Use of DES-Treated Rats as an Animal Model for Assessment of Pituitary Adenoma Imaging Agents

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Prolactin (PRL) secreting pituitary adenomas are the most common type of pituitary tumors. An imaging agent which specifically localized in prolactinomas would be of considerable clinical value for both initial detection and also for monitoring the effects of dopamine agonist therapy. Tritiated spiroperidol (3HSp) was selected for initial evaluation as a possible imaging agent based on: (1) demonstrated localization in the pituitary and (2) demonstrated binding to human PRL-secreting tumor tissue. DES was implanted in Fischer F344 rats and induced prolactinoma formation was evidenced by increased pituitary weight, elevated serum PRL levels and by an increase in the proportion of PRL-secreting cells in the pituitary. 3HSp concentrations in pituitary and other tissues of DES-treated rats were assessed in female rats and correlation studies showed that a 5-fold increase in serum PRL was associated with a 6-fold increase in both pituitary weight and % dose/organ accumulation of 3HSp. The number of pituitary D₃ receptors per mg of protein in tissue homogenates was similar in both normal and DES-treated females. A blocking study with (+)-butaclamol demonstrated a D₃ receptor-mediated component to 3HSp localization. In summary, an animal model for prolactinoma was characterized. An assessment of 3HSp accumulation indicates that radiolabelled spiroperidol shows excellent potential for detecting PRL-secreting tumors of the pituitary.

Introduction

Prolactin (PRL) secreting pituitary adenomas are the most common type of pituitary tumors. The high incidence of these tumors only became apparent within the past 9–10 years as a result of the development and general availability of a radioimmunoassay for measurement of PRL in serum. These tumors are common in females who usually present with galactorrhea, amenorrhea or infertility although other local effects such as visual disturbances from compression of the optic chiasma may be evident. It is now recognized that approximately 20–25% of all women with amenorrhea have prolactinomas. The detection of prolactinomas currently depends on physical symptoms, elevated serum PRL levels and abnormal CT scans of the sella turcica. However, other disorders such as pituitary cysts may present with both elevated serum PRL and abnormal CT scans. Not only have surgically confirmed prolactinomas been found in patients with normal CT scans and with elevated serum PRL, but abnormal CT scans have a predictive value of only 22% for pituitary tumors in patients with no clinical history of pituitary disease. CT scans do not functionally characterize tumors but merely indicate density changes which are presumed to reflect the presence of a tumor. Thus, diagnosis may be imprecise and often rests on the association of an elevated serum PRL level with a possible CT scan abnormality. Prolactinomas have been demonstrated using [123I]pertechnetate. However, [123I]pertechnetate does not functionally characterize tumors but reflects increased vascularization and vascular permeability associated with tumor presence. Nuclear magnetic resonance (MR) has recently been evaluated for pituitary tumor imaging but MR also does not functionally characterize tumor type.

Thus, an imaging agent which specifically localizes...
in prolactinomas based on some functional character-
istic of the tumor would be of considerable clinical
value. Positive imaging of these tumors would enable
a definite diagnosis of PRL-secreting adenoma to be
made and this would represent an improvement over
existing CT scans. Earlier detection may be possible
and the effects of medical therapy (e.g. bromo-
criptine) on functional status and tumor size could be
monitored in a serial manner.

Prolactin secretion appears to be largely under
dopamine control. Dopamine, which is carried into
the hypothalamic portal blood, may inhibit PRL
secretion by binding to receptors in the pituitary.(14)
The anterior pituitary is thought to contain exclu-
sively postsynaptic D2 receptors.(15,16) Studies indicate
that most human prolactinomas have intact dop-
amine receptor sites on the PRL-producing cells.(17 19)
There are contrasting reports regarding the numbers
of receptor sites in human prolactinomas. One study
by Cronin et al. using spiroperidol found increased
numbers of binding sites(18) while Bression and col-
leagues using 3H-domperidone report decreased num-
bers.(19) Further quantification studies using a uni-
form receptor concentration assay are necessary to
clarify this point. Regardless, the increase in PRL-
secreting cells (mammotrophs) in prolactinomas cou-
pled with the presence of dopamine receptors capable
of binding 3H-neuroleptics(15) raises the possibility of
receptor-mediated imaging of these tumors with a
radiolabelled D2 receptor antagonist.

Development of a suitable imaging agent depends
not only on the synthesis of an appropriate radio-
 pharmaceutical but on the availability of an animal
tumor model with characteristics similar to human
prolactinomas. A recent publication has shown that
implantation of diethylstilbestrol (DES) in Fischer
F344 rats resulted in the induction of PRL-secreting
hyperplasia/tumor of pituitary tissue in almost all
animals within 8-12 weeks after implantation.(20)
Treatment with estradiol had no effect on the affinity
of the dopamine receptor for spiroperidol(20) but the
effect of estrogen on the number of dopamine recep-
tors in the rat pituitary is uncertain and has been
reported to remain constant(21) or to be reduced by
approximately 50%. It2) The presence of functioning
pituitary dopamine receptors together with elevated
serum PRL levels suggests that the DES-treated F344
rat is a suitable animal model for the assessment of
potential imaging agents for prolactinomas.

As we have previously reported on the uptake of
3HSP in the normal pituitary of Fischer F344 rats(21)
and as 3HSP binding to human PRL-secreting tumor
 tissue has been demonstrated,(19) we evaluated 3HSP
in the DES-induced prolactinoma model rats. The
concentration and retention of spiroperidol or
its analogs in any pituitary tumor have not been
determined.

Thus, we have studied (1) the time course of 3HSP
activity in tissues of DES-treated female F344 rats,
(2) the effect of (+)-butaclamol on 3HSP pituitary
concentration, (3) the number of D2 receptors in
normal and DES-treated female pituitary, and (4)
the correlations between 3HSP concentration in the
pituitary, serum prolactin levels and percent and
number of PRL-producing cells in pituitary tissue of
male and female rats treated with DES.

**Materials and Methods**

The following compounds or reagents were ob-
tained from commercial sources: 3H-spiroperidol
(25-30 Ci/mmol) (New England Nuclear), diethyl-
stilbestrol (Aldrich Chemical Co.) avidin-biotin
peroxidase complex (Vector Laboratory), diamino-
benzidine hydrochloride, pargyline (Sigma Chemical
Co.) (+)-butaclamol hydrochloride (Research Bio-
chemicals Inc.). Dow Corning Silastic tubing and
silicone adhesive type A were obtained commercially,
as were the scintillation fluids used in counting,
Ox-triti-stint (Romac) for tissue samples and ACS
(Amersham) for binding assays.

Polyclonal antiserum to rat prolactin was obtained
from the NIADDK. The NIADDK Pituity Hormone
Distribution Program supplied materials and
protocols for the double antibody RIA for rat
prolactin.

Fischer F344 rats, male and female, were pur-
chased (Charles River). Animals were exposed to
alternating 12 h periods of light and dark and re-
ceived rat chow and water *ad libitum* during the
study.

**Tumor model**

Prolactin secreting adenomas were induced by
implanting DES-containing Silastic tubing s.c. into
30 day old rats under ether anesthesia through a
small incision in the back.(20) Control rats were im-
planted with empty Silastic tubing. The DES-
implants were prepared as described except that 3/4
in. lengths of tubing were used and these were filled
with 10 mg of DES. Both blank and DES-implants
were soaked in 2% BSA solution for 24 h prior to
implanting in the rats.

**Immunohistochemical staining**

The anterior and posterior pituitary lobes were
removed separately and the anterior pituitary fixed in
3 mL of 10% formalin for 24 h at 23°C before being
embedded in paraffin. Tissue sections were cut sagi-
tally with a microtome (5 μm) and stained with
hematoxylin and eosin. Other sections were stained
for PRL by immunohistochemical methods.(24) After
inhibiting endogenous peroxidase with 1% methanol-H2O2,
tissues were washed in phosphate buffered saline (PBS),
then treated with normal goat serum to suppress nonspecific binding for 30 min. Rat
anti-PRL serum (produced in rabbits and used at
1:1000 dilution) was applied for 1 h at 23°C. The
tissues were washed with PBS treated with 1:200
dilution of rabbit biotin-IgG made in goat for 30 min,
followed by PBS washes, then incubation with avidin–biotin peroxidase complex for 30 min. Di-
aminobenzidine (DAB) was used as the chromogen (10 mg DAB in 50 mL PBS, pH 7.2 and 0.001% 
H$_2$O$_2$) for 5 min.

Controls consisted of substituting normal rabbit serum for the primary antibody and absorbing each 
antibody with specific antigens for 24 h before performing the assay. Additional controls consisted of 
omitting biotin-IgG or avidin-biotin peroxidase complex. All of these controls resulted in no staining 
of the tissues. The number of cells staining positively for PRL was counted by systematically sampling the 
entire pituitary tissue using a 4 mm$^2$ grid in the microscope ocular. A minimum of 1000 cells per slide 
were counted and scored as negative or positive if a brown-black reaction product was present in the 
cytoplasm.

Serum prolactin assay

Serum PRL was determined for all rats, male and female, control and DES-treated, using a published 
radioimmunoassay procedure.(25)

D$_2$ receptor binding assay

Female Fischer F344 rats under ether anesthesia were killed by decapitation. Normals were 8 weeks of 
age; DES-treated were sacrificed 4 weeks after implant. The pituitaries were rapidly removed and 
washed free of blood in cold saline. The anterior lobes were separated and stored at -70°C until 
assayed. Pituitaries from both normal and DES-treated rats were assayed simultaneously. Tissue sam-
ples were homogenized at low speed with a Tekmar homogenizer using 30 vol of cold buffer (0.25 M 
sucrose, 15 mM Tris, 120 mM NaCl, 5 mM KCl, 2 mM CaCl$_2$, 1 mM MgCl$_2$, 0.1 mM EDTA,(26) 2 µM 
pargyline, 0.1% ascorbate, pH 7.4, 25°C). The ho-
mogenate was centrifuged twice as described.(21) The first pellets were resuspended in Tris buffer (as above 
but omitting sucrose) and incubated for 10 min at 37°C. The homogenates were then assayed for pro-
tein content(26) and diluted with buffer to a final concentration of about 0.2 mg protein/100 µL.

For binding studies, 600 µL samples were prepared in triplicate as described by Cronin and Weiner.(27)

Assays contained about 0.2 mg protein. Membrane bound $^3$HSP was separated by rapid filtration (< 5 s) 
under vacuum over Schleicher & Schuell No. 34 glass fiber filters and washed with 3 x 4 mL cold Tris 
buffer. The filters were placed in scintillation vials and 3 mL scintillation fluid added. The samples were 
stored until translucent, then counted. All values were corrected for background.

Specific binding was defined as the total counts of $^3$HSP minus the counts obtained in the presence of 
1000-fold excess of (+)-butaclamol (pharmacologically active form). Scatchard analysis was per-
fomed to determine the apparent dissociation constant $K_D$, and the maximal number of receptor 
sites, $B_{max}$, for both normal and DES-treated pituitary.

Tissue distribution studies

DES-treated. Female Fischer F344 rats were im-
planted with DES as described above and sacrificed 4 weeks later. Tissue distribution studies were per-
formed as described(23) at 5 min and at 1 and 2 h post injection.

(+)-Butaclamol treated. Female rats implanted 
with DES were treated with (+)-butaclamol (2 mg/kg, n = 6, and 5 mg/kg, n = 6) 45 min prior to 
$^3$HSP injection (25 µCi). Tissue distribution studies 
were performed as described at t = 1 h post $^3$HSP injection.

Correlation studies

Protocol. Correlation studies were similarly per-
formed on male and female rats. Thirty day old 
Fischer F344 rats (12 per group for each time period of 
4 and 8 weeks) were implanted with blanks or DES. After 4 weeks for female rats, and after 4 and 
8 weeks for male rats, the animals were separated into two groups of six animals and treated as follows. All 
animals were killed by decapitation, pituitaries re-
moved and blood collected. Serum was kept frozen 
until use for PRL assay. The uteri of all female rats 
were removed, cleaned of fat, connective tissue and 
excess fluid and weighed. Six were treated as de-
scribed above for tissue distribution studies. Six 
pituitaries were fixed for determination of the per-
centage of PRL-producing cells by immuno-
histochemical staining.

Results

Effects of DES treatment

The effects of DES on uterine and pituitary weight 
determined. Uterine weight was 320 ± 60 mg for 
10 mg DES implanted for 4 weeks. This is compar-
able to 250 mg reported for 4 weeks of treatment with 
5 mg DES(28) As expected, pituitary weights also in-
creased and are presented in Table 3. For both 
males and females, the 10 mg dosage of DES used 
resulted in higher pituitary weights than reported 
after 5 mg DES treatment.(20)

The induction of PRL-secreting tumor was verified 
by the increase in weight of the anterior pituitary, by 
the elevation of serum PRL levels and by an increase 
in the numbers of PRL-secreting cells. In both male 
and female rats, the increase in PRL-secreting cells 
was uniformly distributed in the anterior pituitary.

Figures 1A and B are examples of pituitary tissue 
from normal and DES-treated female rats after im-
munohistochemical staining.

Time course in DES-treated rats

The concentration data of $^3$H-activity in various 
tissues from DES-treated rats is compiled in Table 1.
Table 1. \(^3\)H-spiroperidol activity levels in DES-treated female rats

<table>
<thead>
<tr>
<th>Tissue</th>
<th>5 min</th>
<th>1 h</th>
<th>2 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior pituitary</td>
<td>0.29 (\pm) 0.046</td>
<td>0.221 (\pm) 0.014</td>
<td>0.224 (\pm) 0.035</td>
</tr>
<tr>
<td>Posterior pituitary</td>
<td>(-) (\pm) 0.220</td>
<td>0.097 (\pm) 0.029</td>
<td>0.131 (\pm) 0.016</td>
</tr>
<tr>
<td>Uterus</td>
<td>0.144 (\pm) 0.017</td>
<td>0.123 (\pm) 0.003</td>
<td>0.021 (\pm) 0.005</td>
</tr>
<tr>
<td>Blood</td>
<td>0.026 (\pm) 0.004</td>
<td>0.017 (\pm) 0.002</td>
<td>0.021 (\pm) 0.005</td>
</tr>
</tbody>
</table>

\(n = 3\), Fischer F344 rats sacrificed 4 weeks after 10 mg DES implant.

Data as % kg dose/g, mean \(\pm\) SEM.

Posterior pituitary not adequately distinguishable from anterior pituitary for two of the rats.

Over a time span from 5 min to 2 h, the concentration in anterior and posterior pituitary, uterus and blood was approximately constant for both normal (data from Ref. 23) and DES-treated female rats. In DES-treated animals, anterior pituitary values were approximately 10 times that seen in other tissues.

The posterior pituitary could usually be visually distinguished from the anterior pituitary at 4 weeks after DFS treatment in female rats. However, in female rats implanted with 10 mg DES and sacrificed 8 weeks later, the tumors of all rats \((n = 9)\) appeared necrotic and hemorrhagic. Concentration data in such tumors is of questionable validity so further evaluation was not performed. The posterior pituitary could not be distinguished from anterior pituitary in these rats.

**Butaclamol blocking study**

DES-treated female rats were pretreated with two dosages of \((+)-butaclamol-2 and 5 mg/kg. Results were similar for all tissues examined at both dosage levels and only percent kg dose/g values for 2 mg/kg are presented in Table 2.

**D\(_2\) receptor binding assay**

Scatchard analysis of \(^3\)HSp specific binding to anterior pituitary homogenates from normal and DES-treated female rats was performed. The apparent \(K_d\) is 0.15 \(\pm\) 0.06 nM for normals and 0.19 \(\pm\) 0.08 for DES-treated animals. The maximum number of D\(_2\) receptor sites \((B_{max})\) was also similar for normal (71 \(\pm\) 13 fmol/mg protein) and DES-treated rats (63 \(\pm\) 11).

**Correlation studies**

The relationship between serum PRL levels and the percent of PRL-secreting cells present in control and DES-implanted male and female rats is presented in Table 3. The increase in serum PRL levels to

<table>
<thead>
<tr>
<th>Tissue</th>
<th>% kg dose/g</th>
<th>% Reduction(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior pituitary</td>
<td>0.232 (\pm) 0.014</td>
<td>28 (\pm) 7</td>
</tr>
<tr>
<td>Posterior pituitary</td>
<td>0.238 (\pm) 0.055</td>
<td>—</td>
</tr>
<tr>
<td>Uterus</td>
<td>0.079 (\pm) 0.002</td>
<td>36 (\pm) 4</td>
</tr>
<tr>
<td>Blood</td>
<td>0.016 (\pm) 0.001</td>
<td>—</td>
</tr>
</tbody>
</table>

\(n = 6\), Fischer F344 rats implanted with 10 mg DES. Rats injected with \((+)-butaclamol (2 mg/kg) 45 min prior to \(^3\)HSp injection (25 \(\mu\)Ci). Sacrifice at \(t = 1\) h post \(^3\)HSp injection.

Data as % kg dose/g, mean \(\pm\) SEM.

\(^d\)Percent relative to % kg dose/g at \(t = 1\) h for DES-treated rats (data in Table 1). Only statistical differences are listed.

Table 2. \(^3\)H-spiroperidol activity for (+)-butaclamol treated rats

Table 3. Correlation between serum prolactin levels, anterior pituitary weights, percent prolactin secreting cells and \(^3\)H-spiroperidol concentration at \(t = 1\) h post injection

Table 3. Correlation between serum prolactin levels, anterior pituitary weights, percent prolactin secreting cells and \(^3\)H-spiroperidol concentration at \(t = 1\) h post injection

\(\alpha = 0.05\)
Fig. 1. (A) Normal anterior pituitary gland from a female rat stained for PRL by immunohistochemistry. A black reaction product is present in the cytoplasm of PRL-producing cells. (Immunoperoxidase x 330.)

(B) Pituitary gland from DES-treated female rat stained for PRL by immunohistochemistry. Most of the tumor cells contain immunoreactive PRL. (Immunoperoxidase x 330.)
Assessment of pituitary adenoma imaging agents

1170 ± 110 ng/mL for males and to 2500 ± 199 for females was associated with a 2.5 fold increase in the percent of PRL-secreting cells in the anterior pituitary of both male and female rats at 4 weeks. When placed in conjunction with increasing pituitary weight, this increase in percent of PRL-secreting cells corresponds to a 10 fold increase in the total number of PRL-secreting cells for males and a 15 fold increase for females. Male rats were also evaluated at 8 weeks as the pituitary tumors, in contrast to females at 8 weeks, were smaller, less vascularized and did not appear hemorrhagic (see Time course in DES-treated rats above).

The tissue concentrations of 3H-spiroperidol are also presented in Table 3. Concentration values are presented as % kg dose/g, the normalized tissue concentration, and as % dose/organ which reflects the fraction of the dose administered which localized in the anterior pituitary. In male rats a 10 fold increase in serum PRL level is associated with an 8 fold increase in the % dose/organ and a 4 fold increase in anterior pituitary weight. In female rats a 5 fold increase in serum PRL is associated with a 6 fold increase in % dose/organ and a 6 fold increase in anterior pituitary weight. Figure 2 shows the correlation between % dose/organ and serum PRL levels in male and female rats in graphic form.

The correlation between percent PRL cells with % dose/organ and % kg dose/g is also contained in Table 3. Percent dose/organ values in the posterior pituitary are minimally affected by treatment with DES (less than 2 fold increase) and are the same for male and female rats at all time intervals. Anterior pituitary values increased dramatically, as stated above. In sharp contrast to % dose/organ increases, the % kg dose/g values relative to control values remained approximately constant for males and females at 4 weeks and showed a 50% decrease in males at 8 weeks. It is interesting that the 6 fold increase in % dose/organ for females and the 8 fold increase for males correlate with a 2.5 fold increase in the percent of PRL-producing cells for both female and male rats.

Discussion

Time course in DES-treated rats

The dissociation constants of 3HSp from human anterior pituitary and from human PRL-secreting pituitary adenomas are similar \([K_D = 2.2 ± 0.7\) and \(3.1 ± 1.4 \text{nM}, \text{respectively (mean ± SEM)}\). The similarity in \(K_D\) suggests that the time course for 3HSp uptake by tumor tissue may be the same as in normal tissue. Comparison of data in Table 1 with data from normal rats (See Table 1 in Ref. 23) shows that 3HSp uptake appears to be constant from 5 min to 2 h in both normal and tumor pituitary tissue. Percent kg dose/g in anterior pituitary is a normalized value and reflects concentration of injected radioactivity/g tissue. The data suggest that although the pituitary weight has increased 6 fold due to tumor, the concentration/g tissue has remained approximately constant. Because of the similarity in data between normal and DES-tumor induced rats, further time intervals were not evaluated.

Butaclamol blocking study

As with the time course results, the data obtained from rats pretreated with butaclamol are experimentally equivalent for both control(23) and DES-induced tumor bearing rats. That is, the 28 ± 7% reduction observed in anterior pituitary is lower than that reported for cortex and striatum. The reduction

![Graph](Fig. 2. Percent dose/organ vs serum prolactin level in male and female rats after treatment with DES and in controls. Sacrifice was at 1 h post injection. (Correlation factor \(r = 0.9987\).)
in $^3$HSp uptake is supportive that some concentration of $^3$HSp is due to D$_2$ receptor specific binding.

**D. receptor binding assay**

The $K_D$ value observed for normal rats is similar to that reported using F344 male anterior pituitary, 0.10 ± 0.04 nM$^{(29,30)}$ and other rat anterior pituitary tissue$^{(29-32)}$. Likewise the apparent $K_D$ for DES-treated pituitary is comparable to values reported for estradiol treated adult male F344 rats: $0.12 \pm 0.02$ and $0.15 \pm 0.03$ nM for 15 and 90 days of estradiol treatment, respectively$^{(28)}$.

The $B_{max}$ values reported here are similar to those reported for male F344 rats.$^{(28)}$ These data suggest that DES treatment did not significantly alter the observed $B_{max}$ which is in agreement with data obtained using estrogen treated adult male F344 rats$^{(28)}$ and adult female Sprague-Dawley rats.$^{(41-52)}$ and contrasts with data obtained from female Wistar rats.$^{(29)}$ $B_{max}$ determination is in terms of mg pituitary protein and does not include any correction for the percent of PRL-secreting cells (see following discussion).

**Correlation study**

When % dose/mg pituitary is calculated by dividing % dose/organ by anterior pituitary weight (data in Table 3), the value is 0.0024 ± 0.0005% dose/mg and is independent of sex or length of DES treatment. This similarity suggests that, although pituitary weight increased, the relative uptake/mg tissue has remained constant. If one assumes that $^3$HSp localization in the pituitary is dependent on at least an initial complex formation with the D$_2$ receptor, then one might expect that the concentration of D$_2$ receptors/mg tissue has also remained constant. Data presented earlier in D$_2$ receptor assay show that the concentration of D$_2$ receptors in DES induced rat prolactinoma is approximately the same as in controls. Consideration of the D$_2$ receptor concentration in connection with the (for females) 15 fold increase in the number of PRL-secreting cells suggests that the number of D$_2$ receptors per PRL-secreting cell has been reduced. The relationship between increases in % dose/organ and increases in the number of PRL-secreting cells may also be interpreted as support for reduction of number of D$_2$ receptors per cell. For males, the number of PRL cells increase about 1.3 times faster than % dose/organ; for females, this rate of increase is about 2.7. Although the relationship differs for males and females, apparently uptake as % dose/organ is not directly correlated with increasing number of PRL cells.

In general terms, for both male and female rats at 4 weeks, increasing serum PRL levels were accompanied by increases in the percent and number of PRL-secreting cells and by increases in pituitary size. These increases correlate with increasing % dose/organ values. For males and females, there appear to be different rates of increase of % dose/organ (8 fold for males, 6 fold for females), serum PRL (12 fold for males, 5 fold for females), and number of PRL-secreting cells (10 fold vs 15 fold).

**Prolactinoma imaging assessment**

The goal of the present work was to develop an animal model that could be used to screen radiotracers for their potential as mammotroph (prolactinoma) imaging agents. Based on the observed uptake in rats in DES induced prolactinomas and in normal tissue, radiolabelled spiroperidol shows excellent potential for detecting both PRL-secreting pituitary tumors and normal pituitary. Since the size of the pituitary in humans is at the resolution limit of various brain imaging instruments, early presence of a prolactinoma would need to be inferred from an uptake measurement which could best be performed using single photon tomography. In the DES-stimulated pituitary, both pituitary mass and density of PRL-secreting cells increased with the net effect of increasing the uptake per organ by a factor ranging from a low of 5.8 for female rats at 4 weeks to a high of 19.8 for males at 8 weeks. It is highly likely that increases of this magnitude will lie well outside the normal variation for humans and could be detected even at count rates ranging from 12 to 70 cpm predicted in a worst case analysis of a hypothetical normal pituitary.$^{(23)}$ Since the pituitary is below the brain and since it is surrounded by bone, imaging the pituitary will be similar to imaging a point source in background. One can therefore expect good results in uptake measurements.

Future efforts will use this model and a series of other radiolabelled D$_2$ agonists and antagonists. In other studies, attempts will be made to induce pituitary adenomas in larger animals to permit direct scintigraphy evaluations.

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