	5–25 mg/kg/day	Subcutaneous administration; animals infected with *E. coli* after thermal injury	(53)
M	**Fails to alter body fat or weight in obese men**	**Humans**	**16 mg/kg/day**	**Oral, given dose of 400 mg 4 times/day**	(54)
C	Alters the rate of tumor growth in rats with DMBA-induced mammary tumors	Rats	16 mg/kg/day	By gastric intubation for 21 days; 2 mg/rat twice a day; effect different in ovariectomized and intact female rats	(55)
N	Enhances long-term potentiation in dentate gyrus	Rats	10–30 mg/kg	DHEA-S administered intravenously in Nutralipid	(56)

Table I. Continued

Category	Action	Species	Dose	Route of administration and comments	Reference
CV	**Lowers serum cholesterol in obese, postmenopausal women**	**Postmenopausal women**	**20 mg/kg/day**	**Oral, 400 mg 4 times/day for 28 days; double-blinded, placebo-controlled, crossover study. Raised serum insulin without change in glucose levels. No change in weight or body fat. Significant androgenic action at this dose**	(57)
N	Enhances hypnotic and hypothermic effect of ethanol and pentobarbital	Rats	20 mg/kg	Intraperitoneal administration of DHEA and DHEA-S caused fall in body temperature; both enhance response to ethanol	(58)
I	**Transiently improves immune function in AIDS patients**	**Human**	**11–32 mg/kg/day**	**Oral, given for 16 weeks; no dose-limiting side effects seen**	(59)
M	**Reduces LDL cholesterol and body fat but not insulin sensitivity in normal men**	**Lean men**	**21 mg/kg/day**	**Oral, 400 mg 4 times/day in normal healthy men for 4 weeks**	(60)
M	**No effect on energy metabolism, weight, or lean body mass**	**Lean men**	**21 mg/kg/day**	**Oral, 400 mg 4 times/day; no side effects seen after 4 weeks. Serum levels of DHEA were 9 times higher than during placebo**	(61)
M	Decreases body weight	Rats	21 mg/kg/day	Intraperitoneal injections of 50 mg/kg 3 times weekly for 9 weeks; only works while consuming high fat diet in young animals	(62)
M	Antagonizes the effect of dexamethasone on induction of hepatic enzymes	Mice	25 mg/kg	Intraperitoneal injection	(63)
N	Enhances hippocampal primed burst potentiation	Rats	24–48 mg/kg	Subcutaneous administration of DHEA-S; neither lower nor higher doses worked; suggest U-shaped curve	(64)
M	**Weight loss in obese**	**Obese humans**	**34 mg/kg/day**	**Oral; 4 grams of etiocholanedione given daily; a metabolite of DHEA. Cannot be converted to androgens**	(65)
N	Improves memory	Mice	35 mg/kg/day	Given subcutaneously; needs twice as much by oral route or only 0.02 as much if given into cerebral ventricles	(66)
N	**Improves some functions in multiple sclerosis patients**	**Humans**	**40 mg/kg/day**	**Oral; uncontrolled, nonrandomized study in which some patients had response in mood and other CNS functions**	(67)

Table I. Continued

Category	Action	Species	Dose	Route of administration and comments	Reference
C	Prevents mammary tumors induced by N-methyl-N-nitrosourea	Rats	32–64 mg/kg/day	Administered as 0.04% or 0.08% supplement in chow; mammary tumors reduced from 70% in control to 0%	(68)
I	Improves survival in animals treated with endotoxin	Mice	5–100 mg/kg	Administered by intraperitoneal injection before lipopolysaccharide; TNF response blocked by DHEA	(69)
CV	Decreases serum cholesterol and body weight	Obese dogs	30–75 mg/kg/day	Oral for 3 months; obese lost weight; both obese and lean had lower cholesterol	(70)
M	Induces peroxisomal proliferative response	Rats	60 mg/kg/day	Given by intraperitoneal injection for 4 days; DHEA-S is more effective than DHEA	(71)
N	Alters expression of GnRH in brain	Rats	60 mg/kg/day	Given by intraperitoneal injection for 2 days; results varied in males and females	(72)
I	Inhibits dexamethasone-induced suppression on lymphocyte proliferation	Mice	60 mg/kg/day	Subcutaneous administration for 3 days before 60 mg/kg dexamethasone	(73)
CV	Reduces LDL cholesterol while on low-fat diet	Rhesus monkey	60 mg/kg/day	Oral; effect not seen on high-fat diet; DHEA also altered thyroxine levels	(74)
CV	Reduces serum cholesterol	Rhesus monkey	60–75 mg/kg/day	Oral; 8 weeks of treatment; affects mostly the cholesterol in LDL fraction	(75)
I	Inhibits glucocorticoid-induced involution of thymus	Mice	80 mg/kg/day	Subcutaneous injection for 3 days with DHEA before recieving equal amount of dexamethasone	(76)
M	Induction of hepatic glycerophosphate dehydrogenase	Rats	40–160 mg/kg/day	Oral; actinomycin blocked effect; levels increased 3–5-fold in 7 days	(77)
M	Elevates state 3 mitochondrial respiration	Zucker rats	100 mg/kg	Given by gastric intubation route; effect seen by 3 hr	(78)
M	Induces changes in liver histology and mitochondria	Rats	100 mg/kg/day	Administered as intraperitoneal injections in corn oil	(79)
M	Decreases body weight	BHE rats	120 mg/kg/day	Intraperitoneal injections; lower doses did not cause difference in weights	(80)
CV	Reduction of aortic plaque size in cholesterol-fed rabbits with aortic injury	Rabbits	125 mg/kg/day	Fed for 12 weeks; 50% reduction in plaque size	(81)
M	Induces lipid peroxidation in rat liver mitochondria	Rats	40–480 mg/kg/day	Oral in food; effect seen with low dose and after 3 days of treatment with high dose	(82)

Table I. Continued

Category	Action	Species	Dose	Route of administration and comments	Reference
CV	Inhibits acclereated coronary disease in rabbits	Rabbits	150 mg/kg/day	Oral; rabbits received heterotopic cardiac transplant and a high-cholesterol diet	(83)
C	Inhibits mammary gland chemical carcinogenesis	Rats	160 mg/kg/day	Oral; strongly inhibits promotion/progression of mammary cancers induced by N-methyl-N-nitrosourea	(84)
M	Decreases body weight	C3H mice	193 mg/kg/day	Given orally as 450 mg/kg 3 times/week; Dose of 11 mg/kg/day did not work	(85)
N	Diminishes fat food intake	Zucker rat	200 mg/kg/day	Intraperitoneal injection; doses below 50 mg/kg/day had no effect; macronutrient selection diet; changes in hypothalamic neurotransmitters seen	(86)
I	Prevents lupus-like syndrome	New Zealand Black/New Zealand white Mice	225 mg/kg/day	Given in chow; anti-DNA antibody level decreased and mice live longer	(87)
N	Elevates serotonin in lateral hypothalamus	Obese Zucker rats	240 mg/kg/day	7 days of treatment with a 0.3% supplemented chow diet	(88)
M	Antiobesity effect in castrated rats	Castrated and noncastrated obese Zucker rats	240 mg/kg/day	Given as 0.3% supplement in chow; suggests that conversion of DHEA into androgens by gonads is not needed	(89)
C	Chemopreventive for cancers	Rats	240 mg/kg/day	Given in diet for over 20 weeks after known carcinogens	(90)
C	Inhibits prostaglandin stimulation by tumor promoter	Mice	260 mg/kg/day	Administered in food as 0.2% supplement	(91)
M	Decreases body weight	Sprague-Dawley rat with diet-induced obesity	260 mg/kg/day	Oral; mixed into high-fat diet	(92)
M	Induces hepatic peroxisome proliferation-associated enzymes	Rats and mice	300 mg/kg/day	Given by gastric intubation; had less of an effect on hamsters and no effect on guinea pigs	(93)
C	Inhibits testicular tumors	Fischer 344	360 mg/kg/day	Fed DHEA-containing food for 84 weeks; none of treated animals had Leydig tumors; all controls did	(94)
C	Induces hepatic tumors	Fischer 344	360 mg/kg/day	Fed DHEA-containing food for 70–84 weeks	(95)
M	Decreases body weight	Sprague-Dawley rat	360 mg/kg/day	Fed DHEA-containing chow; rats had medial hypothalamic knife cuts to make hyperphagic; DHEA reduced food intake	(96)

Table I. Continued

Category	Action	Species	Dose	Route of administration and comments	Reference
M	Decreases glucose in insulin-resistant mice	Db/db mice	400 mg/kg/day	Given as 0.2% food supplement; higher dose had no effect; fluorinated analog worked better and had no androgenic effect	(97)
M	Alters liver proteins	(NZBxNZW) F1 mice and BALB/c mice	400 mg/kg/day	Oral administration	(98)
M	Decreases body weight	Zucker rat	480 mg/kg/day	Given as 0.6% supplement in chow; treated lean and obese were lighter	(99)
M	Decreases number of hepatic glucocorticoid receptors	Obese Zucker rat	480 mg/kg/day	Given as 0.6% supplement in chow; 28 days of treatment	(100)
C	Inhibits HMGCoA reductase activity in preneoplastic liver nodules	Rat that had liver tumors induced	480 mg/kg/day	DHEA in food as 0.6% supplement for 3 weeks	(101)
M	Increases hepatic carnitine acyltransferase synthesis at level of transcription	Zucker rats	480 mg/kg/day	Administered as 0.6% food supplement; clofibrate acted similarly	(102)
C	Decreases hepatic nodules and protects against hepatic cancers	Rats with diethylnitrosamine to induce hepatic nodules	480 mg/kg/day	DHEA (0.6%) in food; treated animals had fewer nodules and fewer transitions into cancer	(103)
N	Alters hypothalamic serotonin content	Obese Zucker rats	480 mg/kg/day	Seen after 1 day of feeding DHEA (0.6%) in rat chow	(104)
C	Inhibits bladder cancer induced by butylated hydroxyanisole	F344 Rats	480 mg/kg/day	Some other tumors were enhanced by the addition of DHEA in the diet	(105)
M	Decreases weight gain	Wistar rats	480 mg/kg/day	DHEA in food; DHEA did not inhibit tumor production by dimethylnitrosamine (DMN)	(106)
I	Enhances immune response of older animals	Mice	500 mg/kg	Only one subcutaneous injection of 10 mg/mouse; response monitored 5 weeks after immunization	(107)
I	Improves immune system of mice immunosuppressed by dexamethasone and infected with *Cryptosporidium parvum*	Mice C57BL/6N	500 mg/kg/day	Subcutaneous injection after administration of 6.25 mg/kg dexamethasone	(108)
C	Prevents spontaneous tumors in p53-knockout mouse	P53-knockout mice	600 mg/kg/day	Given as 0.3% supplement in chow; decreased mortality	(109)
M	Prevents obesity and/or hyperglycemia	*Db/db* mice *ob/ob* mice	800 mg/kg/day	Given as 0.4% food supplement; no decrease in food intake	(110)

Table I. Continued

Category	Action	Species	Dose	Route of administration and comments	Reference
I	Decreases spleen mass and other immune changes; animals lived longer	Mice AZB/W F_1	800 mg/kg/day	Given as 0.4% addition to chow; not all immune functions were improved	(111)
I	Inhibits murine natural killer cell differentiation	Mice that were lethally irradiated	900 mg/kg/day	Given as 0.45% addition to chow; affected differentiation of progenitors	(112)
M	Decreases hepatic triglyceride production and increases cholesterol production	Mice	900 mg/kg/day	Given as 0.45% supplement in food; also changed pattern of protein phosphorylation of liver proetins	(113)
I	Decreases lymphopoiesis but not myelopoiesis	Mice	900 mg/kg/day	Given as 0.45% supplement in chow; androgen-unresponsive mice also responded; clofibrate (a peroxisomal proliferator) did not act the same way	(114)
I	Protects against viral encephalitis	Mice	1000 mg/kg	Subcutaneous injection on the same day as the infection; mortality reduced by 50%	(115)
I	Protects against viral infection	Mice	1000 mg/kg	Subcutaneous injection 4 hr before infection	(116)
C	Protects against colorectal carcinoma	Mice	1200 mg/kg/day	Given as 0.6% supplement in chow	(117)

Note. The letter in the first column refers to the area in which the article is grouped (N = neurologic; I = immunologic; CV = cardiovascular; C = oncologic; M = metabolic.) The species and amount of DHEA given are recorded. Boldface type indicates DHEA given to humans.

of DHEA are needed. Further, when administered directly into the cerebral ventricles, actions are seen with very low doses. This latter observation is consistent with the opinion of Baulieu (118) that DHEA is a neurosteroid.

The very large doses that need to be administered by the oral route may reflect poor absorption and/or rapid clearance of DHEA. Few studies evaluate the absorption, tissue distribution, metabolism, and clearance of DHEA in experimental animals. Longcope and Tast (119), however, report that DHEA is poorly absorbed from the gastrointestinal track of monkeys (absorption = 16.3%) and that its metabolic clearance rate is 2601 liters/day. Further, the conversion ratio of orally administered DHEA is 63.3% whereas after intravenous administration, conversion is only 9.3%. Thus after oral administration the amount of active hormone absorbed that makes it past the portal circulation is probably quite low.

In Zucker rats we have reported (120) that the serum level of DHEA-S in obese and lean rats consuming a diet containing 0.6% DHEA in their food for 28 days is 30.5 and 13.8 μmole/l respectively. These serum values can be com-

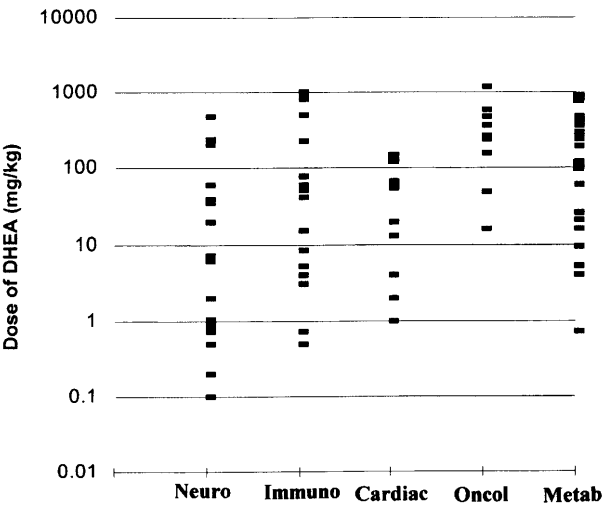

Figure 1. Doses of DHEA employed in studies reviewed. The doses of DHEA expressed as mg/kg utilized in the studies reviewed in Table I are displayed. Studies are divided into categories based upon the major thrust of the paper. Neuro = neurologic; Immuno = immunologic; Cardiac = cardiovascular; Oncol = oncology; and Metab = metabolic.

pared to 5.0 μmole/l that we reported (121) for boys in Tanner Stage V. The intake by these animals was on the order of 480 mg DHEA/kg/day. Thus, although the animals consumed very large quantities of hormone, serum values are only 3–6-fold higher than in young humans. Labrie *et al.* (122) compared the effects of giving DHEA by a subcutaneous route to an oral route. They concluded that if the effect of a dose administered subcutaneously is considered unity, then the same amount of DHEA administered by mouth is only 3% as effective. In unpublished studies, we found that DHEA (100 mg/kg) suspended in propylene glycol and injected into the peritoneal cavity of Zucker rats is very rapidly absorbed with DHEA-S levels reaching a peak of nearly 136 μmole/l in less than 1 hr. Thereafter, levels fall rapidly and within 24 hr serum values are only 4% of those seen at 1 hr. Thus, we find that DHEA is rapidly cleared from the serum of rats. In summary, although the amount of DHEA administered to experimental rodents *via* the oral route is high, evidence suggests that absorption may be poor and metabolism extensive. More investigators need to report serum levels of DHEA after treatment; levels may not be as elevated as anticipated from intake data.

No studies exist on the chronic, parenteral administration of DHEA to humans. However, several studies have reported the serum levels of DHEA after oral administration. Mortola and Yen (57) reported that after 28 days of administration at a dosage of 20 mg/kg/day, DHEA levels rose to 65.1 μmole/l. These levels are nearly 20-fold higher than baseline in this group. They are also about 7 times higher than the upper limit of normal for younger women. Nestler's group reported that after the administration of 21 mg/kg/day of DHEA to lean men (60) or 17 mg/kg/day to obese men (54) for 28 days, the levels of DHEA-S were 38.8 μmole/l and 39.8 μmole/l respectively. These values were about 5 times greater than baseline. Welle *et al.* (61) used a similar protocol and found DHEA-S values of 67.1 μmole/l in lean men. Other reports evaluated 'lower' doses of DHEA supplementation. Beer *et al.* (33) administered nearly 2 mg/kg/day to men for 16 days and found DHEA-S levels rose to 20.2 μmole/l. Van Vollenhoven *et al.* (35) administered 3 mg/kg/day to women and reported that the serum level of DHEA-S rose to nearly 32 μmole/l. Yen's group (24) administered doses of 50 mg/day to older individuals and found that serum levels rose to approximately 12 μmole/l in the morning. Casson *et al.* (21–22) reported comparable results. These values are just above the upper end of the normal range for young adults. The attainment of this level has led to this dose being referred to as the 'physiologic' replacement dose. All these data are presented graphically in Figure 2. The average serum DHEA-S level in healthy 'younger' adults is around 7.5 μmole/l. Thus nearly any dosage of DHEA above 1 mg/kg/day (50 mg/day) pushes the serum levels into clearly supraphysiologic ranges.

Direct comparisons between humans and rats are impossible; however, from the few comparable reports available, one may speculate that rodents clear DHEA more rapidly than humans, and larger doses must be given to rodents by the oral route in order to duplicate the values found in humans given daily doses of 1–20 mg/kg/day.

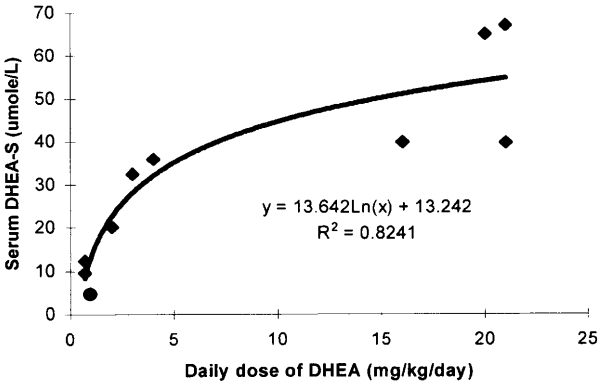

Figure 2. Serum DHEA-S levels attained after administration of DHEA. Results of serum DHEA-S given in references 20–22, 24, 33, 35–36, 54, 57, and 60–61 after the oral administration of DHEA to humans is plotted.

Neurologic Effects. Contrary to the statements of many commentators, rodents do produce DHEA in their adrenals (123). However, serum levels are so low that they are essentially unmeasurable using assays designed for clinical applications. Thus, the physiologic significance of DHEA's actions in the periphery of rats and mice might be questioned. On the other hand, DHEA is clearly synthesized in the brains of rodents (118). Thus, special attention must be paid to actions taking place in the central nervous system.

Examination of Table I and Figure 1 shows that the trials in which the smallest doses of DHEA produce positive effects are those employing parenteral injections while monitoring behavior. Doses below 0.1 mg/kg affect rodent learning and memory. DHEA is anxiolytic in mice and reduces stress in rats.

There are also reports that very large doses of DHEA affect nervous function. The three that used the highest dose (86, 88, 104) were characterized in this review as having an effect on neurological tissues because they changed hypothalamic neurotransmitters or eating behavior. In two of these cases, DHEA was administered in the food. If these three reports on the effect of DHEA are set aside, the greatest number of DHEA's actions on the nervous system require doses below 60 mg/kg, and many require less than 10 mg/kg.

Four papers suggest that DHEA has an action in the nervous system of humans (20, 24, 48, 67), and there are some tantalizing similarities between the actions of DHEA in humans and animal models. DHEA reduces anxiety, despair, and aggression in rodents (19, 32). Yen's group reported (24) that humans experience a feeling of "improved well-being" after receiving DHEA in a prospective, blinded study. Regelson *et al.* (67) reported that subjects with mul-

tiple sclerosis had an improvement in mood upon receiving DHEA at 40 mg/kg/day. (In a related vein, Salahuddin *et al.* (124) recently found that DHEA levels are lower in those with chronic fatigue syndrome as compared to healthy controls or those with depression.) Friess *et al.* (48) reported that the administration of a single 7-mg/kg dose of DHEA at night alters rapid eye movement in humans, suggesting that DHEA has actions within the central nervous system. Finally, a very recent report (20) shows that DHEA is able to treat depression successfully in six patients who had low DHEA levels. Unfortunately, the latter study was neither blinded nor placebo-controlled. To be fair, although all these reports are positive, other authors looked for an effect of DHEA on mood and were not able to see a statistically significant effect (23).

Several possibilities exist for how DHEA might act in the central nervous system. Majewska and co-workers reported that the GABA receptor contains a binding site for DHEA-S (125). They proposed that DHEA-S could be a GABA antagonist. Alternately, Abadie *et al.* (104) reported that DHEA elevates hypothalamic serotonin in rats. Central serotonin levels have been associated with changes in food intake, mood, and aggression in humans. Prasad *et al.* found that DHEA and DHEA-S *in vitro* affect chloride channel transport (125a).

Immunity. DHEA has a beneficial action on immune function. At doses less than 5 mg/kg, DHEA affects the immune system of both experimental animals and humans. Much of the data at these doses involves experiments utilizing subjects with 'suppressed' immune systems. For example, DHEA improves the immune system of older animals (44), burned animals (45), and those treated with antigen excess (43). Similarly, DHEA improves the immune function in humans with suboptimal immune systems: older humans who are being vaccinated (25–26), women who have lupus (35), and (at only slightly higher doses—11–32 mg/kg/day) those with HIV infection (59). Once again, although there are positive reports that DHEA improves immune function, others (16, 27) report that DHEA does not alter the immune response. Further, even in the positive reports, the magnitude of the effects in humans is modest.

The potential physiologic pathways involved in these actions of DHEA include changes in interleukins (42), cytokines (38), and lymphocyte viability (52). All can be altered by DHEA administration. Supporting these possibilities are reports of receptors for DHEA in lymphoid tissues, both in human (126) and murine (127) cell lines.

The observation that DHEA can improve the activity of an immune system suppressed by physiologic stressors suggested to several investigators that DHEA may be an antiglucocorticoid. (This subject has been reviewed by Kalimi *et al.* in Ref. (128)). May *et al.* (76) demonstrated that DHEA is able to inhibit glucocorticoid-induced thymic involution. Others reported (50) that DHEA prevents glucocorticoid hypertension in rats, and we reported (63) that DHEA prevents glucocorticoid induction of tyrosine aminotransferase in liver and kidney as well as ornithine decarboxylase in the kidney. One study reported (100) that DHEA reduces the number of glucocorticoid receptors in liver when expressed as number of receptors/mg cytosolic protein. Whether these actions are at all significant in humans is not clear. No study has evaluated directly the interaction of glucocorticoids and DHEA in humans nor has any study demonstrated that these antiglucocorticoid events take place at physiologic concentrations of hormones in humans.

Many studies have investigated very large doses of DHEA (>200 mg/kg) on the immune system. These warrant closer scrutiny. Several involve feeding DHEA-supplemented food. As before, this raises the question of how much steroid is actually absorbed and the half-life of any that is. In other trials using these very high doses, the hormone was tested using very acute and demanding paradigms. For example, Rasmussen *et al.* (108) showed that 500 mg/kg/day are needed to protect mice whose immune system had been suppressed by both dexamethasone *and* infection with *Cryptosporidium parvum.* Likewise, two groups (115–116) showed that 1000 mg DHEA/kg is able to reduce *mortality* in mice acutely infected with lethal infective vectors.

One might hypothesize that the experiments in the field of immunity can be divided into two groups: those that improve a senescent or suppressed immune system, requiring around 10 mg/kg/day or less, and those that need much higher doses (>200 mg/kg/day) but utilize tests that acutely overwhelm the immune system. We have presented a preliminary report that at lower doses, DHEA enhances the survival of obese Zucker rats that are made septic, but at higher doses DHEA decreases survival (129). This biphasic response is similar to what one sees with glucocorticoids in adrenally insufficient animals; at low doses, glucocorticoids improve host response, but at higher doses glucocorticoids suppress it. This division of effects is generally felt to reflect the 'physiologic' and 'pharmacologic' actions of glucocorticoids.

Finally, it has been reported that DHEA has an effect on the immune system of androgen-unresponsive mice (114). This suggests that DHEA has an action independent of its conversion into androgens.

Cardiovascular. Barrett-Connor's report (4) that DHEA-S levels are inversely related to the likelihood of men having a myocardial event has been one of the most stimulating and oft-quoted reports in DHEA literature. Although the authors have since modified their original conclusions (2), a number of independent groups still suggest that DHEA may be cardioprotective in men (3, 5–6). Surprisingly, for all this excitement, only a few have tried to evaluate whether exogenous DHEA demonstrates actions that might provide a mechanism for this finding. Still, although few in number, the reports are very promising.

Actions that may be pertinent to the cardiovascular system are listed in Table I under the category of CV. Investigators have evaluated only a narrow dosage range. Figure

1 shows that doses between 1–100 mg/kg have been examined. In humans an even smaller dosage range has been examined. At the lowest levels, DHEA affects dermal ischemia caused by a burn (31). At 4 mg/kg it improves circulation in muscle damaged by ischemia (37). These reports suggest that DHEA has an action, either direct or indirect, on vascular reactivity. DHEA affects the clotting system; at 2 mg/kg/day (50 mg 3 times a day in men), DHEA reduces plasminogen activator inhibitor (33) and at approximately 13 mg/kg DHEA inhibits platelet aggregation (51). Taken as a whole these studies offer exciting avenues to account for DHEA's reported beneficial actions on the vascular component of cardiovascular events.

One of the more exciting reports in the area of cardiovascular risk was that of Nestler *et al.* (60), who reported that the administration of about 21 mg DHEA/kg/day resulted in a decrease in serum LDL levels in lean men. This report rapidly led to an additional study (54) evaluating the same total dose of DHEA (1600 mg/day) in obese men. In this trial no significant effects were seen on lipids. An additional study (61) in lean men using 21 mg/kg/day of DHEA also showed no effect on body fat or energy metabolism. Although these latter results were discouraging, other positive studies require note: DHEA has been shown to: 1) lower the cholesterol levels in obese, postmenopausal women (dose = 20 mg DHEA/kg/day) (57), 2) decrease cholesterol in obese and lean dogs (30–75 mg DHEA/kg/day) (70), and 3) reduce serum cholesterol in monkeys (60 mg DHEA/kg/day) (74–75). The effect in the latter model was obscured when a high-fat diet was consumed (74). Experiments in rodents also point to an effect on serum lipids, but as the lipid transport systems of these animals are quite different from humans, the significance of these findings is of only supportive interest. Thus, in summary, there are reports that DHEA does not affect lipid levels in humans (diet not specified—high-fat?) and two reports that it does lower cholesterol in humans when given at doses around 20 mg/kg. Further, there are reports that DHEA alters cholesterol in dogs and monkeys when doses of 30–75 mg/kg/day are utilized. The lipids of humans might respond if higher doses of DHEA were administered.

In a very direct study of DHEA in models of cardiovascular disease, two groups have reported (81, 83) the effect of dietary DHEA on cholesterol-fed rabbits. In each case, similar dosage schedules of 125–150 mg/kg/day led to clear beneficial effects; there was a 50% reduction in the degree of cardiac vessel stenosis without a change in serum lipids. This suggests that DHEA may have an effect on the vascular reactivity component of atherosclerosis.

In considering that DHEA may have an affect on vascular tissue as opposed to serum lipids, a recent report by Ridker *et al.* (30) may be pertinent. They found that men who had myocardial infarctions had higher levels of c-reactive protein than healthy, matched controls. The authors suggest that inflammation may be an important component in the cardiac events of these individuals. In this light, it is tempting to speculate that besides any effect on lipids and clotting mechanisms, DHEA might exert its beneficial actions on atherosclerosis by its effects on the immune system.

Cancer. Probably the most confusing area of DHEA research is in evaluating its potential role in cancer biology. There are nearly as many observations suggesting that DHEA promotes cancer as there are that it retards tumors. Indeed, these reports often use the same animal model, the same authors, and the very same dosage. Rao *et al.* (94–95) reported that when administered at a dosage calculated to be about 360 mg/kg/day, DHEA inhibits testicular tumors but promotes hepatic tumors in rats. In nearly all cases in which DHEA has an action that may be relevant to cancer induction, progression, or regression, high doses are used (>100 mg/kg/day).

Nearly all of the studies investigating tumors were done in rodents, and the main observations involved the liver. All investigators who looked at the liver of rodents receiving DHEA reported that DHEA increases the size of the liver, changes its color, and induces a wide range of hepatic enzymes. DHEA also causes peroxisome proliferation (93). How this effect applies to hepatic tumors and how relevant these findings are to humans is not yet clear. However, these studies may eventually lead to significant insights into the mechanism of DHEA action. Peters *et al.* (71) reported that both DHEA and clofibrate only act in animals that have a functional PPAR-alpha receptor. They concluded, "DHEA-S or one of its metabolites, may thus serve as an important endogenous regulator of liver peroxisomal enzyme expression *via* a PPAR alpha-mediated pathway."

Since DHEA is now readily available at over-the-counter sources in the United States, if it causes hepatic problems, a rash of case reports may appear. In this light it is important to note that DHEA was administered to humans in doses as high as 32 mg/kg/day for 16 weeks (59) with no reported dose-limiting side effects. This dosage is nearly 50 times the currently utilized daily dose of 0.7 mg DHEA/kg/day that is 'suggested' in the over-the-counter preparations. Other researchers (60) have administered 21 mg/kg/day of DHEA to lean males and have reported no statistically significant change in liver enzymes although one out of four of the males had a mild elevation in serum levels while on the medication.

Metabolism. The fifth and final area of activity in which DHEA has been investigated is in the realm of obesity, herein more generally referred to as metabolism. Nearly every obese animal that can be studied (Zucker rats, rats with medial hypothalamic knife cuts, diet-induced obese rats, *db/db* mice, *ob/ob* mice, and obese dogs) have had their obesity reduced by DHEA. Most of these studies involve the administration of high doses (most often over 200 mg/kg/day) of DHEA as a dietary supplement over a period of weeks to months.

Cleary (131) has summarized a variety of evidence concluding that DHEA affects mitochondrial respiration, and this may be the cause of the weight loss. Whether DHEA

also affects food intake is not agreed upon. In some reports it affects food intake, especially when a high-fat diet is administered (86, 104). As most rodent chows are low in fat, this may account for some of the reported differences between research groups. When administered to rhesus monkeys, DHEA altered food intake transiently (74). Differences between species, the sex of the animals, and the ages of the animals may also be important. Finally, DHEA acted in both castrated and intact male Zucker rats (89), suggesting that conversion of DHEA in the testes is not a necessary step.

Although DHEA has clear antiobesity actions in obese animals, results in humans have been disappointing. One early study (60) that involved lean men demonstrated that body fat decreased with DHEA administration, but all subsequent studies failed to report changes in body weight or fat (54, 61). However, it is important to note the very narrow range of doses used and that diets have never been controlled. In the initial positive study, the dose of DHEA was nearly 21 mg/kg/day. A similar dosage was used in a subsequent study in lean men that showed no effect (61). In studies of obese men, a maximum of about 17 mg/kg/day was used (54). A more recent blinded, placebo-controlled study (65) using etiocholanedione, a metabolite of DHEA, found that at 32 mg/kg/day there was weight loss.

Certainly if animal studies are to be any guide, the doses used in human studies are inadequate. Ignoring the rodent data, weight loss is seen in dogs (70) but only with doses around 60 mg/kg/day. The potential impact of diet also should not be overlooked. Cleary *et al.* reported (62) that at a calculated dose of 21 mg/kg/day, DHEA only produced weight loss in animals that were consuming a high-fat diet. Further, it is not clear whether DHEA would be more effective if taken at certain times of the day; with meals, for example. Discontinuation of DHEA leads to rebound hyperphagia in rats (88). It may be that too infrequent a dosing schedule leads to unrecognized periods of food overconsumption that obscure weight loss.

Besides obesity, DHEA may prove beneficial in reducing insulin resistance. The chronic treatment of obese Zucker rats leads to a lowering of insulin levels, a change that can be interpreted as an improvement of insulin resistance (120). Buffington *et al.* (36) reported a single case of a diabetic whose insulin resistance decreased with DHEA treatment. No one had been able to reproduce these promising positive results until a recent abstract by Ibanez *et al.* (132) in which they showed a 14-day course of 50-mg DHEA improved the response to an intravenous glucose challenge. The patient group selected was special—hyperandrogenic women with low or normal levels of DHEA. Whether this is the first of many reports of effects of DHEA in unique patient groups remains to be seen.

Summary and Overview

In many ways the endocrinology of DHEA can be likened to that of cortisol. Both are made in the adrenal, and both affect the nervous system, immunity, and intermediary metabolism. Indeed, the fact that DHEA antagonizes glucocorticoid action (128) links them even further.

Additional insight might come from an appreciation of how glucocorticoids work. These hormones act in cells that have high affinity receptors that mediate the 'physiologic' actions that take place at 'low' levels of steroids. Glucocorticoids also exert distinct actions that take place at much higher 'pharmacologic' doses. The subcellular mechanisms of these actions are still unclear; possibly they involve low-affinity receptors or nonreceptor-mediated pathways. Review of the information in Table I suggests that DHEA may act similarly. A number of distinct actions take place at low doses of DHEA whereas others require much larger doses. Those actions that take place at low doses may reflect the 'physiologic' properties of DHEA. These involve certain functions in the CNS like enhancing information processing and improving memory as well as modulating mood. They may also involve controlling aspects of the immune system, especially when the system is suppressed and, maybe most particularly, when it is suppressed by chronic disease (mediated by glucocorticoids?). DHEA may also have a 'physiologic' role in controlling vascular tone, endothelial function and clotting mechanisms. As noted above there are reports of DHEA receptors in lymphocytes. There are also reports of DHEA binding sites in other tissues, notably liver (133–135).

On the other hand, DHEA's actions in models of sepsis, tumorigenesis, and obesity seem to require 'pharmacologic' doses. That pharmacologic doses of steroids can be clinically useful should not be ignored. Most of the clinical usage of glucocorticoids involves prescribing pharmacologic doses; glucocorticoids are frequently employed to treat diseases of inflammation like lupus and asthma and use supraphysiologic doses.

One of the major impediments to accepting DHEA as a member of a distinct class of steroidal hormones has been the failure to identify conclusively a receptor for it. A mounting collection of papers have reported intracellular as well as membrane-binding sites for DHEA (133–135). None of these reports, however, involves the rigorous proofs needed to establish that the receptors comprise a distinct nuclear-steroid binding family. The studies have simply demonstrated cellular binding species for DHEA. Whether these putative receptors can be translocated to the nucleus, undergo structural changes, and activate nuclear sites is unclear. In this regard, however, the reports of Li *et al.* (72) and Garcia de Yebenes *et al.* (47) are pertinent. Both studies reported that the administration of DHEA alters the levels of mRNA in neuronal tissues. These reports support the hypothesis that DHEA interacts with nuclear sites.

One reason that receptors may not yet be characterized for DHEA is that no synthetic, high-affinity DHEA analog is available in radiolabeled form. Such analogs are crucial for investigating binding; direct demonstrations of glucocorticoid receptors using tritiated cortisol are difficult (136)

if not impossible. Glucocorticoid receptors were demonstrated consistently only after radiolabeled triamcinolone acetonide and dexamethasone were prepared. These steroids have very low dissociation rates from the glucocorticoid receptor. Thus, it may not be possible to characterize DHEA receptors until a radioactive species that has a low dissociation rate is available.

Another impediment to accepting DHEA as a member of a distinct family of steroid hormones has been the paucity of *in vitro* cell assays that respond to DHEA. Roberts *et al.* (14), have shown that DHEA increases viability of neuronal cells in tissue culture. However few study DHEA in these systems. The dependence of glucocorticoid action on receptor binding has been demonstrated most clearly in models like the GH3 cell and the AtT-20 cell. As yet, no such accepted model exists for DHEA.

Conclusion

The goal of this report was to analyze the actions of exogenous DHEA with the hope of delineating its actions. Indisputable activities, especially at the cellular level, have yet to be defined. The most fruitful areas appear to involve neurologic and immunologic tissues. Other actions may reflect pharmacologic properties.

As DHEA antagonizes the actions of glucocorticoids, does not affect electrolytes, works in androgen-insensitive animal models, and does not appear to have either estrogenic or progestogenic actions, it suggests that DHEA is in a separate category of steroid hormones. We have proposed (137) that this group be called the Regnantoids, a reflection of its wide range of actions and the high concentration of DHEA-S in the serum of young adults. Once the specifics of DHEA's biology are recognized, more effort will be directed toward developing analogs that posses suitable pharmacologic properties, and the biology of DHEA at both physiologic and pharmacologic concentrations can be more readily exploited.

1. Svec F, Porter JR. Dehydroepiandrosterone and the endocrine aging process. Current Opinion in Endocrinology and Diabetes **3:**117–124, 1996.
2. Barrett-Connor E, Goodman-Gruen D. The epidemiology of DHEAS and cardiovascular disease. Ann NY Acad Sci **774:**259–270, 1995.
3. Nestler JE, Clore JN, Blackard WG. Dehydroepiandrosterone: The "missing link" between hyperinsulinemia and atherosclerosis? FASEB J **6:**3073–3075, 1992.
4. Barrett-Connor E, Khaw KT, Yen SSC. A prospective study of dehydroepiandrosterone sulfate, mortality, and cardiovascular disease. New Eng J Med **315:**1519–1524, 1986.
5. Mitchell LE, Sprecher DL, Borecki IB, Rice T, Laskarzewski PM, Rao DC. Evidence for an association between dehydroepiandrosterone sulfate and nonfatal, premature myocardial infarction in males. Circulation **89:**89–93, 1994.
6. Contoreggi CS, Blackman MR, Andres R, Muller DC, Lakatta EG, Fleg JL, Harman SM. Plasma levels of estradiol, testosterone, and DHEAS do not predict risk of coronary artery disease in men. J Androl **11:**460–470, 1990.
7. Barrett-Connor E, Goodman-Gruen D. Dehydroepiandrosterone sulfate does not predict cardiovascular death in postmenopausal women: The Rancho Bernardo Study. Circulation **91:**1757–1760, 1995.
8. Gordon GB, Shantz LM, Talalay P. Modulation of growth, differentiation, and carcinogenesis by dehydroepiandrosterone. Adv Enzyme Regul **26:**355–382, 1987.
9. Heinonen PK, Koivula T, Pystynen P. Decreased serum level of dehydroepiandrosterone sulfate in postmenopausal women with ovarian cancer. Gynecol Obstet Invest **23:**271–273, 1987.
10. Williams DP, Boyden TW, Pamemter RW, Gohman TG, Going SB. Relationship of body fat percentage and fat distribution with dehydroepiandrosterone sulfate in premenopausal females. J Clin Endocrinol Metab **77:**80–85, 1993.
11. Wisniewski TL, Hilton CW, Morse EV, Svec F. The relationship of serum DHEA-S and cortisol levels to measures of immune function in human immunodeficiency virus–related illness. Am J Med Sci **305:**79–83, 1993.
12. Young J, Couzinet B, Nahoul K, Brailly S, Chanson P, Baulieu EE, Schaison G. Panhypopituitarism as a model to study the metabolism of dehydroepiandrosterone (DHEA) in humans. J Clin Endocrinol Metab **82:**2578–2585, 1997.
13. Flood JF, Morley JE, Roberts E. Memory-enhancing effects in male mice of pregnenolone and steroids metabolically derived from it. Proc Natl Acad Sci USA **89:**1567–1571, 1992.
14. Roberts E, Bologa L, Flood JF, Smith GE. Effects of dehydroepiandrosterone and its sulfate on brain tissue in culture and on memory in mice. Brain Res **406:**357–362, 1987.
15. Singh VB, Kalimi M, Phan TH, Boadle-Bider MC. Intracranial dehydroepiandrosterone blocks the activation of tryptophan hydroxylase in response to acute sound stress. Mol Cell Neurosci **5:**176–181, 1994.
16. Degelau J, Guay D, Hallgren H. The effect of DHEAS on influenza vaccination in aging adults. J Am Geriatr Soc **45:**747–751, 1997.
17. Wright BE, Svec F, Porter JR. Central effects of dehydroepiandrosterone in Zucker rats. Int J Obes Relat Metab Disord **19:**887–892, 1995.
18. Araneo BA, Woods ML, Daynes RA. Reversal of the immunosenescent phenotype by dehydroepiandrosterone: Hormone treatment provides an adjuvant effect on the immunization of aged mice with recombinant hepatitis B surface antigen. J Infect Dis **167:**830–840, 1993.
19. Melchior CL, Ritzmann RF. Dehydroepiandrosterone is an anxiolytic in mice on the plus maze. Pharmacol Biochem Behav **47:**437–441, 1994.
20. Wolkowitz OM, Reus VI, Roberts E, Manfredi F, Chan T, Raum WJ, Ormiston S, Johnson R, Canick J, Brizendine L, Weingartner H. Dehydroepiandrosterone (DHEA) treatment of depression. Biol Psychiatry **41:**311–318, 1997.
21. Casson PR, Andersen RN, Herrod HG, Stentz FB, Straughn AB, Abraham GE, Buster JE. Oral dehydroepiandrosterone in physiologic doses modulates immune function in postmenopausal women. Am J Obstet Gynecol **169:**1536–1539, 1993.
22. Casson PR, Faquin LC, Stentz FB, Straughn AB, Andersen RN, Abraham GE, Buster JE. Replacement of dehydroepiandrosterone enhances T-lymphocyte insulin binding in postmenopausal women. Fertil Steril **63:**1027–1031, 1995.
23. Wolf OT, Neumann O, Hellhammer DH, Geiben AC, Strasburger CJ, Dressendorfer RA, Pirke KM, Kirschbaum C. Effects of a two-week physiological dehydroepiandrosterone substitution on cognitive performance and well-being in healthy elderly women and men. J Clin Endocrinol Metab **82:**2363–2367, 1997.
24. Morales AJ, Nolan JJ, Nelson JC, Yen SCC. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. J Clin Endocrinol Metab **78:**1360–1367, 1994.
25. Araneo B, Dowell T, Woods ML, Daynes R, Judd M, Evans T. DHEAS as an effective vaccine adjuvant in elderly humans: Proof-of-principle studies. Ann NY Acad Sci **774:**232–248, 1995.
26. Evans TG, Judd ME, Dowell T, Poe S, Daynes RA, Araneo BA. The use of oral dehydroepiandrosterone sulfate as an adjuvant in tetanus and influenza vaccination of the elderly. Vaccine **14:**1531–1537, 1996.
27. Dannenberg HD, Ben-Yehuda, Zakay-Rones Z, Gross DJ, Friedman G. Dehydroepiandrosterone treatment is not beneficial to the immune response to influenza in elderly subjects. J Clin Endocrinol Metab **82:**2911–2914, 1997.
28. Khonam O, Vu L, Yen SS. Activation of immune function by dehy-

droepiandrosterone (DHEA) in age-advanced men. J Gerontol **52:**M1–7, 1997.
29. Hashimoto S, Katou M, Dong Y, Murakami K, Terada S, Inoue M. Effects of hormone replacement therapy on serum amyloid P component in postmenopausal women. Maturitas **26:**113–119, 1997.
30. Bergeron R, De Montigny C, Debonnel G. Potentiation of neuronal NMDA response induced by dehydroepiandrosterone and its suppression by progesterone: Effects mediated *via* sigma receptors. J Neurosci **16:**1193–1202, 1996.
31. Araneo BA, Ryu SY, Barton S, Daynes RA. Dehydroepiandrosterone reduces progressive dermal ischemia caused by thermal injury. J Surg Res **59:**250–262, 1995.
32. Prasad A, Prasad A, Prasad C. Dehydroepiandrosterone (DHEA) decreases behavioral despair in rats selected for mixed despair and anxiety, but not despair alone. J Investig Med **44:**6A, 1996.
33. Beer NA, Jakubowicz DJ, Matt DW, Beer RM, Nestler JE. Dehydroepiandrosterone reduces plasma plasminogen activator inhibitor type 1 and tissue plasminogen activator antigen in men. Am J Med Sci **311:**205–210, 1996.
34. Haug M, Ouss-Schlegel ML, Spetz JF, Brain PF, Simon V, Baulieu EE, Robel P. Suppressive effects of dehydroepiandrosterone and 3-B-methylandrost-5-en-17-one on attack towards lactating female intruders by castrated male mice. Physiol Behav **46:**955–959, 1989.
35. Van Vollenhoven RF, Engleman EG, McGuire JL. An open study of dehydroepiandrosterone in systemic lupus erythematosus. Arthritis Rheum **37:**1305–1310, 1994.
36. Buffington CA, Pourmotabbed G, Kitabchi AE. Case report: Amelioration of insulin resistance in diabetes with dehydroepiandrosterone. Am J Med Sci **306:**320–324, 1993.
37. Lohman R, Yowell R, Banton S, Araneo B, Siemionow M. Dehydroepiandrosterone protects muscle flap microcirculatory hemodynamics from ischemia/reperfusion injury: An experimental *in vivo* study. J Trauma **42:**74–79, 1997.
38. Spencer NFL, Poynter ME, Hennebold JD, Mu HH, Daynes RA. Does DHEAS restore immune competence in aged animals through its capacity to function as a natural modulator of peroxisome activities? Ann NY Acad Sci **774:**200–216, 1995.
39. Schurr MJ, Fabian TC, Croce MA, Vamavas LE, Proctor KG. Dehydroepiandrosterone, an endogenous immune modulator, after traumatic shock. Shock **7:**55–59, 1997.
40. Araneo BA, Shelby J, Li GZ, Ku W, Daynes RA. Administration of dehydroepiandrosterone to burned mice preserves normal immunologic competence. Arch Surg **128:**318–325, 1993.
41. Caims BA, Yamamoto H, Smith D, Ramadan FM, Meyer AA. Dehydroepiandrosterone fails to improve immunoglobulin synthesis and lymphocyte mitogenic response after burn injury. J Burn Care Rehabil **15:**509–514, 1994.
42. Daynes RA, Dudley DJ, Araneo BA. Regulation of murine lymphokine production *in vivo.* II. Dehydroepiandrosterone is a natural enhancer of interleukin 2 synthesis by helper T cells. Eur J Immunol **20:**793–802, 1990.
43. Kim HR, Ryu SY, Kim HS, Choi BM, Lee EJ, Kim HM, Chung HT. Administration of dehydroepiandrosterone reverses the immune suppression induced by high-dose antigen in mice. Immunol Invest **24:**583–593, 1995.
44. Garg M, Bondada S. Reversal of age-associated decline in immune response to pnu-immune vaccine by supplementation with the steroid hormone dehydroepiandrosterone. Infect Immun **61:**2238–2241, 1993.
45. Araneo B, Daynes R. Dehydroepiandrosterone functions as more than an antiglucocorticoid in preserving immunocompetence after thermal injury. Endocrinology **136:**393–401, 1995.
46. Wright BE, Porter JR, Browne ES, Svec F. Antiglucocorticoid action of dehydroepiandrosterone in young obese Zucker rats. Int J Obes Relat Metab Disord **16:**579–583, 1992.
47. Garcia de Yebenes E, Hong M, Pelletier G. Effects of dehydroepiandrosterone (DHEA) on pituitary prolactin and arcuate nucleus neuron tyrosine hydroxylase mRNA levels in the rat. J Neuroendocrinol **7:**589–595, 1995.
48. Friess E, Trachsel L, Guldner J, Schier T, Steiger A, Holsboer F. DHEA administration increases rapid eye movement sleep and EEG power in the sigma frequency range. Am J Physiol **268:**E107–113, 1995.
49. Pashko LL, Schwartz AG, Abou-Gharbia M, Swern D. Inhibition of DNA synthesis in mouse epidermis and breast epithelium by dehydroepiandrosterone and related steroids. Carcinogenesis **2:**717–721, 1981.
50. Shafagoj Y, Opoku J, Qureshi D, Regelson W, Kalimi M. Dehydroepiandrosterone prevents dexamethasone-induced hypertension in rats. Am J Physiol **263:**E210–213, 1992.
51. Jesse RL, Loesser K, Eich DM, Qian YZ, Hess ML, Nestler JE. Dehydroepiandrosterone inhibits human platelet aggregation *in vitro* and *in vivo.* Ann NY Acad Sci **774:**281–290, 1995.
52. Ben-Nathan D, Lustig S, Kobiler D, Danenberg HD, Lupu E, Feuerstein G. Dehydroepiandrosterone protects mice inoculated with West Nile virus and exposed to cold stress. J Med Virol **38:**159–166, 1992.
53. Gianotti L, Alexander JW, Fukushima R, Pyles T. Steroid therapy can modulate gut barrier function, host defense, and survival in thermally injured mice. J Surg Res **62:**53–58, 1996.
54. Usiskin KS, Butterworth S, Clore JN, Arad Y, Ginsberg HN, Blackard WG, Nestler JE. Lack of effect of dehydroepiandrosterone in obese men. Int J Obes Relat Metab Disor **14:**457–463, 1990.
55. Boccuzzi G, Aragno M, Brignardello E, Tamagno E, Conti G, Di Monaco M, Racca S, Danni O, Di Carlo F. Opposite effects of dehydroepiandrosterone on the growth of 7,12-dimethylbenz(a)anthracene-induced rat mammary carcinomas. Anticancer Res **2:**1479–1484, 1992.
56. Yoo A, Harris J, Dubrovsky B. Dose-response study of dehydroepiandrosterone sulfate on dentate gyrus long-term potentiation. Exp Neurol **137:**151–156, 1996.
57. Mortola JF, Yen SSC. The effects of oral dehydroepiandrosterone on endocrine-metabolic parameters in postmenopausal women. J Clin Endocrinol Metab **71:**696–704, 1990.
58. Melchior CL, Ritzmann RF. Dehydroepiandrosterone enhances the hypnotic and hypothermic effects of ethanol and pentobarbital. Pharmacol Biochem Behav **43:**223–227, 1992.
59. Dyner TS, Lang W, Geaga J, Golub A, Stites D, Winger E, Galmarini M, Masterson J, Jacobson MA. An open-label dose-escalation trial of oral dehydroepiandrosterone tolerance and pharmacokinetics in patients with HIV disease. J Acquir Immune Defic Syndr Hum Retrovirol **6:**459–465, 1993.
60. Nestler JE, Barlascini CO, Clore JN, Blackard WG. Dehydroepiandrosterone reduces serum low-density lipoprotein levels and body fat but does not alter insulin sensitivity in normal men. J Clin Endocrinol Metab **66:**57–61, 1988.
61. Welle S, Jozefowicz R, Statt M. Failure of dehydroepiandrosterone to influence energy and protein metabolism in humans. J Clin Endocrinol Metab **71:**1259–1264, 1990.
62. Cleary MP, Shepherd A, Zisk J, Schwartz A. Effect of dehydroepiandrosterone on body weight and food intake in rats. Nutrition and Behavior **1:**127–136, 1983.
63. Browne ES, Wright BE, Porter JR, Svec F. Dehydroepiandrosterone: Antiglucocorticoid action in mice. Am J Med Sci **303:**366–371, 1992.
64. Diamond DM, Branch BJ, Fleshner M. The neurosteroid dehydroepiandrosterone sulfate (DHEAS) enhances hippocampal primed burst, but not long-term, potentiation. Neurosci Lett **202:**204–208, 1996.
65. Zumoff B, Strain GW, Heymsfield SB, Lichtman S. A randomized double-blind crossover study of the antiobesity effects of etiocholanedione. Obes Res **2:**13–18, 1993.
66. Flood JF, Smith GE, Roberts E. Dehydroepiandrosterone and its sulfate enhance memory retention in mice. Brain Res **447:**269–278, 1988.
67. Calabrese VP, Isaacs ER, Regelson W. Dehydroepiandrosterone in multiple sclerosis: Positive effects on the fatigue syndrome in a nonrandomized study. In: Kalimi M, Regelson W, Eds. The Biologic Role of Dehydroepiandrosterone (DHEA). New York: Walter de Gruyter, pp 95–100, 1990.
68. McCormick DL, Rao KVN, Johnson WD, Bowman-Gram TA, Steele BE, Lubet RA, Kelloff GJ. Exceptional chemopreventive activity of low-dose dehydroepiandrosterone in the rat mammary gland. Cancer Res **56:**1724–1726, 1996.
69. Danenberg HD, Alpert G, Lustig S, Ben-Nathan D. Dehydroepiandrosterone protects mice from endotoxin toxicity and reduces tumor necrosis factor production. Antimicrob Agents Chemother **36:**2275–2279, 1992.

70. Kurzman ID, MacEwen EG, Haffa AL. Reduction in body weight and cholesterol in spontaneously obese dogs by dehydroepiandrosterone. Int J Obes Relat Metab Disord **14:**95–104, 1990.
71. Peters JM, Zhou YC, Ram PA, Lee SST, Gonzalez FJ, Waxman DJ. Peroxisome proliferator-activated receptor alpha required for gene induction by dehydroepiandrosterone-3beta-sulfate. Mol Pharmacol **50:**67–74, 1996.
72. Li S, deYebenes EG, Pelletier G. Effects of dehydroepiandrosterone (DHEA) on GnRH gene expression in the rat brain as studied by *in situ* hybridization. Peptides **16:**425–430, 1995.
73. Blauer KL, Poth M, Rogers WM, Bernton EW. Dehydroepiandrosterone antagonizes the suppressive effects of dexamethasone on lymphocyte proliferation. Endocrinology **129:**3174–3179, 1991.
74. Christopher-Hennings J, Kurzman ID, Haffa ALM, Kemnitz JW, MacEwen EG. The effect of high-fat diet and dehydroepiandrosterone (DHEA) administration in the Rhesus monkey. In Vivo **9:**415–420, 1995.
75. Haffa ALM, MacEwen EG, Kurzmann ID, Kemnitz JW. Hypocholesterolemic effect of dehydroepiandrosterone administration in the rhesus monkey. In Vivo **8:**993–998, 1994.
76. May M, Holmes E, Rogers W, Poth M. Protection from glucocorticoid induced thymic involution by dehydroepiandrosterone. Life Sci **46:**1627–1631, 1990.
77. Su CY, Lardy H. Induction of hepatic mitochondrial glycerophosphate dehydrogenase in rats by dehydroepiandrosterone. J Biochem (Tokyo) **110:**207–213, 1991.
78. Mohan PF, Cleary MP. Short-term effects of dehydroepiandrosterone treatment in rats on mitochondrial respiration. J Nutr **121:**240–250, 1991.
79. Frenkel RA, Slaughter CA, Orth K, Moomaw CR, Hicks SH, Snyder JM, Bennett M, Prough RA, Putnam RS, Milewich L. Peroxisome proliferation and induction of peroxisomal enzymes in mouse and rat liver by dehydroepiandrosterone feeding. J Steroid Biochem Mol Biol **35:**333–342, 1990.
80. McIntosh MK, Berdanier CD. Strain differences in the dose-response curves of adrenalectomized, starved-refed rats to dehydroepiandrosterone (DHEA). Proc Soc Exp Biol Med **187:**216–222, 1988.
81. Gordon GB, Bush DE, Weisman HF. Reduction of atherosclerosis by administration of dehydroepiandrosterone: A study in the hypercholesterolemic New Zealand white rabbit with aortic intimal injury. J Clin Invest **82:**712–720, 1988.
82. Swierczynski J, Mayer D. Dehydroepiandrosterone-induced lipid peroxidation in rat liver mitochondria. J Steroid Biochem Mol Biol **58:**599–603, 1996.
83. Eich DM, Nestler JE, Johnson DE, Dworkin GH, Ko D, Wechsler AS, Hess ML. Inhibition of accelerated coronary atherosclerosis with dehydroepiandrosterone in the heterotopic rabbit model of cardiac transplantation. Circulation, **87:**261–269, 1993.
84. Ratko TA, Detrisac CJ, Mehta RG, Kelloff GJ, Moon RC. Inhibition of rat mammary gland chemical carcinogenesis by dietary dehydroepiandrosterone or a fluorinated analogue of dehydroepiandrosterone. Cancer Res **51:**481–486, 1991.
85. Cleary MP, Seidenstat R, Tannen RH, Schwartz AG. The effect of dehydroepiandrosterone on adipose tissue cellularity in mice. Proc Soc Exp Biol Med **171:**276–284, 1982.
86. Porter JR, Svec F. DHEA diminishes fat food intake in lean and obese Zucker rats. Ann NY Acad Sci **774:**329–331, 1995.
87. Lucas JA, Ahmed SA, Casey ML, MacDonald PC. Prevention of autoantibody formation and prolonged survival in New Zealand Black/New Zealand White F_1 mice fed dehydroepiandrosterone. J Clin Invest **75:**2091–2093, 1985.
88. Porter JR, Abadie JM, Wright BE, Browne ES, Svec F. The effect of discontinuing dehydroepiandrosterone supplementation on Zucker rat food intake and hypothalamic neurotransmitters. Int J Obes Relat Metab Disord **19:**480–488, 1995.
89. Taniguchi S, Yanase T, Haji M, Ishibashi K, Takayanagi R, Nawata H. The antiobesity effect of dehydroepiandrosterone in castrated or noncastrated obese Zucker male rats. Obes Res Suppl **5:**639S–643S, 1995.
90. Shibata M, Hasegawa R, Imaida K, Hagiwara A, Ogawa K, Hirose M, Ito N, Shirai T. Chemoprevention by dehydroepiandrosterone and indomethacin in a rat multiorgan carcinogenesis model. Cancer Res **55:**4870–4874, 1995.
91. Hastings LA, Pashko LL, Lewbart ML, Schwartz AG. Dehydroepiandrosterone and two structural analogs inhibit 12-O-tetradecanoylphorbol-13-acetate stimulation of prostaglandin E_2 content in mouse skin. Carcinogenesis **9:**1099–1102, 1988.
92. Mohan PF, Ihnen JS, Levin BE, Cleary MP. Effects of dehydroepiandrosterone treatment in rats with diet-induced obesity. J Nutr **120:**1103–1114, 1990.
93. Sakuma M, Yamada J, Suga T. Comparison of the inducing effect of dehydroepiandrosterone on hepatic peroxisome proliferation–associated enzymes in several rodent species. Biochem Pharmacol **43:**1269–1273, 1992.
94. Rao MS, Subbarao V, Yeldandi AV, Reddy JK. Inhibition of spontaneous testicular Leydig cell tumor development in F-344 rats by dehydroepiandrosterone. Cancer Lett **65:**123–126, 1992.
95. Rao MS, Subbarao V, Kumar S, Yeldandi AV, Reddy JK. Phenotypic properties of liver tumors induced by dehydroepiandrosterone in F-344 rats. Jpn J Cancer Res **83:**1179–1183, 1992.
96. Gosnell BA. Effects of dietary dehydroepiandrosterone on food intake and body weight in rats with medial hypothalamic knife cuts. Physiol Behav **39:**687–691, 1987.
97. Pashko LL, Schwartz AG. Antihyperglycemic effect of dehydroepiandrosterone analogue 16 alpha-fluoro-5-androsten-17-one in diabetic mice. Diabetes **42:**1105–1108, 1993.
98. Marrero M, Prough RA, Putnam RS, Bennett M, Milewich L. Inhibition of carbamoyl phosphate synthetase-1 by dietary dehydroepiandrosterone. J Steroid Biochem Mol Biol **38:**599–609, 1991.
99. Shepherd A, Cleary MP. Metabolic alterations after dehydroepiandrosterone treatment in Zucker rats. Am J Physiol **246:**E123–128, 1984.
100. Browne ES, Porter JR, Correa G, Abadie J, Svec F. Dehydroepiandrosterone regulation of the hepatic glucocorticoid receptor in the Zucker rat. J Steroid Biochem Mol Biol **45:**517–524, 1993.
101. Pascale RM, Simile MM, De Miglio MR, Nufris A, Seddaiu MA, Muroni MR, Danni O, Rao KN, Feo F. Inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase activity and gene expression by dehydroepiandrosterone in preneoplastic liver nodules. Carcinogenesis **16:**1537–1542, 1995.
102. Brady LJ, Ramsay RR, Brady PS. Regulation of camitine acyltransferase synthesis in lean and obese Zucker rats by dehydroepiandrosterone and clofibrate. J Nutr **121:**525–531, 1991.
103. Simile M, Pascle RM, De Miglio MR, Nufris A, Daino L, Seddaiu MA, Muroni MR, Rao KN, Feo F. Inhibition by dehydroepiandrosterone of growth and progression of persistent liver nodules in experimental rat liver carcinogenesis. Int J Cancer **62:**210–215, 1995.
104. Abadie JM, Wright B, Correa G, Browne ES, Porter JP, Svec F. Effect of dehydroepiandrosterone on neurotransmitter levels and appetite regulation of the obese Zucker rat. Diabetes **42:**662–669, 1993.
105. Shibata MA, Shirai T, Asakawa E, Hirose M, Fukushima S. Inhibition by dehydroepiandrosterone of butylated hydroxyanisole (BHA) promotion of rat-bladder carcinogenesis and enhancement of BHA-induced forestomach hyperplasia. Int J Cancer **53:**819–823, 1993.
106. Ogiu T, Hard G, Schwartz AG, Magee PN. Investigation into the effect of DHEA on renal carcinogenesis induced in the rat by a single dose of DMN. Nutr Cancer **14:**57–67, 1990.
107. Danenberg HD, Ben-Yehuda A, Zakay-Rones Z, Friedman G. Dehydroepiandrosterone enhances influenza immunization in aged mice. Ann NY Acad Sci **774:**297–301, 1995.
108. Rasmussen KR, Healey MC, Cheng L, Yang S. Effects of dehydroepiandrosterone in immunosuppressed adult mice infected with *Cryptosporidium parvum.* J Parasitol **8:**429–433, 1995.
109. Hursting SD, Perkins SN, Haines DC, Ward JM, Phang JM. Chemoprevention of spontaneous tumorigenesis in p53-knockout mice. Cancer Res **55:**3949–3953, 1995.
110. Coleman DL. Therapeutic effects of dehydroepiandrosterone (DHEA) and its metabolites in obese-hyperglycemic mutant mice. Prog Clin Biol Res **265:**161–175, 1988.
111. Matsunaga A, Miller BC, Cottam GL. Dehydroisoandrosterone prevention of autoimmune disease in NZB/W F_1 mice: Lack of an effect on associated immunological abnormalities. Biochim Biophy Acta **992:**265–271, 1989.
112. Risdon G, Moore TA, Kumar V, Bennett M. Inhibition of murine natural killer cell differentiation by dehydroepiandrosterone. Blood **78:**2387–2391, 1991.
113. Marrero M, Prough RA, Frenkel RA, Milewich L. Dehydroepiandrosterone feeding and protein phosphorylation, phosphatases, and

lipogenic enzymes in mouse liver. Proc Soc Exp Bio Med **193:**110–117, 1990.
114. Risdon G, Cope J, Bennett M. Mechanisms of chemoprevention by dietary dehydroisoandrosterone. Am J Pathol **136:**759–765, 1990.
115. Ben-Nathan D, Lachmi B, Lustig S, Feuerstein G. Protection by dehydroepiandrosterone in mice infected with viral encephalitis. Arch Virol **120:**263–271, 1991.
116. Loria RM, Inge TH, Cook SS, Szakal AK, Regelson W. Protection against acute lethal viral infections with the native steroid dehydroepiandrosterone (DHEA). J Med Virol **26:**301–314, 1988.
117. Klann RC, Holbrook CT, Nyce JW. Chemotherapy of murine colorectal carcinoma with cisplatin and cisplatin plus 3′-deoxy-3′-azidothymidine. Anticancer Res **12:**781–788, 1992.
118. Baulieu EE. Neurosteroids: A new function in the brain. Biol Cell **71:**3–10, 1991.
119. Longcope C, Tast J. Dehydroepiandrosterone metabolism in the female rhesus monkey: Oral versus intravenous administration. Steroids **61:**7–10, 1996.
120. Svec F, Hilton CW, Wright B, Browne E, Porter JR. The effect of DHEA given chronically to Zucker rats. Proc Soc Exp Biol Med **209:**92–97, 1995.
121. Richards RJ, Svec F, Bao W, Srinivasan SR, Berenson GS. Steroid hormones during puberty: Racial (black-white) differences in androstenedione and estradiol—The Bogalusa Heart Study. J Clin Endocrinol Metab **75:**624–631, 1992.
122. Labrie C, Flamand M, Belanger A, Labrie F. High bioavailability of dehydroepiandrosterone administered percutaneously in the rat. J Endocrinol **150:**S107–108, 1996.
123. Hung TT, LeMaire WJ. The effects of corticotropin, opioid peptides and crude pituitary extract on the production of dehydroepiandrosterone and corticosterone by mature rat adrenal cells in tissue culture. J Steroid Biochem Mol Biol **29:**721–726, 1988.
124. Salahuddin F, Svec F, Dinan TG. Low DHEA levels in patients with chronic fatigue syndrome. J Invest Med **45:**56A, 1997.
125. Demirgoren S, Majewska MD, Spivak CE, London ED. Receptor binding and electrophysiological effects of dehydroepiandrosterone sulfate, an antagonist of the GABA-A receptor. Neuroscience **45:**127–135, 1991.
125a. Imamura M, Prasad C. Modulation of GABA-gated chloride ion influx in the brain by dehydroepiandrosterone and its metabolites. Biochem Biophys Res Comm **243:**771–775, 1998.
126. Okabe T, Haji M, Takayanagi R, Adachi M, Imasake K, Kurimoto F, Watanabe T, Nawata H. Upregulation of high-affinity dehydroepiandrosterone binding activity by dehydroepiandrosterone in activated human T lymphocytes. J Clin Endocrinol Metab **80:**2993–2996, 1995.
127. Meikle AW, Dorchuck RW, Araneo BA, Stringham JD, Evans TG, Spruance SL, Daynes RA. The presence of a dehydroepiandrosterone-specific receptor binding complex in murine T cells. J Steroid Biochem Mol Biol **42:**293–304, 1992.
128. Kalimi M, Shafagoj Y, Loria R, Padgett D, Regelson W. Antiglucocorticoid effects of dehydroepiandrosterone (DHEA). Mol Cell Biochem **131:**99–104, 1994.
129. Rau E, Boshell T, Martin L, DeBoisblanc B, Svec F, Porter JR. DHEA effect on mortality caused by experimental sepsis in lean and obese Zucker rats. J Invest Med **43:**46A, 1995.
130. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Eng J Med **336:**973–979, 1997.
131. Cleary MP. The antiobesity effect of dehydroepiandrosterone in rats. Proc Soc Exp Biol Med **196:**8–16, 1991.
132. Ibanez L, Potau N, Oliveras M, Carrascosa A, Taylor AE. Oral DHEA administration improves intravenous glucose tolerance in hyperandrogenic women with low normal DHEA levels. Presented to the 79th Annual Meeting of the Endocrine Society, June 1997, Minneapolis, MN.
133. Yamada J, Sugiyama H, Sakuma M, Suga T. Specific binding of dehydroepiandrosterone sulfate to rat liver cytosol: A possible association with peroxisomal enzyme induction. Biochim Biophys Acta **1224:**139–146, 1994.
134. Imai A, Ohno T, Tamaya T. Dehydroepiandrosterone sulfate-binding sites in plasma membrane from human uterine cervical fibroblasts. Experientia **48:**999–1002, 1992.
135. Kalimi M, Regelson W. Physicochemical characterization of 3H DHEA binding to rat liver. Biochem Biophys Res Commun **156:**22–29, 1988.
136. Svec F, Tate D. Characterization of glucocorticoid receptors bound with corticosterone. J Recept Signal Transduct Res **9:**405–410, 1989.
137. Svec F, Porter JR. Dehydroepiandrosterone and the endocrine aging process. Current Opinion in Endocrinology and Diabetes **3:**117–124, 1996.