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國家衛生研究院整合性醫藥衛生科技研究計畫

以動態磁振造影評估股骨頭骨髓壞死之過程：實驗雞

計畫名稱

95年度成果報告

執 行 機 構： 台北醫學大學

計 畫 主 持 人： 陳榮邦 副教授

本年度執行期間 95 年 1 月 1 日 至 95 年 12 月 31 日

＊＊本研究報告僅供參考用，不代表本院意見＊＊

壹、95年度計畫研究成果摘要

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Animal model, Avascular necrosis, Bone marrow, Chicken, Corticosteroid, Femoral Head, MR Imaging, Osteonecrosis

成 果 分 類：
☐ 癌症基礎與臨床研究(可複選，最多三項)
☐ 分子與基因醫學研究
☐ 臨床研究
☐ 生物技術與藥物研究
☐ 生物統計與生物資訊研究
☐ 醫療保健政策研究
☐ 環境衛生與職業醫學研究
☐ 醫學工程研究
☐ 老年醫學研究
☐ 精神醫學與藥物濫用研究
☐ 疫苗研究
☐ 幹細胞研究
☐ 奈米醫學研究
☑ 其他重要疾病或醫藥衛生問題研究

（1）中文摘要

摘要

在第三年實驗中，將89隻樣本雞根據組織學的發現及年齡，以半定量方式判讀(0,1,2分)，並測量股骨頭髓內壓力(Intramedullary pressure,IMP)。初步的結果顯示與對照組比較，實驗組於「新骨頭形成」、「脂肪細胞增生」和「IMP升高」都呈現顯著，這些數據可做為「以雞為對象研究類固醇誘導骨髓壞死」的貢獻。

緒論

過去，許多科學家嘗試以類固醇來誘發實驗動物產生非創傷性股骨頭骨髓壞死(Osteonecrosis of the femoral head;ONFH)，直至1997年Cui和Wang [1]以來亨雞建立ONFH的動物實驗模式。另外，Ficat [2]認為在發生ONFH時，股骨頭骨隨的動脈血流減少，可能與骨髓內壓升高有關。

為延續前兩年的研究，第三年在實驗組及對照組增加了38隻雞，新增的雞隻經過年齡配對，做統計分析。將89個樣本經由資深骨骼病理學家定義類固醇誘發ONFH的組織改變結果，並做判讀(0,1,2分)，且利用IMP測量實驗組與對照組的差異情形。本報告不包括MRI結果。

方法與結果

(1)發展以膽固醇誘導骨隨壞死的雞隻模型

第 I 期實驗(雞隻個案數：12)

材料與方法：共飼養 12 隻來亨雞(8 公 4 母，年齡 25-27 週)，3 隻對照組，不施打類固醇，9 隻實驗組，依 3mg/kg/week 施打類固醇。分為 0 週組(n=3，1 公 2 母，即對照組)、另外實驗組分為 1 週組(n=1，1 公)、4 週組(n=2，1 公 1 母)、6 週組(n=1，1 公)、8 週組(n=1，1 母)、10 週組(n=3，3 母)、12 週組(n=1，1 母)。

結果：飼養的12隻來亨雞中，其中一隻公雞（佔1/12,8%)在未完成類固醇注射實驗設計期間，因傳染病死亡於33週齡，並隨即進行組織解剖。實驗組與對照組的組織結果顯示，發現實驗組公雞股骨粗隆脂肪增生為100.0%（3/3），對照組則無。母雞中，股骨頸有50.0%（3/6)骨頭增生，股骨粗隆紅血球阻塞66.7%（4/6），對照組則無。然而，股骨粗隆的脂肪細胞增生在母雞中並非顯著。

第 II 期實驗(正常雞隻個案數：23)

延續第一期結果報告，增加正常雞隻。

第 III 期實驗（雞隻個案數：54）

材料與方法：

一　**對照組：**16隻未接受類固醇的母雞。依照年齡週數，區分為三個年齡層【A-1】小於40週（4隻）、【A-2】40-79週（8隻）、【A-3】80週以上（4隻）。

二　**實驗組：**38隻接受類固醇注射的母雞。其中6隻（16%）在未完成類

固醇注射實驗期間即死亡，並未納入組織樣本分析。另有3隻由於技術上的疏失，未納入組織樣本分析。其餘29隻雞同樣依照年齡週數以及類固醇劑量週數分別進入以下分類：

【B-1】年齡小於40週，隔日注射類固醇9mg/kg，注射66次（5隻）

【B-2】年齡40-79週（19隻），再細分為（B-2a）（B-2b）（B-2c）（B-2d）

（B-2a）年齡40-79週，每週注射類固醇3mg/kg，注射12週（6隻）

（B-2b）年齡40-79週，每週注射類固醇3mg/kg，注射19週（6隻）

（B-2c）年齡40-79週，每週注射類固醇3mg/kg，注射40週（4隻）

（B-2d）年齡40-79週，隔日注射類固醇9mg/kg，注射130次（3隻）

【C-3】年齡大於80週，隔日注射類固醇9mg/kg，注射160-180次（5隻）

結果：（A）對照組中，組織樣本分別呈現骨小樑損壞，骨髓壞死、骨頭增生、脂肪細胞增生之程度。對照組中探討年齡對於組織結果之關聯，結果發現，不論是股骨頭部、股骨頸部、股骨粗隆等三個部位的各項組織樣本，年齡與組織結果皆未達統計上顯著關聯（Fisher's Exact test，$P>0.05$）。

（B）另外在年齡小於40週的組別，分別比較股骨頭部、股骨頸部、股骨粗隆三個部位在實驗組與對照組的組織結果。分析結果顯示股骨頸部的骨頭增生（$P=0.0476$)、股骨頭部的脂肪細胞增生（$P=0.0079$)以及股骨頸部的脂肪細胞增生（$P=0.0476$)會與實驗組別有關聯（Fisher's Exact test）。股骨

頸部的骨頭增生，對照組中有50%(2/4)發生，而經由類固醇誘導的實驗組則是100%發生（5/5）。在股骨頭部的脂肪細胞增生，對照組中有0%(0/4)發生，而經由類固醇誘導的實驗組則是100%發生（5/5）。在股骨頸部的脂肪細胞增生，對照組中有75%(3/4)發生，而經由類固醇誘導的實驗組則是100%發生（5/5）。

年齡40-79週組別，分別比較股骨頭部、股骨頸部、股骨粗隆部位在實驗組與對照組的組織結果。結果顯示股骨頭部的骨頭增生（P＝0.0226)會與實驗組別有關聯（Fisher's Exact test)。在股骨頭部的骨頭增生，對照組中有75%（6/8）發生，而經由類固醇誘導的實驗組則是100%發生（19/19)。細部比較年齡40-79週，其劑量和期間差異的類固醇注射，在股骨頭部、股骨頸部、股骨粗隆三個部位於實驗組與對照組的組織結果。結果顯示不論是注射3mg/kg/12週、3mg/kg/19週、3mg/kg/40週或是9mg/kg隔日注射130次，各項組織結果皆與實驗組別無關聯（Fisher's Exact test，P＞0.05)。

年齡大於80週的組別，分別比較股骨頭部、股骨頸部、股骨粗隆三個部位在實驗組與對照組的組織結果。分析結果顯示各項組織結果皆與實驗組別無關聯（Fisher's Exact test，P＞0.05)。

小結：對照組中，年齡對於股骨頭部、股骨頸部、股骨粗隆等三部位各項組織結果無關聯。小於40週的雞隻，隔日注射類固醇9mg/kg，注射66次會

造成股骨頸部的骨頭增生、股骨頭部的脂肪細胞增生、股骨頸部的脂肪細胞增生與對照組有差異。中年40-79週的雞隻，至少須注射3mg/kg/12週，可造成股骨頭部的骨頭增生與對照組有差異。大於80週的雞隻，即使在高劑量且長時間注射後，組織結果也與對照組未有差異。

(2)髓內壓力的測量(IMP)

材料和方法：以 Ficat 和 Arlet 描述的方法來進行 IMP 測量的實驗[2]，共 14 隻雞接受股骨頭測量 IMP。

A2 組的雞中得出 4 個正常結果(左側)(40~79 週齡)，在 B2 組的雞中發現 10 個類固醇誘導的雞(左 6；右 4)(B2a 一個，B2b 兩個，B2c 一個，B2d 六個)。

結果：在正常的中年雞，IMP 在股骨頭約為 12 ~19 mmHg。而在類固醇誘導的雞中，IMP 為 25 ~82 mmHg。而在 B2b 和 B2c 組中其 IMP(51 ~82 mmHg)在股骨頭高於 B2a 和 B2d 組(25 ~44 mmHg)，但 B2d 組中有一隻雞為例外(81 mmHg)。

小結：評估比較 IMP 在正常的中年雞和以類固醇誘導的中年雞。在實驗的結果中，可知中年雞在注射類固醇的含量 3mg/kg/19 週或 3mg/kg/40 週可得到較高的 IMP，而不受更高劑量或長時間影響。

討論和結論

Cui et al[1]初步報告雞模型中類固醇引起的 ONFH 在 83 隻雞中有 48% 的死亡率。發現在 12 隻雞中每週注射 3mg /kg methylprednisolone 連續 12-24 週，有四隻雞在股骨頭有新骨頭形成，不過股骨頭倒塌現象在任何雞皆不明顯，並且未提到多少雞有骨髓壞死的現象。

由本研究第三年的數據可發現，在 89 隻雞中以類固醇誘導的雞死亡率只有 16%。初步的統計結果首次顯示年齡配對可以獲得準確的數據。

由於使用嚴格的科學方法學，我們的最初結果增加新知識如下：

(1)正常雞的股骨病理學的改變，並未隨年紀而有明顯且有意義的不同。

(2)從年輕雞中發現，類固醇引起的雞隻股骨頸裡的新骨形成、股骨頭及頸部的脂肪細胞增生有顯著的病理變化。中年雞在股骨頭裡新骨形成是明顯的。雖然有少數的雞可能是對類固醇敏感而導致骨髓壞死，就統計學上來說，類固醇誘導的雞隻沒有明顯的骨髓壞死或股骨頭倒塌現象。與正常雞比較，類固醇誘導的雞，在股骨頭裡有 IMP 升高的現象。

參考資料

1. Cui Q, Wang G-J, Su C-C, Balian G. Lovastatin prevents steroid induced adipogenesis and osteonecrosis. Clin Orthop Rel Res 1997;344:8-19
2. Ficat RP, Arlet J. Necrosis of the femoral head. In: Hungerford DS, ed. Ischemia and necrosis of bone. Baltimore: Williams & Wilkins, 1980;11-52

（2）英文摘要

ABSTRACT In the 3rd research year, 89 chicken specimens were reassessed with use of a semi-quantitative method (score 0, 1, 2) for various histologic findings and age-matched chickens for statistic analysis. Intramedullary pressure was measured in selected experimental and control animals. Preliminary results indicated that significant changes in new bone formation, fat cell proliferation and elevated IMP can be observed in steroid-induced chickens. These data added new knowledge to the current literatures in steroid-induced 'osteonecrosis' with chicken model.

INTRODUCTION

Many investigators have tried to induce osteonecrosis of the femoral head (ONFH) with steroid in various animal models but failure. In 1997, Cui and colleagues [1] successfully induced ONFH with a chicken model by injection of corticosteroids. In addition, Ficat [2] has postulated that elevated intramedullary pressure (IMP) might result in decrease arterial blood flow to the femoral head and initial the process of ONFH.

With continuum of the two-year results of this project, the 3rd year data added 38 chickens in both normal and experimental groups in order to perform age-match statistic analysis. A total of 89 chicken specimens was reassessed by a senior skeletal pathologist using a semi-quantitative interpretation (score 0, 1, 2) for various histologic findings in order to determine significant changes in the development of steroid-induced ONFH in chickens. Measurement of intramedullary pressure also was performed in selected experimental and control

animals. This report presents re-interpretation of histologic data and IMP results. Results of MRI have been described in the 2nd year report.

METHODS AND RESULTS

(1) Development of steroid-induced 'osteonecrosis' in chicken model

Phase I study (n=12)

Material and methods Twelve white Leghorn chickens (eight female, four male; age 25~27wk) were recruited. Nine experimental chickens received methylprednisolone with dose of 3mg/kg/week via intramuscular injection. All animals were divided into 6 groups and were sacrificed at week 0 (n=3; two female, one male; control, without steroid injection), 1 (n=1; 1M), 4 (n=2; 1F, 1M), 6 (n=1; 1M), 8 (n=1; 1F), 10 (n=3; 3F), and 12 (n=1; 1F), respectively, after steroid injection.

Results One male chicken (1/12, 8%) was dead due to infection at age of 33 weeks (six steroid injection) before the scheduling date for scarification. This animal was sacrificed and prepared for histology immediately. Results of histologic findings revealed fat cell proliferation in the femoral intertrochanteric area (3/3) of male experimental chickens as compared to none in male control animal. In female chickens, there was new bone formation in the femoral neck (3/6) and red blood cell pooling in the intertrochanter (4/6) as compared to none in the control group. The fat cell proliferation in the intertrochanter was not remarkable in females, however. The femoral necks of most specimens were easily broken due to unknown reasons.

Phase II study (n=23) Recruited more normal chickens for MRI study.

Phase III study (n=54)

Material and methods **(A)** Sixteen white Leghorn female chickens were recruited. All chickens did not receive methylprednisolone and acted as a control group. These chickens were divided into 2 main groups by their age of scarification as follows: (A-1): age ≦40wk, n=4; (A-2): 40~79wk, n=8; (A-3): ≧80wk, n=4. **(B)** A total of 38 white Leghorn female chickens were recruited. Six chickens (6/38, 16%) were dead during induction period before the scheduling time for scarification. These animals were not recruited for histologic analysis. Another three chickens were excluded due to technical failure during preparation for histologic specimens. Finally, 29 chickens were recruited and categorized into three groups by age at time of scarification as follows: (B-1): age ≦40wk, n=5; steroid, 9mg/kg/every other day for 66 times of injections; (B-2): 40~79wk, n=19; (B-2a) steroid, 3mg/kg/week ×12 times of injections, n=6; (B-2b) steroid, 3mg/kg/week ×19 times of injections, n=6; (B-2c) steroid, 3mg/kg/week ×40 times of injections, n=4; (B-2d) steroid, 9mg/kg/every other day ×130 times of injections, n=3; (C-3): ≧80wk, n=5; steroid, 9mg/kg/every other day ×160~187 times.

Results **(A)** In the control group, histological specimens revealed some degree of trabecular bone loss, bone marrow necrosis, new bone formation, and fat cell proliferation. However, there were no statistical significant differences among three age groups analyzed with various histologic parameters in three anatomic femoral sites (P>0.05, Fisher's Exact test). **(B)** In this age-match comparison (age <40 weeks), there were statistical significant differences of

new bone formation in the femoral neck (P=0.0476), fat cell proliferation in the femoral head (P=0.0079) and neck (P=0.0476) between normal and steroid-induced chickens (A1 vs. B1) (Fisher's Exact test). In the femoral neck, new bone formation was noted in 5/5 (100%) steroid-induced animals as compared to 2/4 (50%) control chickens. In the femoral head, there were 5/5 (100%) animals with fat cell proliferation as compared to none in control group. In the femoral neck, fat cell proliferation was noted in 5/5 ((100%) experimental group versus 3/4 (75%) control animals. In age-match comparison (age, 40~79wk), only new bone formation in the femoral head showed statistical significant differences between control and steroid-induced groups (P=0.0226) (A2 vs. B2, Fisher's Exact test). There were 19/19 (100%) chickens with steroid induction exhibited new bone formation in the femoral head as compared to 6/8 (75%) control animals. The dose and duration of steroid injection were not related to the differences of new bone formation in the femoral head (B2a vs A2; B2b vs. A2; B2c vs,. A2; all P values higher than 0.05 by Fisher's Exact test). In age-match comparison (age≧80wk), there were no statistical significant differences among three age groups analyzed with various histologic parameters in three anatomic femoral sites (P>0.05, Fisher's Exact test).

Summary In normal chickens, there were no obvious differences of various histologic findings in various femoral sites by age. For chickens young than 40 weeks, steroid injection of 9mg/kg/every other day for 130 times could induce significant new bone formation in the femoral neck and fat cell proliferation in the femoral head and neck. For the middle-age chickens, there was significant change in new bone formation in the femoral head after steroid

injection with dose of 3mg/kg/week for at least 12 times. For the ageing chickens, there was no significant histologic change at all even after high-dose and long duration of steroid injection.

(2) Measurement of intramedullary pressure

Material and methods Measurement of intramedullary pressure (IMP) was performed in 14 chickens (14 hips) with the method described by Ficat and Arlet [2]. There were four normal hips (left) obtained from those animals in A2 group (age, 40~79wk) and 10 steroid-induced chicken hips (6 left, 4 right) obtained from those chickens in B2 group (B2a in one, B2b in 2, B2c in 1, B2d in 6).

Results In normal middle-age chickens, their IMPs were 12~19 mmHg at the femoral head. In steroid-induced age-matched chickens, their IMPs were 25~82mmHg at the femoral head. The IMPs of animals in group B2b and B2c (51~82mmHg) depicted higher IMPs than that of the chickens in group B2a and B2d (25~44mmHg), except one B2d chicken got an IMP of 81mmHg.

Summary For the middle-aged chickens, elevation of IMP was observed in steroid-induced animals as compared to normal animals. IMP remained higher when steroid injected with 3mg/kg/week ×19 times or ×40 times rather than higher dose with longer duration.

DISCUSSION AND CONCLUSION

Cui et al preliminary reported steroid-induced ONFH in chicken model with a mortality rate up to 48% in 83 chickens. They found new bone formation in the femoral head in 4/12 chickens with 3mg/kg methylprednisolone IM

injection per week for 12 ~ 24 weeks. However, femoral head collapse was not apparent in any chickens, and lack of mention how many chickens had focal marrow necrosis.

In our study, the mortality rate of steroid-induced chickens was only 16% in 89 chickens. In the 3rd year data, our preliminary statistic results was the first report to show age-matched animals in order to obtain accurate data comparison among normal controls versus steroid-induced chickens. With use of the strict scientific methodology, our initial results should add new knowledge as follow: (1) normal chicken growth without significant differences of histologic changes in proximal femur by age. (2) For young group, steroid-induced chickens had significant histologic changes in new bone formation in the femoral neck and fat cell proliferation in the femoral head and neck. For the middle-age group, new bone formation in the femoral head was remarkable. By statistic, there was not apparent of steroid-induced chickens progressing to bone marrow necrosis or collapse of the femoral head, although sporadic cases might sensitive to steroid resulting in bone marrow necrosis. There was evidence of IMP elevation in the femoral head in steroid-induced chickens as compared to normal animals.

References

1. Cui Q, Wang G-J, Su C-C, Balian G. Lovastatin prevents steroid induced adipogenesis and osteonecrosis. Clin Orthop Rel Res 1997;344:8-19

2. Ficat RP, Arlet J. Necrosis of the femoral head. In: Hungerford DS, ed. Ischemia and necrosis of bone. Baltimore: Williams & Wilkins, 1980;11-52

貳、95年度計畫著作一覽表

Journal

序號	計畫產出名稱	產出型式	Impact factor	致謝對象
	無			

Patent

序號	計畫產出名稱
	無

Book

序號	計畫產出名稱
	無

Conference Paper

序號	計畫產出名稱
1	Chan WP, Kuo TF, Cheng CJ, Lin MF, Jiang CC. Dynamic Gadolinium-enhanced MR Imaging in Assessment of Osteonecrosis of the Femoral Head: Chicken Model. Vancouver , Canada . (International). The 106th Annual Meeting of ARRS, 2006; A132. 2006

Technical Report

序號	計畫產出名稱
	無

參、95年度計畫重要研究成果產出統計表

註：群體計畫(PPG)者，不論是否提出各子計畫資料，都必須提出總計畫整合之資料

(係指執行95年度計畫之所有研究產出結果)

科技論文篇數			技術		
	國　內	國　外	類　型	經　費	項　數
期　刊 論　文	0篇	0篇	技　術 輸　入	千元	項
研討會 論　文	0篇	1篇	技　術 輸　出	千元	項
專　著	0篇	0篇	技　術 擴　散	千元	項
專　利	0項	0項	技　術 報　告	千元	項
			技　術 創　新	千元	項

〔註〕：

期刊論文：指在學術性期刊上刊登之文章，其本文部份一般包含引言、方法、結果、及討論，並且一定有參考文獻部份，未在學術性期刊上刊登之文章（研究報告等）與博士或碩士論文，則不包括在內。

研討會論文：指參加學術性會議所發表之論文，且尚未在學術性期刊上發表者。

專　　著：為對某項學術進行專門性探討之純學術性作品。

技術報告：指從事某項技術之創新、設計及製程等研究發展活動所獲致的技術性報告且未公開發表者。

技術移轉：指技術由某個單位被另一個單位所擁有的過程。我國目前之技術轉移包括下列三項：一、技術輸入。二、技術輸出。三、技術擴散。

技術輸入：藉僑外投資、與外國技術合作、投資國外高科技事業等方式取得先進之技術引進國內者。

技術輸出：指直接供應國外買主具生產能力之應用技術、設計、顧問服務及專利等。我國技術輸出方包括整廠輸出、對外投資、對外技術合作及顧問服務等四種。

技術擴散：指政府引導式的技術移轉方式，即由財團法人、國營事業或政府研究機構將其開發之技術擴散至民間企業之一種單向移轉（政府移轉民間）。

技術創新：指研究執行中產生的技術，且有詳實技術資料文件者。

肆、95年度計畫重要研究成果

註：群體計畫(PPG)者，不論是否提出各子計畫資料，都必須提出總計畫整合之資料

計畫之新發現、新發明或對學術界、產業界具衝擊性(impact)之研究成果，請依性質勾選下列項目。

☑1. 研發或改良國人重要疾病及癌症的早期診斷方式及治療技術

☐2. 發展新的臨床治療方式

☐3. 發展新生物製劑、篩檢試劑及新藥品

☐4. 瞭解常見疾病及癌症之分子遺傳機轉

☐5. 瞭解抗癌藥劑對癌細胞之作用機制

☐6. 提供有效的疾病預防策略

☐7. 利用生物統計與生物資訊研究，推動台灣生技醫藥研究，促進生物技術與基因體醫學之發展

☐8. 醫療保健政策相關研究

☐9. 瞭解環境毒理機制及重金屬對人體健康的影響

☐10. 研發適合臨床使用的人造器官及生醫材料

☐11. 縮短復健流程並增加復健效果的醫療輔助方式或器材之研究應用

☐12. 改進現有醫療器材的功能或增加檢驗影像的解析能力

☐13. 其他重要疾病或醫藥衛生問題研究

一、 計畫之新發現、新發明或對學術界、產業界具衝擊性（impact）之研究成果，請敘述其執行情形。

目前建立股骨頭骨髓壞死(ONFH)模型的研究仍有不少限制，如沒有年齡配對的對照組作比較，或沒有利用統計方法做嚴謹分析。本研究首次提出以雞隻模式做年齡配對的方式作統計分析，以瞭解ONFH 病理過程之機轉，發現無法以此模型誘導至雞隻產生股骨塌陷或有意義骨髓壞死，僅個別雞隻產生骨髓壞死，因此類似人類 ONFH 模式迄今仍無法建立，釐清以往沒有統計分析的誤差。

二、 計畫對民眾具教育宣導之研究成果（此部份將為規劃對一般民眾教育或宣導研究成果之依據，請以淺顯易懂之文字簡述研究成果，內容以不超過 300 字為原則）

「股骨頭骨髓壞死」這名詞對民眾來說可能較陌生，它是骨折外髖關節最常見而且是難纏的病症，常發生於中年酗酒者或服用類固醇病人。發生的原因相當複雜，其中有研究指出可能是股骨頭的血管堵塞，造成骨細胞營養中斷而壞死，或是骨髓內血液滯留導致骨內壓增加而造成骨髓壞死。患者早期會覺得髖關節僵硬、疼痛，進而影響到活動功能。這是一種進行性的病變，最後導致股骨頭塌陷，需要做大手術置換髖關節。唯有早期發現早期治療才能減輕症狀，並可能預防往後的繼發性關節失能。

本研究採用類固醇藥物注射於實驗動物，我們採用來亨雞，是由於雞與人類同是由兩腿承載全身的重量，理論上可誘發「股骨頭骨髓壞死」，並以磁振造影(MRI)觀察其疾病發展之機轉，迄今僅發現骨髓

脂肪細胞增加及新生骨之形成，對類固醇誘發至骨頭塌陷之機轉仍有待突破。

三、 簡述年度計畫成果之討論與結論，如有技術移轉、技術推廣或業界合作，請概述情形及成效

本年度為全程計劃之第 3 年，目前有些數據(如脂肪數目量化分析)仍在分析中，因此尚無全程計畫成果之討論與結論，此部分將依規定時間 2007 年 2 月前完成統計。

四、 成效評估（技術面、經濟面、社會面、整合綜效）

技術面：第一、二年實驗已成功建立實驗雞之動態顯影 MRI (DCE-MRI) 的成像條件，並建立類固醇誘發股骨頭骨髓壞死(ONFH)之實驗雞模式。第三年更積極增加正常雞隻與誘發 ONFH 雞隻數目，並首先做以年齡配對為基礎的有效統計。

經濟面、社會面：本研究係基礎研究，以瞭解致病機轉為主，並未立刻可以影響到這兩個構面。

整合綜效：本實驗之結果將可能影響未來 ONFH 隻動物模式建立之方式。

五、 下年度工作構想及重點之妥適性

本研究年度為最後一年成果報告。

六、 檢討與展望

對第一、二年實驗已有超出預期的具體成果，如 DCE-MRI 的技術及 ONFH 雞模型之建立，並以誘發出 ONFH 前期之實驗雞隻，做出有效統計，初步結果已於去年美國放射線學會年會(ARRS)報告。第三年更擴大 ONFH 雞隻誘發，及組織切片之分類與重新判讀，並增加對照組年齡配對作有效設計，且克服了骨髓內壓測量之困難，降低雞隻飼養死亡率僅到 16%，對將來誘發實驗雞模型之技術將有具體貢獻。

伍、95年度計畫所培訓之研究人員

註：群體計畫(PPG)者，不論是否提出各子計畫資料，都必須提出總計畫整合之資料

種類				人數	備註
專任人員	1.	博士後研究人員	訓練中		
			已結訓		
	2.	碩士級研究人員	訓練中	1	本研究目前聘有專任碩士及研究助理1人
			已結訓		
	3.	學士級研究人員	訓練中		
			已結訓		
	4.	其他	訓練中		
			已結訓		
兼任人員	1.	博士班研究生	訓練中		
			已結訓		
	2.	碩士班研究生	訓練中		
			已結訓		
醫師			訓練中		
			已結訓		

特殊訓練課程（請於備註欄說明所訓練課程名稱）

陸、參與95年度計畫所有人力之職級分析

註：群體計畫(PPG)者，不論是否提出各子計畫資料，都必須提出總計畫整合之資料

職級	所含職級類別	參與人次
第一級	研究員、教授、主治醫師	2人
第二級	副研究員、副教授、總醫師、助教授	1人
第三級	助理研究員、講師、住院醫師	0人
第四級	研究助理、助教、實習醫師	1人
第五級	技術人員	1人
第六級	支援人員	1人
合計		6人

〔註〕：

第一級：研究員、教授、主治醫師、簡任技正，若非以上職稱則相當於博士滿三年、碩士滿六年、或學士滿九年之研究經驗者。

第二級：副研究員、副教授、助研究員、助教授、總醫師、薦任技正，若非以上職稱則相當於博士、碩士滿三年、學士滿六年以上之研究經驗者。

第三級：助理研究員、講師、住院醫師、技士，若非以上職稱則相當於碩士、或學士滿三年以上之研究經驗者。

第四級：研究助理、助教、實習醫師，若非以上職稱則相當於學士、或專科滿三年以上之研究經驗者。

第五級：指目前在研究人員之監督下從事與研究發展有關之技術性工作，且具備下列資格之一者屬之：具初（國）中、高中（職）、大專以上畢業者，或專科畢業目前從事研究發展，經驗未滿三年者。

第六級：指在研究發展執行部門參與研究發展有關之事務性及雜項工作者，如人事、會計、秘書、事務人員及維修、機電人員等。

柒、參與95年度計畫所有人力之學歷分析

註：群體計畫(PPG)者，不論是否提出各子計畫資料，都必須提出總計畫整合之資料

類別	學　歷　別	參與人次
1	博士	2 人
2	碩士	2 人
3	學士	0 人
4	專科	0 人
5	博士班研究生	1 人
6	碩士班研究生	0 人
7	其他	1 人
合計		6 人

捌、參與95年度計畫所有協同合作之研究室

註：群體計畫(PPG)者，不論是否提出各子計畫資料，都必須提出總計畫整合之資料

機構	研究室名稱	研究室負責人
無		

玖、九十五年度計畫執行情形

註：群體計畫(PPG)者，不論是否提出各子計畫資料，都必須提出總計畫整合之資料

一、請簡述原計畫書中，九十五年預計達成之研究內容

原計畫於第三年增加對照組及誘發 ONFH 雞隻以便做有效統計，並預期於年底進行組織分析及電腦軟體開發以便分析脂肪細胞數目。本研究目前進度比預期超前，如雞隻數目增加近 38 隻，全程實驗雞隻共 89 隻，係目前研究最大數目。

並已完成年齡配對統計、組織切片全部重新判讀及增加骨髓內壓測量。脂肪細胞數據正在分析中，將於全程總報告呈現。

二、請詳述九十五年度計畫執行情形，並評估是否已達到原預期目標（請註明達成率）

第三年增加對照組及誘發 ONFH 雞隻以便做有效統計。目前進度比預期超前，如雞隻數目增加近 38 隻，全程實驗雞隻共 89 隻，係目前研究最大數目。並已完成年齡配對統計、組織切片全部重新判讀及增加骨髓內壓測量。

在我們的研究過程中，從第三年的數據可以發現在 89 隻雞中以類固誘導的雞的死亡率只有 16%。我們的初步的統計結果是第一份顯示年齡與動物相配可以獲得準確的比較數據在對照和實驗組中。

由於使用嚴格的科學方法學，我們的最初結果應該增加新知識如下：

(1)股骨病理學的改變並沒有隨年紀而有明顯有意義的不同在正常雞的成長中。

(2)從年輕雞中發現，類固醇引起的雞在新骨頭在股骨頸裡的形成和在股骨頭和頸裡的脂肪細胞增生方面有顯著的病理變化。對中年雞來說，在股骨頭裡新骨頭的形成是驚人的。就統計學上來說，在類固醇誘導的雞隻中有不明顯的骨髓壞死或者股骨頭的倒塌的，雖然有少數的雞可能是對類固醇敏感而導致骨髓壞死。 在與正常的雞相比較類固醇誘導的雞裡，在股骨頭裡有 IMP 升高的證據。

拾、附錄

本研究計畫中之研究成果圖片及表格部份因涉及專利資料，而不宜彙編入冊或上網公告。

本計劃初步結果於去年美國放射線學會年會(ARRS)報告。

拾壹、本年度之著作抽印本或手稿

skeletal dysplasia related to thalidomide or aminopterin therapy during pregnancy will be presented. The pathophysiologic basis for the bone findings will be explored.
Format: A pictorial review of skeletal manifestations will be presented in a didactic format, using radiographic imaging supplemented, where appropriate, by CT and MR imaging.
Teaching Points: The increasing use of pharmaceuticals makes it incumbent upon the radiologist to be able to recognize iatrogenic skeletal disease. Understanding the pathophysiologic basis for the abnormalities will assist the radiologist in identifying the pertinent findings. Physician awareness of the risks of various drugs will stimulate the monitoring of the skeletal system for their adverse effects, allowing for timely intervention whenever possible.

E249. Osteonecrosis of the Femoral head: Initial Experience Using Dynamic Gadopentate Dimeglumine-enhanced MR Imaging

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Objective: To assess intramedullary hemodynamic changes relating to severity of osteonecrosis of the femoral head (ONFH) using dynamic contrast-enhanced MR imaging (DCE-MRI).
Materials and Methods: Twelve patients (14 symptomatic ONFH) who underwent DCE-MRI and had subsequent core decompression and biopsy of the femoral head were reviewed. DCE-MRI was obtained with use of T1-weighted (300/25) sequence on a coronal plane at 16-s acquisition time for each image for 5 minutes after bolus injection of 0.2 ml/kg of gadopentate dimeglumine. Another 13 normal volunteers (26 asymptomatic hips) were recruited as control. Severity of ONFH was graded from 0 (elevated intramedullary pressure only) to II (collapse) by MRI findings.
Results: In the femoral head, the peak (and rate) percentage of enhancement was 4.17±1.85 (rate, 3.49±1.86) for control hips, 3.74±3.05 (3.57±0.15) for stage 0 ($n = 3$ hips), 19.35±10.33 (12.10±6.87) for stage I ($n = 5$), and 46.56±25.40 (17.72±4.45) for stage II ($n = 6$) ONFH (Kruskal-Wallis test, $p < 0.001$). In the femoral neck, the peak (and rate) was 7.40±6.26 (7.79±8.28) for control hips, 6.95±6.45 (13.15±13.41) for stage 0, 12.62±4.81 (13.22±11.36) for stage I, and 73.67±11.91 (27.72±7.14) for stage II ONFH ($p < 0.001$). The peak (and rate) of the intertrochanteric areas was 7.23±4.56 (6.96±5.39) for control hips, 9.43±4.69 (12.01±7.74) for stage 0, 20.24±16.02 (11.82±5.76) for stage I, 41.81±21.31 (20.80±7.37) for stage II ONFH ($p < 0.001$). Control hips versus stage I and II ONFH were significant in various femoral sites (Mann-Whitney test, $p < 0.001$).
Conclusion: Increased intramedullary perfusion in various femoral sites was noted with progression of severity of ONFH as assessed by DCE-MRI.

E250. Dynamic Gadolinium-enhanced MR Imaging in Assessment of Osteonecrosis of the Femoral Head: Chicken Model

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Objective: To assess hemodynamic changes of various stages of osteonecrosis of the femoral head with use of dynamic contrast-enhanced MRI (DCE-MRI) in a chicken model.
Materials and Methods: Twenty-nine white Leghorn female chickens were recruited as experimental group. Each animal received methylprednisolone (3 mg/kg, IM) every other day. All chickens received DCE-MRI before steroid injection (baseline) and before scarification at week 0, 12, 19, 40, respectively, after steroid injection. DCE-MRI was performed by using T1-weighted imaging at 12-sec intervals for 7 minutes synchronous after intravenous bolus injection of gadopentetate dimeglumine. Histology was staged from I to III. Another 20 chickens without steroid injection were recruited as control group.
Results: In the femoral head, the peak percentage of enhancement in stage I ($n = 4$ chickens), II ($n = 13$) and III ($n = 12$) diseases was 84.6±14.3, 103.5±44.8, 84.4±27.8, respectively ($p = 0.47$). The peak of the femoral neck was 92.3±13.6 for stage I, 91.7±44.8 (II), 84.21±3.3 (III), respectively ($p = 0.56$). The peak of the intertrochanteric areas was 101.8±13.7 (stage I), 116.2±48.5 (II), 80.6±23.9 (III), respectively ($p = 0.03$). Pooling of RBC was remarkable in the intertrochanteric areas on histology. In control animals, the peak in three various femoral sites of three age groups (week 25, 30, 35) revealed no statistical significant ($p > 0.05$).
Conclusion: Our results supported Ficat's hypothesis that intramedullary stasis in the intertrochanteric areas can be a common pathway to initial the ischemic process of osteonecrosis of the femoral head, and DCE-MRI is feasible in detection of such hemodynamic changes in a chicken model.

E251. Advanced Imaging Features of Gout

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Objective: The purpose of this study is to define the imaging characteristics of gout on magnetic resonance imaging (MRI), computed tomography (CT) and 18F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) imaging.
Materials and Methods: Retrospective review was made of the MRI ($n = 17$), CT ($n = 6$) and FDG-PET ($n = 2$) studies in 14 patients with a documented diagnosis of gout. Twenty-one joints and two bursae were affected. There were 9 males and 5 females, with a mean age of 53 years (range = 24–84 years). Imaging studies were reviewed for the presence/location of tophi and osseous MR signal changes. Tophi were evaluated for size, signal characteristics and enhancement pattern with MRI, density on CT, and degree of uptake on PET imaging.
Results: Gouty involvement included the MTP joint ($n = 4$), midfoot ($n = 4$), knee ($n = 4$), lumbar spine ($n = 2$), thoracic spine ($n = 1$), SI joint ($n = 2$), hindfoot ($n = 1$), wrist ($n = 1$), IP joint of the finger ($n = 1$) and MCP joint ($n = 1$). Bursitis was identified in the prepatellar ($n = 1$) and olecranon ($n = 1$) bursae. MRI examinations demonstrated tophi in all cases. Longest dimension of individual or conglomeration of tophi averaged 4 cm (range = 0.9–16 cm). All but 4 tophi demonstrated signal intensity isointense to skeletal muscle on T1-weighted images: one was slightly hyperintense to muscle and three had mixed isointense/hypointense signal. All cases demonstrated intermediate signal within at least portions of the tophi on fluid-sensitive sequences; hypointense signal was also common, but varied according to the specific sequences obtained. All tophi demonstrated enhancement on gadolinium-enhanced MRIs; most were intense, peripheral and heterogeneous. All tophi imaged with CT were denser than skeletal muscle; two demonstrated distinct foci of calcification. The first patient undergoing FDG-PET imaging had moderate uptake in the lumbar spine, midfoot and MTP joints. The second patient had marked uptake in the thoracic and lumbar spine, and mild uptake in the SI joints.
Conclusion: Although gout most commonly involved the feet and knees, a multitude of joints were affected. Gouty tophi were isolated or multifocal, and ranged greatly in size. MRI and CT demonstrated characteristic imaging findings. Most tophi were isointense to muscle on T1-weighted sequences, isointense/hypointense on fluid-sensitive sequences, and enhanced intensely. All tophi were denser than skeletal muscle, with occasional calcification on CT. Uptake by gouty tophi on FDG-PET imaging was marked, moderate or mild.

E252. The Reverse Total Shoulder Prosthesis: Imaging Features and Complications

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Background: A new generation of total shoulder prosthesis, known as the "reverse shoulder prosthesis" (RSP), has been introduced into the United States as of April, 2004. The RSP has a novel design which reverses the usual ball and socket arrangement of the shoulder, placing a ball in the glenoid fossa and a flat surface in the position of the humeral head. In patients with advanced rotator cuff arthropathy, failed hemiarthroplasty with rotator cuff disease or superior subluxation of the humerus due