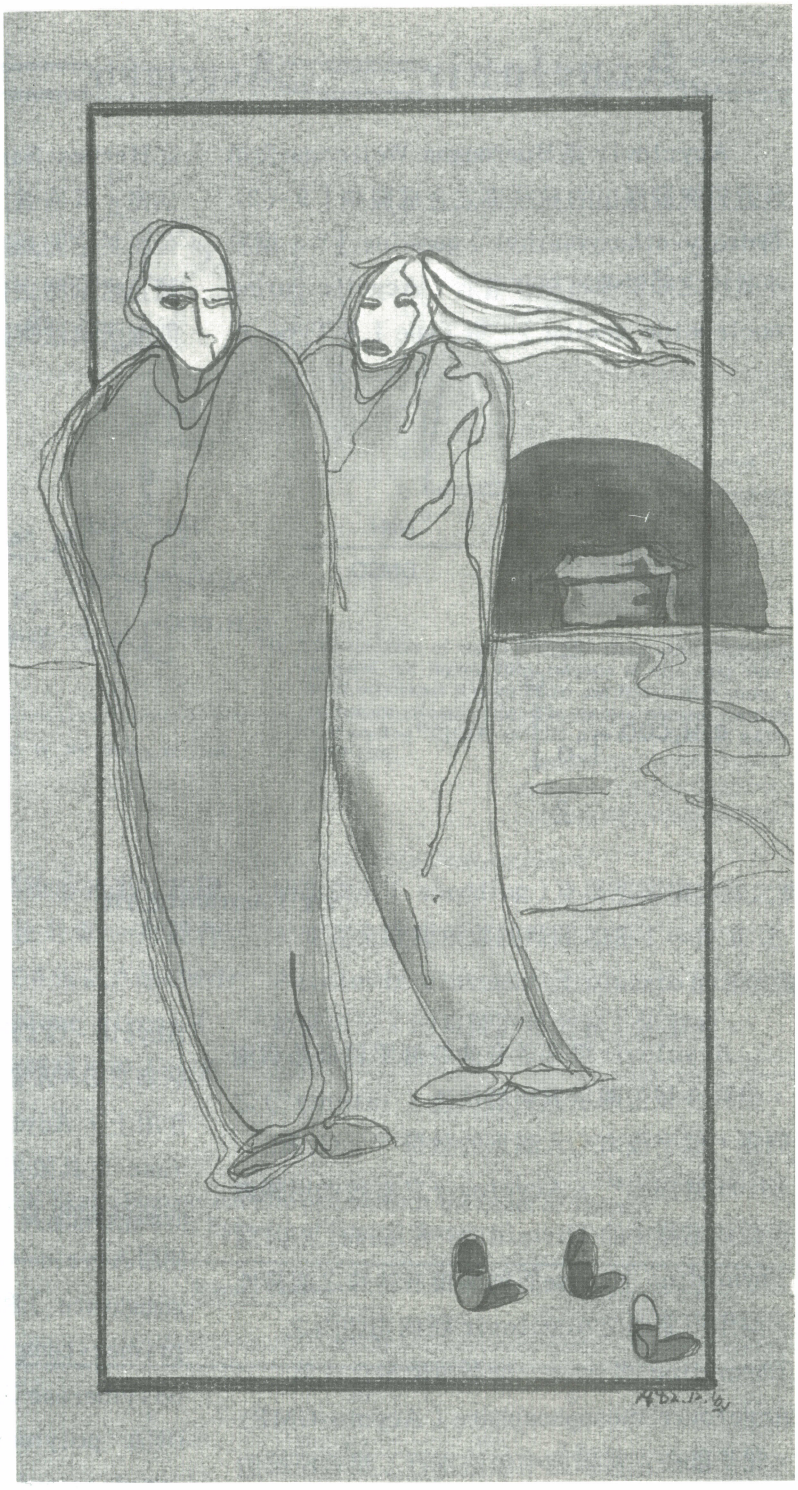
抗皰疹病毒的新藥



ACYCLOVIR

陳國棟教授校閱
蕭秋彬
張薰文　　執筆

Acyclovir Acyclovir Acyclovir

Acyclovir 爲Burroughs Wellcome公司最近研究發展出的抗病毒之合成製劑［9—(2-hydroxy-ethoxymethyl) guanine ］[1]，屬於非環狀之類似嘌呤核苷構造（Acyclic purine nucleoside analog），對Type Ⅰ及Type Ⅱ之Herpes Simplex病毒，Varicella zoster病毒，具有強力之抑制作用，值得我們重視的是在於它對病毒體有特殊之選擇性，因而對人體正常細胞之毒性作用極低，此爲一般抗病毒製劑所無法突破之優點。

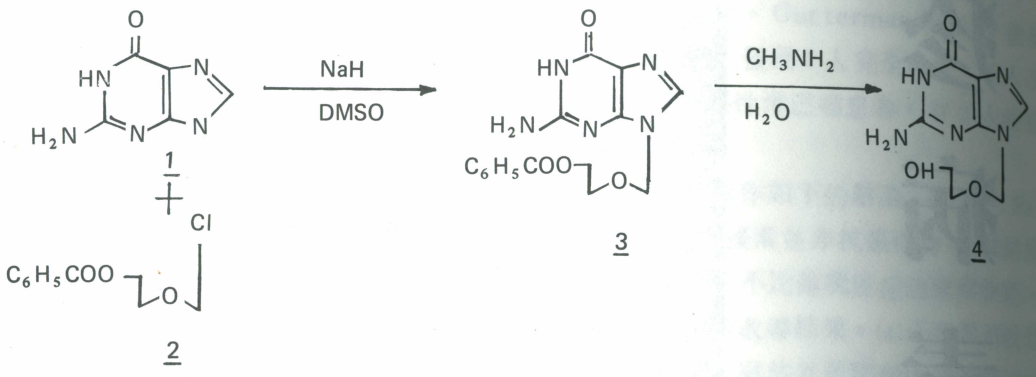


Fig 1 Acyclovir之合成

Acyclovir雖確能有效控制單純疱疹病毒，但許多報告顯示其對潛伏性（latency）之病毒，似乎沒有令人滿意的效果[2]。G. B. Elion 曾指出[3]，Acyclovir之有效作用關鍵是在病毒體中的Thymidine Kinase，亦因爲Thymidine Kinase而對病毒有特殊之選擇性。其作用原理是Acyclovir經病毒體內之Thymidine Kinase 激發而磷酸化成爲Acyclovir monophosphate（Acyclo-GMP），此步驟在正常細胞中無法進行；接著經細胞酶之作用使Acyclo-GMP 轉變爲Acyclovir triphosphate（Acyclo-GTP）；在接受Acyclovir 治療之疱疹細胞體內所存在的Acyclo-GTP 較未受感染之細胞體中之Acyclo-GTP多出40～100倍；另外在抑制病毒之DNA聚合酶（DNA polymerase)之作用上，Acylo-GTP較Cellular polymerase 更具效果；尤其在type Ⅰ及type Ⅱ之疱疹病毒的DNA聚合酶（DNA polymerase)使用Acyclo-GTP 爲酶作用物（Engyme substrate）和混淆Acyclo-GMP 到DNA的primer-template 方面，較一般細胞的polymerase之應用要多得多。另外病毒的DNA polymerase Acyclo-GMP-termin-ated template強力結合，所以不但可以成功地抑制病毒的繁衍，也可因爲它的特殊選擇性而使正常未受感染的細胞所受到Acyclovir的毒性作用，降低到病毒細胞所受的300～3000分之一。

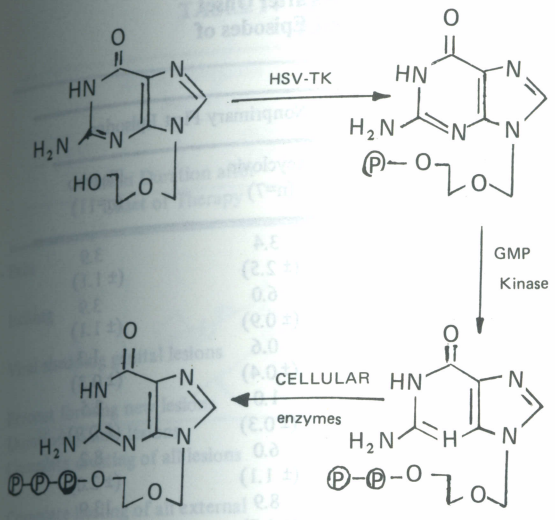


Fig. 2. Enzymatic conversion of acyclovir to its mono-, di-, and triphosphate forms.

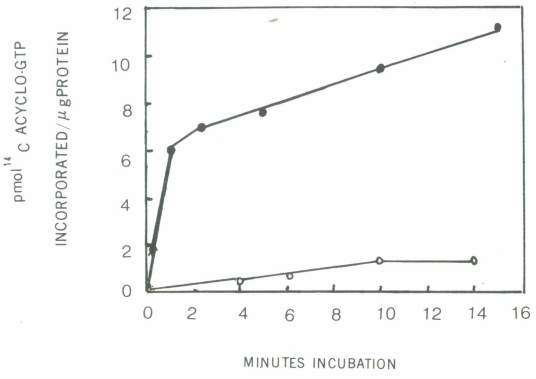


Fig. 3. Incorporation of acyclo-[^{14}C]GMP (from acyclo-GTP) into an activated calf thymus DNA template in vitro using Vero cell DAN polymerase α (open circle) and HSV-1 (H29 strain) DNA polymerase (closed circle). The reaction mixtures contained 24 = M acyclo-[^{14}C]GTP, and 100 μ M each of dCTP, dATP, and dTTP [10].

曾有一篇臨床報告顯示其治療效果[4]；於陰部疱疹病毒感染之患者，69位是第一次發作型，111位爲反覆發作型，在5％之Acyclovir ointment治療及以polyethylene glycol（PEG）爲安慰劑軟膏治療的兩組比較下；在病毒溢出（sheddiag）及局部痛癢症狀之消除，或完全痊癒所須的時間如表Ⅰ～表Ⅱ之Acyclovir ointment及placebo的相互對照結果所示，均有統計學意義上的療效。

TABLE I Viral Type, Duration and Size of Lesions at the Onset of Therapy in Patient with First Episodes of Genital Herpes

	Primary Disease		Nonprimary Disease	
	Acyclovir (n=28)	Placebo (n=23)	Acyclovir (n=7)	Placebo (n=11)
HSV 2 isolated	23	20	6	11
HSV-1 isolated	5	3	1	0
Mean duration (days) of lesions prior to onset of therapy	4.3	4.7	3.5	2.8
Mean no. lesions at onset of therapy	22.7 (± 12.5)	21 (± 10.2)	17.8 (± 10.8)	9.6 (± 12.3)
Mean lesion area (mm^2) at onset of therapy	478 (± 192)	615 (± 253)	199 (± 92)	83 (± 32)

( )=S.D.

TABLE II Duration of Symptoms and Signs of Genital Herpes after Onset of Topical Acyclovir Therapy in Patients with First Episodes of genital Herpes

Mean Duration (days) after Onset of Therapy	Primary First Episodes		Nonprimary First Episodes	
	Acyclovir (n-28)	Placebo (n=23)	Acyclovir (n=7)	Placebo (n=11)
Itching	3.6 (± 0.8)	8.0 (± 1.5)	3.4 (± 2.5)	3.9 (± 1.1)
Pain	5.2 (± 0.6)*	7.0 (± 0.7)	6.0 (± 0.9)	3.9 (± 1.1)
Dysuria	4.4 (± 6.1)	5.0 (± 0.9)	0.6 (± 0.4)	1.3 (± 0.3)
Viral shedding from lesions	2.3 (± 0.4)‡	5.6 (± 0.8)	1.0 (± 0.3)	2.5 (± 0.9)
Time to crusting of lesions	8.5 (± 0.9)*	12.9 (± 1.3)	6.0 (± 1.1)	8.2 (± 2.0)
Duration of lesions	11.2 (± 1.3)*	15.8 (± 1.4)	8.9 (± 1.7)	13.9 (± 3.5)

( ) = S.E.M.
* $p < 0.05$ Mantel Cox statistic.
† $p < 0.001$ Mantel Cox statistic.
‡ H 0.001 Mantel Cox statistic.

TABLE III Epidemiologic, Clinical, and Virologic Characteristics of Patients with Recurrent Genital Herpes

	Acyclovir-Treated (n=51)	Placebo-Treated (n=60)
Mean age	31.6	29.9
Percent caucasian	96	92
Male	31	35
No. HSV-2 isolated	51	60
Mean no. months prior genital herpes	47 (± 47)	37 (± 36)
Mean no. prior episodes genital herpes	24 (± 21)	21 (± 22)
Mean no. days since last episode	63 (± 50)	49 (± 60)
Stage of lesions at onset of therapy:		
Vesicular	76%	67%
Pustular	22%	25%
Ulcerative	4%	8%
Mean no. lesions at onset of therapy	7.6	6.0
Mean lesion area at enrollment	64.5 (± 17.7)	50.6 (± 13.6)
Mean titer of HSV isolated frp, lesions at enrollment	$10^{3.3}$ (n=26)	$10^{3.6}$ (n=27)

( )=S.D.

而 111 位反覆發作型，如表 III 及表 IV之 Acyclovir 治療及安慰劑治療之比較所示，雖然可減短在病區病毒消失之時間，但不管在男或女，對其局部症狀並沒甚麼療效，故局部治療對第一次感染後之再發或反覆感染之陰部疱疹效果不良，故是否該考慮採用口服或靜脈注射途徑來治療？在另一篇報告[5]則顯示口服 Acyclovir 在第一次感染及復發感染之治療，均有不錯的效果，在統計上有 29 位第一次發作，61 位反覆發作，用雙盲試驗，實驗組服用 200mg acyclovir，一天 5 次，計 5 天其對照組則服用安慰劑（placebo），結果顯示出不管在第一次發作型或反覆發作型均能獲致統計學上有意義的效果。如下列數表（表V～表VIII）

TABLE IV Mean Duration (Days) of Signs and Symptoms of Disease in Patients with Recurrent Genital Herpes

Mean Duration after Onset of Therapy	Males		Females	
	Acyclovir-Treated (n=31)	Placebo-Treated (n=35)	Acyclovir-Treated (n=20)	Placebo-Treated (n=25)
Pain	2.2 (± 0.4)*	3.2 (± 0.7)	1.6 (± 0.4)	1.8 (± 0.4)
Itching	2.0 (± 0.4)	2.0 (± 0.5)	2.3 (± 0.8)	1.9 (± 0.5)
Viral shedding genital lesions	1.0 (± 0.2)†	2.2 (± 0.4)	0.4 (± 0.2)	1.1 (± 0.3)
Percent forming new lesions	39%	46%	40%	30%
Duration of new lesions	3.3	4.1	4.0	3.7
Complete crusting of all lesions	3.5 (± 0.4)	5.0 (± 0.9)	4.6 (± 0.6)	4.3 (± 0.5)
Complete healing of all external lesions	7.6 (± 0.6)	9.7 (± 0.8)	6.6 (± 0.7)	5.6 (± 1.1)

* $p < 0.05$ Mantel Cox analysis.
† $p < 0.01$ Mantel Cox analysis.

TABLE V Assessment of Effcacy Relative to Severity at Presentation of Recurrent Genital Herpes (Men only)

	Severity Score			
	≤6		>6	
	Acyclovir (n=6)	Placebo (n=13)	Acyclovir (n=9)	Plasebo (n=12)
Mean score	5.0	4.9	9.1	7.8
Viral shedding (days)*	0.8	2.1	0.9	4.3
Healing time (days)*	4.7	7.5	5.2	9.0
Pain resolution (days)*	0.7	1.8	2.4	3.8

* Mean value.

TABLE VI Effect of Oral acyclovir on Initial Genital Herpes (Men and Woemn)

	Median Value (days)		
	Acyclovir (n=13)	Placebo (n=11)	One-tailed p Value
Duration of viral shedding	1.0	8.0	< 0.001
Time to crusting	3.5	9.0	< 0.01
Time to compiete healing	5.5	11.0	< 0.01
Duration of pain	3.5	4.5	< 0.05
Duration of all symptoms	3.5	4.5	< 0.05
Cessation of new lesions (no. with lesions)	0.0* (0)	2.0* (5)	< 0.05

* Mean value (days).

TABLE VIII Effect of Oral Acyclovir on Recurrent Genital Herpes (Men only)

	Median Value (Days)		
	Acyclovir (n=15)	Placebo (n=25)	One-Tailed p Value
Duration of viral shedding	0.5	2.5	< 0.001
Time to crusting	3.0	4.0	< 0.01
Time to complete healing	5.0	7.0	< 0.001
Duration of pain	2.0	2.5	NS (0.13)
Duration of all symptoms	2.0	2.5	NS (0.17)
Cessation of new lesions (no. with lesions)	0.0* (0)	1.3* (6)	< 0.05

* Mean value (days)
NS = not significant.

TABLE VII Patient Characteristics at Presentation

	Initial Genital Herpes		Recurrent Genital Herpes	
	Acyclovir (n=15)	Placebo (n=14)	Acyclovir (n=28)	Placebo (n=33)
No. virologically confirmed	14	11	20	29
No. men	6	7	15	25
No. women	8	4	5	4
Age (years)*	26.4	23.4	30.4	29.9
Duration lesions (days)*	2.9	2.5	0.9	1.1
Extent/severity score*	13.4	3.0	7.9	6.6
No. with vesicles	4	6	17	24
No. with pain	13	11	17	26

* Mean value.

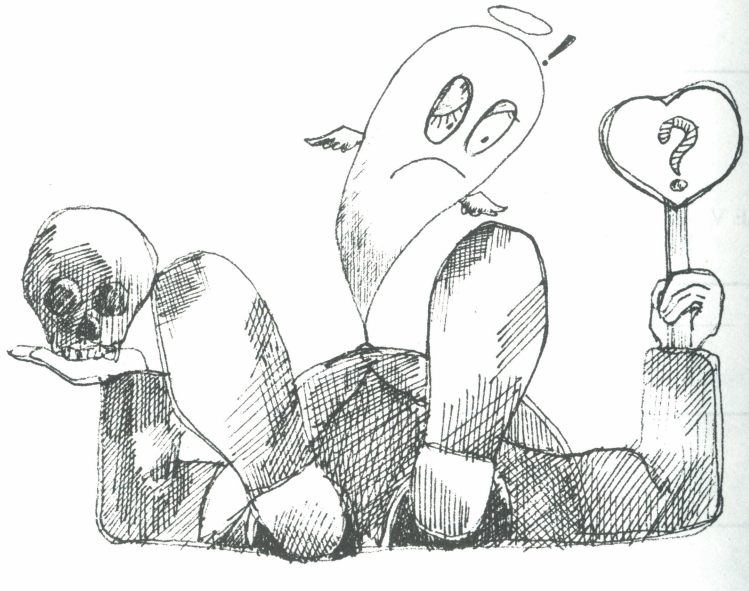
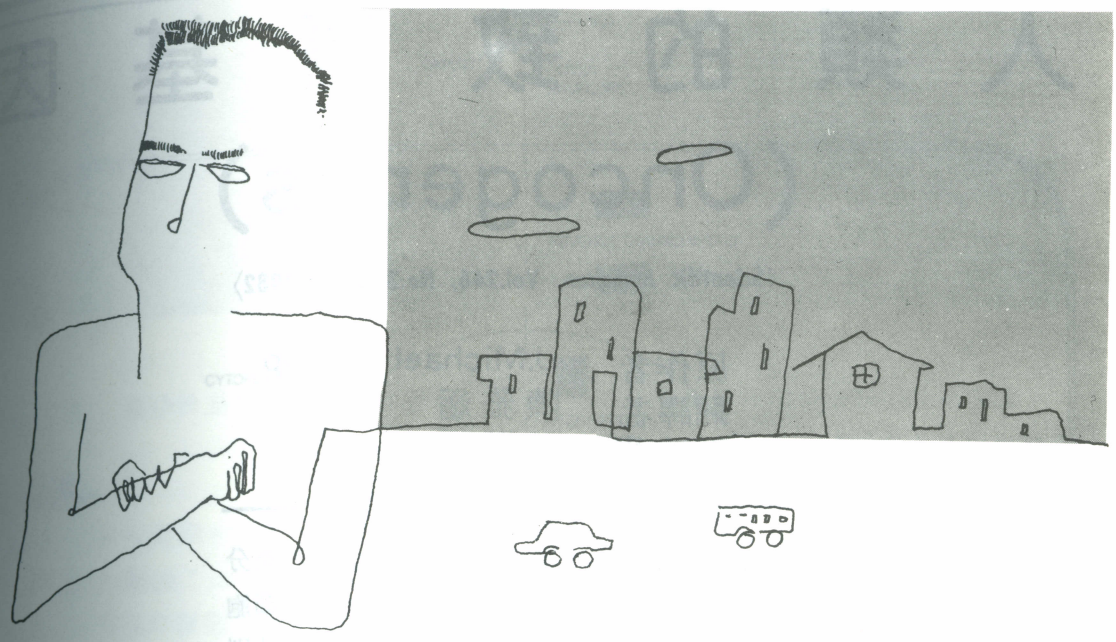


TABLE IX MAIN DIFFERENCES BETWEEN PATIENTS TREATED WITH ACYCLOVIR AND PLACEBO

	Primary patients			Female patients			All patients		
	Acyclovir (n=12)	Placebo (n=8)	p	Acyclovir (n=12)	Placebo (n=12)	p	Acyclovir (n=15)	Placebo (n=15)	p
Viral shedding time (all lesions)	2.0	8.8	<0.001	2.0	7.5	<0.001	2.0	8.5	<0.001
Healing time (all lesions)	9.0	15.0	<0.05	7.0	12.5	<0.05	7.0	14.0	<0.001
Duration of new lesion formation	0.0	2.0	<0.01	0.0	1.5	<0.05	0.0	2.0	<0.05
Duration of vesicles	2.5	5.0	NS	2.5	4.5	NS	3.0	5.0	NS
Duration pain	3.5	5.0	NS	4.0	4.0	NS	4.0	4.0	<0.05
Duration all symptoms	6.3	8.8	NS	6.8	7.3	NS	6.5	8.5	

Results are given as median time in days.



至於靜脈注射Acyclovir治療陰部疱疹其報告不多，且只限於第一次感染發作之病人，Mindet et al[6] 對30位初患嚴重陰部疱疹患者進行靜脈內插管慢性給藥之雙盲試驗，（即每8小時給與75mg／kg的Acyclovir或安慰劑manmitol）其結果亦出現不錯的效果，且亦無嚴重的副作用，如表 IX .

陰部疱疹在英、美已成爲相當受到重視而且其擾人的問題一直在增加。據英國的統計，這四年來因性接觸傳染疾病來求診病人，於19799576病例中，陰部疱疹佔42％[7]，其嚴重性可想而知，故而有" God punishment "之稱。以陰部疱疹之臨床治療報告來介紹Acyclovir；一方面借此說明今日醫藥進步一日千里，另一方面回想當年penicillin治療淋菌感染的威風，而今日抗藥性菌體漸日增多，醫藥之進步是否能及得上大自然之演變？今日Acyclovir的突破，抗Acyclovir之疱疹病毒亦漸有人報告[8]，醫藥之進步實在無法抵抗得了" God punishment "，所以要防止疱疹病毒（尤其是陰部疱疹）感染最好仍是預防重於治療，潔身自愛重於事後之補救。

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