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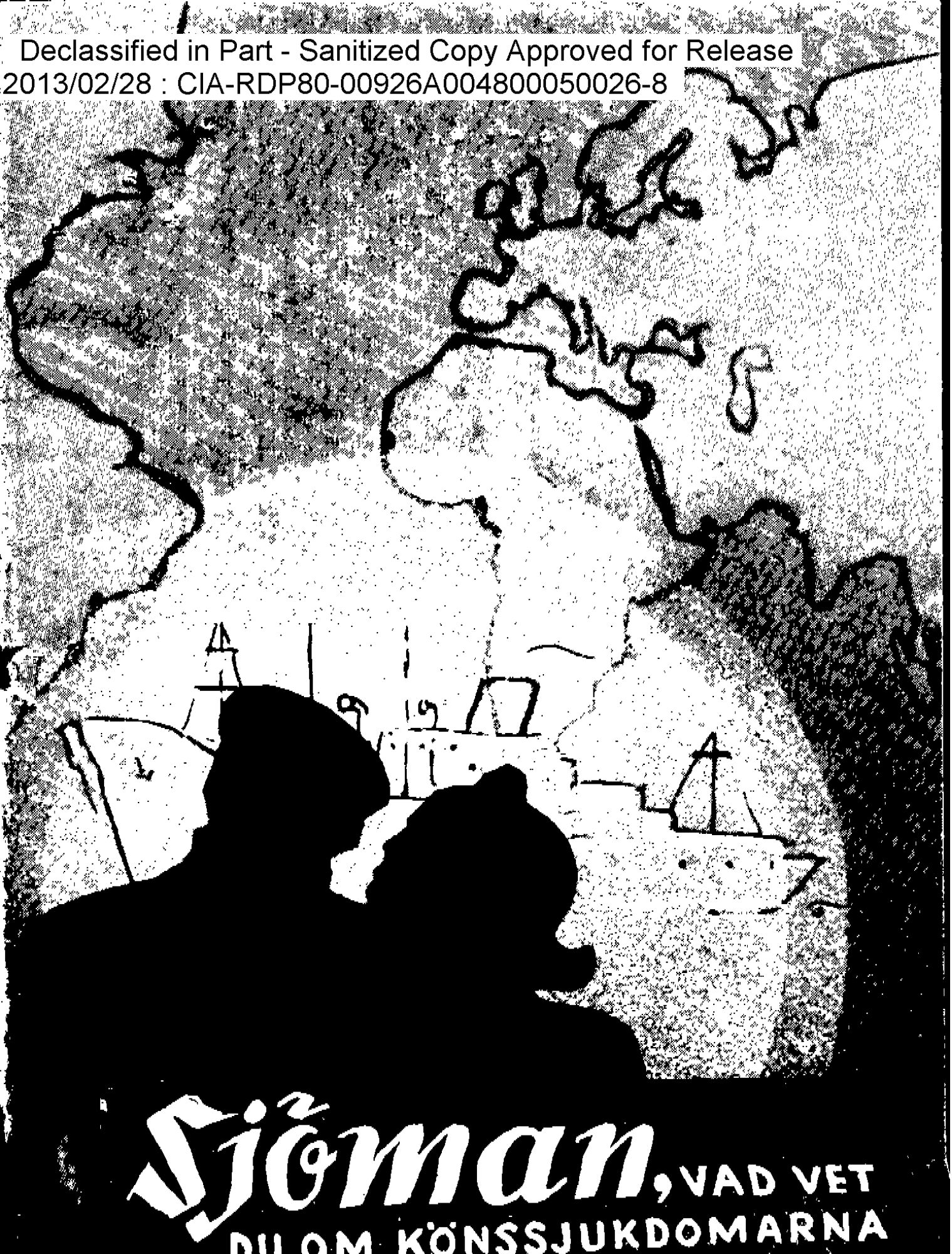

Sjöman, VAD VET DU OM KÖNSSJUKDOMARNA

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Sjöman,

Sailors / Seamen

vad vet du om könssjukdomar ?

What do you know about V. D. ?

FÖRENINGEN FÖR KÖNSSJUKDOMARNAS BEKÄMPANDE r.f.

Helsingfors, 1947
Kauppalehti Oy:s Boktryckeri

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FÖRORD.

Eder, sjömän, havets raska gossar, tillängas denna skrift. Som ni vet är sjömannen borta i främmande hamnstäder ofta i fara att utsättas för venerisk smitta långt mer än de, vilka leva sitt liv i hemmets och familjens skyddande atmosfär. För er är det därför av största vikt att känna till dessa sjukdomar, deras symptom och behandling, och framför allt att veta, hur man skall undvika dem. Mången äldre sjöman har kanske i skrytsamma ordalag berättat för de unga "första resans gossarna" om sina bravader och sjukdomar. — Hade det icke varit förståndigare att i stället giva dem några goda råd och en faderlig varning?

Läsen nu alla, både äldre och yngre, denna lilla bok och lägg på minnet de råd ni finna goda.

Finlands Redareförening r.f. och Finlands Maskinmästarförbund r.f. hava givit sitt stöd åt Föreningen för Könssjukdomarnas Bekämpande r.f. vid tryckningen av denna skrift.

Helsingfors den 22 november 1946.

FÖRENINGEN FÖR KÖNSSJUKDOMARNAS BEKÄMPANDE.

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SMITTOFARAN.

Könssjukdomarna äro sedan gammalt spridda runt jordklotet och ha nu efter kriget yttermera tilltagit i oroväckande grad. I Finland konstaterades år 1945 över 28.000 nya fall av könssjukdomar. Huru mycket skall det då ej finnas av dem annorstädes i världen? Vad tror ni t.ex. om den hamnstad där bortom haven, dit eder båt kanske just som bäst är på väg? Här vore kanske plats för eftertanke. Ja, man borde förstås vara litet försiktigare, medger ni. — Men hur går det nu vanligen till? Jo, kommen till staden efter den långa sjöresan viker ni in på en krog och tar er ett glas eller fler. Till ert sällskap sällar sig kanske ett par flickor och med dessa tömmas återigen glasen för att befästa den nya vänskapen. Så fortsätter man, och efter en rundtur i staden slutar det hela med en natt hos flickorna. I början, när ni var nyktrare, märkte ni tydligt, huru härjade, smutsiga och illaluktande dessa flickor i själva verket var. Men alkoholen, som försvagar förståndet och sinnena, fick dem att framstå som frestande blommor. Ni märkte kanske inte, att de sminkade läpparnas kärlekslöften voro utslitna fraser, och att rösten vart honungslenare alltefter omfånget hos er plånbok?

I större hamnstäder hämtas till fartyget genom speciella agenter adresskort över bordeller, som stå under s.k. läkarkontroll. Dessa bordeller äro vanligtvis belägna nära hamnen, med ingång från gatan. Musik, sång och dans locka de nyfikna att sticka sig in. — Och vari består nu den mycket omreklamerade läkarkontrollen? Kanske undersökas flickorna en gång i veckan, men ingalunda var gång en klient avlägsnat sig. Efter den senaste läkarbesiktningen ha flickorna måhända redan upprepade gånger varit i tillfälle att skaffa sig nya könssjukdomar, vilka de sedan lämna som minne åt sjömännen. Aldrig bör man invagga sig i den tron, att en dylik "kontroll" skulle eliminera smittofaran. Det har mången lättrogen person själv fått ångra.

SMITTOFARANS BEKÄMPANDE.

Hur skall man då skydda sig för smitta? Det säkraste sättet är naturligtvis att slå dövörat till för alla frestelser och helt enkelt gå förbi både krogar och bordeller. I de stora städerna finnas nog bättre och mera bestående sevärdheter. Det erfordras bara viljestyrka och förmåga att behärska sig. Återhållsamhet är aldrig skadligt för hälsan, varken för kropp eller själ, fastän man ofta för att försvara sin egen svaghet vill inbilla sig motsatsen. I de allra flesta fall medför emellertid en prostituerad eller lättfångad flicka fara för smitta.

Om ni trots allt idkat könsumgänge med en dylik flicka, kan ni dock själv ännu göra en hel del för att förebygga sjukdomen. Det gäller i så fall att handla

snabbt. Men även om flera timmar skulle ha förgått efter könsumgänget, bör man dock icke försumma att ännu försöka en prohibitiv (förhindrande) behandling.

Det hade givetvis varit bra om könsdelarna redan före könsumgänget blivit besmorda med en för detta ändamål avsedd skyddssalva. Efter könsumgänget är det bäst att genast urinera. Därefter rengöres urinröret. Om till förfogande finnes en stark, 10—20 % protargollösning, räcker det att i denna lösning doppa en med vadd omlindad tändsticka, vilken sedan införes en eller högst 2 centimeter in i urinrörsmynningen och kvarhålles där 2—3 minuter. Detsamma kan upprepas med en ny sticka. Med samma lösning rengöres även förhudens insida och trakten kring urinrörsmynningen. Det vore alltså bra om varje sjöman vid sådana tillfällen hade i sin västficka en liten flaska med 10—20 % protargollösning eller 5 % albarginlösning och litet vadd.

Om man endast har att tillgå en svag (½—2 %) protargollösning, kan man använda denna till insprutning i urinröret på samma sätt som vid behandling av dröppel, men då endast en fjärdedels spruta.

Efter urinrörets rengöring insmörjas könsdelarna (även innanför förhuden) omsorgsfullt med skyddssalvan.

En åtgärd, som även under de mest primitiva förhållanden kan genomföras, är vanlig enkel rengöring med tvål och vatten. Könsdelarna och huden däromkring intvålas grundligt och tvättas noggrant, dock bör man undvika att irritera huden.

Ett ganska gott medel mot smitta är preservativet eller den s.k. kordongen. Den skyddar dock icke alla för smittan utsatta områden, och dessutom förefinnes faran,

att preservativet går sönder. Säkrast är att genomföra den redan tidigare nämnda förebyggande behandlingen, även om preservativet förblev helt, ty den möjligheten finnes, att vid preservativets avlägsnande någon enstaka bakterie trots allt lyckats inträngа i könsdelarna.

Ju tidigare skyddsbehandlingen göres, desto säkrare är dess verkan. Om ni varit berusad och glömt alla försiktighetsåtgärder, gör vad ni kan ännu dagen därpå, ty ibland kan även en försenad behandling ännu vara till nytta.

KÖNSSJUKDOMAR.

Vi ha här nyss berört smittofaran vid könssjukdomar och dessas förebyggande. Om det trots allt skulle hända er en malör, är det bra för er att veta, vilka och hurudana de veneriska sjukdomarna äro.

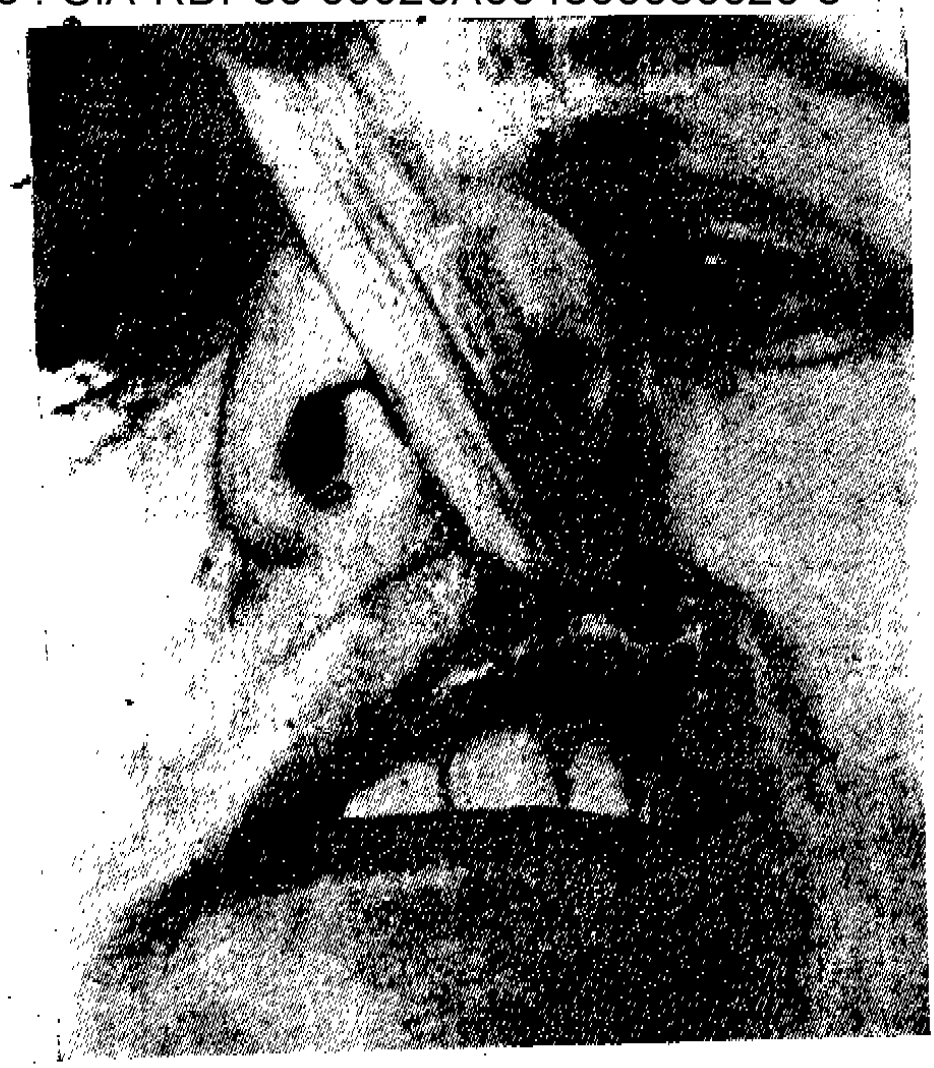
Det finnes 4 olika slag av könssjukdomar. (Man kan ibland ha två eller flere av dessa sjukdomar samtidigt utan att de ändra sin karaktär.)

Syfilis
Dröppel eller gonorrhoea
Mjuk schanker eller ulcus molle
Negerschanker eller lymphogranuloma inguinale.

Syfilis.

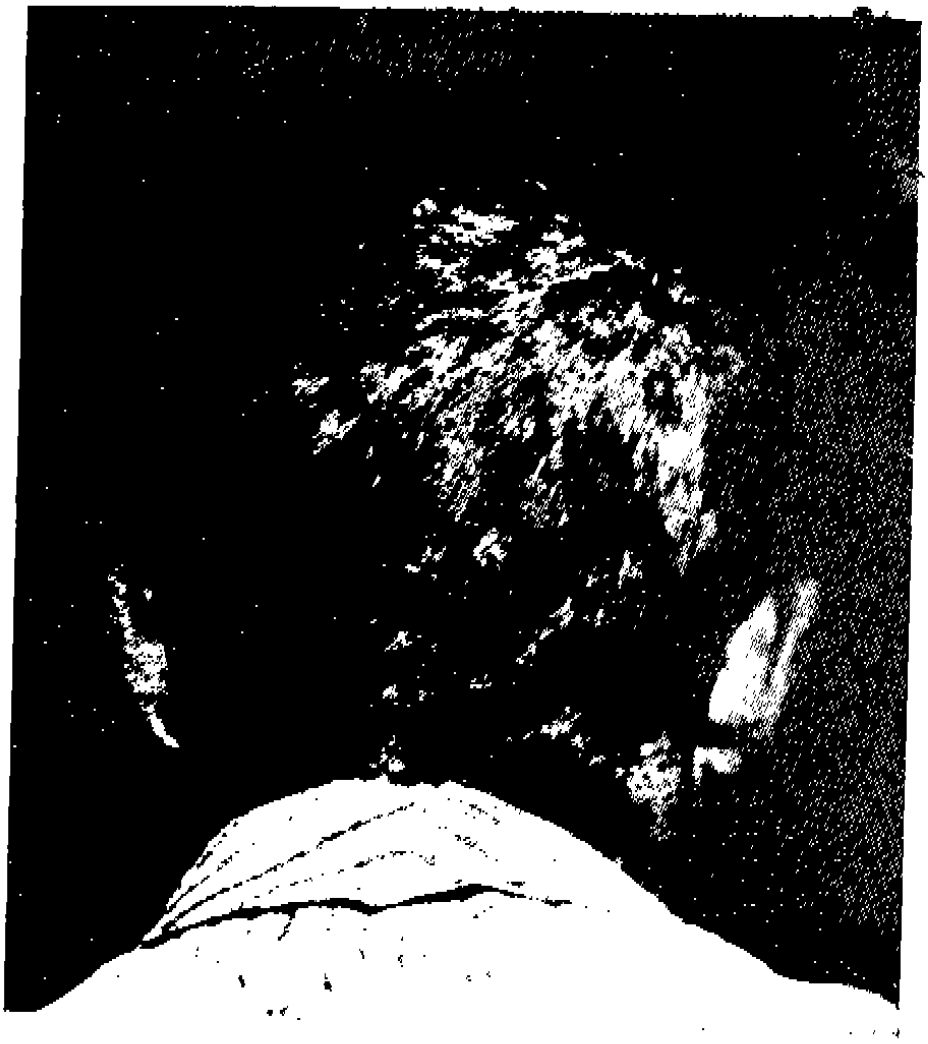
Före kriget förekom det i vårt land ca. 1.000 nya fall av syfilis per år. Enbart år 1945 konstaterades färsk syfilis hos 5.381 personer.

Denna sjukdom förorsakas av en fin, trådliknande mikrob, *spirochaeta pallida*. Genom frisk hud och slem-



Det första syfilis-såret (Primärstadium).

hinna har denna sannolikt icke kraft att tränga in, men om man har en den allra minsta skråma, kan mikroben tränga sig in i kroppen och framkalla syfilis. Spirochaeta pallida dör i 40 graders värme, och för torka är den mycket ömtålig. Däremot trivs den utmärkt i rumstemperatur och fuktighet och hålles så vid liv långa tider. Därför kan man också stundom erhålla sjukdomen genom förmedling av besudlade föremål. I regel överföres sjukdomen från en person till en annan antingen genom könsumgänge, eller genom kyssar.



Håravfall i fläckar förorsakad av syfilis i andra stadiet.

Efter en tid av ungefär tre veckor uppstår på det besmittade stället först ett sår. Det kan likna ett obetydligt skavsår och ömmar vanligen icke. Dess rand brukar kännas något hård. Såret innehåller ofta rikligt med spirocheter. Sjukdomen sprider sig härifrån hastigt vidare. Såret läkes visserligen av sig självt, men sjukdomen tilltager och sprider sig till andra ställen i kroppen. De närmast såret befintliga lymfkörtlarna kännas redan tidigt något hårda och svullna, men ömma vanligen föga.

Utslag under det andra stadiet av syfilis.

Några veckor senare uppstå på huden talrika bleka (ibland rätt otydliga), brunröda fläckar, eller i andra fall små papulösa (eller finneliknande) upphöjningar, vilka icke klia eller fjälla av sig. Detta är ett tecken på att sjukdomen inträtt i sitt andra stadium. Genom det s.k. Wasserman-provet kan detta konstateras i blodet. Utslaget försvinner av sig självt, och det händer ibland, att patienten icke ens märkt det. Efter denna första utslagsperiod uppkomma de mest olikartade utslag. Ibland händer det att håret lossnar, så att huvudsvålen ter sig som en maläten päls.

Samtidigt kan patienten även lida av allmän symptom, såsom irriterande huvudvärk, aptitlöshet, otålighet o.s.v. Rösten blir ofta hes, halsen känns sjuk, och patienten tror sig lida av angina.

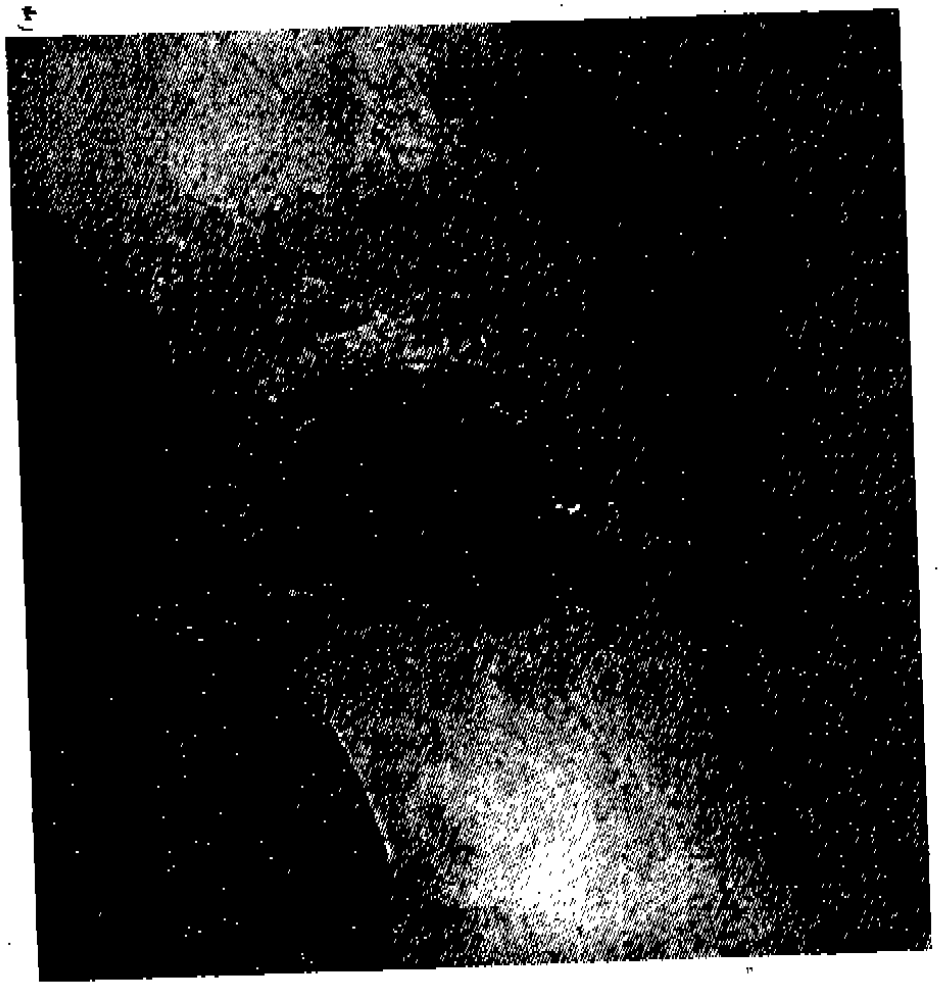
Symptomen i det andra stadiet försvinna efter hand. De kunna också vara så svaga, att patienten icke alltid lägger någon större vikt vid dem. I synnerhet kan så vara fallet, om en tid förflutit sedan könsumgänget, och smittofaran redan råkat i glömska. I sin okunnighet om det rätta sakförhållandet tillmäter patienten sin krämpa icke någon större betydelse. Eventuellt tänker han kanske minst av allt på en venerisk åkomma. Så fortsätter syfilis i lugn och ro sin förstörelse.

Följer så en skenbart sjukdomsfri period, vars längd kan vara några månader, ett år eller ett tiotal år.

I det s.k. tredje stadiet kan sjukdomen placera sig i vilken del av kroppen som helst. Vanligen uppkomma svårläkta sår. Sjukdomen kan skada både ben- och broskvävnader, lever och njurar samt förorsaka svåra fel i hjärtat och blodkärlssystemet. Ofta förkortar den livslängden betydligt.

Ryggmärgslidanden och förlamning med tyåtföljande invaliditet kan bliva följden av syfilis. Det händer icke sällan, att patienten får tillbringa återstoden av sina levnadsår på ett sinnessjukhus. Under åren 1939—44 ha enbart på de finska sinnessjukhusen behandlats 2.002 fall av sjukdomar i nervsystemet som förorsakats av gammal syfilis.

För att undvika dessa svåra recidiv och följdtillstånd måste behandlingen av syfilis ske på ett så tidigt stadium som möjligt. I behandlingen ingår salvarsan- och vismut-



Sår på benet i det tredje stadiet av syfilis.

insprutningar, vilka hos oss numera givas i serier om 10 injektioner. Emellan behandlingsserierna är det c:a 4—6 veckors viloperiod. För att resultatet av behandlingen skall lyckas, är det absolut nödvändigt, att läkarens föreskrifter med allra största noggrannhet efterföljas. Om sjukdomen behandlas på relativt tidigt stadium och behandlingen fullföljes omsorgsfullt, kan sjukdomen helt botas. Under senare stadier kan genom behandling ernås, om ock ej alltid en fullständig läkning, så dock en avsevärd förbättring.

En botad syfilis medför ingen immunitet. Den skyddar m.a.o. icke mot ny smitta.

Dröppel eller gonorrhoea.

Enligt statistiken förekom i vårt land före kriget c:a 8.000 fall av dröppel årligen. För år 1945 steg siffran till c:a 23.000. Sjukdomen framkallas av en bakterie, den s.k. gonokokken. På fullvuxna smittar sjukdomen knappast på annat sätt än genom könsumgänge.

Samma person kan insjukna i dröppel flera gånger, ty immunitet förekommer icke.

Dröppelns inkubationstid varierar mellan 3—10 dygn, varefter en (i början klar, senare varig) flytning från urinröret blir synlig, åtföljd av sveda vid urinering. Dröppeln förorsakar nämligen en katarr i urinröret.

Om sjukdomen icke i tid behandlas, kan den sprida sig och förorsaka en blåskatarr med ofta påkommande urinträngningar. Sjukdomen kan även sprida sig till bitestiklarna, som då svälla märkbart och bli ytterst ömma. Om denna komplikation är dubbelsidig, efterlämnar den ofta sterilitet (förlust av fortplantningsförmåga).

Dröppeln kan även förorsaka en svår ledinflammation, event. med styv led som påföljd. Trakten omkring leden sväller märkbart och själva leden känns mycket öm. Den av dröppel förorsakade ledinflammationen angriper oftast endast en led och icke såsom den vanliga ledgångsreumatismen flera leder samtidigt. Genom orena händer kan dröppelsmittan överföras på ögat med t.o.m. blindhet som följd. Det må nämnas, att utslag vanligtvis icke förekomma vid denna sjukdom.

Om ni trots förebyggande behandling märker dröppelsymptom, vänd eder då i närmaste hamn till läkare. På egen hand företagen behandling kan försvåra saken och t.o.m. åstadkomma svåra skador. Sjukdomen kan kvarstå, även om besvären skenbart försvunnit. Tablettkurer tagna utan läkarordination kunna t.o.m. bliva livsfarliga.

Mjuka schankern eller ulcus molle.

Schankern förekommer i Finland rätt oregelbundet, men den kan ofta förekomma rikligt utomlands. Även den förorsakas av en bakterie. Några dagar efter erhållen smitta uppkommer på könsorganet eller i dess närmaste grannskap ett sår, som är mjukt och ömmande. Ibland uppstår även en lymfkörtelsvullnad i ljumskvecket. Längre sprider sig sjukdomen icke. Såret bör rengöras och förbindas. Om lymfkörtlarna svullnat i högre grad, bör man intaga sängen.

Om ett sår (eller flera) uppkommit på könsorganen eller i trakten däromkring, är det alltid skäl att misstänka, att det kanske härleder sig av syfilis. Det är därför bäst att härvid genast besöka läkare och att dessutom efter några månader låta taga ett blodprov (även om läkaren ansett att såret icke var syfilitiskt).

Negerschankern eller lymphogranuloma inguinale.

Negerschankern är en hos oss mindre vanlig könssjukdom, i synnerhet nu, då sjöfarten till sydligare länder varit inställd. Även den är mycket smittosam. Lång-

varig och svårbehandlad kräver den alltid sjukhusvård. Dess inkubationstid är längre än mjuka schankerns, och dess primärsår kan ofta vara nästan omärkligt. I stället bildar den envisa fistulerande körtelpaket (s.k. buboner) i ljumskvecket, som lämnade åt sig själva ofta behöva många månader för att läkas. Hos kvinnan är den ofta en svår och plågsam sjukdom, som t.o.m. kan medföra döden.

LAGEN OM KÖNSSJUKDOMARNA OCH BEHANDLINGENS REGELBUNDENHET.

I Finland trädde lagen om könssjukdomarna i kraft år 1943. På grund av denna lag har varje person rätt till avgiftsfri vård. Person, vilken icke efterkommer läkarordinationen, kan förpassas till sjukhus. En speciell tjänsteläkare ombesörjer utforskningen av smittokällan. Polisen står vid behov till hans förfogande.

Såsom vi redan upprepade gånger framhållit, är villkoret för ett tillfrisknande från dessa sjukdomar följande:

1. att behandlingen påbörjas så snart som möjligt,
2. att behandlingen sker systematiskt,
3. att den icke avbrytes för tidigt.

I slutet av vår lilla bok återfinnes en förteckning över sjukhus och polikliniker världen runt, där ni kan bli i tillfälle att erhålla sakkunnig vård och hjälp.

Efterkom med noggrannhet de råd ni erhållit!

SKABB OCH FLATLÖSS.

Till könssjukdomar räknas skabben och flatlusen icke, ehuru man ofta får dem på köpet samtidigt som någon av könssjukdomarna.

Skabben framkallar kliande nippor mellan fingrarna, vid mellangärdet, på fötterna och på könsorganen. Klådan är värst om natten. Utslaget smittar synnerligen lätt till den som ligger i samma bädd. Skabben behandlas med en därför tillverkad salva efter speciell ordination.

Flatlusen bebor trakterna kring könsorganen. I enstaka fall förekommer den även i armhålan. Man får den vanligtvis av sin sängkamrat. Om man noggrannt iakttager huden, märker man huru flatlusen rör sig. Den förorsakar klåda. I fartygets läkeskåp finnas läkemedel som döda lusen.

Både skabb och flatlöss sprida sig hastigt från man till man genom kläder, bekvämlighetsinrättningar o. dyl. Därför är det av stor vikt att genast genom omsorgsfull behandling förgöra dem.

ÄKTENSKAPET OCH FRAMTIDEN.

Kanske vill ni invända, att ni lever som ni själv behagar, och att ingen har med den saken att göra, samt att ni själv svarar för edra handlingar. Det bekymrar eder kanske föga, om ni besmittar en flicka, som går från man till man. Men har ni besinnat, att denna flicka fortsätter att sprida sjukdomen bland edra kamrater?

Ni har kanske en kär hustru eller fästmö, som väntar er hem. Tänk om ni belönade hennes trohet med en gåva av detta slag, som kanske kunde förstöra hela hennes liv. Könssjukdomarna äro nämligen för kvinnan vida farligare än för mannen.

Dröppeln hos kvinnan kan sprida sig till äggledarna, där den är svår att behandla och vanligtvis medför sterilitet. Som påföljd kan även räknas bukhinneinflammation och någon gång t.o.m. förlust av livet.

Kvinnan har svårt att märka en begynnande syfilis, emedan första sårnaden oftast icke blir synlig. Om symptomen till andra stadiet dessutom förbliva otydliga, kan sjukdomen nå sitt tredje stadium utan att det stackars offret anar det. Hos oss födas årligen bortåt 150 syfilitiska barn, av vilka en del med bästa tänkbara vård icke kunna fås till självförsörjande medborgare. Sjukdomen går under havandeskapet från modern över på barnet. Ett syfilitiskt barn blir i fysiskt och psykiskt hänseende undermåligt och får till följd av sin faders misstag oskyldigt lida hela sitt liv. Om modern under havandeskapet erhåller ordentlig behandling, kan hon däremot föda ett friskt barn.

Även negerschankern är betydligt riskablare för kvinnan än för mannen. Den kan förorsaka henne långvarigt lidande och en smärtsam död.

Om ni vid hemkomsten från er resa är sjuk, bekänn det då för er hustru. Utsätt henne icke för sjukdomens alla faror. Om ni först senare, efter det ni redan varit med eder hustru, märker sjukdomssymptomen, så kom ihåg, att den av eder tidigare förvärvade och nu först

utbrutna sjukdomen under sin inkubationstid kan ha överförts på er hustru. Dölj icke dessa fakta för henne, även om ni därmed kanske kunde äventyra hennes kärlek. Om ni redan har familj eller står i beredskap att bilda en sådan, kan ni icke påstå, att det liv ni lever vore eder ensak. Ni bär ansvaret för er hustrus hälsa och för edra barns framtid och välfärd.

Har ni varken hustru eller fästmö, så har ni dock er "idealflicka". Ni saknar ett hem, där ni efter edra seglatser kunde få vila ut i hemtrevnad och lugn. Så purpurglödande hamnstadsflickornas „kärlek" än är, är den dock tekniskt beräknad. Den njutning de erbjuda är en förrädisk dryck, som för stunden berusar, men efterlämnar en besk smak i munnen.

Kära vän. Du lever bara ett liv. Tänk dig för, lönar det sig verkligen för en njutningsmättad sekund att förstöra sin dyrbara hälsa och gå miste om möjligheterna till lycka?

Sjöman, om du misstänker, att du blivit besmittad med könssjukdom, så vänd dig då genast till en läkare! I följande förteckning angives orterna där du kan erhålla sakenlig och förstklassig vård. På de flesta av dessa orter är behandlingen för sjömän avgiftsfri.

Undvik att anlita utländska privatläkare, ty de kunna möjligen fordra ett stort arvode och för behandlingens förstklassighet finnes ej någon garanti.

Det är möjligt, att förteckningen på dina ställen är bristfällig på grund av eventuella förändringar som ägt rum under kriget. Så fort det finnes möjligheter att kontrollera adresser bifogas de som tillägg till denna skrift.

I slutet av denna skrift finnes en förteckning över finska beskickningar och konsulat i utlandet.

KÄNNER DU TILL MÄRKET?

En stor fara för vårt falle är könssjukdomarna.

Med följande märke har godkänst för Föreningen för Könssjukdomarnas Bekämpande r.f. Motivet är tre varningstrianglar — de tre viktigaste könssjukdomarna.

Föreningen för Könssjukdomarnas Bekämpande r.f. svarar skriftligen på frågor rörande könssjukdomarna och deras behandling. Adr. Unionsg. 45 B 23, Helsingfors.

Om ni misstänker att ni blivit besmittad med någon könssjukdom, så låt en läkare undersöka Eder och låt för säkerhets skull taga blodprov för att få reda på huru saken förhåller sig. I fall något är oklart — så fråga!

EUROPA

BELGIEN

ANTVERPEN

Centraal Kliniek
33—37 rue Jardin des Arbalétriers (Schutterhofstr.)
Croix-Rouge de Belgique Schulstraat 15
Hôpital Ste-Elisabeth
45, Rue Longue de Hôpital (Lange Gasthuisstraat)

GENT

Clinique Centrale
6, Rempart St-Jean (Sint Jansvest)
Hôpital Civil la Biloque
2, rue Kluyskens (Kluyskenstraat)

OSTENDE

Hôpital Civil Rue de l'Hôpital (Gasthuisstraat)

DANMARK

KÖPENHAMN

Konsultationsstuen, Kommunehospitalets 4. Afd.,
Gammeltoftsgade
Polikliniken for Hud- og Kønssygdomme,
Rigshospitalet, Frederik d. V's Vej
Konsultationsstuen

Rudolph Berghs Hostpital Tietgensgade
Kliniken, Enghavevej 42
Kliniken, Nørrebrogade 18 A
Kliniken, Østerbrogade 56 D
Kliniken, Wildersgade 29

FÄR-ÖARNA

Thorshavn, Vestmanhavn &
Suderf: Länsläkare och provinciallläkare

ISLAND

REYKJAVIK
St. Joseph Hospital

FRANKRIKE

AJACCIO (Korsika)
Dispensaire d'Hygiène sociale Bd. Lantivy

ARCACHON
Dispensaire d'Hygiène sociale 35 Cours Tartas

BASTIA (Korsika)
Hôpital Civil

BAYONNE
Bureau de Bienfaisance 14, rue Dover
Service de dermato-vener., Hôpital

BORDEAUX
Dispensaire central 82 bis cours d'Albret
Dispensaire Ferdinand-Petit,
244 cours Balguerie Stuttenberg
Consultations Hôpital Boursier
Dispensaire de la Cie des Chemins de fer du Midi
14, rue Pelleport

BREST
Disp. Maritime de Inst. Prophylactique,
60, Quai de la Douane
Hôpital 8, rue Traverse

CAEN

Dispensaire géré par Office Public d'Hygiène sociale, 73 rue du Vaugueux

Disp. privé de la Miséricorde, Quai Vendeuvre

CALAIS

Hôpital

CHERBOURG

Hôpital Pasteur 46 rue Val de Saire

DIEPPE

Hospices civils

DUNKERQUE

Disp. du Bureau de Bienfaisance, 10 rue Faulconnier

FÉCAMP

Hôpital, rue St. Nicolas

LE HAVRE

Hôpital Général 55 bis rue Gustave Flaubert

Dispensaire de l'Institut prophylactique, 4 rue Fleurus

HONFLEUR

Dispensaire de l'Office publique d'Hygiène sociale rue Alphonse Allais

LORIENT

Hôpital Bodëlio

MARSEILLE

Dispensaire maritime Esplanade de la Tourette

Dispensaire de l'Hotel-Dieu Place Daveil

Dispensaire d l'Hôpital de la Conception, 136, rue Saint-Pierre

NANTES

Office central des Oevres d'Hygiène sociale, 6, rue Jean V.

Centre antivénérien de l'Hotel Dieu, 13, Quai Moncousu

NICE

Centre de prophylaxie Hôpital Saint Roch 4, Place Defly

PORT-VENDRES
Dispensaire International Quai de la Douane

La ROCHELLE
Hôpital, 49, rue Thiers

ROCHERFORT
Hôpital civil, 8, rue Emile-Combes

ROUEN
Dispensaire central 1, rue de Germont

Les SABLES d'OLONNE
Dispensaire d'Hygiène sociale, Hôpital-Hospice

SAINT-BRIEUC
Dispensaire central 76, ru de quintin

SAINT-MALO
Hôtel-Dieu 4, rue d'Estrées

SAINT-NAZAIRE
Hôpital

SÈTE
Dispensaire departemental rue de l'Hôpital

TOULON
Dispensaire central

HOLLAND

AMSTERDAM
Poliklinik Conradstraat 18
Westerpark
Binnen-Gasthuis Grimburgwall 10

ROTTERDAM
Poliklinik Nieuwehaven 87
Havnepoliklinik Institut for Tropesygdomme
Wijde Nieuwsteeg 4

VLIESSINGEN
Poliklinik Hospital St. Joseph, Van Dishoekstraat
Hospital Bethesda Koudekerkstraat

IRLAND

BELFAST
- Royal Victoria Hosp.
- Mater Infirmorum Hosp.
- Union Infirmary

DUBLIN
- Dr. Steevens Hospital Stevens Lane
- Sir Patrick Dunn's Hosp.

LIMERICK
- City Home & Hospital

LONDONDERRY
- City and Country Infirmary

NORGE

AALESUND
- Læge A. Mathiesen Skansetorvet

ARENDAHL
- Stadslægen Torvet

BERGEN
- Poliklinik Jon Smörsgate 11

DRAMMEN
- Stadslægen Ole Steensgate 18, Bragernes

FREDRIKSTAD
- Stadslægen Storgaten 20

HALDEN
- Læge Ulstad Storgaten 3

HAUGESUND
- Stadslægen Kirkegaten 147

KRISTIANSAND
- Stadslægen Dronningensgaten 41

KRISTIANSUND N.
- Stadslægen Fosnagaten 1

OSLO
- Poliklinik St. Olavs Plads 5

PORSGRUNN
Stadslægen Storgaten 88

SARPSBORG
Stadslægen Torvet

STAVANGER
Læge Tronslin, Muségaten 10

TRONDHEIM
Stadslægen

TÖNSBERG
Stadslægen

PORTUGALIEN

LISSABON
Dispensaire de Prophylaxie sociale, Pl. du Brèsil
Hôpital Do Desterro Rua Desterro

OPORTO
Hôpital Anglais Calcada de Monchique
Hôpital St. Antonio

SPANIEN

ALGECIRAS
Station Sanitaire

ALICANTE
Station Sanitaire

ALMERIA
Station Sanitaire

BARCELONA
Station Sanitaire

BILBAO
Station Sanitaire

BURRIANA
Station Sanitaire

CADIZ
Station Sanitaire

CARTAGENA
Station Sanitaire

CORUNA
Station Sanitaire

FERROL
Station Sanitaire

GANDIA
Station Sanitaire

GIJON
Station Sanitaire

HUELVA
Station Sanitaire

PORT MAHON
Station Sanitaire

MALAGA
Station Sanitaire

PALMA de MALLORCA
Station Sanitaire

PASAJES
Station Sanitaire

ST. SEBASTIAN
Station Sanitaire

SANTANDER
Station Sanitaire

SEVILLA
Station Sanitaire

TARRAGONA
Station Sanitaire

VALENCIA
Station Sanitaire

VIGO
Station Sanitaire

VILLAGARCIA
Station Sanitaire

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STOR-BRITANNIEN

ENGLAND

BARROW-IN--FURNESS
North Lonsdale Hospital

BARRY
County Council Clinic Woolands Road

BIRKENHEAD
General Hospital

BOSTON
V.D. Clinic Holland (County) Sanatorium London Road

BRISTOL
Guardian House Maudlin Street

CARDIFF
Royal Infirmary
Royal Hamadryad Seamen's Hospital

CHATHAM
Clinic at 36 New Road, Rochester

DOVER
Royal Victoria Hospital

GOOLE
Bartholomew Hospital

GRAVESEND
22, Cobham Street

GRIMSBY
38, Queen Street

HULL
Health Department Mill Street

IPSWICH
Eeast Suffolk and Ipswich Hospital

KING'S LYNN
West Norfolk and Lynn Hospital

LIVERPOOL
Central Clinic Mill Road Infirmary
Royal Infirmary
Seamen's Dispensary
Cleveland Square, Paradise Str. 15—20

LONDON
Guy's Hospital S.E. 1.
Miller General Hospital Greenwich S.E. 10.
Royal Albert Dock Hospital (West Ham)
St. Bartholomew's Hospital, E.C. 1.
St. Paul's Hospital Endell Street, W.C. 2.
St. Thoma's Hospital S.E. 1.
Seamen's Hospital Soc. Dreadnought Hospital, Greenwich
Whitechapel Clinic Turner Street, Mile End, E.C. 1.
St. John's Hospital Mordan Hill, Lewisham
West London Hospital Hammersmith Road, W. 6.

LOWESTOFT
Lowestoft & North Suffolk Hospital

MANCHESTER
Ancoats Hospital
Manchester & Salford Hosp. for Skin Diseases
Royal Infirmary
St. Luke's Hospital

MIDDLESBROUGH
Municipal Hospital

NEWCASTLE — on — TYNE
General Hospital

NEWPORT (Mon)
Royal Gwent Hospital

PLYMOUTH
City Hospital, Greenbank

POOLE
Royal Victoria & West Hants Hospital,
Boscombe, Bournemouth

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PORT TALBOT
County Council Clinic

PORTSMOUTH
Royal Portsmouht Hospital

PRESTON
Preston Royal Infirmary

ROCHESTER
36, New Road

SOUTHAMPTON
New Clinic, Vicarage Grounds, East Park Terrace

SOUTH SHIELDS
Municipal Clinics Stanhope Road

SUNDERLAND
Royal Infirmary

SWANSEA
General & Eye Hospital

WEST HARTLEPOOL
Mill House, Stranton Green

SKOTLAND

ABERDEEN
Aberdeen City Hospital
Royal Infirmary

AYR
Heathfield Hospital

EDINBURGH
Edinburgh Royal Infirmary

GLASGOW
Bellahouston Dispensary, 87, Paisley Road
186, Broomielaw
Victoria Infirmary
Western Infirmary
67, Black Street

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GRÅNGEMOUTH

Royal Infirmary, Falkirk

LEITH

Seamen's Dispensary 65, Shore Street

MEDELSHAVETS flottbos

GIBRALTAR

The Colonial Hospital

CYPERN

Famagusta V.D. Clinic

Larnaca V.D. Clinic

Limassol V. D. Clinic

MALTA

Central Civil Hospital Piazza San Calcedonio, Floriana

VALETTA

King George V Merchant Seamen's Memorial Hosp.

SVERIGE

GEFLE

Stads Poliklinik Södra Strandgatan 16

GÖTEBORG

Holtermanska sjukhus Holtermansgatan

Social Huset

HALMSTAD

Dr. H. Laurell, Köpmansgatan 2

HÄLSINGBORG

Thure Roringsgatan 4

HÄRNÖSAND

Dr. Sinkowsky

KARLSTAD

Poliklinik

LULEÅ

Dr. Börje Kjellander

MALMÖ

Malmö Stads Poliklinik Allmänna Sjukhuset

NORRKÖPING
Poliklinik, Generalsgatan 5

SÖDERHAMN
Dr. F. Fex Kungsgatan 4

STOCKHOLM
Kornhamnstorget 4
Döbelusgatan 59
Jungfrugatan 27
St. Göran Hospital

SUNDSVALL
Dr. G. Hedberg, Nybrogatan 21

UMEÅ
Dr. O. S. Wahlin, Storgatan 52

VÄSTERÅS
Poliklinik

AMERIKA

NORD-AMERIKA

CANADA

MONTREAL
Hôpital Notre Dame 1560 Sherbroke Str. E.
Hôpital General 66 Dorchester Str. E.
Hôpital St-Luc 1058 St. Denis Street

St. JOHN
134 Sydney Street

VANCOUVER
640 Hastings Street W.

U. S. A.

NEW YORK
Red Hook-Gowanus Clinic 250 Baltic Street, Brooklyn
Central Clinic 130 Leonard Str., Man.
Central Harlem Clinic 2238, 5th Avenue, Man.
Eeast Harlem Clinic 158 East 115th, Man.

Kips Bay-Yorkville 411 E. 69th Street, Man.
Lower West Side 303 9th Avenue, Man.
Meinhard Clinic 130 E. 101st Str., Man.
Washington Clinic 123 Wooster Street, Man.
Mott Haven Health Center 349 E 140th, Bronx
Tremont Clinic, 1880 Carter Ave., Bronx
Astoria Clinic 12—26 31st Avenue, Astoria, L.I.
Bushwick 186 Grove Street, Brooklyn
Jamaica West Clinic 92—18 149th Street, Jamaica
Williamsburg—Greenpoint, 151 Maujer Str., Brooklyn

CAMDEN N.J.
Cooper Hospital 6th and Stevens Sts.

JACKSONVILLE, Fla.
Duvall County Hospital Foot of W. 10th Street

Los ANGELES, California
City Clinic 116 Temple Street
Graves Skin & Veneral Clinic 737 N. Broadway
White Memorial Clinic 312 N. Boyle

NORFOLK, Virginia
Venereal disease Clinic Grigsby Place

PORTLAND, Oregon
University of Oregon Out-Patients Clinic Marquam Hill

SAN FRANCISCO, California
Policlinic 1535 Jackson Street
Stanford University Hospital 2398 Sacramento Str.
University of California Luetic Clinic,
3rd and Parnassus Avenues

SAN PEDRO
City Clinic City Hall

SYD-AMERIKA

BRASILIEN

BAHIA
Centro de Saude Rua dos Artistas, Carcia No. 14
Centro de Saude Rua J.J. Seabia
Centro Se Saude Calcado de Bomfim 22

RIO de JANEIRO
Hosp. Gaffre Guinla Rua Mariz Barros 369
SANTOS
Gaffre & Guinle Praca de Republica

URUGUAY

MONTEVIDEO
Dispensario Central 18 de Julio 1892
Dispensario No. 1. 25 de Mayo 174
Dispensario No. 2 Calicia 873
Dispensario No. 1 och 2 ligga nära till hamnen.

ARGENTINA

BUENOS AIRES
Consultorium No. 1 Calle Viamonte
ROSARIO
Dispensario antivenero del Departamento de Higiene, Puerto de Rosario

CHILE

ANTOFAGASTA
Dispensario No. 7 Avenida Matta 1040
COQUIMBO
Dispensario No. 22 Aldunate 972
IQUIQUE
Dispensario No. 6 Barros Arana 1095
SAN ANTONIO
Dispensario No. 14 Alberto Barros 330
TALCAHUANO
Dispensario No. 10 Bilbao 353
TOCOPILLA
Dispensario No. 26 Washington 1364/1376
VALPARAISO
Dispensario No. 9 Chacabuco 484
Dispensario No. 13 Cochrane 414

FINLAND

HELSINGFORS
Dr. Y. Salminen, Katrinegatan 3

KEMI
Dr. V. Lindberg

KOTKA
Dr. O. Rysä

ULEÅBORG
Dr. U. J. Matinolli

BJÖRNEBORG
Dr. L. Sandell

RÄFSÖ
Dr. G. Svensk

TORNEÅ
Dr. N. Soilunen

ÅBO
Dr. C-G. Schauman

VASA
Dr. K. J. Leineberg

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BESKICKNINGAR OCH KONSULAT

NEDERLÄNDERNA

AMSTERDAM: Konsul Key Jzn, Gerrit, Houthaven 24, Finlands Konsulat, Scott, Watkin

JAVA Batavia: Konsul Haasmann, Leopold Th., Soerabajaweg 8, Haasmann, Batavia centrum, Java

VÄST-INDIEN Willemstad (Curacao): Konsul Mensing, W. F. G., P.O. Box 125; c/o Messrs Mensing & Co

AMERIKAS FÖRENTA STATER

WASHINGTON: Utomord. sändebud och befullm. minister Jutila, Kalle Teodor, 2144 Wyoming ave.
Leg.råd. v. Numers, Sigurd Waldemar
Handelsattaché Smedslund, Ragnar
Leg. sekreterare Munkki, Olavi

NEW YORK: Gen. Konsul Niskanen, Wille
v. Konsul Lindén, Kurt, 53 Broadway

ARGENTINA

BUENOS AIRES: Leg. sekreterare Mikkola, Erkki Veli Viljo, Calle Montevideo 1693

BELGIEN

ANTVERPEN: Konsul Tuominen, Leo, Kipdorp 55

BELKISKA KONGO, Léopoldville: Konsul van Ruyteghem, Theo J. Ch. Léopoldville

BRASILIEN

RIO DE JANEIRO: Utomord. sändebud och befullm. minister Orasmaa, Niilo Y. G., Rua Duvivier 43, Copacabana
Attaché Mäkelä, K.

BAHIA: V. konsul Gama da Costa Santos, Aloysio, Bahia

PORTO ALEGRE: Konsul Heitmann, Ernst, Caixa Postal 209, Rua Mostardeiro 257

SANTOS: V. konsul Mossige, Olav, Rua 15 de Novembro 183

SAO PAULO: Konsul Arnesen, Finn B., Caixa Postal 1926

BRITTISKA RIKET

LONDON: Finlands polit. attaché Wuori, Eero, 79 Addison Road, London, W. 14
Leg. råd von Knorring, Helge
Leg. sekreterare Ingman, Martti
Handelsattaché Krogius Ali. Teleg. adr. Finlandia Hammer.

CARDIFF: Konsul Beecher, Archie, Atlantic Buildings, Mount, Stuart Square

GLASGOW (Skotland): Konsul Graham, William Richardson, 12 Waterloo Str. Glasgow C 2

HULL: Konsul Good, Ambrose, Burnett avenue, Scale Lane

LIVERPOOL: Konsul Holmes, Livingstone, 55/South Castle street

SYD-AFRIKA

CAPE TOWN: Sekreterare Ranta, Yrjö, adr. Swedish Consulate

BULGARIEN

SOFIA: Gen. konsul Karakaschoff, Wladimir, Rue Aksakoff 5II

BURGAS: Konsul Petroff, Mathien, Bourgas

GDANSK

GDYNIA-GDANSK: V. konsul Wuoma, Julius Arvid

DOMINIKANSKA REPUBLIKEN

CIUDAD TRUJILLO: Konsul du Breil, Hipolito, Ciudad Trujillo, S.D.

SPANIEN

MADRID: Beskickningens adr.: Giunta del Berro al Final de La Calle de Eduardo Aunos
Konsul Cortés, Antonio, Calle de Ferrez 4
V. konsul Krabbe-Knudsen, Fr.

ALICANTE: V. konsul de Armona y Esparza, Róman, Ciudad Jardin, Calle C. n:o 15

ALMERIA: V. konsul Terriza-Abad, Juan, Calle Aguilar

BARCELONA: V. konsul Fritsch-Catarineu, José, Aviño 33

BILBAO: V. konsul Røvig, Arne T., Calle 2 de Navarra 2

CADIZ: Konsul Grosso-Portillo, Antonio Luis, Feduchy 14

CARTAGENA: V. konsul Guardiola-Diaz, Ricardo, Calle del Aire 11 y 13

LA CORUNA: V. konsul Pedregal-Santullano, Ismael, Plaza de Orense 4

MALAGA: V. konsul Ojeda-Suarez, Francisco, Marques de Larios 6

PALMA DE MALLORCA: V. konsul Manera-Rovira, Enrique, Avenida Antonio Maura 19

SAN SEBASTIAN: Konsul Harmens, Wilhelm Magnus, Calle Prim 7

SANTANDER: V. konsul Lopez Doriga, Miguel, Paseo de Pereda 32

SEVILLA: Konsul Justel-Santamaria, Victorio, Calle Adriano 59—61

TARRAGONA: V. konsul Boada-Pigué, Juan; Calle de Gobernador Gonzalez 35

VALENCIA: Konsul Moroder-Gomez, Ricardo

VIGO: V. konsul Barbini, Vittorio, S. Maria del Giglio 2516

KANARISKA ÖARNA

LAS PALMAS: V. konsul Levy-Arata, Emilio (Sveriges konsulat)

IRAN

TEHERAN: Utomord. sändebud o. befullm. minister Yrjö-Koskinen, Arno, adr.: Ankara

ISLAND

REYKJAVIK: Gen. konsul Andersen, Christian Ludvig, Hafnarhusid, Truggvagötu

SIGLUFJORD: V. konsul Jónsson, Alfons, adr.: Gránugata 11

ITALIEN

BARI: V. konsul Girone, Nicola, Via San Domenico 9

CATANIA: V. konsul Comoni, Ferruccio, Via Museo Biscari 10

FIRENZE: Konsul Weil, Federico, Borgo degli Albizzi 27

GENOVA: Konsul Boesgaard, Einar Nils Laurberg, Piazza San Siro 10

V. konsul von Tangen Kielland, Christopher

MESSINA: V. konsul Saccà, Francesco, Via Natoli 59

MILANO: Gen. konsul Weil, Federico, Via Piatti 9

PALERMO: V. konsul Grillo, Renato, Via Malaspina 11

SAVONA: V. konsul Frumento, Filippo, Via San Lucia 1

TORINO: Konsul Cibrario, Luigi, Via Ettore De Sonnaz 21

TRIEST: Konsul Giugia, Matteo

VENEZIA: Konsul Barbini, Vittorio, S. Maria del Giglio 2516

COLUMBIA

CARTAGENA: V. konsul Escallon, Carlos, Apartado postal 50

GREKLAND

CALAMATA: V. konsul Pastras, Christos

VOLO: V. konsul Panas, Constantin

CUBA

HAVANNA: Konsul Evertz, Guillermo, Avenida de Belgica 10

LIBERIEN

MONROVIA: Konsul Lowndes, Alfred, c/o Messrs Paterson, Zochonis & Co. Ltd

LUXEMBURG

LUXEMBURG: Konsul Arendt, Max, 22 rue Joseph II

MEXIKO

MEXICO CITY: Konsul Grönroos, Leo Karl

VERA CRUZ: V. konsul Barranco, Gabriel Luis, Apartado 211

NORGE

OSLO: Utomord. sändebud och befullm. minister Tarjanne, P. K., Thomas Helteysgt. 1
Gen. konsul. Bödtker, Johannes Mathias
Konsul Stephanson, Robert
Leg. sekreterare Brotherus, Heikki

AALESUND: V. konsul Wesenberg, Hjalmar, Finnlands Vicekonsulat

ARENDAL: V. konsul Thorsen, Thorlief

BERGEN: Konsul Gjestland, Birger, Finnlands konsulat

DRAMMEN: V. konsul Rudolf, Jörgen, Finnlands Vicekonsulat

FREDRIKSTAD: V. konsul Knudsen, Sigurd, Finnlands Vicekonsulat

HALDEN: V. konsul Röd, Alf.

HARSTAD: V. konsul Galschiödt, O.

HAUGESUND: V. konsul Haaland, Chistian

KIRKKONIEMI: V. konsul Nilsen, Mangor, Finnlands Vicekonsulat

KRISTIANSAND: Konsul Hegermann, Ditlev, Sparebankens gård

KRISTIANSUND: V. konsul Arentz-Hansen, Ludvig, Finnlands Vicekonsulat

LARVIK: V. konsul Mürer, Carl Johan, Finnlands Vicekonsulat

MANDAL: V. konsul Christensen, Christen Andreas, Finnlands Vicekonsulat

MOSS: V. konsul Vogt, Carsten, Finnlands Vicekonsulat

SANDEFJORD: V. konsul Virik, Haldor

SARPSBORG: V. konsul Iversen, Einar

SKIEN: V. konsul Bertelsen, Carl Ferdinand, Finnlands Vicekonsulat

STAVANGER: Konsul Bjelland, Ragnvald

TROMSSA:
TROMSÖ: } Konsul Wennevold, Eivind

TRONDHEIM: Konsul Ellingsen, Johan, Finnlands Vicekonsulat

TÖNSBERG: V. konsul Berg, Thorvald

VESISAARI:
VADSÖ: } V. konsul Esbensen, Andreas Brodtkorb, Finnlands Vicekonsulat

VUOREIJA:
VARDÖ: } V. konsul Valle, Ingvald, Finnlands Vicekonsulat

PÅVSTOL

VATIKANEN: Utomord. sändebud Holma, Harri G., Via dei Monti Parioli 49

T.f. leg. sekreterare Stenius, Göran

PARAGUAY

ASUNCION: Gen. konsul Heikel, Paul

PORTUGAL

LISSABON: Gen. konsul Wang, Otto, Rua do Arsenal 160

OPORTO: V. konsul da Rocha Romaritz, Claudino Rua do Infante D. Henrique 75

SETUBAL: V. konsul Liverio, Alexandre, Setubal

VILA REAL DE SANTO ANTONIO: V. konsul Ramirez, Emilio, Avenida da Republica 37

MADEIRA Funchal: Konsul Gomes, Joâo Marcello, Rua Murras 41

POLEN

WARSZAWA: Utomord. sändebud och befullm. minister Järnefelt, Eero, Hotel Polonia
Leg. sekreterare Pyykkö, Matti
GDYNIA: V. konsul Wuoma, Julius Arvid

FRANKRIKE

PARIS: Utomord. sändebud och befullm. minister Helo, Johan, 30 Cours Albert Ier, Paris (VIIIe)
Leg. sekreterare Enckell, Ralph
Attaché Suomela, Pentti

PARIS: Konsul Brusin, Kaarlo, 11 rue de la Pépinière, Paris (VIIIe)
Konsul Enegren, Eino

ANNOMASSE: T.f. konsul Frondeville, J. M. F., 1 rue de la Fancille (Haute Savoie)

BORDEAUX: Konsul Videau, Georges Louis Armand 135, Cours de Midoc (Gironde)

BREST: V. konsul Reillard, Ad., 21, rue Aiguillon (Finistère)

CALAIS: V. konsul Pagniez, Paul Edouard Benoist Joseph, 198, rue des Quatre Coins. (Pas de Calais)

CHERBOURG: V. konsul Quoniam, Camille Théodore 9, Quai de l'Entrepot. (Manche)

DIEPPE: V. konsul Porte, Charles, Quai du Cours Bourbon (Seine Inf.)

NANTES: Konsul Beaupère, Paul Luis, 37, rue Lame riciere (Loire Inf.)

NIZZA: Konsul Powilewicz, Charles Marcel, 20, Quai Lunel,

ROUEN: Konsul Fondeville, Jean Marie Francois 15, rue Lézurier de la Martell

ROUEN: V. konsul Fondeville, Bernard

ST. MALO: V. konsul Sabatier, Lucien

STRASSBOURG: Konsul Belot, Henri, 15, rue des Juifs (Bas-Rhin)

ORAN: V. konsul Dehaen, Albert, 5, rue El-Moungar

RUMÄNIEN

BUKAREST: Gen. konsul Chrissoveloni, Nicolae Jean
GALATZ: Konsul Popa, Ervin Apostol P, Galatz

SVERIGE

STOCKHOLM: Utomord. sändebud och befullm. minister Gripenberg, G., Västra Trädgårdsgatan 13
Leg. sekreterare Pohjanpalo, Taavi, leg. råd.
Leg. sekreterare Ahlqvist, Eric
Leg. sekreterare Palas, Reino
Tidningsattaché Frietsch, Carl Olof
Gen. konsul Salén, Sven Gustaf
Konsul Lindwall, Edward Wilhelm
V. konsul Sjödin, Erik Fr.

GÄVLE: Konsul Nordström, Erik Gustaf
GÖTEBORG: Gen. konsul Numelin, Ragnar, Wasagatan 23
HAPARANDA: Konsul Svensk, Åke
HALMSTAD: V. konsul Westerberg, Nils O., Gjuterivägen
HUDIKSVALL: V. konsul Arndt, Johan Eric Hamngatan 21
HÄLSINGBORG: V. konsul Börjesson, B. A., Järnvägsgatan 7
HÄRNÖSAND: V. konsul Ramström, Herman Robert, Skeppsbron 17
KALIX: V. konsul Larson, Åke, Kalix
KALMAR: V. konsul Trolle, Carl Harald, Storgatan 16
KARLSHAMN: V. konsul Samuelson, Ernst Ivar, Drottninggatan 51
KARLSKRONA: V. konsul Tordson, Per Lennart, Ronnebygatan 49
KARLSTAD: V. konsul Johnson, Johan H., Karlstad, Rosenbad 2
KIRUNA: V. konsul Hammarén, Harald, Norra Skolgatan 3
KRISTIANSTAD: V. konsul Borg, Nils August, Barbarkgatan 7
LANDSKRONA: V. konsul Weibull, Carl Walfrid, Landskrona, Östra Infartsvägen 39

LULEÅ: V. konsul Lindgren, Ernst Oscar, Nygatan 2
LYSEKIL: V. konsul Berg, Wilhelm, Finska Vicekonsulat
MALMÖ: Konsul Könsberg, Nils Allan, Skeppsbron 5
V. konsul Sirén, Ernst Bertil

NORRKÖPING: Konsul Hellman, Gösta, Sandgatan 12 A
OSKARSHAMN: V. konsul Svensson, Carl Otto Knut, Oskarshamn, Skeppsbron 3

OXELÄSUND: V. konsul Ström, Ture Viktor, Percy Tham Ab.
SKELLEFTEÅ: V. konsul Lundström, Karl Edvard, Skellefteå
SUNDSVALL: Konsul Tigerman, Gösta
STRÖMSTAD: V. konsul Hessel, Karl Arthur, Rådhuset
SÖDERHAMN: V. konsul Sandberg, John Helge Samuel, Dammgatan 3

TRELLEBORG: V. konsul Christensen, Axel Emil, Trelleborg, Hamngatan 20

UDDEVALLA: V. konsul Sanne, Johan Herman, Uddevalla, Norra Hamngatan 4

UMEÅ: Konsul Forsman, Johan Edvard, Kungsgatan 48
VISBY: V. konsul Ihre, Jacob Henrik Olaus, Visby, Transhusgatan 25

VÄSTERVIK: V. konsul Flink, Yngve Fredrik, Kvarngatan 19
YSTAD: V. konsul Larsson, Lars Wilh., St. Östergatan 21
ÖRNSHÖLDSVIK: V. konsul Norén, Alf., Villagatan 12

SOCIALISTISKA RADREPUBLIKERNAS FÖRBUND

MOSKVA: Utomord. sändebud och befullm. minister Sundström, Cay, Krapotkinski per 15/17
Leg. sekreterare Vanamo, Jorma Jaakko
Leg. sekreterare Pulkkinen, Paavo

SCHWEIZ

BERN: T.t. chargé d'affaires, Leg. sekreterare Leppo, Heikki
Gen. konsul Schanwecker, Carl, Villa Sommerlust, Wabern
GENÈVE: Konsul Wieland, Ph.

BASEL: Konsul Hofmann-Hess, W, Gerbergasse 4
LAUSANNE: Konsul Krafft, Agènor, 2, rue St. Pierre
LUGANO: Konsul Wullschleger, Fritz, Via Bellavista 3
LUZERN: V. konsul Åkerson, Kurt, Sonnbühlstrasse 3
ZÜRICH: Konsul Hatt-Bucher, Heinrich, Löwenstrasse 17

DANMARK

KÖPENHAMN: Utomord. sändebud och befullm. minister Hynninen, P. J., Hammerensgade 5
Leg. sekreterare Nyberg, Charles
Attaché Makkonen, Veikko
Gen. konsul Høyvald, Einar
Konsul von Christierson, Tönne

AALBORG: V. konsul Kjeldsen, Einar Peter, Nørresundby
AARHUS: Konsul Östergaard, Peder Jensen, Norrebrogade 43
ESBJERG: V. konsul de Molade, Johannes, Nygaardsvej 77
FAABORG: V. konsul Petersen, Johannes, Østerbrogade 18
FREDERICIA: V. konsul Jørgensen, Carl, Fredericia
FREDRIKSHAVN: V. konsul Høy, Carl Johan Danmarksgade 47
HADERSLEV: V. konsul Outzen, Andreas Henrik, Storegade 80
HELSINGØR: Konsul Bang, Erik, Helsingör
HORSENS: V. konsul Raackman, Kai, Horsens
KALUNDBORG: V. konsul Christensen, Marinus, Kalundborg
KOLDING: Konsul Christensen, Oskar, Jernbanegade 52
KORSØR: Konsul Mogensen, Erik Carl Julius, Havnegade 17
NAVSKOV: V. konsul Krøyer, Tønnes Georg, Nygade 4
NESTVED: V. konsul Grönholt, Rasmus Nielsen, Jernbanegade 3
NYBORG: V. konsul Schmidt, Bertil Peter
ODENSE: Konsul Henningo, Ove, Dronningensgade 3
RANDERS: V. konsul Høyer, Harald Sand, Carrøesgade 2
RØNNE: V. konsul Bidstrup, Elfred, Rønne
SVENDBORG: V. konsul Høyvald, Emil, Møllergade 64

SØNDERBORG: V. konsul Falkenberg, Peter Christen, Norre Havnegade 70

VESTERVIG: V. konsul Jepsen, Poul Carl Christian, Vestervig

TURKIET

ANKARA: Utomord. sändebud och befullm. minister Yrjö-Koskinen, Aarno Sakari, Günes Sokak 3, Kavaklidere
Handelsattaché Kala, Toivo Ilmari

ISTANBUL: Gen. konsul Tüten, Husseyin Sabri
V. konsul Weckman, K. B.
V. konsul Tammivuori, R. Olavi

ANKARA: Konsul Ahmet Hanifoglu, Ankara

MERSINA: Konsul Fevzi Yakup, Mersina

SAMSUN: Konsul Süleiman Balcam Messfut, Samsun

URUGUAY

MONTEVIDEO: Gen. konsul Mc Lean, Jorge

I fall Ni önskar upplysning i frågor om könssjukdomar och behandlingen av desamma, kan ni skriftligen vända Er till Föreningen för könssjukdomarnas bekämpande r.f. Adr.: Helsingfors, Unionsg. 45 B. 23.

FÖRENINGEN FÖR KÖNSSJUKDOMARNAS BEKÄMPANDE r.f.

A B C of Sex Hygiene

Tämä on Maikki.
Maikissa on eräs tauti.
Sen tavallinen nimi on
"pahatauti" tai"kuppa".
Maikin taudin oikea ni-
mi on syfilis. Maikki
sai syfiliksen eräästä
miehestä. Syfilis voi-
daan todeta verikokeella.

Detta är Maj.
Hon plågas av en sjukdom.
Den kallas vanligen en
"ful sjukdom" eller "syff".
Sjukdomens rätta namn är
syfilis. Maj fick den av
en man. Syfilis kan
konstateras medelst
blodprov.

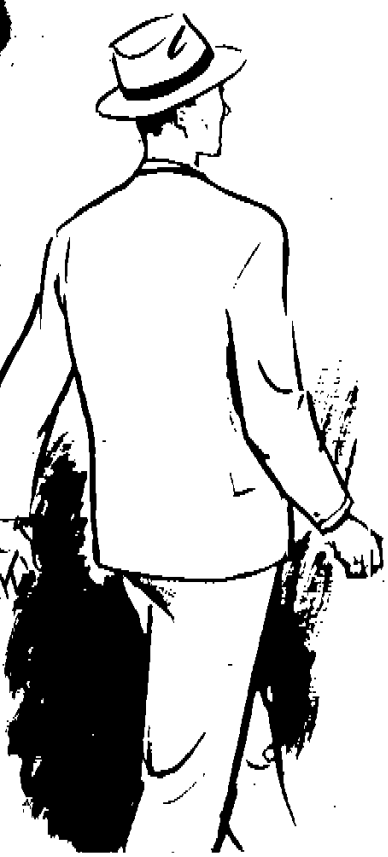
Tämä on Jukka.
Jukka lähti "juhlimaan"
Maikin kanssa.
Hän sai Maikista syfi-
liksen. Syfilis leviää
sukupuoliyhdynnän väli-
tyksellä. Syfilis on
aina saatu jostakusta
toisesta henkilöstä.
Taudin alkuoireet jää-
vät usein huomaamatta.

Detta är John.
John gick ut och "festa"
med Maj. Han fick syfi-
lissmitta av Maj. Syfi-
lis sprides genom
könsumgänge. Syfilis
kommer alltid från någon
annan person. Sjukdomens
första symptom bli ofta
obeakjade.

Maikin sukuelimissä oli ollut aikaisemmin pieni haavautuma (ennen kuin hän tapasi Jukan.) Maikki ei mennyt lääkäriin. Haavauma katosi. Kuitenkin Maikki tunsi pitkät ajat olevansa kehnossa kunnossa. Hän ei tietänyt sairastavansa syfilistä.

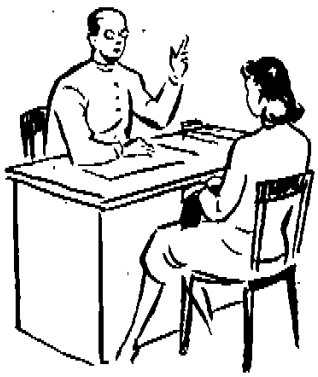
Majs könsorgan hade haft en liten sårbildning. Maj gick ej till läkare. Sårbildningen försvann. Men länge kände sig Maj vara vid dålig vigör. Hon visste ej att hon led av syfilis.

KLINIKKA



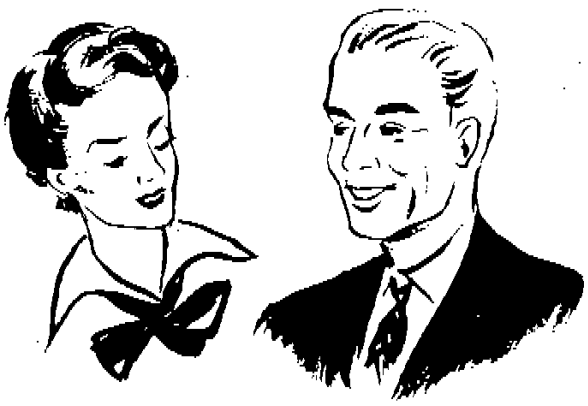
Myöhemmin huomasi Jukkakin itsessään haavauman. Jukka meni lääkäriin, joka paransi hänet. Lääkäri selitti, että Jukka oli saanut syfiliksen sukupuoliyhteyden välityksellä jostakusta, joka sairasti tuota tautia. Jukka tiesi, että "tuo joku" oli Maikki.

Senare konstaterade aven John en sårbildning. Han gick till en läkare som botade honom. Läkaren förklarade att John hade fått syfilis genom könsumgänge med någon, som hade denna sjukdom. John visste att denna "någon" var Maj.



Jukka lähetti Maikin lääkäriin.
Lääkäri tutki Maikin.
Hän selitti, että Maikissa oli syfilis. Hän lupasi hoitaa myös Maikkia. Maikki tulee pian terveeksi.

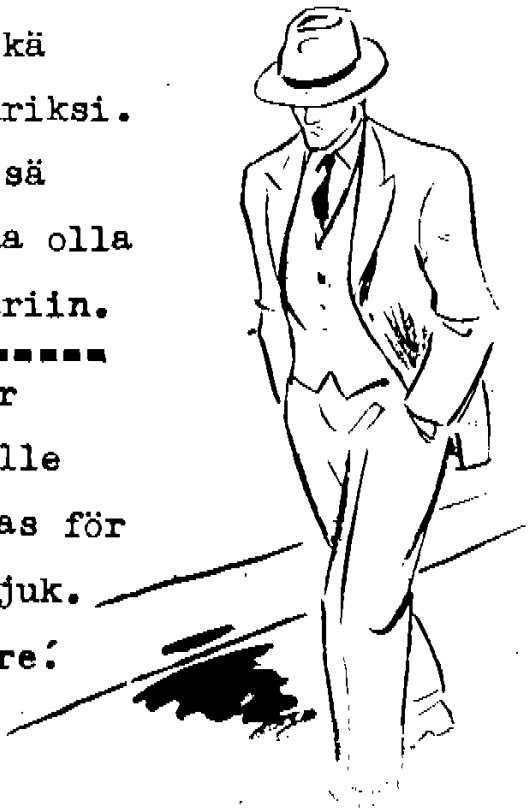
John sände Maj till läkare.
Denna undersökte Maj och förklarade att Maj hade syfilis. Han lovade sköta Maj. Maj blir snart frisk.



He ovat ystävyksiä. He eivät ryhdy sukupuoliyhteyteen ennen kuin ovat naimisissa. Heihin ei voi syfilis tarttua. Naimisiin ehdittyään he saavat terveitä lapsia. Heleä ja Heikkiä odottaa onnellinen koti.

Här äro Helen och Henrik. De äro goda vänner. De inlåta sig ej på könsumgänge förrän de äro gifta. De kan ej bli besmittade av syfilis. Sedan de gift sig få de friska barn. De komma att få ett lyckligt hem.

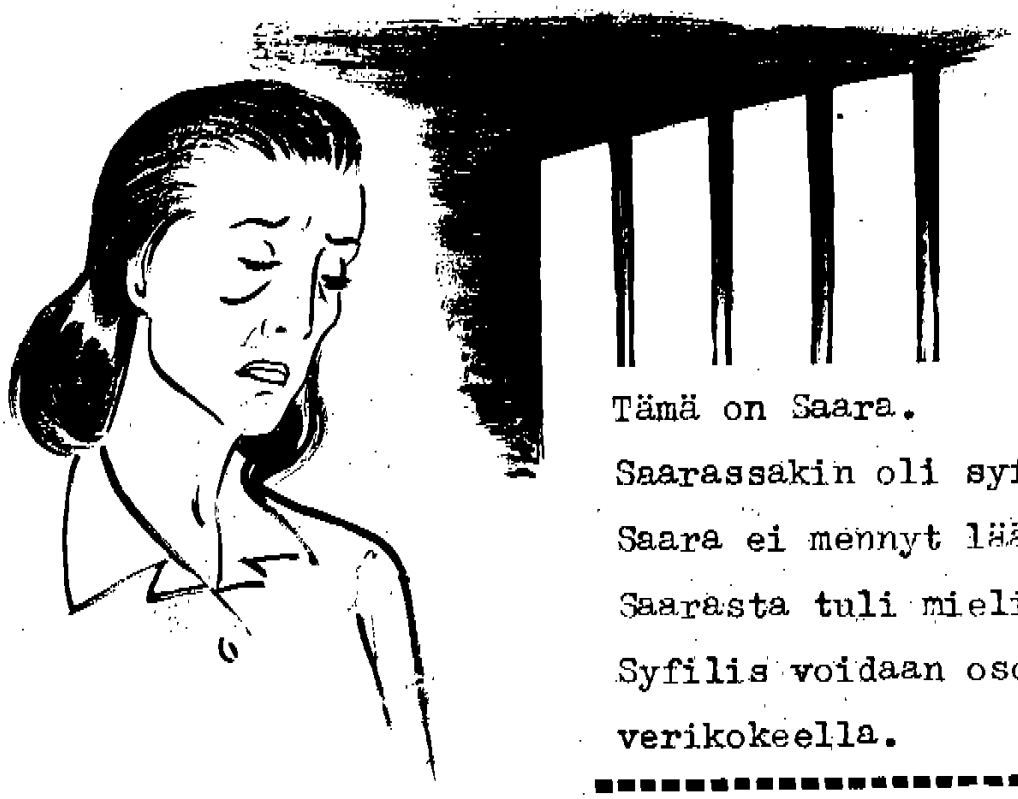
Kallea väsyttää aina. Hän ei pysty kunnolliseen työhön. Kalle ei tiedä, mikä häntä vaivaa. Häntä haukutaan laiskuriksi. Mutta Kalle on todella sairas. Hänessä saattaa olla syfilis. Hänessä saattaa olla gonorrea. Kallen pitäisi mennä lääkäriin.



Kalle känner sig alltid trött. Han är oförmögen till ordentligt arbete. Kalle vet ej vad som felas honom. Han kallas för en lätting. Men Kalle är verkligen sjuk. Han kan ha syfilis. Han kan ha gonorre. Kalle borde gå till en läkare.

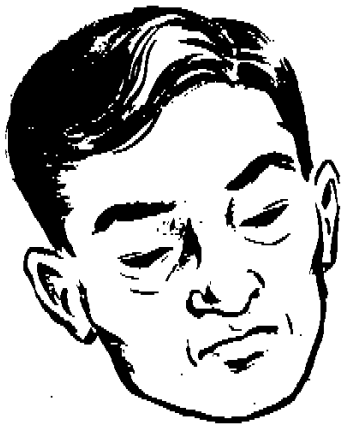
Tämä on Jammu.
Jammussakin oli syfilis.
Hän ei mennyt lääkäriin.
Hän kuoli ennen aikojaan.
Syfilis hänet otti hengiltä.

Detta är Jammu. Även han har syfilis. Han gick ej till läkare. Han dog i tidig ålder. Syfilis tog livet av honom.



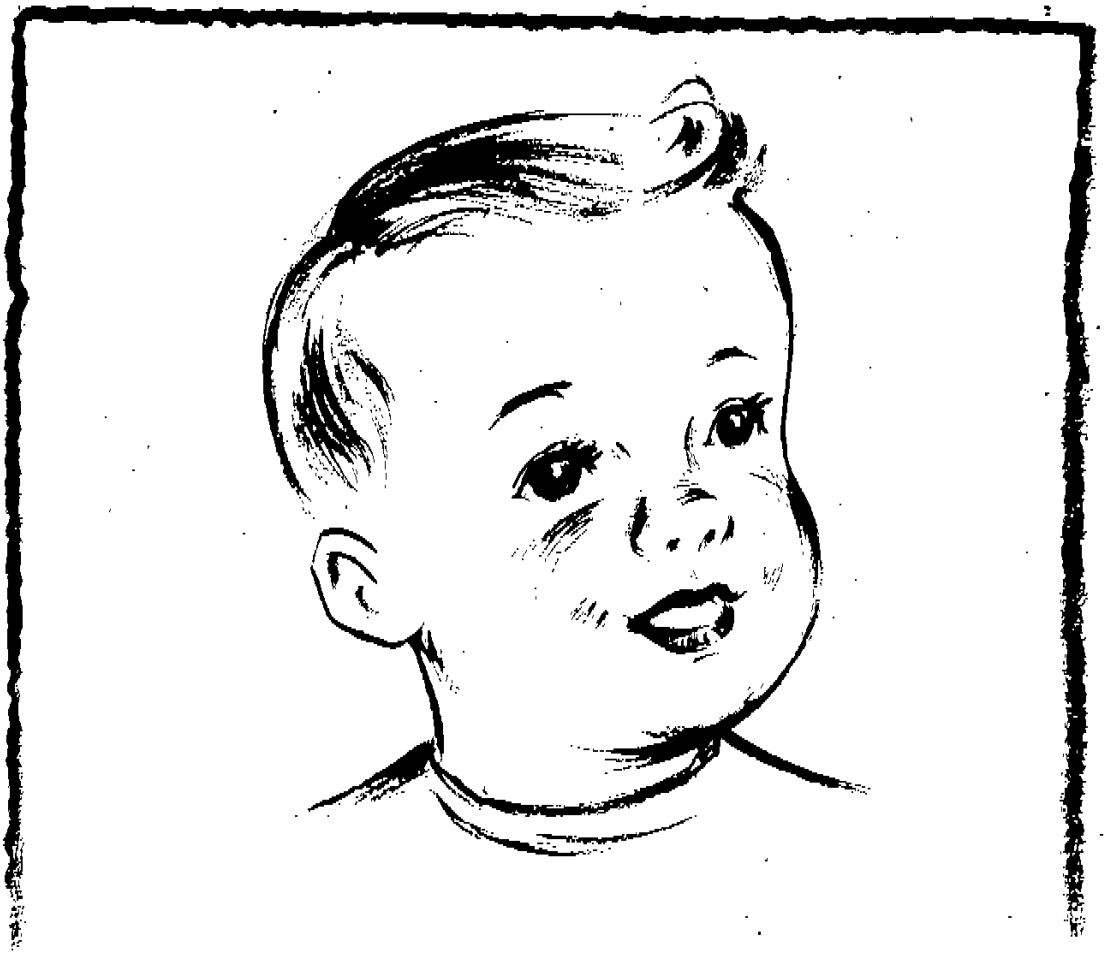
Tämä on Saara.
Saarassakin oli syfilis.
Saara ei mennyt lääkäriin.
Saarasta tuli mielipuoli.
Syfilis voidaan osoittaa verikokeella.

Detta är Sara. Även Sara hade syfilis. Sara gick ej till läkare. Sara blev vansinnig. Syfilis kan påvisas medelst blodprov.



Tämä on Ville. Villessä oli syfilis. Hän meni naimisiin Sylvin kanssa. Syfilis tarttui hänestä Sylviin. Sylvin esikoinen syntyi kuolleena. Sylvin toisessa lapsessa oli syfilis jo syntyessä. Lapsi ei elänyt monta viikkoa.

Detta är Ville. Ville hade syfilis. Han gifte sig med Sylvi. Även Sylvi blev syfilisbesmittad. Sylvis första barn kom dödfött till världen. Även det andra barnet hade syfilis redan vid födelsen. Barnet levde ej många veckor.



Tämä vekara on Jaakko. Hänen vanhempansa ovat terveitä.
Ja hän on itsekin terve. Naapurin poika ei elänyt kauan. Hänen vanhemmissaan oli syfilis. Poika sai tartunnan jo ennen syntymäänsä, koska äitiä ei hoidettu raskauden aikana.

Denna byting heter Jacke. Hans föräldrar äro friska, och även själv är han frisk. Grannens gosse levde ej länge. Hans föräldrar hade syfilis. Gossen fick smiltan redan före sin födelse, då hans mor ej blev omskött under graviditetstiden.

ei ole syfilistä. Mutta Hertassa on eräs toinen tauti. Sitä nimitetään yleensä "tippuriksi". Hertan taudin toinen nimi on gonorrea. Hertta sai gonorrean eräästä miehestä. Gonorrea tarttuu sukupuoliyhdynnässä, jos toisessa henkilössä on gonorrea. Hertta meni lääkäriin.

Lääkäri paransi hänet muutamassa tunnissa. Lääkäri selitti lisäksi, että gonorrea saattaa tarttua Herttaan uudestaankin. Hän selitti myös, millä tavoin tämän taudin voi välttää. Mutta Hertta unohti kaiken. Ja pian hän sairastuikin uudestaan, koska oli ryhtynyt sukupuolisuhteisiin erään toisen gonorreaa sairastavan miehen kanssa.

Detta är Hertta. Hertta har ej syfilis. Men hon har en annan sjukdom. Den kallas i allmänhet dröppel. Sjukdomens andra namn är gonorré. Hertta fick sjukdomen av en man. Gonorré smittar genom könsumgänge, om den andra parten har gonorré. Hertta gick till en klinik. Läkaren förklarade vidare, att Hertta kan få gonorrésmittan på nytt. Han förklarade även hur sjukdomen kan undvikas. Men Hertta glömde allt. Snart insjuknade hon på nytt, ty hon hade varit i könsumgänge med en annan man som hade gonorré.

Tämä on Paavo. Eräänä päivänä Paavo huomasi saaneensa gonorrean. Hän osti apteekista jotakin lääkettä. Paavo haaskasi paljonkin rahaa lääkkeisiin, mutta ei parantunut. Lääkäri olisi parantanut hänet muutamassa tunnissa. Miksi Paavo ei mennyt lääkäriin? Hän olisi voinut saada hoidon ilmaiseksi.

Detta är Paul. En dag upptäckte Paul att han fått gonorré. Han köpte på apoteket någonslags medicin. Paul slösade mycket pengar på medicin, men blev ej bättre. Läkaren hade botat honom på några timmar. Varför gick Paul ej till läkare? Han hade kunnat erhålla behandlingen gratis.

[illegible]än on kunnon tyttö.
Kaikki pitävät hänestä. Pojat ihailevat häntä. He kunnioittavat häntä.
Hilkka osaa elää siivosti. Hilkkaan eivät sukupuolitaudit tartu.

Detta är Hilkka. Hon är en bra flicka.
Gossarna beundra henne. De högakta henne. Hilkka kan leva ordentligt. Hon blir ej besmittad av könssjukdomar.

On viisasta elää siivosti.

Kom alltid ihåg:

Det är klokt att leva ordentligt

Syfiliksen alkuoireet: haavauma, ihottumat ym. voivat hävitä hoidottakin tai jäädä huomaamatta, mutta tauti ei parane. Sydämen ja aivojen vioittumat tulevat esille vasta monien vuosien kuluttua. Ja äidistä tauti tarttuu lapseen jo raskauden aikana - lapsi usein kuolee tai vioittuu vaikeasti. Tauti voidaan osoittaa verikokeella. - On lääkkeitä, joilla se paranee.

Gonorrean seurauksia on mm. hedelmättömyys. Sen aiheuttajan voi lääkäri helposti osoittaa ja nykyisin hoito kestää vain vuorokauden.

Virkalääkäri hoitaa sukupuolitauteja maksutta.

Sukupuolitauteja koskeviin kirjeellisiin kyselyihin vastaa Sukupuolitautien Vastustamisyhdistys (H:ki, Humalistonk. 1.B.33).

Fakta:

De första syfilissymptomen: sårbildning, utslag mm. kunna försvinna även utan vård eller bli obeaktade, men sjukdomen finnes kvar. De rubbningar sjukdomen åstadkommit i hjärnan och nerverna framträda först efter åratal. Barnet får sjukdomen av sin mor redan under graviditetstiden - det dör ofta eller får svåra defekter. Sjukdomen kan konstateras medelst blodprov. Den kan botas med läkemedel.

Gonorré förorsakar bl.a. sterilitet. Dess förorsakare kan läkaren lätt påvisa och numera går den att bota på ett dygn.

Tjänsteläkaren behandlar könssjukdomarna gratis.

På skriftliga frågor beträffande könssjukdomar svarar Föreningen för Könssjukdomarnas Bekämpande (H:fors, Hummelg. 1.B.33).

Lehtisen laatimat

Sukupuolitautien Vastustamisyhdistys r.y.

Broshyren har utgivits av

Föreningen för Könssjukdomarnas Bekämpande r.f.

Helsinki 1949. OFFSET Oy:n offsetpaino.

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Eripainos Suomen Lääkärilehdestä N:o 15, 1951

	1923	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	
Syphilis TAULU I	0.9	0.5	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.6	0.6	0.5	0.6	0.4	0.5	0.7	0.4	0.3	0.3	0.5	0.3	0.4	0.3	0.1	0.1	0.4	0.2	0.6	‰ 55a : Per 1000 of Pop
Gon. TAULU I	2.9	2.6	2.7	2.6	3.4	3.2	3.3	3.1	2.9	2.9	2.9	3.1	2.7	2.6	2.7	2.6	2.7	2.6	2.1	2.6	2.1	2.4	2.1	1.9	1.7	1.9	2.4	1.6	‰ 55a Per 1000 of Pop
Syphilis TAULU II	1922	1729	1859	1782	2536	2544	2469	2501	2490	2501	2391	2251	2141	1775	1472	1426	1501	1423	1233	2064	3270	5234	2998	3566	4769	3164	1845	865	391	Tapauksia ; Cases
Gon. TAULU II	1516	1989	1935	1950	1230	1055	1033	1578	1088	1056	1093	1617	1039	1866	2548	1865	1568	1866	1834	2223	4290	4205	2556	1865	1559	1261	1459	662	629	
Syphilis ♂ TAULU III																	0.45	0.46	0.45	0.68	0.98	1.40	0.84	1.23	1.51	0.90	0.45	0.21	0.11	‰ 55b Per 1000 of male Pop
Syphilis ♀ TAULU III																	0.23	0.19	0.19	0.46	0.70	1.04	0.64	0.73	0.89	0.64	0.32	0.18	0.08	‰ 55a Per 1000 of fem Pop
Gon. ♂ TAULU IV																	3.61	3.19	3.41	3.99	4.12	5.61	5.23	3.96	6.83	5.57	4.41	2.89	2.66	‰ 55a Per 1000 of male Pop
Gon. ♀ TAULU IV																	0.91	0.74	0.75	0.94	1.20	1.82	1.65	1.25	1.37	1.15	1.31	1.06	1.01	‰ 55a Per 1000 of fem Pop
S. Congenit TAULU V																														Tapauksia ; Cases
S. Congen. 0-4, TAULU V																							80	82	49	66	59	78	53	42	Tapauksia (0-4) Cases (0-4 y.)
S. Congen + TAULU VI																	0.31	0.29	0.23	0.21	0.21	0.21	0.45	0.53	0.50	0.29	0.34	0.28	0.09	0.18	‰ 55a syntyneistä Per 1000 of live births
Syphilis TAULU VIII									140	215	231	242	206	226	248	219	265	164	190	192	168	188	216	266	203	224	173	174		Tapauksia ; Cases
Ulcus molle TAULU III	898	1216	1490	1569	2260	2380	2175	1996	1382	1106	810	622	528	463	572	575	292	155	156	110	62	26	65	32	19	9	9	3	Tapauksia ; Cases
Lymphogr. ing. T. X													32	163	119	36	29	12	13	9	5	4	2	2	2	2	2	0	Tapauksia ; Cases

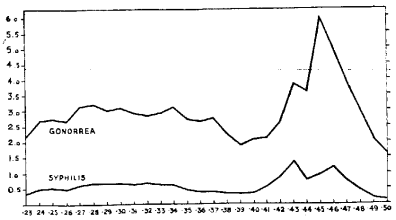
Taulu 11. Luvut taulukoissa 1—10. *Table 11.* Numbers in Tables 1—10.

Tilastoja sukupuolitaudeista Suomessa.

S. Härö.

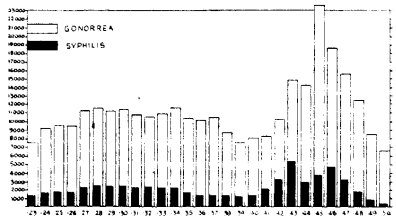
Viime vuosina on maassamme voitu todeta tarttuvassa vaiheessa olevien sukupuolitautien ilahduttavassa määrässä vähentyneen. Nopeasti on sotien jälkeen saavutettu tilanne, joka hyvin kestää vertailun esim. Ruotsin esimerkillisenä pidetyn sukupuolitilanteen kanssa. (5) Hermosyfilis ja synnynnäinen syfilis eivät toistaiseksi kuitenkaan mainittavasti näytä vähentyneen. Sukupuolitauteja koskevia tilastoja on julkaistu useissakin yhteyksissä, (1, 4, 5) mutta erikoisesti käytännöllisessä vastustamistyössä on kaivattu yhteenvetoa, johon esim. propagandassa voidaan vedota. Oheiset käyrästöt ja pylväiköt perustuvat Lääkintöhallituksen vuosikertomuksiin ja julkaisemattomiin tilastoihin samoinkuin Tilastollisen Päätoimiston antamiin tietoihin. Armeijan sukupuolitautiluvut on lisätty siviililukuihin ja perustuvat taulukoissa 1—4 olevat tiedot vv. 1923—47 Putkosen (4) julkaisemaan tilastoon. Suhdeluvut $^0/_{00}$:ssa on laskettu rekisteröidyn väestön keskiväkilukuun verrattuna. Taulu 5, joka esittää todettuja Lues congenita tapauksia, on 0—4 vuotiaiden osalta vuosina 1943—47 osittain arvioitu, koska ikäryhmitys tilastoissa oli tällöin 0—2 vuotta ja vasta myöhemmin 0—4 vuotta. Taulussa 7 on sairaalahoitoon otetut syfilispotilaat esitetty viisivuotiskausittain yhdistettyinä keskiarvoina. Taulukosta 11 voidaan tarvittaessa etsiä luvut, joihin graafiset esitykset perustuvat.

Tilastoja sukupuol. udeista Suomessa.



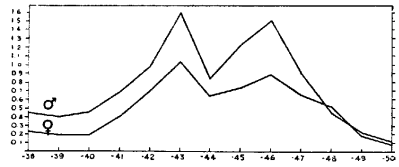
Taulu 1.
Ilmoitettuja Lues recens ja Gonorrhea tapauksia $^0/_{00}$:ssa väestöstä 1923—50.

Table 1.
Reported Cases of Early Syphilis and Gonorrhea 1923—50 per 1000 of Population.



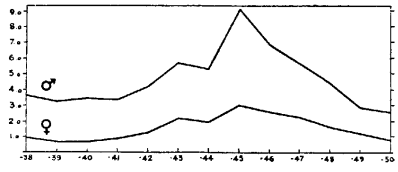
Taulu 2.
Ilmoitettujen Lues recens ja Gonorrhea tapausten määrä vuosittain 1923—50.

Table 2.
Number of Reported Cases of Early Syphilis and Gonorrhea 1923—50.



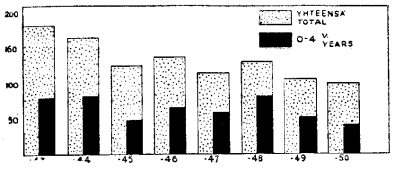
Taulu 3.
Ilm. Lues recens tapauksia naisilla ja miehillä $^0/_{00}$:ssa nais- ja miespuolisesta väestöstä. 1938—50.

Table 3.
Reported Male and Female Cases of Early Syph. per 1000 of Male and Female Population.



Taulu 4.
Ilm. Gonorrhea tapauksia naisilla ja miehillä $^0/_{00}$:ssa nais- ja miespuolisesta väestöstä 1948—50.

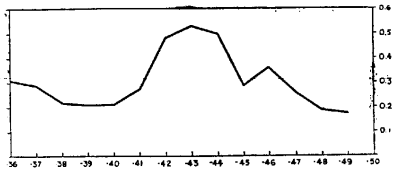
Table 4.
Reported Male and Female Cases of Early Syph. per 1000 of Male and Female Population.



Taulu 5.
Todettuja Lues congenita tapauksia 1943—50.

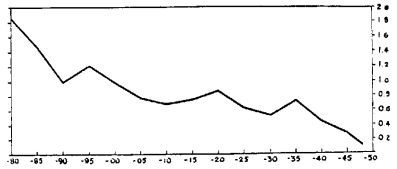
Table 5.
Reported Cases of Congenital Syphilis 1943—50.

Incidence of Venereal iseases in Finland.



Taulu 6.
Lues congenita. Alle 1 v. iässä kuolleet vuosittain $^0/_{00}$:ssa syntyneistä 1936—49.

Table 6.
Syphilis Infant Mortality Rate per 1000 Live Births 1936—49.

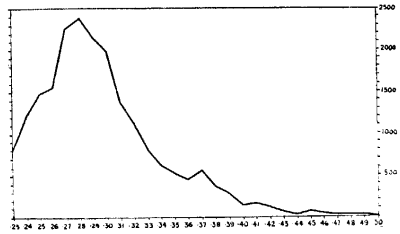


Taulu 7.
Syfiliksen vuoksi sairaalahoitoon otetut $^0/_{00}$:ssa väestöstä 1879—1948.

Table 7.
Syphilities Hospitalized per 1000 of Population 1879—1948.

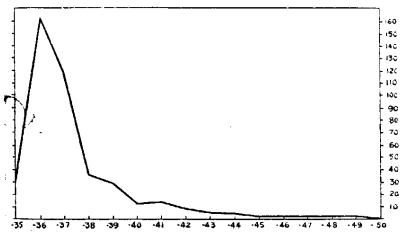
Taulu 8.
Syfiliksen aiheuttaman mielisairauden vuoksi ensi kertaa sairaalahoitoon otetut 1930—49.

Table 8.
Cases of Neurosyphilis Hospitalized for the First Time per 1000 of Population 1930—49.



Taulu 9.
Ilmoitettuja Ulcus molle tapauksia 1923—50.

Table 9.
Reported Cases of Chancroid 1923—50.



Taulu 10.
Lymphogranuloma inguinale. Ilmoitetut tapaukset 1935—50.

Table 10.
Reported Cases of Lymphogranuloma Venerum 1935—50.

Syfilis förorsakar förändringar i blodet och kan påvisas nästan samtidigt som såret uppstår. Förändringarna i blodet försvinner inte, varför sjukdomen alltid kan påvisas genom blodprov. Om blodprovet är negativt, behöver man inte oroa sig för sjukdomen. Blodprov kan tagas av varje läkare.

DRÖPPEL är en könssjukdom, som förorsakas av bakterier, som lever på könsorganens slemhinna. Sjukdomen smittar genom könsumgänge. Några dagar efter det man blivit besmittad, uppstår sveda i könsorganen och nästan samtidigt avsöndrar slemhinnorna var, som yttrar sig i flytning t. ex. från urinröret. Hos män är symptomen för det mesta tydliga, men hos kvinnor däremot ofta obetydliga. Sjukdomen kan obemärkt utbreda sig och åtföljes då av ledsamma sviter. Ifall sjukdomen ej behandlas, kan den förorsaka långvariga inflammationer t. ex. i kvinnans äggstockar, och den kan förorsaka ofruktsamhet såväl hos män som kvinnor. De bakterier, som förorsakar dröppel, tränger sig i allmänhet inte genom slemhinnan, ej heller åstadkommer sjukdomen förändringar i övriga organ.

Dröppel kan snabbt botas.

Penicillinbehandling förgör dröppelbakterierna förvånansvärt hastigt och har härigenom väsentligt underlättat läkarens arbete. Endast en läkare kan med säkerhet igenkänna denna sjukdom och behandla den.

Även behandlingen av dröppel är kostnadsfri.

Men könssjukdomarna är ingalunda de enda ledsamma följderna av ett lättsinnigt könsumgänge. En ung människa kan förlora sin självaktning, hon förmår ej upprätthålla de ideal, som hon har skapat sig i sitt hem, i sin skola eller i skriftskolan. Gör ditt liv innehållsrikt, intressera dig för allt, som är gott, studera och roa dig på ett rätt sätt. Detta är det bästa sättet att undvika dåligt sällskap och dåliga seder. Ett sådant liv åtföljes av såväl andlig som materiell välsignelse.

FÖRENINGEN FÖR KÖNSSJUKDOMARNAS BEKÄMPANDE. — MEDICINALSTYRELSEN.

Helsingfors 1949. Statsrådets tryckeri

Vi litar på ungdomen...

(Also printed in Finnish, but these are all gone)

Ungdomen har numera mycket större frihet än förut. Var tids ungdom får själv välja sitt sällskap och sina intressen, den övervakas inte nära på samma sätt som tidigare generationers.

MEN ungdomen har även ansvar för sin framtid — större ansvar än förut. Ehuru den har stora möjligheter att utveckla sig i göd riktning, kan den även på mångahanda sätt förminska sina möjligheter att leva ett lyckligt liv. Den kan låta sig förfalla i slöhet och försumma sin utveckling, sina studier och kroppsövningar. I dåligt sällskap kan den förvärva sig dåliga seder, t. ex. missbruk av tobak och alkohol. Det händer därvid lätt, att ungdomen glömmer såväl sin själsliga utveckling som sina andliga behov.

..... Kort sagt. *Med större frihet följer större ansvar.*

KÖNSDRIFTENS överraskande styrka förnimmer den nutida människan redan rätt tidigt. Ifall vi inte har en god andlig beredskap, förmår vi inte tygla den och råka lätt in på villovägar. Könslivet och de i sammanhang därmed stående faktorerna intresserar naturligtvis de unga, men vanligtvis är det så, att sådana „typer" som skrävlar och säger oanständigheter, har de minsta kunskaperna om könslivet och dess allvar.

Kunskap gör tvetydigheter smaklösa.

TILLFÄLLIGA FÖRBINDELSER FÖRE ÄKTENSKAPET ÄVENTYRAR VÅR LIVSLYCKA OCH VÅR SJÄLVAKTNING. Då man låter ett av sina ideal förfalla, förlorar man samtidigt tilltron till sin förmåga att hålla fast vid de övriga. Självdisciplin härdar vår kropp och vår själ. Tillfälliga förbindelser medför svårigheter av olika slag av vilka de själsliga icke är de enda. Det är ett faktum, att könssjukdomarna i de flesta fall sprida sig just på denna väg.

Könssjukdomarna är sjukdomar, som nästan uteslutande smittar genom intimt könsumgänge. De är mycket allvarsamma sjukdomar, som endast kan botas genom läkarbehandling. Obehandlade kan de förorsaka lyten för hela livet.

Ingen insjuknar i en könssjukdom utan eget förvållande. Ett säkert och — märk väl — det enda säkra sättet att undvika könssjukdomar, är att undvika alla förbindelser med trivelaktiga män eller kvinnor..... att undvika könsumgänge utom äktenskapet. Könssjukdomarna är en följd av ett lättsinnigt sedeslöst liv.

VIKTIGA FAKTA.

I vårt land förekommer två olika slag av könssjukdomar: *syfilis* och *dröppel* eller *gonorrhé*. Årligen förekommer i vårt land c. 15,000 fall, vilket är c. 4 gånger mera än t. ex. i Sverige. Efter krigen har antalet fall i hög grad tilltagit. Förut förekom dessa sjukdomar nästan uteslutande i städerna, men numera är de lika vanliga på landsbygden.

SYFILIS

förekommer i alla länder. Upphovet till denna sjukdom är en korkskruvformad mikro-organism, en s. k. spiroket, som är nära besläktad med bakterierna och kan överföras från en person till en annan. Den är farlig ej endast för dig själv, utan även för din tillkommande maka (make), emedan den lever i organismen i åratal. En väntande moder, som lider av syfilis, nedsmittar sitt barn redan före födseln.

..... Denna sjukdom smittar i allmänhet endast genom könsumgänge, då spiroketen tränger genom slemhinnorna in i kroppen. Någon gång kan även sjukdomen smitta genom en kyss eller via ett dryckeskärl, som den sjuke använt. Då 2—8 veckor förflutit sedan man blivit besmittad, uppstår på det ställe, där spiroketen trängt genom slemhinnan, ett litet sår, i allmänhet endast 1 cm i genomsnitt, men ibland kan såret vara så obetydligt, att man inte observerar det. Om någon vecka läkes såret, men samtidigt sprider sig spiroketerna i organismen och påbörjar sitt förstörelseverk. Ifall den sjuke icke blir behandlad, uppstår om någon vecka på huden ett karakteristiskt utslag och den sjuke har temperaturstegring och besväras av huvudvärk. Även långvarig inflammation i svalget och heshet kan ibland tyda på syfilis. Ibland förstoras endast lymfkörtlarna och håret faller fläckvis av. En svår omständighet är, att även dessa symptom kunna vara rätt obetydliga, så att den sjuke ej uppsöker läkare. Detta är ödesdigert, ty sjukdomen håller sig härefter dold och först flere år senare uppflammar den helt oväntat på nytt. Den förstör då vår kropps ädlaste organ såsom hjärnan, hjärtat och blodkärlen eller levern o. s. v. Då kan ej ens den bästa möjliga behandling längre förnya de förstörda vävnaderna, i bästa fall kan man förhindra sjukdomens vidare fortskridande.

SYFILIS KAN BOTAS.

Ju förr behandlingen påbörjas, dess bättre resultat. Så snart behandlingen påbörjas, försvinner risken för smitta, varför sjukdomen icke behöver åstadkomma avbrott i arbetet. Endast läkaren igenkänner med säkerhet sjukdomen och kan behandla den. ...

Behandlingen är enligt lag kostnadsfri.

VERIKOE ON OTETTAVA RASKAUDEN ALKAESSA, SEKÄ TOISTETTAVA SEN LOPPUPUOLELLA.

Syfilis voidaan aina parantaa äidistä, mutta hänen lapsensa terveyttä ei voida aina ehdottomalla varmuudella turvata, ellei hoitoa aloiteta hyvissä ajoissa ennen lapsen syntymää.

Verikoe on siis otettava raskauden alkaessa, mutta se on myöskin toistettava raskauden loppupuolella. Hoito on heti aloitettava.

Penisilliini on nopein ja varmin lääke. Meilläkin on penisilliiniä saatavissa raskaiden kuppatautisten äitien hoitamiseksi. **Hoito on ilmaista.**

Penisilliinin tähän tarkoitukseen on lahjoittanut Y.K:n Lastenapu (UNICEF)

ÄITI ....

Äiti — olet suuressa vastuussa lapsellesi ja koko yhteiskunnalle. Pieni verimäärä, joka kokeessa tarvitaan, ottaa harteiltasi suurimman osan vastuusta. Pyydä siis se ottamaan heti — parempi myöhään — kuin liian myöhään.

Saanko pojan vaiko tytön?

Ei taitavinkaan lääkäri voi vastata siihen, mutta syfiliksestä voidaan lapsemme varmasti pelastaa.

Cartoons for mothers who have Syphilis

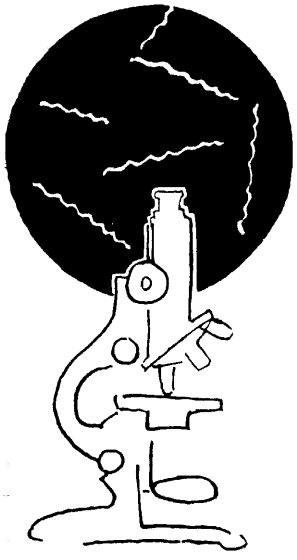
KERTOMUS ÄIDEISTÄ JOISSA OLI SYFILIS

SUKUPUOLITAUTIEN VASTUSTAMISYHDISTYS RY — LÄÄKINTÖHALLITUS

JOKAINEN ÄITI....

haluaa saada terveen lapsen ja hän tietää, että sen vuoksi on hänen saatava paras hoito jo raskauden aikana. Ja kun lapsi on syntynyt, voi äiti ylpeänä näyttää lastansa, joka terveenä ja rakkaudella hoidettuna hymyilee tyytyväisenä koko uudelle suurelle maailmalle. Mutta kaikki lapset eivät ole yhtä onnellisia.

SYFILIS — SYNTYMÄTTÖMÄN LAPSEN PAHIN VIHOLLINEN



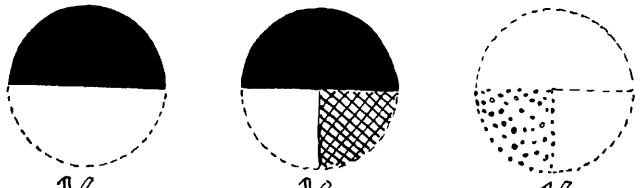
Sadat lapset syntyvät maailmaan, jossa heitä odottavat onnettomuus ja kärsimykset. Nämä lapset ovat sairaita — he ovat äidiltään saaneet raskauden aikana kalvavan, tuhoavan jopa tappavan sairauden, joka on piillyt äidin ruumiissa näyttämättä mitään ulkonaisia oireita. On tapahtunut sellaista, mitä äiti ei ole osannut lainkaan odottaa — lapsessa on syfilis — syntymättömien lasten pahin vihollinen.

Tällainen lapsi sairastaa synnynnäistä syfilistä eli kuppatautia. Usein isä on tartuttanut taudin äitiin — hänestä taasen lapsi saa tartunnan 5—6 raskauskuukauden aikana.

MITÄ SYFILIS ON?

Se on mikroskooppisen pienen kierteisen olion aiheuttama tauti. Se tarttuu yleensä vain sukupuoliyhteydessä aiheuttaen usein aluksi pienen haavauman tarttumiskohtaan, saattaa myöhemmin aikaansaada kuumetta, ihottumaa ja muitakin oireita, mutta voi myös jäädä aivan huomaamatta. Oireet häviävät muutaman kuukauden kuluessa, mutta tauti ei parane, vaan piilee vuosikausia — jopa kymmeniä.

Hoitamatonta kuppatautia — piileväkin — sairastavan äidin synnyttämistä lapsista on tehty tilastoja. Tällainen on ollut tulos:



1/2 lapsista kuoli ennen syntymää,

1/4 lapsista kuoli alle 3 kk ikäisinä,

1/4 oli enää elossa 3 kk kuluttua.

MITÄ OIREITA ON LAPSESSA?

Eloon jääneitä on siis vain 1/4 ja nämäkin usein ovat sairaita. Ne kehittyvät hitaasti, usein vaivaa lapsia silmäsairaudet, kuulo voi tulla huonoksi, iholla on haavaumia, hampaissa ja luustossa on epämuodostumia. Ja mikä pahinta — henkinen kehitys viivästyy, jopa pysähtyykin. Joskus kehitys voi olla normaalia kouluikään asti, mutta nuoressa lapsessa on syfilis tehnyt jo tuhojaan ja lopuksi oireet ilmenevät sitä pahempina.

AINOANKAAN LAPSEN EI TARVITSE SAIRASTAA SYFILISTÄ

Terveet vanhemmat ovat paras vakuutus terveen lapsen saamisesta. Meillä on olemassa verikokeita, jotka osoittavat ovatko vanhemmat vapaita taudista. Jokaisen äidin on otettava raskauden alkuaikana tällainen koe — neuvolassa se otetaan ilmaiseksi.

ACTA DERMATO-VENEREOLOGICA
VOL. 31 SUPPLEMENTUM 24

TRANSACTIONS
OF THE
INTERNATIONAL SYMPOSIUM
ON THE STUDY OF SYPHILIS

HELD UNDER THE AUSPICES OF
THE STATE MEDICAL BOARD OF FINLAND
AND
THE WORLD HEALTH ORGANIZATION

HELSINKI, FINLAND, 4—10 SEPTEMBER, 1950

HELSINKI
MERCATORIN KIRJAPAINO
1951

Participants in the Symposium in the park of Kumpula Hospital, Helsinki.

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1951

The collection and arrangement of the papers presented, and the roundtable discussions held at the International Symposium for the Study of Syphilis, Helsinki, has been carried out by:
Tauno Putkonen, M.D., M.P.H., and
Frank Reynolds, M.D., M.P.H.

FOREWORD

The year 1950 offered the first real opportunity for taking stock of methods used to overcome the health emergencies inherited from the second world war. Particularly was this true in the field of venereal disease control in Europe. Here, the resolute pursuit of large scale campaigns by National Health Administrations limited opportunities for an exchange of ideas and experiences which would have been a feature of more normal times.

The World Health Organization has shared in the fight against syphilis in a variety of ways in Europe since the end of the war. It now co-sponsors with the Governments of Finland and France consecutive symposia on some aspects of the modern control of syphilis. At these two symposia the experts of at least 16 countries representing the traditional European schools met in round table discussion with their colleagues from the United States of America.

It is always something of an undertaking to attempt reproduction in a readable form of the lively and informal discussions which form an integral part of symposia, and, indeed, represent its true value. The authors of the publication on the International Symposium on the Study of Syphilis in Helsinki are to be congratulated on having completed this difficult task. It is hoped that, by assisting in this publication, the European Office of the World Health Organization will have furthered in some way the exchange of ideas and experience amongst venereal disease experts in other parts of the world.

Norman D. Begg, M.D., D.P.H.
Chief, Special Office for Europe
World Health Organization

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SUMMARY OF TRANSACTIONS

INTRODUCTION

It has been recognized for some time that a different outlook has governed syphilotherapy and serodiagnosis in syphilis in different parts of the world. The uneven production, distribution and availability of penicillin preparations and cardiolipin antigens, with resulting rapid accumulation of scientific data in some countries, while experience is being gained more slowly in others, is only part of the overall picture. A more direct contact between outstanding experts with varied experience in syphilis control would make for a more fruitful exchange of technical information.

To this end the World Health Organization took the initiative to encourage round-table discussions on syphilis in Europe in 1950, resulting in the International Symposia on the Study of Syphilis in Helsinki and Paris, so well organized by the Finnish and French Health Administrations. In this work, Frank Reynolds, M.D., M.P.H. of the Venereal-disease and Treponematoses Section of WHO Headquarters, and Alain Spillmann, M.D. WHO Regional Adviser for Europe, acted as liaison officers with the respective health administrations.

The transactions of the Helsinki symposium are published in English in the present supplement of the Acta Dermato-Venereologica Scandinavica and those of the Paris symposium in Prophylaxie Antivénérienne.

Thorstein Guthe, M.D., M.P.H.
Chief, Venereal-disease and
Treponematoses Section
World Health Organization

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PARTICIPANTS IN THE SYMPOSITUM

MAIN SPEAKERS

Dr. P. Møller, Senior Associate, University Venereal Disease Clinic, National Hospital, Copenhagen, Denmark.

Dr. T. Putkonen, Chief, Kumpula State Hospital for Venereal Diseases, Helsinki, Finland.

Dr. T. Vogelsang, Professor of Bacteriology, Gade's Institute, Bergen, Norway.

Dr. E. Hollström, Assistant Professor in Dermatology and Venereology, Karolinska sjukhuset, Stockholm, Sweden.

Dr. B. Dattner, Associate Professor, New York University and Special Consultant, Rapid Treatment Centre, Bellevue Hospital, New York City, N.Y., USA.

Dr. N. Ingraham, Assistant Professor of Dermatology and Syphilology, School of Medicine and Graduate School of Medicine, Associate Director Institute for the Study of Venereal Diseases, Chief, Division of Venereal-Disease Control, Department of Public Health, Philadelphia, USA.

Dr. M. Pangborn, Senior Biochemist, Division of Laboratories and Research, New York State Department of Health, Albany, N.Y., USA.

Dr. C. Rein, Associate Professor of Dermatology and Syphilology Post Graduate Medical School, New York University — Bellevue Medical Centre, New York City, N.Y., USA.

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Dr. A. Perdrup, Senior Associate, Rudolph Bergh's Hospital for Dermato-Venereology, Copenhagen, Denmark.

Dr. A. Reyn, Assistant Director, Serodiagnostic Department, State Serum Institute, Copenhagen, Denmark.

Dr. S. Donner, Chief, Department of Neuropsychiatry, Kivelä Hospital, Helsinki, Finland.

Dr. O. Enkvist, Chief, Finnish Hospital for Congenital Syphilis, Helsinki, Finland.

Dr. M. Kaila, Professor of Neuropsychiatry, University of Helsinki, Finland.

Dr. A. Oksala, Assistant Physician, Department of Ophthalmology, University Hospital, Turku, Finland.

Dr. T. Olin, Professor, Dermato-Venereological Department, University Hospital, Turku, Finland.

Dr. K. Penttinen, Chief, Virus Institute, Helsinki, Finland.

Dr. K. O. Renkonen, University Professor, Institute of Sero-Bacteriology, Helsinki, Finland.

Dr. Y. Salminen, Medical Officer, City of Helsinki, Finland.

Dr. M. Tuomioja, Chief, Serological Section, State Serum Institute, Helsinki, Finland.

Dr. E. Uroma, Chief, State Serum Institute, Helsinki, Finland.

Dr. A. Ylppö, Professor of Pediatrics, University of Helsinki, Finland.

Dr. H. Thorarinsson, Specialist in Dermato-syphilology, Reykjavik, Iceland.

Dr. N. Danbolt, Professor, Dermato-Venereological Department, University Clinic, Oslo, Norway.

Dr. E. Vogt, Assistant Physician, Serodiagnostic Department, State Institute of Public Health, Oslo, Norway.

Dr. C. H. Flodén, Teaching Consultant, Dermatologic Clinic, Karolinska sjukhuset, Stockholm, Sweden.

Dr. M. Tottie, Assistant Physician, Dermatology and Venereology, University Clinic, Stockholm, Sweden.

Dr. L. Chargin, Associate Clinical Professor of Dermatology and Syphilology, 1 West 85th Street, NewYork, N.Y., USA.

Dr. D. K. Kitchen, New York University — Bellevue Medical Centre, New York, N.Y., USA.

Dr. F. W. Reynolds, Venereal-disease Section, World Health Organization, Palais des Nations, Geneva, Switzerland.

Dr. P. Krag, Serology and Laboratory Aspects, Venereal-disease Section, World Health Organization, Palais des Nations, Geneva, Switzerland.

Messages of Welcome

Professor Oskari Reinikainen, President, The Finnish Medical Board.

It is my pleasure and honour first to extend a welcome to our distinguished guests who represent the Government of Finland. Their presence here is evidence of the interest of the Finnish State in these meetings. It is further my pleasure to extend a warm greeting of welcome to all of the delegates, particularly those from foreign countries.

We are grateful that this important meeting is being held in our country. Syphilology has an important place in the public health programme of our country, and in other countries as well. All physicians, especially those who are specialists in this field, are fully aware of the disastrous consequences of syphilis.

We who have helped to organize this symposium have attempted to secure for the various sections of the conference the foremost specialists in pediatrics, in neurology and in serology.

Medicine is not a subject confined to the borders of any one country. It is truly international, for disease knows no boundaries. Fortunately, this makes it possible for the medical achievements of each country to be added to the common good of all humanity.

A small country like Finland profoundly appreciates the great value of an international organization like the World Health Organization of the United nations (WHO). To the representatives of WHO, I should like to extend our thanks for the help we have gratefully received. We wish sincerely that your work will continue in ever growing strength. We have in Finland a national committee to work with the WHO that has been set up with the consent of our Government and Parliament. We believe we were the first country to do this, and that it is an indication of the importance we attach to the work of WHO.

We are happy to see here representatives from all of the Scandinavian countries. We understand each other well; we co-operate with one another; we are, indeed, brothers, although Finland may be the youngest in the family.

We also wish to greet the representatives of the United States of America. We are profoundly grateful for the effective aid that we have received from the United States during the past years. It is merely the truth to state that those of us who have lived through hardships never will forget the assistance we have

received. We hope you will extend our thanks and greetings to the American Public Health officials and tell them that the numerous bursaries and scholarships which we have received for studies in America have made us very happy indeed, for we have seen how well these studies have been organized and how much good has been done for our medical and public health services as a result of them. Especially is this the case in the field of venereal disease control.

I wish you all welcome once more.

Dr. Frank Reynolds, Venereal-Disease Section, World Health Organization.

It is with great pleasure that I extend to you all on behalf of the Director General of the World Health Organization a sincere and hearty welcome to this sympsium. We hope you will enjoy the meetings and profit from the discussions.

One of the cornerstones of WHO policy is that nations advanced in technical skills and rich in material resources should share these skills and these resources with countries that are comparatively underdeveloped. For this reason our programme for treponemal disease control in Europe is quite different from what it is in the Near East or in South-East Asia.

In Europe we have sought to stimulate the interchange of ideas and concepts of venereal disease control by sponsoring symposia such as that being held here today. We have thought it desirable also to stimulate a wider acquaintance with certain of the newer techniques such as penicillin in therapy and cardiolipin/lecithin antigens in diagnosis. In a few countries in Europe — Finland, Czechoslovakia and Yugoslavia — advisory services and supplies have been made available for national venereal disease control campaigns, whereas in others, such as Italy and Greece, the emphasis has been on suppression of infantile and congenital syphilis.

In the under-developed areas of the world, the WHO programme is based upon the vast needs of many nations, and upon the essential similarity among the several diseases caused by the treponemata. Whether or not one accepts the unitarian concept of the treponematoses, the fact remains that these diseases — syphilis, yaws and bejel — have more points of similarity than points of difference. Of greatest practical importance is the fact that all of these diseases now can be effectively attacked on a mass basis by the application of relatively new techniques.

It is not feasible here to discuss all the various projects with which WHO is presently concerned. There is a venereal disease demonstration team in India; yaws control projects on a mass basis in Indonesia, Haiti and Thailand, and in the near future there will be a bejel control campaign in Iraq. Activities in Afghanistan and the Dominican Republic are scheduled to start during 1950, and next year programmes may be developed for Ceylon, Malaya, Burma and the Philippine Islands. Few of these projects depend entirely upon the regular WHO budget. Most of them are joint WHO/UNICEF enterprises, with WHO

supplying the technical advisory services and UNICEF the supplies and equipment.

In the field of serodiagnosis, there are several important activities. First, information is being collected regarding which of the many serologic tests have gained widest acceptance throughout the world. Second, an exchange of serum specimens has been arranged among several outstanding laboratories in Copenhagen, Paris, London and New York. Third, plans are progressing for the projected International Serologic Conference which may take place in 1952 or 1953.

The principles upon which this overall International Treponematosis Disease Control Programme are based are those recommended by the WHO Expert Committee on Venereal Infections and Treponematoses.

In all these activities WHO looks particularly to the Scandinavian countries, including Finland, for advice, leadership and inspiration. It is a tacit recognition of the leadership of the Scandinavian countries in the control of venereal diseases.

In this symposium we seek an interchange of ideas, regarding several of the most important phases of syphilology: early syphilis, prenatal and congenital syphilis, serology and neurosyphilis. We sincerely hope that all present will join actively in the discussions.

In closing, I should like to express our gratitude to the State Medical Board of Finland, to the WHO Committee for Finland, to the Association for Combating Venereal Diseases in Finland and to the Finnish Dermatological Society for their splendid co-operation in organising this symposium. Many persons have assisted with the details and their help is sincerely appreciated.

Section I: Early Syphilis

Chairman Tauno Putkonen

Problems in the Therapy of Early Syphilis

By

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There has been a marked reduction in the incidence of reported early syphilis in the United States. Physicians and clinics are noting a great decrease in the number of new cases reporting for diagnosis and treatment. In a recent article, Howell (1) gives Chicago as an example for cases that have dropped from 200 to 10 per week. This marked reduction is probably due to two main factors; the introduction of penicillin therapy and the subsequent development of adequate and effective ambulatory schedules that can be easily employed by physicians.

Since the future of the control and ultimate eradication of syphilis lies in the hands of the physician, it is necessary that he be acquainted with, and keep abreast of the recent clinical and laboratory investigations in this field. Syphilis seminars, such as this one, under the auspices of the World Health Organization, play a very important role. They are of great value, in that they allow for informal discussions and exchange of ideas relating to the problems in the treatment of early syphilis. The results of these discussions can then be disseminated to the various teaching institutions and treatment centres throughout the world.

A voluminous amount of data on the efficacy of penicillin therapy in early syphilis has been recorded since the first report in 1943 by Mahoney (2). At that time, however, there was no definite knowledge regarding the total dosage of penicillin required for the satisfactory treatment of early syphilis. As with many new therapeutic agents, some of the earlier reports appeared inconclusive and were interpreted as unsatisfactory. As a result of some of these early studies, there are physicians who still believe that penicillin alone is unsatisfactory for the treatment of early syphilis and should either not be used at all or only when combined with arsenic and bismuth. Why did some of the earlier reports state penicillin to be unsatisfactory in the treatment of syphilis? Where were the errors in the interpretation of results? It is believed that the following discussion may explain some of these discrepancies.

Inadequate dosage

During the last World War, penicillin was urgently needed for many diseases and conditions other than syphilis. In fact, the effectiveness in the treatment of syphilis was unknown until its importance as a life-saving factor in curing other diseases and infections following battle injuries was established. Since supplies of penicillin were limited, very little could be allotted for the treatment of syphilis. As a result, schedules were employed utilizing a total dosage of as little as 600,000 units of aqueous penicillin. It was rapidly learned, that although all patients with early syphilis who received this relatively small amount of penicillin were rapidly rendered non-infectious, the relapse and failure rates were exceedingly high. Some physicians were unduly influenced by these unsatisfactory results. It is now an accepted fact by most investigators that there is a *minimal total dosage* of penicillin that must be administered if one is to obtain satisfactory results. Amounts below this minimal total dosage will result in increasingly high failure rates.

Inadequate duration of therapy

Although M a h o n e y and his associates (3) treated their original patients over a period of seven and a half days, some investigators felt that a more rapid method of therapy was necessary and possible. Some schedules were introduced wherein the treatment was administered in a period of three days or less, and again a high percentage of treatment failures followed. It has been subsequently shown that the time-dosage relationship (4) is most important and that there is a *minimal time* during which penicillin must be administered to be effective. Keeping the total dosage constant, the longer the period taken to administer the penicillin (within certain limits) the more effective was the therapy. The likelihood of curing at least 90% of all patients with early syphilis with any penicillin preparation which will maintain a serum concentration above 0.03 units per cc for a period of 72 to 96 hours, has been suggested by M a h o n e y (5) on the basis of analysis of the data of his group since the beginning of his early schedules. Unless the duration of therapy is adequate, there will be a relatively high incidence of failures. E a g l e (6) has found that the Treponema pallidum is the most sensitive of all the many different pathogenic bacteria which he has studied, and that low concentrations of penicillin are profoundly lethal. The killing time, however, is longer for Treponema pallidum than for other pathogens investigated, indicating again the necessity of maintaining adequate levels of penicillin in the serum and tissues at the site of infection for a sufficient period of time.

Inadequate knowledge of the chemistry of penicillin

Early in the development of penicillin products, little was known about the chemistry of the various chemical structures of this antibiotic. From June of 1943 until the preparation of the various pure fractions of penicillin, there have been

many reports on the use of commercial amorphous calcium penicillin in the treatment of early syphilis. When new techniques were developed for the production of penicillin on a large commercial scale, the chemical character of the antibiotic began to vary. There were variations in the components (penicillin G, F, X, and K) in different commercial lots. With the changes of these constituent parts, there *may* have been variations in the efficacy of this antibiotic in the treatment, of early syphilis. From the end of 1944 to May 1946 the penicillin which was available consisted chiefly of penicillin K. It was reported (7) that penicillin K, unlike penicillin G, was rapidly destroyed or inactivated in the body, and thus was relatively ineffective against the Treponema pallidum. It is quite possible, therefore, that the use of penicillin K during this period might have been responsible for the reported failures in syphilo-therapy. As the situation was corrected and the newer preparations consisted predominately of penicillin G, improved therapeutic results were reported. When the total dosage was raised to 2.4 million units, and the penicillin preparations improved, the percentage of satisfactory results was markedly increased (8, 9, 10, 11).

Inadequate interpretation of serologic response

Although physicians were satisfied with the rapid disappearance time of Treponemata from the early lesions of syphilis and the prompt healing of cutaneous manifestations, they were disappointed by the slow serologic response. This lag in serologic reversal caused fallacious pessimism among those who looked for a more rapid reversal of positive serologic tests for syphilis. It has been shown that months and even years may elapse following successful therapy before serologic tests on all patients treated for early syphilis ultimately become negative. In fact, in old latent syphilis, or in late congenital syphilis, it is only on infrequent occasions that there is reversal to sero-negativity within five years after treatment. As I have pointed out in a previous publication, (12) there are a number of factors that may determine the serologic response to penicillin therapy: (a) stage of the disease, (b) serologic titer prior to the institution of therapy, (c) sensitivity of the serologic tests employed, (d) amount, type and duration of therapy, (e) patient's individual immunologic response. These points will be discussed in detail in another report dealing with problems in the serodiagnosis of syphilis.

When one realizes that the serologic response in high titered early syphilis may be slow; that the serologic reversal in old latent syphilis is not to be expected; and that the persistence of positive serologic tests for syphilis does not necessarily indicate the persistence of infection, it will then be possible to appraise more accurately and intelligently the results of penicillin therapy for syphilis. Furthermore, unless quantitative serologic tests are performed at rather frequent and regular intervals on patients with high titered reactions, it may not be possible to determine whether there is a satisfactory trend following therapy.

Inadequate clinical evaluation

It is true that many investigators are discouraged with penicillin therapy because they are of the opinion that the so-called relapse or failure rate is excessive. Unfortunately, it is often quite difficult or impossible to differentiate between relapse and reinfection. Since syphilis may be «cured» in a relatively short period of time, it is possible for patients to be reinfected by subsequent exposure. In fact, an individual may even be reinfected with his original spirochetes which were deposited in his sexual contact soon after his first infection. There is no question but that such instances of «ping-pong» syphilis are a much more frequent occurrence than hitherto appreciated. Whether or not an adequately treated patient with early syphilis will develop a new chancre at the site of inoculation will depend on the extent of immunity he has developed from his original infection. The degree of immunity is greatly dependent upon the duration of the original infection and it may vary in degree with the size of the original inoculum. From all available evidence from animal experimentation it appears that the extent of immunity in syphilis may be classified roughly into three phases provided the dosage of the challenge inoculum is maintained constant. The first phase of immunity is manifested by the resistence to development of a new primary lesion at the reinoculation site, associated, however, with the increase of Wasserman-type antibodies and positive lymph node transfers. Thus Chesney and Kemp (13) found that rabbits treated for *from 41 to 68 days* after an initial infection and reinoculated with virulent treponemes developed asymptomatic reinfection, as manifested by an increase in serologic titer and the development of spirochete positive lymph nodes, in the absence of a new primary lesion at the injection site. This *first phase* of partial immunity could conceivably be detected in humans treated for a syphilitic infection who subsequently developed a rise in serologic titer with no other clinical evidence of the disease, following exposure to infectious syphilis.

Magnusen and Rosenau (14) demonstrated that a further increase in the duration of the original infection in rabbits resulted in still greater protection. This degree of immunity may be classified as the *second phase.* In animals treated *from 12 to 24 weeks* following an initial syphilitic infection, reinoculation resulted in an asymptomatic reinfection which was manifested solely by positive lymph node transfers, unaccompanied by a rise in serologic titer. Unfortunately, such a phenomena of asymptomatic reinfection, without a rise in serologic titer could not be recognized in humans using the present routine method of study.

There is also a *third phase* of immunity in which rabbits will fail to develop new primary lesions, manifest no rise in serologic titer and lymph nodes remain noninfectious on transfer. This type of complete resistance has been demonstrated by Arnold, Mahoney, and Cutler (15) in rabbits with early latent syphilis of *eight months duration* who were then adequately treated with penicillin and challenged 10 days later with an homologous strain of Treponema pallidum. In 47% of these animals, complete immunity was observed.

It may be possible, therefore, that certain patients with early syphilis may develop no immunity or only a partial immunity if therapy is administered very early in their original infection. Such individuals, might, therefore, develop a new chancre (a clinical reinfection) or an asymptomatic reinfection depending upon the degree of immunity they develop as a result of their original infection and to the size of the inoculum on re-exposure. If the only evidence of a reinfection is a rise in serologic titer, it would be almost impossible with our present methods to distinguish this from a serologic relapse. Therefore, the development of new early lesions, or the increase in serologic titer without the appearance of a chancre occurring in patients who had received adequate treatment for a previous infection, does not necessarily indicate a treatment failure. Furthermore, when such reinfections are classified as failures, there is a false reduction in the cure rate.

When physicians realize that the five factors described as «inadequacies» operate in opposition to a favourable evaluation of penicillin therapy, they will undoubtedly appreciate that this antibiotic is by far the best single agent for the treatment of syphilis.

Development of absorption delaying penicillin preparations

The inconvenience and expense entailed originally in the frequent injections (every two to three hours day and night) of aqueous penicillin stimulated many investigators to discover and design superior repository forms, which would maintain penicillin serum concentrations over longer periods of time. These studies were directed along the following lines:

1. *Development of Methods to Alter the Rate of Excretion of Penicillin*

It was observed that patients with certain types of nephropathy maintained serum concentrations following injections for longer periods of time than individuals with normal kidney functions. Later, certain compounds were developed to retard the urinary excretion of penicillin without the altering of desirable functions and of these, caronamide has received the most attention.

2. *Development of Insoluble Salts of Penicillin*

Insoluble penicillin salts and derivatives have been prepared, but unfortunately, many were considered either too toxic or too irritating. The procaine salt of penicillin G however, is less soluble in tissue fluids than the sodium and potassium salts. It is non-toxic and will maintain serum concentrations following injections much longer than the soluble salts (16).

3. *Development of Absorption Delaying Methods*

Early attempts to delay absorption were made by applying an ice-pack to, or a tourniquet below the site of injection. Both proved impracticable as were combina-

tions of penicillin with vaso-constrictors. The most important early advance was that of R o m a n s k y (17) who employed calcium penicillin in an absorption delaying menstrum of 4.8 per cent beeswax in peanut oil. More recently, investigations have been directed towards the use of water repellent agents such as the aluminum salts of stearic acid (18). These investigators at Bristol Laboratories described a combination containing procaine penicillin (small particle size) in peanut oil jelled with 2% aluminum monostearate. Their animal evaluation disclosed that the serum concentration of penicillin was maintained much longer with this product than with a comparable amount of penicillin in peanut oil and beeswax or any of the other products studied. A single injection (16) of one cubic centimeter (300,000 units) maintained a serum concentration of penicillin above 0.03 units per cubiccentimeter for 96 hours in approximately 90% of the 173 patients studied. In a subsequent report K i t c h e n and his associates (19) were able to show that the daily injection of 1 cubic centimeter (300,000 units) daily for 15 days resulted in a progressive serum accumulation of penicillin. This began with a serum concentration of 0.1 unit per cubic centimeter, 24 hours following the first injection, attaining an average of about 0.4 unit per cubic centimeter by the eighth day, and maintaining this same high level thereafter. A similar phenomenon resulted from the injection of the same amount of penicillin at 48 hour intervals, but the accumulation rate was slower and the serum concentration level lower at the end of the eighth day, being approximately 0.2 units per cubic centimeter. In the same publication we also reported serum concentrations of penicillin following the single injection of this penicillin preparation as follows:

Schedule 1. 1.2 million units (4 cubic centimeters) one depot.

Schedule 2. 2.4 million units (8 cubic centimeters) one depot.

Schedule 3. 2.4 million units (4 cubic centimeters) in each of two depots.

Schedule number 1 produced a peak level of approximately 0.5 units per cubic centimeter in one hour and remained above 0.03 units per cubic centimeter for 6 to 8 days. Schedules 2 and 3 produced serum levels of approximately identical magnitude. The one hour peak concentration for these was approximately 1 unit per cubic centimeter. A gradual decline in the level which fell below 0.03 units per cubic centimeter occurred in about 8 to 10 days in most patients. With this information, our group at New York University-Bellevue Medical Centre (20) initiated four schedules of treatment for early syphilis.

The ultimate objective in the treatment of syphilis from the public health standpoint is to effect eradication of this disease. This will eventually be accomplished by methods which will actually «cure» or render non-infectious patients in the early stages. We were, therefore, concerned in our work and in this study, with early syphilis and have chosen subjects in the primary and secondary stages of the disease for this evaluation. This report is not concerned with speculations as to the therapeutic management and outcome of patients with old syphilis, where irreversable, anatomical or serologic changes may have occurred. These studies were started in May of 1948. Since they were the first patients to be treated

on single injection schedules with the new penicillin preparations, and since we did not wish the possibility of a high failure and relapse rate, we did not administer less than a single injection of 1.2 million units in any schedule. Simultaneously with the treatment schedules, sera were assayed for the concentration of penicillin produced and maintained by the injections of these varying amounts of this product. The four treatment schedules were as follows:

Schedule 1. A single injection of 4 ccs (1.2 million units).
Schedule 2. A single injection of 8 ccs (2.4 million units).
Schedule 3. A single injection of 4 ccs once a week for two weeks (2.4 million units).
Schedule 4. A single injection of 4 ccs once a week for four weeks (4.8 million units).

At this time, I shall only report on the results obtained in those patients whe received single injections of 4 or 8 ccs of procaine penicillin in oil and aluminum monostearate (schedules 1 and 2).* Since there was no appreciable difference noted in the results obtained with these single injection schedules they will be considered as one group. Onehundredandone had been followed for from 6 to 20 months at the time of this report (August 1950). When last examined, (see Table I)

Table 1. *Treatment of Early Syphilis with One Injection of 1.2 or 2.4 Million Units of Procaine Penicillin in Oil and Aluminum Monostearate* (*R e i n et al*)

Serologic Cure	81 (80.2 per cent)
Serologic Improvement	11 (10.9 per cent)
*Retreatment	9 (8.9 per cent)
Total	101

*4 reinfection
2 persistent high titered serologic reaction one year following therapy
3 relapse or reinfection

81 (80.2 per cent) had negative serologic reactions with the complement fixation and Kahn tests, 11 had shown reductions in serologic titers and 9 were retreated for the following reasons: 4 were reinfected; 3 relapsed or were reinfected; 2 had a Kahn titer of more than 16 units one year following completion of therapy.

Although the data presented in this report are inadequate for valid conclusions at this time, it appears that there is no advantage in weekly injections of procaine penicillin G in oil and aluminum monostearate in the treatment of early syphilis.

The second study upon which we wish to report briefly is that of L o v e m a n, B u s c h m e y e r, Z a u g, and F l i e g e l m a n (21) carried out at the University of Louisville. The same penicillin preparation was used in their

*Grateful acknowledgement is made to Bristol Laboratories, Inc., Syracuse, N. Y. for making this work possible by a grant-in-aid plus their product, Flo-Cillin «96».

study as in the study reported from the New York University-Bellevue Medical Centre group. A total of 102 patients were selected for this study, of which 20 were in the seronegative primary stage, 29 were in the seropositive primary stage, and 53 had secondary syphilis. Each patient was subjected to a clinical and serologic examination prior to therapy, at weekly intervals while under treatment, and at monthly intervals thereafter for one year. Spinal fluid examinations were made from the 6 to 12 month following completion of therapy. Each patient received one injection of 1 cc (300,000 units) of procaine penicillin G in oil and aluminum monostearate once a week for 4 weeks (for a total of 1.2 million units). These patients were followed for from 2 to 18 months. Of these there were 42 white and 58 coloured patients. Fifty were males and 52 were females.

It will be noted (see Table II) that 89.3 per cent had attained serologic cure

Table II. *Treatment of Early Syphilis with Four Weekly Injections of 300,000 Units of Procaine Penicillin in Oil and Aluminum Monostearate* (L o v e m a n *et al*)

Serologic Cure	82	(80.4 per cent)
Serologic Improvement	7	(6.8 per cent)
*Retreatment	13	(12.7 per cent)
Total	102	

*2 reinfections
5 serologic relapse or asymptomatic reinfection
6 clinical relapse

or serologic improvement. In this study, 10.7 per cent were classified as failures, of which 5 were serologic relapses or asymptomatic reinfections and 6 were clinical relapses.

These results would seem to indicate that the results obtained at the New York University-Bellevue Medical Centre with a single injection of 4 ccs were somewhat better.

The third study is that of W r i g h t, N i c h o l s o n and A r n o l d (22) from the Venereal Disease Research Laboratory Staten Island, N.Y. They believed that a single injection treatment of syphilis would be possible for the following reasons:

1. A 72 hour treatment schedule (200,000) units of crystalline sodium G every 2 hours for 36 doses) gave excellent results as judged by more than 2 years of observation.

2. As little as 300,000 units of microcrystalline procaine penicillin with 2% aluminum monostearate would produce a detectable level of penicillin in the blood for 72 hours in 97% of the patients tested.

The same type of penicillin preparation was used by this group as in the two previous studies discussed in this report. They decided to use a single injection of 300,000 units because other investigators were using single injections of larger doses. Furthermore, they felt it would be worthwhile to ascertain whether the low dosage would suffice.

This study was composed of 99 patients with early syphilis, who were observed from 1 to 16 months. At 9 months, a follow-up on 50% of the patients revealed that 6 were retreated for serologic relapse and 5 for clinical relapse, with a cumulative failure rate of 15.3 per cent (see Table III). It was of special interest, how-

Table III. *Treatment of Early Syphilis with One Injection of 300,000 Units of Procaine Penicillin in Oil and Aluminum Monostearate (Wright et al)*

Serologic Cure	65 (66.6 per cent)
Serologic Improvement	23 (23.2 per cent)
*Retreatment	11 (11.1 per cent)
Total	99

*6 serologic relapse
5 clinical relapse

ever, that 66% had attained and maintained seronegativity. This is obviously not an optimal schedule of treatment. In their series of 386 patients, who received 200,000 units of aqueous penicillin G every two hours for 36 doses, the cumulative failure rate at the end of 9 months was only 1.1 per cent. Even after 2 years, the cumulative retreatment rate was only 6.3 per cent and most of them were considered to be reinfections. The investigators conclude, therefore, that:

«1. Maintenance of a detectable serum penicillin level for 72 hours is not a guarantee of cure in early syphilis.

2. A single injection of 300,000 units of propenalate does not provide a sufficiently high cure rate in early syphilis to be used in this country».

The fourth and last report is that of Doctors Chargin, Sobel and Rosenthal (23). This group had already reported on two other series of patients at the New York City Board of Health. The first series (24) of patients received daily injections of 300,000 units of penicillin in peanut oil and beeswax for 16 days for a total of 4.8 million units. The second series (25) received similar injections of the same type of penicillin preparation twice a week for a total of 8 weeks for a similar total of 4.8 million units. The satisfactory results in these two series were almost identical with a relapse rate of about 4%. In considering means of improving the therapeutic results and, if possible, to reduce this relapse rate, they instituted therapy in a third series of patients which had for the object, the answer to the question: «does combined treatment with penicillin, marpharsen and bismuth yield better results in early syphilis than penicillin given alone?» The study was carried out in the clinics of the Department of Health of New York City. Of 540 initially admitted unselected cases of early syphilis, 470 completed the full or nearly full course of treatment (see Table IV). The study covers a period of a little more than two years. The treatment consisted of the administration of penicillin G in oil and beeswax or of procaine penicillin in aluminum monostearate, given daily for 10 consecutive days (omitting Sundays): the total therefore, was 6,000,000 units. By far the majority of patients received the pro-

Table IV. *Treatment of early syphilis with ten daily injections of 600,000 units of Procaine Penicillin in Oil and Aluminum Monostearate plus Mapharsen and Bismuth (Chargin et al)*

Serologic Cure	264	(85.4 per cent)
Serologic Improvement	35	(11.3 per cent)
Serologic Fastness	6	(1.9 per cent)
*Retreatment	4	(1.3 per cent)

*2 reinfection
1 clinical relapse
1 serologic relapse

caine penicillin. The penicillin therapy was followed by semi-weekly intravenous injections of marpharsen for 10 successive weeks (dose 0.045 to 0.06) and this in turn by 1 to 1½ ccs of a 10% suspension of bismuth in oil for 10 weeks. In some the marpharsen and bismuth were given concurrently. The entire treatment, therefore, covered a period of from 10 to 16 weeks. In their summary the authors state that the a priori expectation of a higher «cure» rate with combined therapy has not been realized since the satisfactory outcome in the three studies are about the same. So far as the effect upon the clinical manifestations is concerned, all three schedules, of course, furnish highly satisfactory results. The outstanding difference was the low retreatment rate with a combined schedule (approximately 1 per cent as compared to the 3.9 per cent in the 16 day plan).

Any therapeutic regime designed with the view ultimately to eradicate syphilis must be primarily concerned with actually curing or rendering non-infectious the disease in early stages. Accumulated experiences definitely indicate that this can be accomplished with penicillin alone and that the adjuvant use of heavy metals or fever therapy does not appreciably increase the cure and improvement rate of the disease.

The question of what disposition to make of a patient in whom penicillin or any other treatment has failed deserves special attention. The report of Thomas and Landy (26) from Bellevue Hospital discloses that more than 4,000 patients have received various forms of therapy. Of these, 689 have been retreated one or more times with penicillin because of relapse or reinfection. Of these, 409 have been followed upon completion of the last treatment for 12 to 53 months Three hundred and thirty-three (81.4) were seronegative, 67 (16.4) had positive Kahn tests in dilutions of 1: 2 or less, and 9 (2.2) had persistent Kahn titers in dilutions of 1: 4. Mahoney's results (27) show that approximately 80% of all failure may be successfully retreated with penicillin. So far, we have not encountered evidence of a true resistance to penicillin therapy. Thus, retreatment with penicillin after failures is indicated rather than subjecting the patient to years of administration of toxic chemotherapy with arsenic and bismuth.

I should like to suggest the following schedule for the treatment of all patients with early syphilis. On the first day, administer one injection of 4 ccs of procaine penicillin in oil and aluminum monostearate (1.2 million units), then, if possible, arrange to give that patient one injection of 1 cc once a day for 6 addi-

tional days or 600,000 units twice a week for three weeks. The advantage of this plan of therapy is that an adequate dosage of penicillin is administered on the first day of treatment. Should that patient fail to return for additional therapy, the physician can have the assurance that he has better than a 90 per cent chance of rendering that patient non-infectious and «curing» his infection.

By-effects of penicillin therapy

A great deal has been reported on the subject of reactivity to penicillin when administered by different routes. Most workers agree that approximately 5 per cent of all the patients receiving the soluble penicillin salts (sodium, potassium or calcium) by injection will manifest some degree of skin response in one form or another. This was viewed early as a complication of great importance, since drug sensitivity in the past had proved to be most bothersome and often precluded the administration of an indicated medicament. Thomas (28) reporting on the incidence of sensitivity in 10,000 patients treated with penicillin for syphilis, analyzed the severity of the situation. In most instances skin eruptions were not considered sufficiently important to withold penicillin by injection. It is now well recognized that the urticaria appearing in the average patient sensitive to the antibiotic may disappear in a few days even on continuation of treatment. During this time large doses of antihistaminic drugs administered by mouth may help considerably.

In Chargin's last report (23) he writes, «during the first few months of our study, POB (penicillin in oil and beeswax) of the fluid variety was employed in treatment, and during this period approximately 10% of the patients showed reactions. Later, with a change to procaine penicillin there was a remarkable drop in reaction to about 1%. The type of penicillin reactions observed were chiefly urticarial, immediate or delayed, contact type of dermatitis and activation of fungus sites. In none was it found necessary, except for a short period, to interrupt treatment». Our own observations to date following the intramuscular injections of procaine penicillin in oil and aluminum monostearate in over 3,000 patients indicated that the sensitivity rate is definitely less (approximately 1%) with this product than with the older salts of penicillin used in the past. Severe reactions to penicillin can occur and in 1947 Sawicky and I reported two such patients (29). The following classification of common reactions to penicillin was previously reported by Romansky (30):

A. Toxic Reactions
   1. Intrathecal penicillin reactions
   2. Herxheimer reaction — Not peculiar to penicillin, but common to all potent spirocheticides and antibacterial agents
   3. Therapeutic paradox

B. Allergic Reactions
   1. Pruritus, urticaria, angioneurotic edema, asthma, serum-sickness-like reaction and anaphylaxis-like reaction (immediate or delayed)
   2. Erythematovesicular desquamating type
   3. Contact dermatitis type
   4. Experimental
      (a) Arthus type
      (b) tuberculin type
      (c) anaphylaxis
      (d) photosensitization (?)

In a cursory perusal of the recent literature, I was able to find reports of 7 fatalities following penicillin therapy. Of these, 3 are questionable. In 1, a febrile course terminated fatally 9 days after an abdominal operation for carcinoma. It is not possible in this case to exclude carcinoma as a cause of death. The second patient was suffering from a streptococcal septicemia which may have been the cause of death instead of the penicillin reaction. The third patient was a 53 year old man treated for a furuncle on the neck with two daily intramuscular injections of penicillin in an absorption delaying vehicle. Four days later he developed a pruritic rash which became generalized and began to exfoliate. Anuria, dyspnea, nausea and vomiting developed. He died approximately 15 days later. The patient had a history of nephritis and post-mortem examination revealed that death was due to a chronic glomerulonephritis and exfoliative dermatitis. When one realizes that millions of patients have received penicillin therapy, and yet there are so few reported fatalities, penicillin can be considered an extremely safe form of treatment for syphilis.

Conclusion

Hitherto, confusion has existed regarding the proper place of penicillin in the treatment of syphilis. The possible reasons for this misinterpretation of the problems are discussed. If we are to judge by the majority of reports in the literature to date, penicillin is the drug of choice in the therapy of early syphilis and combined therapy with arsenic and bismuth appears to be of no additional value. There is complete agreement that the administration of penicillin alone in early syphilis results in: (1) the rapid disappearance of Treponema pallida from lesions; (2) the rapid healing of skin and mucous membrane lesions; (3) the reversal to seronegativity of serologic tests in more than 90 per cent of the patients during the first two years following therapy; and (4) the completion of therapy on an ambulatory basis in the majority of patients. Another tremendous advantage of penicillin therapy is its safety, since arsenical therapy by any schedule carries a definite irreducible risk of reaction and even death. To place into effect the best ambulatory schedule for the treatment of early syphilis will require the close

collaboration of investigative clinicians throughout the world and a longer observation period. International meetings of this type, which have been made possible by the World Health Organization, where therapeutic problems can be fully discussed, will help tremendously in solving this problem.

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Clinical results and by-effects in early syphilis with combined arsenical-bismuth treatment

By

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The introduction of penicillin treatment of syphilis marks a forward step of such magnitude that its full significance, 7 years after its adoption, is not yet fully realised, although the drawbacks of this treatment have not been entirely clarified.

However, 7 years of intensive research work, largely carried out in the United States, have thrown some light upon the advantages and disadvantages of penicillin. They will be briefly summarised here, and the results will be compared with those of combined arsenical-bismuth treatment.

Advantages:

1) Penicillin is non-toxic.
   It may, like any other effective antisyphilitic treatment, produce a Herxheimer reaction, but in the early stages of the disease this reaction is of no importance.
2) Penicillin treatment may be completed in a fraction of the time required for effective treatment with arsenical-bismuth preparations.
   Satisfactory results have been reported from treatment with 4—5 million units during 8—14 days. Extension of the cure beyond that period is stated to serve no useful purpose [T h o m a s (16)].
   Some workers claim to be able to cure early syphilis with a single injection of penicillin [M a h o n e y (8)] in a high proportion of cases.
   From an epidemiological point of view it is an immense advantage that the treatment may be concentrated in the shortest possible period, thereby reducing the difficulties in retaining the patients.

Disadvantages:

1) 10—20 per cent relapses in penicillin treatment are reported. The relapses are stated to be most frequent 3—9 months after treatment, and infrequent after 2 years [T h o m a s (16); B u r c h a r d t (2)]. Some of the relapses

are believed to be reinfections. In the available literature, very few reports mention any attempts to confirm the allegation of reinfections. This might be effected, for instance by looking for sources of infection among the persons with whom the patient associates. One work in which such a research was made reported 7 per cent of probable reinfections and 5 per cent relapses (Schoch & Alexander (14)].

2) A certain number of relapses within the first 2 years will not be ascertained. Most statistics have a large number of patients who fail to turn up for control. The annual loss ranges between 20 and 60 per cent. The number of relapses is hardly less among this category of patients. In the case of clinical relapses, the patients may apply for treatment, but the sero-relapses will remain undetected and may manifest themselves as an outbreak of tertiary syphilis several years later.
3) Thus far, nothing can be said as to the number of relapses occurring long after the completion of the treatment. No penicillin treated syphilis patients have as yet been under observation long enough for their final destiny to be ascertained.

Combined arsenical-bismuth treatment.

The appraisal of this treatment is to some extent impeded by the same factors as those which apply to penicillin treatment. As yet, reliable information is still missing on the results achieved by successful intensive treatment — particularly with a view to preventing late syphilitic complications. As will be seen below, most of the patients observed for long periods originate from times when it was believed sufficient to administer a small number of salvarsan (arsphenamine) injections.

In Denmark, 551 patients treated in the years 1910—1914 were kept under observation for 3—9 years by Pontoppidan (12). These patients were given a few salvarsan injections (not exceeding 6) and 50—100 mercurial ointment treatments. In this material he found 22 per cent clinical and 10 per cent serological relapses.

Lomholt (7) in a more recent material of about 1,800 patients treated between 1920 and 1927, found 5 per cent clinical and 10 per cent serological relapses. These patients had been treated rather more intensively than Pontoppidan's patients, 3—7 salvarsan injections of 60 or 40 ctgm. having been administered in addition to about 50 mercurial ointment cures and 2—3 series of bismuth injections.

Padget (11), in his carefully examined material from 1939 observed 551 patients through 10 years and found 15 per cent clinical relapses. This high figure is surprising since the patients were treated at a time when the importance of intensive therapy was realised. However, the explanation must be that the patients did not attend the treatments. (Thus, he reported that the 246 best treated patients received continuous treatment for 6 months, either with arsphenamine,

bismuth, mercury, or neosalvarsan «albeit many of them had only a few injections»). Consequently, the intensity of the treatment and the results both conform to Lomholt's results.

The Cooperative clinical group in U.S.A. (3) found 9 per cent relapses in 167 patients treated for one year with combined arsenical-bismuth cure. Irregular treatment causes the number of early relapses to increase considerably [Thomas (16)].

Garnier (4) found 5 per cent serological relapses in 98 patients observed for 4—19 years. All the relapses were found among patients with secondary syphilis; there were no relapses at all among patients with primary syphilis. The treatment consisted of 2 series of combined salvarsan-bismuth. His results conform to Moore's statement (9) that a successfully completed arsenical-bismuth treatment results in 95 per cent recovery.

However, the foregoing material represents early clinical or serological relapses.

The question is now: What are the chances for the patients to avoid the late syphilitic complications?

The answer to this question appears to depend on the course of the early syphilis.

Padget (11) found that in the cases without early relapses the chances of cure were 72 per cent, but in the cases involving early relapses the prospects of cure were only 28 per cent. Correspondingly, the incidence of neuro-syphilis was 6 times as high in the patient group with sero-relapses. (36 per cent and 6 per cent).

In a large Swiss material, Burchardt (1) found 6.8 per cent late complications in poorly treated patients compared to 0.9 per cent in successfully treated patients with early lues.

The patients in this material were observed for 10—15 years; well-treated patients received 3—4 series (totalling 18—24 grammes) of neosalvarsan and 3—4 grammes of bismuth. He succeeded in carrying out post-treatment examinations of only 20 per cent of the total number of the 475 patients treated.

Among 467 patients treated from 1913 to 1920 and observed through 29—36 years, Nielsen (10) found 13 per cent serious late complications. The complications were 4 times as frequent when treatment was begun in the secondary stage as when they were treated in the primary stage.

These patients were treated with 3—6 injections of arsphenamine and with mercury ointments.

Advantages:

The mentioned investigations seem to confirm that intensive combined salvarsan-bismuth treatment at the earliest possible stage will reduce the number of early and late relapses of syphilis to 5 per cent, probably even less.

Disadvantages:

However, there are serious disadvantages in this treatment:

1) Its by-effects may be so strong that the treatment must be interrupted; in some cases it has even caused death. According to Burchardt (1) neosalvarsan is responsible for vomiting and nausea in 14 per cent of the patients, exanthema in 14 per cent, erythrodermias in 0.9 per cent, icterus in 3. 6per cent, and mors in ½ per cent.
   Among 5,526 patients Genner (5) found 3 per cent with erythema, 2 per cent with icterus, 3 per cent with albuminuria, 1 per cent with arthralgia and subjective by-effects (nausea, etc.)

2) The treatment extends over a period which is so long that many patients will fail to complete it.
   Inadequate treatment with arsenical-bismuth may be worse than no treatment at all. [Padget (11); Harrison (6)].

There is hardly any answer which covers all the aspects of the question as to which treatment is preferable.

In some countries the patients cannot be prevailed upon to complete a protracted cure. In the United States the percentage of duly completed treatments is reported to be only about 25 [Thomas (16)], but other workers estimate the figure at 50 per cent, [Reynolds (13)].

In this connection, the penicillin treatment offers advantages of such significance that the 10—20 per cent relapses within the first 2 years, and the lack of knowledge of potential late relapses must be considered the lesser evil.

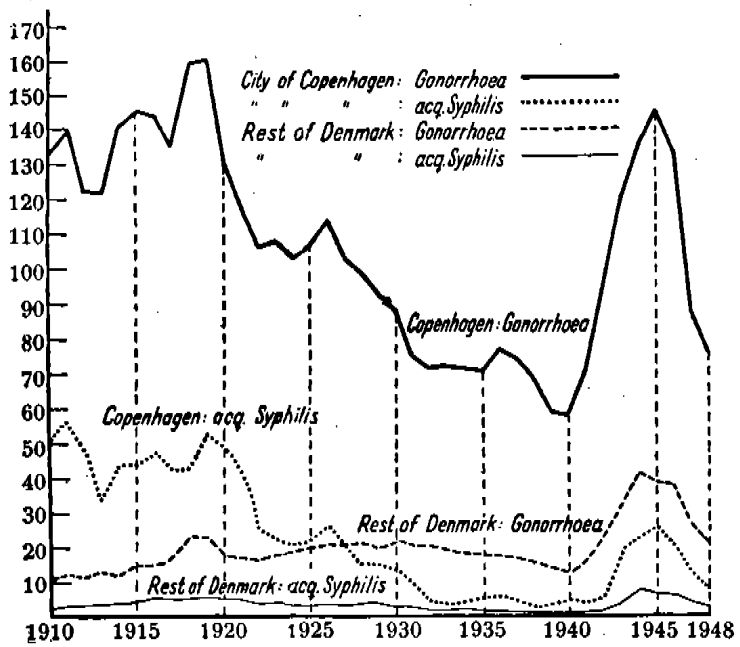
In other countries, for instance in Scandinavia, conditions are different. The difficulties in treating and observing the patients through a long period are much less here, partly because the population is not numerous, and partly because the possibilities of leaving the town or country are less. It may also be significant that it is easier to explain the character of their disease to the patients, because these countries provide easy access to free, expert treatment. In these circumstances treatment which gives the patient upwards of 95 per cent chances of cure is preferable even if it does take time.

A combination of arsenical-bismuth- and penicillin treatment which reduces the period of treatment would appear to be advantageous. However, American experiments have resulted in the same number of relapses as the penicillin treatment alone. From the previously reported investigations, a limited number of salvarsan injections are known to give comparatively many relapses.

In Denmark another factor is significant: The number of syphilis cases is declining rapidly.

As will be seen from the curve (15), the incidence of early syphilis for 1948 was 4 per 10,000 inhabitants. The corresponding figure for 1949 was only 2.4, and the incidence is expected to decline still further. Hence, this disease is likely to lose its epidemical significance, since patients with early infectious syphilis become so few that they no longer constitute any danger to the population.

For the patients themselves, however, the risk of the serious late symptoms



Notified Cases of Gonorrhoea and Acquired Syphilis per. 10,000 population in Copenhagen and Rest of Denmark 1910–1948.

is so decisive that the primary aim of a treatment must be to prevent this complication.

Vigorous combined arsenical-bismuth treatment seems capable of preventing the late consequences of syphilis.

It still remains to be proved that penicillin has the same effect. The comparatively large number of early relapses suggest that caution should be exercised.

Author's investigations.

A comparison between the two forms of treatment of a homogeneous and carefully observed patient material would help to clarify these problems.

In Denmark, experience with penicillin treatment of syphilis is still rather scarce. On account of the declining incidence of the disease it will also be difficult in the future to obtain sufficiently large materials.

Hence, I had to confine my investigation to the combined arsenical-bismuth treatment. The objective of the investigation was to find the answers to the following questions:

1) How frequent are the by-effects of intensive arsenical-bismuth treatment?
2) To what extent have the patients been prevailed upon to attend the treatment?
3) For how long has it been possible to observe the patients after the completion of the treatment?
4) How many relapses and sero-resistant cases are found after this treatment?

Patient material.

For my examinations I selected the patients who attended the University Clinic of Venereology at the National Hospital in Copenhagen during the years 1940—45. This material has the advantage that it is larger than that of the immediately preceding and of the following years.

At the same time, however, there was the drawback that because of the war it was more difficult to control the patients than is the case under normal conditions. Many patients moved to other parts of the country or even went abroad, and the activities of the Register of Births, Marriages and Deaths were partially suspended with the result that the addresses of patients failing to attend the treatment were more difficult to find. Hence, the percentage of attendance was undoubtedly lower than in normal Danish patient materials.

A number of patients had their disease diagnosticated by the National Hospital but preferred treatment by their own doctor or by another clinic. In the cases where the National Hospital has been notified that such patients reported for treatment elsewhere, they are excluded from this material.

A small number of patients (36) stayed away after 1—2 months' treatment without having been ascertained to have reported elsewhere. Since it has been impossible to follow the course of their disease or to ascertain by-effects, if any, these 36 patients are also disregarded (but they have been included in Table No. 6).

From 1940 to 1945 the Clinic of Venereology at the National Hospital diagnosticated 1,207 cases of primary or secondary syphilis. 582 patients of this material got then treatment on other clinics; the material thus consists of 625 patients, viz. 292 men and 333 women.

Table 1. *Sex distribution of patients over the years 1940—45.*

	Men:	Women:
1940:	22	16
1941:	20	18
1942:	24	30
1943:	76	77
1944:	83	96
1945:	67	96
	292	333

Table 2. *Distribution by age*

Under 20 years	65
20—25 »	207
25—30 »	134
30—40 »	163
over 40 »	56

Table 3. *Distribution by disease*

Primary syphilis — WR	162
Primary syphilis + WR	143
Secondary syphilis	320

Treatment.

Treatment was intermittent. As shown in Table No. 4, weekly injections of neosalvarsan and bismuth were administered. Treatments were given concurrently for the first 6 weeks, after which bismuth was given alone. In 1944 and 1945 mapharsen was administered instead of neosalvarsan in 177 cases. Effects and by-effects of this arsphenamine substance have not been found essentially different from those of neosalvarsan. There was a pause of 1 to 2 months between the series.

Table 4. *Schedule of doses*

	Men	Women		
Neosalvarsan	gr. 0.75	gr. 0.60	6 times	once a week
Bismuth	» 0.3	» 0.25	10 »	» » »
or:				
Mapharsen	» 0.06	» 0.04	6 »	» » »
Bismuth	» 0.3	» 0.25	10 »	» » »

Table 5. *Series of treatment*

	Number of patients:
2 series of treatment	111
3 » » »	325
4 or more series of treatment	189

Thus, about 84 per cent have received 3 series of treatment or more. 2 series were mostly given to patients with sero-negative primary lesions whose diseases showed no complications.

For the purpose of recording the patients' attention to the treatment, they have been divided into 4 groups.

1) Attended the treatment well, i.e. they were not more than twice up to one week late for treatment.
2) The patients of this group had to be summoned by letter once or twice, but this did not delay the treatment by more than a fortnight or a month.
3) In this group there were repeated interruptions of the treatment which was completed 3—4 months later than desirable.
4) This category of patients turned up only after numerous reminders. They received written notices 5—6 times, and were summoned for treatment through the police 2 or 3 times. However, the treatment was ultimately completed, but with 5—8 months' delay.

Table 6. *Completion of treatments.*

1st group	(0—14 days' delay)	356
2nd »	(½—1 month's »	149
3rd »	(1—5 months' »)	36
4th »	(5—8 » »)	84 (+36)

The table shows that more than 50 per cent of the patients attended to the treatment satisfactorily. 76 per cent of the patients (groups 1 and 2) completed their treatment without unreasonable delay.

As already mentioned, the possibilities of exercising careful control over the patients were somewhat reduced as a result of the war. The percentage of the attendance in a Danish material today is likely to be considerably higher.

By-effects.

The intensive and comparatively well-attended treatment is likely to involve a comparatively large number of by-effects. Particularly the bismuth doses were rather large, and consequently caused bismuth-coloration of gingivae in a fairly large number of patients. It may not be quite justifiable to mention this harmless consequence of bismuth treatment among the by-effects. The bismuth treatment was not discontinued in any of the cases ascertained, but the doses were reduced to two-thirds or one-half.

Table 7. *By-effects of combined arsenical bismuth treatment*

No by-effects	279	(44%)
Bismuth line	199	(32%)
Bismuth stomatitis	85	(13%)
Arthralgia	89	(14%)
Vomiting, nausea	63	(10%)
Albuminuria	15	(2%)
Dermatitis	18	(3%)
Icterus	44	(7%)
Death	1	(0.16%)

The table shows that almost one-half of the patients escaped by-effects. However, it must be justifiable to classify the next large group, bismuth seams, under this category, because often this symptom was not noticed by the patient at all, and did not cause interruption of the treatment. Hence, it may be said that more than 75 per cent did not experience any inconvenience from the combined arsenical-bismuth treatment.

As was to be expected after the vigorous bismuth treatment, the number of stomatitides is comparatively large (13 per cent). It caused the bismuth treatment to be discontinued, but in many cases the symptom occurred at such a late stage that the discontinuation hardly influenced the result of the treatment.

The number of bismuth arthralgias was also comparatively large (14 per cent). About one-third of these patients also had stomatitis.

Vomiting and nausea was found in 10 per cent of the patients. It was relieved by administering the mapharsen or neosalvarsan injection in glucose, or by changing the preparation.

Albuminuria (2 per cent) was transient in all patients.

Several of the dermatitides (3 per cent) generally amounted to slight, itching erythema at the end of a series of treatment. No attempt was made to distinguish the bismuth dermatitides from the salvarsan-rashes. Only a few cases required hospital treatment.

The number of icterus cases was comparatively large (7 per cent). Most of the cases were found in 1943—44 (27 out of 44). Since it has been demonstrated that they originated from epidemic hepatitis transferred by infected syringes or cannulas, this unpleasant complication can be avoided with certainty.

Only 1 death was demonstrated to result from the treatment. The patient was a 25-year old man with secondary lues. Two days after the second injection he was hospitalised while unconscious and suffering from cramps, and he died on the same day. Dissection revealed encephalitis haemorrhagica.

Three other patients are known to be dead, but they all died 1—3 years after the completion of the treatment. In 1 case the cause is known to be nephritis with cerebral oedema. In the other 2 cases the cause is not known, but at the last controls, 6 months and 12 months before death, the W.R. was negative. The disease or its treatment are hardly responsible for the death.

As already mentioned, seroreactions were carried out before the beginning of each series of treatments.

Table 8. *Seroreactions: Wasserman, Kahn, and Meinicke.*

Negative in 0 to 6 months	471	75%
» » 6 to 12 »	101	16%
» later than 1 year	33	6%
positive for the entire period of observation	19	3%

The table shows that the reactions was negative in 91 per cent of the patients one year after the beginning of the treatment. 3 per cent showed declining reactions, but did not become entirely negative during the period of observation.

Table 9. *Length of observation*

Observation for 0—1 year	55	9%
» » 1—2 years	185	30%
» » 2—5 »	312	50%
» » more than 5 years	73	11%

Consequently, 61 per cent remained under clinical control between 2 and 10 years. It would be of the greatest interest to follow the patients for an even

longer period. In Denmark this is made possible by special circumstances. All Wassermann reactions in this country are carried out by the State Serum Institute in Copenhapen which has a central register of all syphilis patients in Denmark. Blood tests [W.R.] are practised extensively, for instance on nearly all patients who are admitted to hospital. This is illustrated by the fact that in a population of 4 million people 400,000 blood specimens were tested for W.R. in 1948.

The central register makes information about syphilis patients available, regardless of the place where they have been examined or treated in this country. The Wassermann Register obliged the writer by providing information at short notice concerning a large number of the patients included in this investigation. This is a task of considerable magnitude, since the Register, for reasons of discretion, does not describe the syphilis patients by name, but only by the initial of their surname, date of birth, and time of infection. The writer applied for information about 572 patients, and the register succeeded in identifying them all, except 13 patients.

Additional information was provided about 184 patients with the result that the period of observation was prolonged appreciably.

Table 10. *Information from the Wassermann Register on 184 patients examined by clinics after completion of their treatment.*

	Number of patients:
Observed for 0—1 year	0
» » 1—2 years	3
» » 2—5 »	95
» » more than 5 years	86

Table 11. *Observation periods for 625 patients on receipt of additional information from the Wassermann Register*

	Number of patients:	
Observation period 0—1 year	28	4%
» » 1—2 years	131	22%
» » 2—5 »	311	50%
» » more than 5 years	155	24%

It should be borne in mind that an increase in the observation time within the period 2—5 years will not be reflected by Table No. 11.

The information received from the Register has been extremely valuable, considering that the material in question only covers the last 10 years.

In the case of about one-third of the patients, 5 years of observation will thus be the maximum period.

A blood test carried out within the last 18 months is available for 253 patients.

The Wassermann Register has been very helpful also in another respect, viz.

by summing up the relapses. The material included 19 relapses, 10 of which were found through the Register. From the information available, 7 of the relapses are believed to be re-infections and 12 of them seem to be serorelapses. One patient was first re-infected (with chancre and spirochaete pallida) and a few years later suffered a serorelapse.

The number of patients with relapses was thus 18 (3 per cent).

Unfortunately examinations of spinal fluid have not been carried out in sufficient numbers to make an evaluation serve any useful purpose.

The examination corroborates the view that in Denmark a combined arsenical-bismuth treatment may be profitably administered. Hence, it is doubtful whether a new treatment should be introduced. The advantages of the new treatment are obvious, but the effects in regard to the ultimate results are not yet known.

I am indebted for assistance from the Wassermann Register and wish to thank its acting chief, Alice Reyn M.D. For useful advice received for the preparation of this article, my acknowledgements are due to Professor H. Haxthausen, M.D., and to Johs. P. Nielsen, assistant medical officer.

Summary

The disadvantages of the treatment of syphilis with arsenicals and bismuth are:

1) The possibilities of by-effects.
2) The difficulty in ensuring that the patient pursues to conclusion a treatment, which is of long duration.

The extent to which these two aspects of the question affect Scandinavian countries is discussed in this paper, research having been directed principally along the following channels:

1) The by-effects observed during treatment.
2) The patients' attendance record during the course.
3) Observation of cases after completion of treatment.

Evidence was gathered from 625 cases of early syphilis treated by the University Clinic of Venerology at the National Hospital, Copenhagen, between 1940 and 1945.

1) 75 per cent showed no serious by-effects. About 25 per cent experienced by-effects sufficient to cause interruption of the treatment, which was later resumed. The treatment caused one death.
2) 76 per cent of the patients attended for treatment satisfactorily (i.e., they completed the course with less than one month's delay.)
3) 61 per cent of the cases were followed up by the Clinic for periods of two

years, and in 13 per cent additional information was received from the Central Registry of Syphilis in Denmark.

19 relapses occurred, of which 7 were probably re-infections.

The conclusion is that the arsenical-bismuth treatment of syphilis in Denmark yields satisfactory results.

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Round Table Discussion: Early syphilis.

I. Remarks of Discussion Leaders.

Dr. Malcolm Tottie (Stockholm): **Epidemiological Aspects of Modern Antisyphilitic Treatment.**

A new case of syphilis offers manifold problems to the attending physician What is his duty? How far should he go? The patient suffers from an acute disease. A medical decision must be made, so that the patient obtains the best possible treatment. In order to find out the kind, stage, and earlier course of the disease a careful history is required, as well as clinical and laboratory examinations.

What will be the best treatment for the patient? Probably that which gives the best prospects of cure, and which involves at the same time a minimum of risk and trouble.

The physician has not only the task of curing the individual patient. He also has obligations toward the community. Each person who is the carrier of an infectious disease must be treated as a potential danger to the community. Therefore, the physician must take measures to assure that the community runs the smallest possible risk, but without forgetting his primary task: rapid, definite cure of the patient.

But not only the patient himself is a potential danger to the community. For some time, longer or shorter, he has been the bearer of an infection which he may have given to others. These persons, the potentially infected, will require some kind of intervention, partly for their own sake, partly to prevent their spreading the infection.

How does the venereologist in Sweden and perhaps in other Nordic countries look upon this problem? The diagnosis made, the patient must immediately be cured. I believe that most of us are of the opinion that antisyphilitic treatment «for safety's sake» should be given only in exceptional instances. Such preventive treatment will always convey to the patient a feeling of insecurity. If he has the slightest neurotic disposition, each pathological change later in life will make him believe that »it probably was syphilis after all». Such a person is often faced with insoluble problems when he must answer questionnaires from insurance companies, or when he asks for a certificate of health. Nor will the physician be quite satisfied with this kind of treatment.

How is syphilis treated in Sweden? There are no uniform principles. We tend to work along familiar lines with arsenic and bismuth, but use penicillin as an expedient. In Sweden it is supposed that most of the patients follow up their treatment in a satisfactory way. With the low rate of venereal disease that prevails in our country, the number of serious reactions caused by treatment is relatively small, but there are some, of course.

It is possible that experience in other parts of the world will bring about other modes of treatment. Fortunately, the number of our cases of syphilis is very small — last year only about 705 new cases of infectious syphilis in the whole country. It goes without saying that large series for comparison of results from various methods of treatment cannot be studied.

Each physician diagnosing cases of early infectious syphilis is obliged by law to try to obtain the name of the person from whom his patient acquired the infection. He shall also endeavour to find out to what person or persons the patient may have communicated the infection. A report on source of infection and eventual contacts shall be made out by the physician and sent to the Inspector of Health, who undertakes the epidemiological investigation. By means of letter, telephone call, visit of a social worker or policeman, he summons the person in question to a medical examination. To give you an idea of the results of this kind of investigation, I might mention that the number of cases of syphilis, gonorrhea and soft chancre reported during a period of five years was 86,000. In about 40,000 of these cases, that is about 45 per cent, names were given of sources of infection and contacts. It must be admitted that most of the cases were gonorrhea, there being only about 6,000 cases of syphilis, and further that many sources of infections were not registered; the two correspondents might have gone together to the doctor or the social worker found the source of infection without recourse to the Health Inspector. It is much to be regretted that in spite of very careful investigations, more than 50 per cent of the sources of infection and contacts cannot be found. A great number of persons (about 20%), however, acquire their infections abroad.

In combating syphilis, the epidemiological investigation is especially important. This is much easier to carry out in a country, where the main part of the population is permanently resident than in countries where people move about a great deal. It has proved that social workers, employed by VD Out-Patient Departments have succeeded in checking real epidemics.

It is extremely important that the patient goes early to the doctor, but is quite as important that the doctor who examines the patient does his utmost to establish the diagnosis as early as is possible. It is certainly true that doctors in countries with a low syphilis rate easily disregard the diagnosis of syphilis, and thus lose valuable time. In recent years intensive propaganda regarding prevalence of venereal diseases may have influenced some people and made them consult a physician earlier than otherwise would have been the case. We do not

believe, however, that this knowledge will prevent many persons from infecting others before they know of the disease themselves.

Whether the now common use of antibiotics for the treatment of many different kinds of disease is of importance in syphilis — which may perhaps suppress some of the overt manifestations of the disease — cannot be decided at this time, as we have not yet had enough experience. It cannot be denied, however, that as we now have ample quantities of penicillin and the public make great demands upon the physicians, penicillin is perhaps too often used.

From the public health point of view it would be highly desirable if the doctors could come to an understanding as to which form of treatment will be the best for the future of the patient. It is incontestable that in a small country with few cases of syphilis the curative aspects of the treatment must be given the same stress as the epidemiological aspects; whereas countries with high morbidity must consider especially the necessity of rendering as many persons as possible non-infectious as quickly as is possible.

Dr. Axel Perdrup (Copenhagen): **Penicillin versus Arsenical-Bismuth Treatment in Early Syphilis.**

During the last quarter of a century Danish syphilologists have been using combined arsenical-bismuth treatment given in three or more series over a long period of time — knowing that this treatment will cure nearly 100 per cent of the patients.

The special conditions in Denmark include: a small country with a homogenious population, well-organized public health services, adequate antivenereal disease legislation, all of which make it possible to get most of the patients to follow treatment of long duration. The number of new cases of syphilis is rapidly decreasing, and with no imminent danger of an epidemic of the disease, our greatest problem is to provide security of recovery to each individual patient. This means that in this country a probable epidemiological gain from a rapid treatment scheme will, in my opinion, not be able to compensate for a loss in recovery rate.

Nevertheless, because of the above-named special conditions in Denmark and because of the centralization of all serologic work in one laboratory, our registration of the results of serologic tests of all known syphilitic persons enables us to follow our patients longer than is possible in most other countries. For this reason we have thought it desirable to obtain a series of penicillin-treated patients, and this we started in February 1949.

We who treat patients with penicillin often are asked: What is your opinion of penicillin treatment as compared with arsenical-bismuth treatment? The only answer I can give as of the present is that thus far I have met with no case in which I regret that I chose penicillin.

In order to form the basis of a more objective comparison between a series of cases of early syphilis well treated with neoarsphenamine and bismuth, I have analysed our early syphilis cases from the year 1945, and thus have two

series which are from the same clinic, the same city, the same social milieu, examined by identical serologic tests in the same laboratory.

Our penicillin series has been observed for only a short time, since our clinic started this sort of treatment only 18 months ago. We intend to continue the penicillin treatment and thus enlarge our material and to follow the results for as long a period of time as is possible.

Both series contain only patients with early mucocutaneous syphilis, and all latent cases were excluded. The penicillin-treated cases received 600,000 units of procaine penicillin (without aluminum monostearate) daily for ten days. Some patients (sailors and prostitutes) in whom there may be some difficulty in obtaining suitable follow-up, received two such penicillin courses with an interval of two weeks. Serologic tests were done every fourteen days for three months, once a month until negative for three months and thereafter every third month. Clinical symptoms disappeared rapidly in all cases. We have thus far had three cases of known reinfection and one case that may be a relapse. Only 54 patients have been observed for more than 6 months and only 15 for more than a year, hence it is too early to draw definite conclusions.

The neoarsphenamine-bismuth series, which I want to compare with our penicillin series as regards serologic tests dates from 1945. The patients were treated with three or more series, each series consisting of eight injections of about 0.06 Gm. of neoarsphenamine and 20 cg. of bismuth hydroxide. Our treatment schedule was to give the patients two full courses after serologic tests had become negative. The maximum was 6 courses, the minimum was 3 courses.

Three hundred and seventy four patients with early mucocutaneous syphilis were treated in our clinic during 1945, but of these, 203 attended for only a short period. There were 171 who took the treatment satisfactorily. Most of these we have been able to follow for a long period, either through our own records or through the index of the State Serum Institute. These patients form the basis for comparison with the penicillin series.

The comparison of these two series which I am presenting today is a very preliminary one. We have planned a long term follow-up study.

Regarding clinical symptoms, I have made no statistical analysis, but it is my impression that these disappear equally well with both treatments. In respect of the serologic tests, we use three reactions — Wassermann, Kahn and Meinicke. The Wassermann and Kahn are indicated in degrees giving a logarithmic expression of the titer. The Meinicke is reported merely as strong, weak, doubtful or negative. The sensitivity of the reactions and the method of expressing the results were the same during the entire period of observation of both series.

In this table, figures outside the parentheses represent the neoarsphenamine-treated series, and figures within the parentheses, the penicillin-treated series. The proportion of the series which became seronegative at various periods of time is indicated.

The table shows the time required for the Wassermann and the Kahn to

Table I. *A Comparison of the Response of Seroreactions to Treatment with Arsph.-Bi and with Penicillin in Patients with Early Syphilis.*

I	II	III	IV	V	VI	VII	VIII
Wassermann titer	Total number of pt.s being sero+ at start of treatment	Number of patients getting sero÷ in first 3 months	% of total number	Number of patients getting sero÷ in 3—6 months	% of total number	Number of patients being sero+ more than 6 months after start of treatment	% of total number
less than 7 or «skew» or with a faint Meinicke	46 (21)	45 (20)	98 (95)	1 (1)	2 (5)	0 (0)	0 (0)
7—9	16 (8)	8 (4)	50 (50)	4 (2)	25 (25)	4 (2)	25 (25)
10—12	47 (11)	19 (2)	40 (18)	18 (5)	38 (45)	10 (4)	21 (36)
over 12	25 (10)	8 (1)	32 (10)	11 (5)	44 (50)	6 (4)	24 (40)
Total	134 (50)	80 (27)	60 (54)	34 (13	25 (26)	20 (10)	15 (20)
Kahn titer less than 7 or «skew» or with a faint Meinicke	48 (22)	45 (21)	94 (96)	3 (1)	6 (4)	0 (0)	0 (0)
7—9	38 (11)	19 (3)	50 (27)	9 (6)	24 (55)	10 (2)	26 (18)
10—12	47 (15)	16 (2)	34 (13)	21 (6)	45 (40)	10 (7)	21 (47)
over 12	1 (2)	0 (1)	— (—)	1 (0)	— (—)	0 (1)	— (—)
Total	134 (50)	80 (27)	60 (54)	34 (13)	25 (26)	20 (10)	15 (20)

First row of each column: Neoarsph.-Bi series; in parentheses: penicillin series.
»Skew» means that WR ≥ 2 Kahn or Kahn ≥ 2 WR.
Of the neoarsph.-bi series 37 sero÷patients stayed seronegative
» » penicillinseries 10 » » »
» » » 8 patients had a slightly positive rapidly disappearing seroreaction immediately after treatment (obs. time three months or more).

become negative. Starting at the bottom of the table, it will be noted that patients who were seronegative at the start of treatment remained seronegative during the period of observation, with the exception of 8 penicillin-treated patients who had a slight and transiently positive reaction just following the beginning of the treatment. Later all became and remained seronegative.

The upper part of the table shows the results of the Wassermann tests. Cases were divided into four groups: patients with weakly positive reactions (Wassermann titer 1—6, or if higher, part of a «skew» reaction in which there is a significant discrepancy among the three serologic tests), and three groups of cases with increasingly high serologic titers.

Considering the stronger serologic reactions (titre 7—9), it will be noted that only 50 per cent of patients become seronegative in three months and that 25

per cent are still positive after six months. In this group of patients there are no differences between the two series. With still more strongly positive serologic tests, (titer 10—12, and over 12), the percentage of patients becoming seronegative decreases with the elevation of the serologic titer. It may here appear that more penicillin-treated patients remain seropositive than is true with the arsenical-treated group, but the difference is not significant.

The lower portion of the table, depicting the results of the Kahn reactions, shows essentially the same results at with the Wassermann reactions.

This analysis shows, therefore, that serologic reactions respond approximately the same whether patients are treated with neoarsphenamine or with penicillin. It further shows the importance of dividing the series into groups depending upon the strength of the reactions. It also confirms the value of initiating treatment before strongly positive serologic reactions have had time to develop.

Table II. *The behaviour of weakly positive seroreactions.*

		Number of cases	
		WR+ Kahn−	WR− Kahn+
Arsph.-bi	before treatment	7	3
	during or after treatment	3	27
Penicillin	before treatment	10	0
	after treatment	26	8
	transient reaction immediately after treatment	5	0

The next table shows the behavior of those faintly positive serologic reactions we often meet before and after treatment. It is well known that the Wassermann is the first test to appear after a recent infection, and it is also known that after treatment with neoarspenamine-bismuth, the Kahn is more likely to remain persistently positive. It is therefore unusual that among our penicillin-treated cases, it was the Wassermann rather than the Kahn that tended to remain positive the longer. I have no satisfactory explanation for this observation.

Before concluding, I should like to mention a few problems that I should like to have discussed here today. I should like to know your ideas on penicillin dosage. We do not want to run any risk, but, of course, we do not want to waste penicillin needlessly. Another problem is the question of the need for spinal puncture in well-treated cases of early syphilis that have become clinically and serologically cured. To what extent is this procedure necessary? Another difficult matter is the question of the advisability of prophylactic treatment, i.e., the treatment of exposed persons during the incubation period of the disease. In our country, it seems to be possible to control those persons who have been exposed so that they can receive prompt treatment if they develop the disease. It is in many ways a disadvantage not to know whether a person is really infected or not. I will admit that in pregnant women, it may be wise to use prophylactic treatment.

Finally, I should like to propose a manner of registering and centralizing case records for scientific purposes. As it is now, it is only possible to follow many patients by sending out questionnaires which busy practitioners do not like to answer. If every doctor could order from the health authorities forms of a size that suited *him*, and that contained the necessary questions about symptoms and treatment, and would use these forms as case records, they could be sent in to the health authorities at regular intervals, the data copied and the original form returned to the physician. In this way it might be possible to gather information from large groups of patients, at least in a small country such as ours.

Dr. Yrjö V. Salminen (Helsinki): **Reinfection in Early Syphilis after Combined Neosalvarsan and Bismuth Treatment.**

Reinfection usually has been considered to be rare in the course of syphilis. Most of the cases published in the first decades of the 20th Century do not stand up well under critical analysis. Halley and Wassermann (6), who analysed 676 cases described in the literature, found that only 229 of them (approximately one third) fulfilled strict criteria for reinfection. The subject was discussed extensively at the International Dermatology Congress in Copenhagen in 1930 by Truffi (15), Stokes (12), Brown (3) and Hoffmann (7), who were in agreement as to the difficulties of differentiating reinfection from infectious relapse.

Bernard (2) in 1926 and Stokes (11) in 1931 published quite similar criteria to establish the fact of reinfection. Stokes allowed for three degrees of stringency, but accepts as incontrovertable only those cases which fulfill all of the requirements outlined.

Laterly more moderate criteria have been suggested. Moore (10) accepts as reinfections cases that meet the following requirements: 1) a first infection must have been diagnosed either by the demonstration of *Treponema pallidum* in open lesions or by positive serologic tests; 2) After an interval following antisyphilitic treatment and at a site other than that of the primary lesion of the original infection, there must develop a lesion with characteristics of a chancre and in which treponemes can be demonstrated; 3) At the time of the supposed second infection, the serologic test must be negative and under observation for a period during which treatment is purposely withheld, the serologic test becomes positive or the patient develops manifestations of secondary syphilis. Thomas (13) accepts these criteria and emphasizes that the new chancre must be at a different site from the original one. Moreover, he considers it important that the patient be known to have been exposed to a person with infectious lesions.

After the year 1930, a more intensive and shorter treatment for early syphilis came into acceptance in many places. The fact that serologic tests now show greater sensitivity than formerly makes it possible to follow cases more closely both before treatment and after it. These circumstances have brought about an essential change, and experience has shown that relapses are becoming somewhat less

frequently reported, whereas there is evidence of more and more reinfections in the literature — Cannon (4), Klauder and Butterworth (9), Tobias (14), Kopp and Solomon (9), Hahn (5), Allison (1).

With the growing tendency to dispense with arsenicals and bismuth in the treatment of syphilis in favour of penicillin, the question of relapse versus reinfection becomes more important. Before the change to penicillin is complete, it is desired to report the cases of reinfection which have been seen at the Venereological Clinic for men in Helsinki.

The investigation comprises 1089 cases of syphilis observed in the years 1945—1949. Among this group, 69 patients had previously had syphilis for which they had been given treatment that was considered to be adequate. These patients were seen in the clinic with evidence of infectious syphilis. Table I shows these cases classified by years.

TABLE I.

Year	1945	1946	1947	1948	1949	Cases total
Diagnosed cases of syphilis	33	37	193	117	63	1089
Probable reinfection	19	24	8	12	7[1]	69

[1] The same case anew second time.

These 69 cases from the material of the study and the author has personally examined and treated each one. For corroboration of the previous diagnosis of syphilis, a careful anamnesis was taken, including details regarding the first infection, the site of the chancre, the swelling of the regional lymph nodes, the eventual discovery of *T. pallida* in the chancre, the seroreactions. Inquiries were made as to the treatment received, when it was terminated, and the serologic results obtained following treatment. On appearance of the new symptoms inquiries were made particularly as to the following items: the possibilities of infection, the time when infection might have been acquired, and the source of infection. The site of the previous chancre was always found either because of a scar or through information obtained from the patient. *T. pallida* were sought by dark-field examination and serologic tests were carried out on the blood serum. Spinal fluid examination was made if it had not already been undertaken during the interval between the first infection and the appearance of new symptoms. The following treatment had been previously used in these cases: seronegative primary syphilis — two combined courses of 10 × (Bismuth 0.2 Gm. plus neosalvarsan 0.6 Gm); seropositive primary syphilis and secondary syphilis — four combined courses or more. The treatment was intermittent and the length of the intervals between the courses was from 5 to 6 weeks.

The age groups of the patients appear in Table II. This shows that the average age of the patients was 28 years when the first infection was diagnosed and 33.6 years on appearance of the new symptoms. The interval between the first infection and the symptoms of reinfection was 5.6 years, on the average.

TABLE II.

Age	<—20	20—25	26—30	31—35	36—40	41—45	46—>	Average age	Cases
First infection	9	15	22	16	5	1	1	28	69
Probable reinfection ..	—	10	14	21	11	7	6	33.6	69

The cases have been grouped according to the serologic reactions. The first group contains 27 cases in which the seroreactions were negative during the first infection as well as on appearance of new symptoms, and 12 cases in which the seroreactions were positive when the first infection was diagnosed but negative on the appearance of new symptoms. Of the remaining 30 cases, 29 gave positive seroreactions at the time their new symptoms developed, and one was a case of congenital syphilis. This last patient developed new symptoms of primary syphilis at the age of 46 years.

Stokes' criteria of reinfection have been followed as far as is possible in the analysis, but all of the cases do not meet all of these difficult demands. Thirty-nine cases meet all save the following: that the physical examination be negative two years after treatment; that the source of the infection be known; and that the secondary eruption appear not less than twenty days after the chancre. The remaining 30 cases in addition to the above considerations fail to meet the following requirements: three negative blood tests for one year after treatment; and serologic reactions of the second infection negative at the onset and and changing to positive. Owing to these deficiencies, these 30 cases were excluded. One of the cases, however, was so unusual that it is worthwhile to describe it in detail.

A mother and her five months old son came on Nov. 7, 1899 to the Dermatological Department of the University of Helsinki. On examination it was found that the mother suffered from venereally acquired syphilis and the boy from congenital syphilis (papular syphilide on face and anal region, ozena). To this infant were given 40 doses of mercury ointment by inunction. Later, in 1916, the patient received several intramuscular injections, but this was the entire treatment administered. At the age of 46 years the patient came to the clinic (May 7, 1945) with all of the usual manifestations of primary syphilis. Treatment was started with arsenicals and bismuth and the clinical and serological response was entirely favorable.

Comments

Of interest is the high average age of the patients at the time the first infection was diagnosed, as well as the high average age at which the new symptoms appeared. This may be explained by the circumstance that most men from 20 to 46 years of age were in the Army and under war conditions were more frequently exposed to syphilitic infection than normally. Peace returned in 1944, and thereafter the number of new cases of syphilis reached a postwar peak in 1946, but after this a sharp decrease became evident. It was discovered that an unusually large num-

ber (69 cut of 1089 cases) had previously had syphilis. They had been given treatment that was considered to be sufficient, but now they had evidence of recurrent manifestations of the disease. What is the explanation? If these were relapses, why did they occur more frequently during the post-war years and with symptoms of primary syphilis? On the other hand, it can readily be visualized that conditions in the immediate post-war period would be especially condusive to increasing the number of reinfections. The fact that the 69 cases which previously had been treated were the ones that developed primary syphilis speaks in favour of reinfection rather than relapse. Only some of the patients had been examined and shown to be symptom-free two years or more after the treatment (one of S t o k e s' criteria). This deficiency does not, in the author's opinion, militate against reinfection.

Great difficulty arises with S t o k e s' requirement that the source of the second infection be identified. During the confusion of the post-war conditions it was possible to discover the sources of infection in only five of our cases. A missing source of infection should not invalidate the possibility of reinfection in cases where the anamnesis indicates the incubation period to be of the usual duration. Most of the cases meet the requirement that the blood serologic test of second infection be negative and change to positive. The seroreactions were continuously negative in a few cases. After the second infection had been diagnosed and treatment started blood samples were taken several times within an interval of a few days. However, the author could not justify the withholding of treatment until the seroreaction turned positive, considering the best interests of his patients. Another requirement of S t o k e s is that there must be an interval of 2 years or more between the first and second infection. In what way the cases reported herein meet this requirement appears most clearly in Table III. Six cases with negative seroreactions both during the first infection and on the appearance of new symptoms are presented with an interval of less than two years.

TABLE III.

Less than 2 years	More than 2 years	More than 4 years
6	63	29

In the case of congenital syphilis which had had rather inadaquate treatment, two explanations may be advanced for the appearance of symptoms of primary syphilis after 46 years. Here either there was spontaneous cure and reinfection, or a superinfection occurred. The entire clinical picture gainsays relapse.

It is believed therefore that 39 cases meet the requirements of all the most important criteria of S t o k e s, as well as those of M o o r e. The remaining 30 cases are considered to be probable reinfections.

Stokes claims to have observed one case of reinfection out of 228 cases of early syphilis. Moore and Kemp report one case in a group of 131 infections. In our experience, however, reinfections are far more frequent than this, occurring in one out of 28 cases, or 3.6 per cent of 1089 diagnosed cases of syphilis.

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II. Discussion

Q: *Should arsenicals and bismuth be given together with penicillin in the treatment of early syphilis?*

Dr. Danbolt. Our problem in Norway is similar to that in the other Scandinavian countries. Combined treatment with arsenicals and bismuth was introduced in Oslo by Bruusgaard 30 years ago. He found that patients who received one course (15 injections of neoarsphenamine and 15 injections of bismuth) had a relapse rate of about 16%; whereas patients who received two such courses had a failure rate of 7 per cent. This represents follow-up observations on approximately 30% of the original material. Nevertheless, the results in general were good.

In the Autumn of 1946 sufficient penicillin became available in Norway to enable us to treat cases of syphilis. On the basis of a trip to the United States

(where I visited Philadelphia and Baltimore, and was particularly impressed by the experimental work of Eagle on the synergistic action of penicillin and arsenicals and by the opinion expressed by Moore at that time that the two should be combined), I chose to recommend penicillin together with arsenicals and bismuth, and this scheme has been used in Norway since January 1947.

A follow-up study of these cases was made recently. We were able to obtain a one year follow-up on 69 of 85 patients treated. Among these there were five failures including reinfections. At the end of two years observation, the failure rate was approximately 7 per cent. These results are good — so good that we are continuing this form of therapy.

Some research workers report that penicillin affects only multiplying spirochetes and that organisms in the resting phase will not be influenced. If this is so, perhaps it is safest to use combined therapy, since the action of arsenic is different from penicillin in this respect.

I should like to know the more recent American experiences in this matter.

Dr. Rein. I wish Dr. Danbolt could have visited New York prior to going to Philadelphia and Baltimore in 1946. We in New York have complete confidence in penicillin alone and have abandoned arsenicals and bismuth in the treatment of early syphilis.

We have used penicillin in both long and short courses, and noted very little difference in the results. In one study, for example, the results with penicillin-oil-beeswax given 300,000 units once a day for 6—14 days were not significantly different from those obtained with one injection of 300,000 units of P.O.B. twice a week for 8 weeks — approximately the same total dosage.

I mentioned in my formal paper the studies now going on in Dr. Thomas' Clinic. We believe that with penicillin alone in adequate dosage we accomplish everything we can with penicillin plus arsenic and bismuth. We must remember that the «synergistic» concept was established in experimental animals and with sub-curative amounts of the two medications. With curative amounts of penicillin, there is no need for adjunctive therapy.

Since Dr. Chargin is here, I hope he will tell us about his recent experiences along these lines.

Dr. Chargin. I appreciate the privilege of discussing this subject. Having been through the days when mercury alone was used in the treatment of syphilis, and through the days of arsenicals and bismuth, I have lived to see metal chemotherapy almost completely replaced by penicillin in the United States.

Our opinions are based on extensive studies with large numbers of patients, and we have concluded that penicillin is preferable because it is effective and *it is safe*, whereas chemotherapy is not. In terms of therapeutic effectiveness we now obtain almost 100% favourable results with penicillin alone in seronegative primary syphilis, 92.5% favourable results in seropositive primary syphilis, and 77.6% favourable results in secondary syphilis. In early latent syphilis the results

are less good, but no worse than with arsenic and bismuth. The reports of various investigators differ considerably, depending often on the sensitivity of the serologic tests employed in determining serologic »cure».

Does the addition or arsenicals and bismuth make the treatment better? In a series of 476 cases, we found: in seronegative primary syphilis, no difference; in seropositive primary syphilis, no difference; and in secondary syphilis, the percentages also were comparable. We have observed a difference however in the relapse rates. which under combined treatment dropped to less than 1 per cent, We do not yet know the full explanation of this.

Dr. P u t k o n e n. Do you mean by «relapse rate» the same as »failure rate?»

Dr. C h a r g i n. Because of the difficulties in differentiating relapse from reinfection, we have made no distinction between them. But I do not refer to a «retreatment» rate, which is quite another thing.

Dr. T o t t i e: Do I understand that the difference in the failure rates between penicillin alone and penicillin plus arsenic-bismuth is less than 1 per cent?

Dr. R e i n. I think the important point is that with penicillin alone the relapse rate is somewhat higher than when penicillin plus arsenic are used together.

Dr. P u t k o n e n. We all can readily appreciate the differences of opinion in this question. I think that our experiences in the Northern European countries are not greatly different from those in America. Is this opinion shared by others from the Scandinavian countries?

Dr. D a n b o l t. We have gone over to penicillin, but have awaited more information, longer follow-up and larger series of cases.

Dr. D a t t n e r. Regarding the differences Dr. C h a r g i n has reported between patients who receive penicillin alone and those who receive penicillin plus arsenic and bismuth, how long was the therapy with arsenic and bismuth continued after the penicillin was stopped?

Dr. C h a r g i n. About 10—12 weeks.

Dr. D a t t n e r. In that case, the failure rate would surely be lower because you continue the treatment longer, and thus prevent more reinfections and relapses. This would definitely influence the statistics involved.

Dr. R e y n o l d s. I am quite prepared to believe that when penicillin treatment is followed by a course of 10—12 weeks of metal chemotherapy there will

be a somewhat lower «failure» rate than if penicillin alone is given — if only because the incidence of »ping-pong» infections would be reduced.

The question I think we have to answer is: Do we increase the percentage of »successes» sufficiently to compensate for the inevitable increase in toxicity that results from the added arsenic? If so, I think it should be given; if not, penicillin alone should be used.

Dr. R e i n. I think we can accomplish everything with penicillin alone that can be accomplished with combined therapy. Retreatments with penicillin alone have been entirely satisfactory in our experience.

I recently had the opportunity of reviewing some of the reports WHO has on endemic syphilis. In one village in rural Yugoslavia, Dr. G r i n was able to examine *all* the persons and to treat with penicillin alone *all* those with endemic syphilis. Follow-up studies ten months later revealed no recurrences — probably because the possibility of reinfection was removed. It seems to me that if all infected persons were to receive adequate amounts of penicillin alone, this would be adequate.

Dr. P e r d r u p. Since bismuth is essentially non-toxic and its action might be considered prophylactic, why not follow penicillin with a course of bismuth?

Dr. R e i n. Prophylactic treatment of this nature, to afford a complete guarantee against reinfection, would have to be continued for the remainder of the patients's sexually active life.

Q: *What is the optimum dosage of penicillin in the treatment of early syphilis?*

Dr. R e i n. In order to cure patients with early syphilis it is necessary to maintain a therapeutically effective penicillin level for from six to eight days. Any schedule of administration and any time-dose relationship, that will do this is highly efficacious.

A single injection of 1.2 million units of penicillin in oil with 2% aluminum monostearate will give a serum concentration of 0.03 units for 6 days in 90% of the cases. A single injection of 2.4 million units will give an effective serum concentration for 9 days in 90% of the cases.

May I make one more comment on the subject of penicillin versus penicillin plus arsenic and bismuth? Dr. D a n b o l t mentioned that Dr. J. E. M o o r e once advised combined therapy. At the last meeting of the American College of Physicians, Dr. M o o r e and I participated in a panel discussion during which this question was raised. Dr. M o o r e specifically stated that in his opinion penicillin alone was adequate, provided satisfactory blood levels were maintained 6—8 days. I think the duration of therapy is important, for it now seems clear that there is a minimum period of time over which the treatment must be prolonged.

Q: *Do the data now available show any advantage of penicillin in oil with aluminum monostearate over crystalline penicillin G? Is particle size important?*

Dr. K i t c h e n. The search for a slowly absorbed penicillin preparation has led to the development of many products, but the most suitable one is the procaine salt of crystalline penicillin G. By suspending this in oil and gelling it with aluminum monostearate, it is possible to maintain serum concentrations for days at a time following a single intramuscular injection.

The important thing is to maintain the serum penicillin level. If injections of penicillin in oil with aluminum monostearate are given daily there is a cumulative effect. If injections are given every forty-eight hours there is also a cumulative effect but on a lower level. A single injection of 2.4 million units (8 cc) will give levels in excess of the theoretical minimally effective concentration for 8—9 days in the vast majority of cases.

The particle size of the penicillin crystals is an important factor in suitable maintenance of the serum level. Ordinarily 50—60 % of the crystals are below five microns, but by careful screening this can be increased to 90 per cent. There may be other factors as well, such as the electrical charge and other physical-chemical considerations, but these are still imperfectly understood.

Dr. R e y n o l d s. I have recently received from Dr. B a u e r, Chief of the Venereal Disease Division of the United States Public Health Service, the latest data they have on the comparative results with aqueous penicillin G and penicillin G in oil with 2% aluminum monostearate. When only cases of secondary syphilis are considered and the total dosage is constant, the cumulative failure rates with these two preparations have been almost identical. There would be little reason to expect anything different in terms of therapeutic efficacy.

The advantage of penicillin-oil-monostearate lies in the convenience with which it can be administered, since far fewer injections are required to produce comparable serum concentrations over comparable periods of time.

Q: *Among patients treated for early syphilis with penicillin, when should a lumbar puncture be performed?*

Dr. D a t t n e r. It is a generally accepted fact (based largely on work carried out in Scandinavian countries) that if the spinal fluid is negative 3—4 years after infection, it will not revert to positivity, provided no reinfection occurs. Hence, it would be logical to postpone the spinal fluid examination for 3—5 years after the patient has been treated. The difficulty is that if this is done, many patients are lost from follow-up.

On the other hand, if the spinal fluid examination is made too early it is possible to miss later developments, since during the first few years reactivation of the syphilitic process is always possible. For practical purposes, I should prefer to set the date later than earlier.

Dr. M ø l l e r: Do I understand that if a patient is treated with penicillin for primary or secondary syphilis and the spinal fluid is found to be negative one year later, that it is still possible for him to develop a positive spinal fluid 3—4 years later?

Dr. D a t t n e r. In my experience, I have never seen a spinal fluid relapse, if 12—18 months following therapy the spinal fluid is negative. Yet to be on the safe side, because of the possibilities of late relapses or reinfections, it would be better to perform or repeat the spinal fluid examination later.

Dr. M ø l l e r. Then the possibility exists for a neurorecurrence following penicillin therapy of early syphilis?

Dr. D a t t n e r. Yes, the possibility exists, but it must be a rare occurrence.

Q: *Is prophylactic treatment of contacts justifiable?*

Dr. R e i n. I have had no personal experience with prophylactic or abortive therapy, largely because I agree with Dr. P e r d r u p that this is a dangerous procedure. We have a considerable amount of data in America that suggests that the procedure may have a public health value in reducing the reservoir of infection. After all, about 50% of all contacts of patients with primary syphilis develop the disease and by treating contacts before their disease becomes evident we may be preventing further spread. The danger lies in undertreatment.

Actually, we are using prophylactic therapy every time we treat a patient for ganorrhea. With penicillin, the physician has at his disposal a drug that is efficacious in the treatment of both diseases. When penicillin was adopted by the American Armed Forces as the standard treatment for gonorrhea, it was anticipated that a concomitantly acquired syphilitic infection would be masked by the penicillin, and many reports of this type have appeared in the literature. In most instances the patient acquires syphilis concomitantly with the gonorrheal infection. Promiscuous patients, however, may acquire syphilis immediately prior to or soon after becoming infected with gonorrhea. The amount of aqueous penicillin (usually 200,000 to 400,000 units) which is adequate for the cure of gonorrhea is definitely inadequate for the concomitant syphilitic infection. In such patients the following may occur:

1) *Abort.* If the patient received penicillin very early in the course of the gonorrheal infection, and the syphilis is only of a few days' duration, then relatively small amount of penicillin may be sufficient to abort or cure the syphilis. This has been corroborated by animal experiments where small amounts of penicillin administered a few days after infection were sufficient to effect a cure.

2) *Mask.* If the concomitant syphilitic infection is a few days older, the same amount of penicillin may prevent the appearance of the primary or secondary

lesions. In such instances the only evidence of syphilis is the development of positive serologic tests several weeks or months following treatment of the gonorrhea.

3) *Delay.* In still older infections, penicillin therapy will tend to delay the appearance of the early cutaneous manifestations for several months after the disease has been acquired.

Dr. T o t t i e. I am very glad to hear this, because this is a subject which has been widely discussed in Sweden. I agree that it is dangerous to administer treatment to exposed persons. What can we tell them after such treatment? Should they be checked month after month? Should we do one or more spinal punctures? Only by controlling these persons as closely as patients treated for clinical syphilis can we be sure they are cured. Otherwise, it is a dangerous practice.

I have followed the American Navy experiences with oral penicillin prophylaxis with great interest. Perhaps this practice is justifiable when the chances of infection are great. Certainly it is a simple procedure, but perhaps it should be carried out before exposure.

Dr. P u t k o n e n: I recall that during the first post-war Scandinavian Dermatological Congress there was considerable opposition to the use of penicillin in the treatment of gonorrhea because of the possible masking of early syphilis. I think we now generally agree that penicillin should not be withheld from gonorrhea patients because of this slight danger.

Q: *How long after therapy for early syphilis can infectious relapse occur?*

Dr. S a l m i n e n. We have already discussed the difficulties of differentiating relapse from reinfection. Certainly the majority of the clinical manifestations of syphilis we observe up to four or five years after infection are of the secondary variety, although relapses are very infrequent after that time.

Dr. T o t t i e. The problem of differentiating relapse from reinfection is of considerable importance from the epidemiological point of view. With a reinfection we must look for new sources of infection; whereas with a relapse, we worry less about other persons and can concentrate more on retreating the patient.

Dr. R e i n. I think we occasionally have much the same problem in the absence of clinical symptoms. A patient is treated and the serologic tests become negative. Some months later, the tests revert to positivity. Usually this is considered to be a serologic relapse, but there is the additional possibility of asymptomatic reinfection, which I am sure occurs. These patients also deserve epidemiologic reinvestigation.

Q: *Are quantitative serologic tests helpful in differentiating a reinfection from a relapse?*

Dr. R e i n. At the Army Medical Centre we had the opportunity of frequent clinical and serologic follow-ups of patients with penicillin-treated early syphilis.

A battery of serologic tests was performed with serums of such patients at weekly and monthly intervals. From our observations we feel it may be possible to distinguish between relapse and reinfection by carefully conducted serologic studies at frequent intervals. Following penicillin therapy in patients with early syphilis, there is usually a progressive reduction in serologic titer. In reinfection the patient usually attained and maintained complete seronegativity followed by the development of a darkfield-positive, sero-negative lesion at a new site. Shortly afterwards such patients developed sero-positive reactions with rapidly increasing titers. Reinfections can also occur in individuals who still have positive serologic reactions from their original infection. In treatment failures or relapse there was noted a sudden increase in serologic titer followed in about one month by evidence of a clinical relapse. If penicillin-treated patients would be subjected to serologic examinations at weekly or monthly intervals, it might be possible to predict a clinical relapse about one month before there is any clinical evidence, by a progressive increase in serologic titer on repeated examinations. Therefore, a rise, in titer followed by the development of a syphilitic lesion is suggestive of relapse, whereas the development of a new syphilitic lesion followed by a rise in titer is suggestive of reinfection. It is of utmost importance to educate patients to the great need of reporting to physicians for serologic and clinical examinations at regular monthly intervals for at least one year following the completion of penicillin therapy.

Dr. P e r d r u p. It has been our experience that true relapses have some of the characteristics of syphilitic infections of longer duration. That is, the serologic relapse is slower in developing a higher titer and the serologic response to treatment also is slower. Reinfections evolve the same way as first infections, and respond similarly to treatment.

Q: *When can patients treated with penicillin for early syphilis safely marry?*

Dr. C h a r g i n. I recall F o u r n i e r's statement on this point. After expressing the opinion that a man whose infection was of at least four years duration could safely get married, F o u r n i e r added: ». . . but not to my daughter, because we can't be absolutely sure.»

We cannot be sure, but we have reason to believe that patients who have received suitable penicillin therapy for early syphilis and whose clinical and serologic response is prompt and maintained throughout one year seldom will exhibit recurrent infectious lesions, and hence can with reasonable safety get married.

Dr. R e i n. In many cases this is largely an academic question. I once inquired of a group of applicants for marriage licenses regarding the question of premarital sexual contacts and found that about 85% already had had sexual intercourse with the prospective marital partner. In this question, patients seldom follow the doctor's advice!

Section II: Syphilis in Pregnancy and Congenital Syphilis

Chairmen Arvo Ylppö and Ole Enkvist.

The Value of Penicillin Alone in the Prevention and Treatment of Congenital Syphilis

By

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The complete suppression of congenital syphilis by prenatal treatment of the syphilitic woman, a cherished dream of many French research workers dating back at least as far as the eighteenth century [Mahon and Lamauve (1804), Swediaur (1809), Bertin (1810), Fournier], was placed in the realm of possibility by the invaluable pioneer contributions in the application of arsenicals and bismuth to this field by the distinguished Scandinavian investigators Boas and Gammeltoft and in other European studies. It is now rendered distinctly probable through the discovery and use of penicillin. In parts of the world where good syphilis control measures are possible and where adequate prenatal care has been realized, fresh cases of syphilis acquired before birth have already seen marked reduction and, from the theoretical standpoint need no longer exist. The value of penicillin in preventing the passage of syphilis from mother to child approaches perfection. Its ability to readily permeate the placenta makes it possible to treat adequately and to cure the fetus already infected *in utero*. In the increasingly unusual instance in which a newborn syphilitic infant may result, the effect of penicillin, immediately applied, in seemingly eradicating this disease has become almost a certainty. For these reasons it is to be hoped that this tragedy of the family and of society may cease long before the complete control of adult syphilis, becomes a realization.

The experience which forms the basis for this detailed discussion on the prevention and treatment of congenital syphilis with penicillin goes back to the fall of 1943 at the University of Pennsylvania [1] and has been gradually expanded to

[1] This work was coordinated by the Institute for the Study of Venereal Disease (John H. Stokes, M.D., Director), and the Department of Dermatology and Syphilology of the School of Medicine. The following individuals contributed actively to the program: Herman Beerman, M.D., John W. Lentz, M.D.; Elizabeth K. Rose, M.D. and Paul György, M.D. (Department of Pediatrics); Alice M. Kresge, R. N., Jane Barbara Taylor, R. N. and Henrietta M. Hanna, R. N. (supervision of attendance follow-up); Verna M. Stein (Serologist); Emily Stannard (Statistician).

include the much larger case material available at the Philadelphia General Hospital [1]. This work has been the subject of a series of previous reports the cases from which, with considerable augmentation, more prolonged period of observation, and better clinical control, are included in the present study. Since the prevention of congenital syphilis is from every standpoint the most important aspect of this program, the material dealing with the syphilitic pregnant woman will be presented first.

Syphilis and Pregnancy

Material

This is a study of the outcome of pregnancy in 1959 women with syphilis. Four hundred and eighty-four of these were contributed by the University of Pennsylvania and 1475 by the Philadelphia General Hospital. The group includes 179 (9%) White and 1790 (91%) non-White women, with a median age of 21.5 years for those with early syphilis and of 31.3 years among the small series of cases with late syphilis included, as described below, for purposes of comparison. Of these women 1063 received penicillin either before or during their pregnancy. The only basis for selection of cases other than presence of syphilis and stage of disease, to be discussed more fully in the analysis material presented below, was the duration of medical follow-up of the infant after birth. It was the desire in this study to keep under observation all surviving infants with at least monthly physical examinations, blood serologic tests and, where indicated, roentgenograms of the long bones, for a period of not less than six months. This was accomplished in about 77% of cases, many of the infants being observed at intervals beyond the first half year of life to the age of one year, two years or even longer. All cases are included, however, in which the surviving infant was followed for at least sixty days and in whom at the time of the last medical observation there seemed no reasonable doubt as to the presence or absence of syphilis. Cases followed for less than sixty days or in whom the diagnosis at the time of last observation was in doubt have been excluded from the analysis. Most experts working actively in this field would feel that, using as a basis for selection the criteria just described, the margin of resultant diagnostic error would be very small, possibly in the magnitude of one percent.

For adequate clinical statistical analysis of the value of penicillin in the prevention of congenital syphilis, it was felt that three types of control groups were necessary. In the first place, since normal, or non-syphilitic, pregnancy does not invariably result in the birth of a full term living infant, it was felt that data on the results from *a comparable group of pregnancies from which syphilis had been excluded,* in so far as possible, were a requisite. This information was obtained

[1] Division Dermato-Syphilology, Department of Medicine (Service Norman R. Ingraham, Jr., M.D.), the following staff members contributed actively to this study: Virgene S. Wammock, M.D., O.M. Carrozzino, M.D., Ira L. Schamberg, M.D., Nellie Clair, R. N. ((attendance follow-up), Michael J. Burke (Statistical Epidemiologist, Department of Public Health).

through inclusion in the study of *such* a control group giving outcome of pregnancy in 10,323 mothers at the Philadelphia General Hospital for the years 1945 to 1949 inclusive, in whom syphilis was ruled out by negative medical history, physical examination and blood serologic tests. These years coincide approximately with the period when the major portion of the penicillin treated syphilitic pregnant women were observed.

Secondly, it seemed necessary to obtain information concerning the *effect of untreated syphilis on the outcome of pregnancy* in comparable material over a period concurrent with the study. Such information, though contained in earlier publications is rather meager in the medical literature and, from other sources, would not necessarily be comparable with the results of this study. In the ten years 1940 to 1949 inclusive it was possible to derive information at the Philadelphia General Hospital on the outcome of 302 untreated syphilitic pregnancies, 220 with early syphilis and 82 cases with late syphilis at the time of delivery.

In controlling the results of penicillin therapy in this field it also seemed highly desirable to have information in a comparable series of cases concerning the outcome of pregnancy when arsenic and bismuth, which it is proposed be replaced by penicillin, is employed. Such a group of adequately studied pregnant women with early syphilis was found at the Philadelphia General Hospital for the interval January 1940 to August 1946 inclusive. This space of time partially overlaps the period, starting in the fall of 1943, when data were collected on the penicillin treated series. Information on the arsenic bismuth treated series ceases to become available after 1946 because such therapy was discontinued at that time. This group of cases numbers 594 who received varying amounts of arsenical and bismuth, as given in more detail in the analyses below, either before or during pregnancy.

Anticipated Results of Pregnancy as Shown by Control Groups

The probability of having a normal full term living infant among patients from a control group comparable to the syphilis material at the Philadelphia General Hospital is about 86 in 100 when the possibility of syphilis has been excluded (Table I). Full term still born infants or neonatal deaths are very infrequent (about one-half of one percent each). Premature infants, more than two-thirds of whom are born alive and survive the neonatal period, occur in slightly less than 13 percent of total deliveries.

In comparison, the toll of *untreated active early syphilis* is enormous. A few normal full term living infants will be born in the untreated syphilitic group, but the probability of a dead or diseased child exceeds four in five pregnancies. In the tabular compilation, all of the differences between the untreated early syphilis group and the control group are statistically significant. The possibility of obtaining a living infant who survives the neonatal period is only 60 chances in one hundred. Two-thirds of these babies, moreover, will have active congenital syphilis. The possibility that the syphilitic infant will be premature is only slightly

Table I. *Effect of u n t r e a t e d syphilis on outcome of pregnancy at Philadelphia General Hospital compared with results from non-syphilitic pregnancies*

Outcome of Pregnancy	Syphilis Status of Mother					
	Non-Syphilitic		Untreated Early Syphilis		Untreated Late Syphilis	
	Number	Percent	Number	Percent	Number	Percent
Normal Full Term Living Infant..	8,897	86.25	40	18.2	61	74.4
Living Syphilitic Infant	—	—	90	40.9	2	2.4
*Premature Non-Syphilitic Infant	930	9.00	5	2.3	2	2.4
Neonatal Death						
Full term infant	49	0.46	4	1.8	1	1.2
*Premature infant	177	1.70	26	11.8	6	7.4
Stillborn						
At full term	57	0.54	40	18.2	10	12.2
Premature (miscarriage)	213	2.05	15	6.8	0	0.0
Total	10,323	100.00	220	100.0	82	100.0

* A premature infant is defined as weighing *less than* 5 lbs. (2.27 kg.)

increased in the syphilitic as compared to the normal control group (21 percent and 13 percent respectively), but the likelihood that the diseased premature infant will survive the neonatal period is only one-sixth that of the otherwise healthy premature infant. The probability that the outcome of pregnancy will be a stillbirth at term is increased more than 32 times in the untreated mother with early syphilis.

Duration of syphilis at the time of pregnancy has an important effect on the outcome. Untreated women with syphilis of more than four years duration have a probability of 3 normal full term living infants in 4 pregnancies (Table I). While this difference is statistically significant, the only other figure in this compilation which will stand the test for accuracy is the percentage occurrence of stillbirths at term which is still about 22 times the probability shown by the normal control group. The likelihood of obtaining a living syphilitic infant, between two and three percent among the untreated women with late syphilis, is not significantly greater than the incidence of this accident in the treated syphilis material to be presented. For this reason, conclusions based upon the effect of treatment in preventing congenital syphilis in any series which includes a substantial number of patients with late syphilis is hardly valid without correction for duration of disease. All of our subsequent analyses on the usefulness of treatment during pregnancy are, accordingly, based only upon the study of women with early syphilis.

Arsenic and Bismuth in the Prevention of Congenital Syphilis

For comparison with the results of penicillin therapy to be presented the value of types of syphilis treatment used immediately before the advent of the antibiotics is summarized in Table II. This shows, as has been known for many

Table II. *Effect of arsenic and bismuth in prevention of congenital syphilis outcome in early syphilis and pregnancy at Philadelphia General Hospital analyzed as to amount of treatment given and compared to non-syphilitic control group*

Outcome of Pregnancy	Non-Syphilitic Control Group		Treatment Status of Syphilitic Mother			
			*Small amounts of arsenical before or during pregnancy		More than ten weeks of arsenical during pregnancy	
	Number	Percent	Number	Percent	Number	Percent
Normal Full Term Living Infant..	8,897	86.25	138	65.1	244	91.4
Living Syphilitic Infant	—	—	28	13.2	6	2.2
Premature Non-Syphilitic Infant ..	930	9.00	6	2.8	2	0.7
Neonatal Death						
Full term infant	49	.46	6	2.8	5	1.9
Premature infant	177	1.70	8	3.8	0	0.0
Stillborn						
At full term	57	.54	20	9.5	9	3.4
Premature (miscarriage)	213	2.05	6	2.8	1	0.4
Total	10,323	100.00	212	100.0	267	100.0

* Less than 20 weeks arsenical treatment with or without bismuth prior to pregnancy and/or less than 10 weeks arsenical treatment with or without bismuth during pregnancy.

years, that small amounts of treatment given either before or during pregnancy, quantities well below the standards normally employed in bringing about the «clinical cure» of syphilis, are capable of having a markedly favorable effect on the outcome of pregnancy. Less than 20 weekly injections of a trivalent arsenical preparation, such as neoarsphenamine or a phenarsine derivative, given before pregnancy with or without bismuth, or less than 10 injections of an arsenical given during pregnancy, are capable of giving normal full term living infants almost two times in three. When more than 10 weeks of arsenical therapy is given during pregnancy, with or without bismuth, the results of pregnancy in all categories analyzed are superior to those obtained in the normal control group with the exception of some slight tendency to an increase in the number of infants stillborn at term, but here, the difference will not bear the test for statistical significance. Better than 91 percent normal full term living infants resulted and only 2.2 percent living syphilitic infants.

Aqueous Penicillin by Frequent Injection in Hospitalized Patients

With the syphilitic pregnant woman, as with other types of syphilis, initial trials and still by far the greatest experience has been with aqueous penicillin by injection at 2, 3 or 4 hour intervals. It was soon found, through trial and error, that amounts of penicillin incapable of stopping progression of the disease in the adult or preventing infectious relapsing lesions were likewise not capable of preventing infection of the fetus in a satisfactory percentage of cases. Nonetheless, as with previous chemotherapy using arsenic and bismuth, even small amounts of peni-

Table III. *Effect of penicillin in the prevention of congenital syphilis. Outcome when aqueous penicillin is used by frequent injection, during pregnancy analyzed as to total dose: whether greater or less than 2.4 million oxford units*

Outcome of Pregnancy	Total Dose Penicillin to Syphilitic Pregnant Woman			
	Less than 2.4 million units		2.4 million units or more	
	Number	Percent	Number	Percent
Normal Full Term Living Infant ..	13	62	435	94.0
Living Syphilitic Infant	5	23	5	1.1
Premature Non-Syphilitic Infant ..	0	00	2	0.4
Neonatal Death				
Full term infant	0	00	1	0.2
Premature infant	1	5	4	0.9
Stillborn				
At full term	2	10	11	2.3
Premature (miscarriage)	0	0	5	1.1
Total	21	100	463	100.0

cillin (total dosage of 300,000 or less up to 1.2 million Oxford units) are capable of producing a markedly favorable effect on the outcome of pregnancy (Table III). Optimum results, better than 90 percent normal living full term infants and about one percent living syphilitic infants, seem to be reached by total dosage of 2.4 million Oxford units when aqueous penicillin is used. Total dosages of 4.0 to 6.0 million Oxford units have been employed in periods from 7 to 12 days but significantly improved outcome of pregnancy has not been procured over those obtained from the use of 40,000 units crystalline G sodium (or potassium) penicillin in aqueous solution every three hours for a total of 60 injections. This last mentioned form of treatment, however effective, has, in the process of evolution and from consideration of practicability and convenience, been largely replaced. It has no great advantage apparently from the therapeutic standpoint over the use of the currently available more slowly absorbed penicillin preparations which require less frequent administration.

Slowly Absorbed Penicillin Given During Pregnancy

Our experience with the use of penicillin in absorption delaying vehicle in the treatment of the syphilitic pregnant woman commenced in the fall of 1945. With increasing accumulation of favourable results and improvement in the vehicles available for treatment it has now completely replaced the use of aqueous penicillin in our clinics. The plan has been to maintain a satisfactory concentration of penicillin in the maternal and fetal tissues for a period of eight to ten days. The results of the three different treatment courses utilized are summarized in Table IV. The initial requirement of once daily injection has more recently been modified to give less frequent injection though with total dosage of from 4.8 to 6.0 million Oxford units. Application of the usual tests for statistical significance show no

Table IV. *Effect of penicillin in the prevention of congenital syphilis. Outcome when penicillin in absorption delaying vehicle is used during pregnancy; three different schedules and total dosages analyzed*

Result of Pregnancy	Method of Treatment						Total All Three Types	
	Total dose 4.8 mill. units		6.0 mill. units		6.0 mill. units			
	Number inject. 8		10		5			
	Number days 8		10		9			
	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Normal Full Term Living Infant	116	89.2	51	88	11	90	178	89.0
Living Syphilitic Infant	3	2.3	1	2	1	10	5	2.5
Premature Non-Syphilitic Infant..	0	0.0	0	0	0	0	0	0.0
Neonatal Death								
Full term infant ..	1	0.8	0	0	0	0	1	0.5
Premature infant..	3	2.3	1	2	0	0	4	2.0
Stillborn								
At full term	6	4.6	5	8	0	0	11	5.5
Premature (miscarriage)	1	0.8	0	0	0	0	1	0.5
Total	130	100.0	58	100	12	100	200	100.0

difference between the results obtained with the three different methods of treatment employed using slowly absorbed penicillin. In the aggregate they have resulted in 89 percent normal full term living infants and 2.5 percent living syphilitic infants. There was no statistical significance in the minor differences in results obtained from aqueous penicillin by frequent injection when compared to slowly absorbed penicillin given once daily or even less frequently. The choice of exact type of drug and frequency of administration will accordingly be determined from questions of convenience or suitability to the particular situation prevailing rather than from concern for any difference in therapeutic efficiency.

Treatment Given Prior to Conception in the Prevention of Congenital Syphilis

If penicillin is an effective method of treatment in most cases of acquired syphilis in the adult woman, the next pertinent question has to do with the need for repetition of therapy during subsequent pregnancies if medical care has been adequate prior to conception. This consideration has led to withholding penicillin during pregnancy in instances in which women have had a normal response to treatment given before pregnancy. It has also led to a reevaluation of the outcome of pregnancy and the necessity of retreatment when adequate amounts of arsenic and bismuth were given prior to conception.

The appraisal of our own experience in this field shows that adequate preconceptional therapy with either arsenic and bismuth or penicillin give results which

Table V. *Prevention of congenital syphilis; treatment of the syphilitic woman before but not during pregnancy; results from penicillin therapy compared with arsenic and bismuth*

Outcome of Pregnancy	Type of Treatment Given Before Conception			
	more than 20 weeks of arsenical with or without bismuth		2.4 million oxford units or more of penicillin	
	Number	Percent	Number	Percent
Normal Full Term Living Infant ..	106	92.2	345	91.0
Living Syphilitic Infant	0	0.0	2	0.5
Premature Non-Syphilitic Infant ..	4	3.5	3	0.8
Neonatal Death				
Full term infant	1	0.8	2	0.5
Premature infant	4	3.5	9	2.4
Stillborn				
At full term	0	0.0	13	3.4
Premature (miscarriage)	0	0.0	5	1.4
Total	115	100.0	379	100.0

again do not differ statistically from those obtained when adequate amounts of treatment given during pregnancy (Table V). Among 115 mothers at the Philadelphia General Hospital who received more than 20 weeks of arsenical treatment with or without bismuth prior to conception, but no specific treatment for syphilis during pregnancy, more than 92 percent normal living full term infants resuted and *no* living syphilitic infants. With 379 mothers who received a total dose of 2.4 million units or more of penicillin prior to conception but no specific treatment for syphilis during pregnancy, 91 percent normal full term living infants resulted and only 2 (0.5%) living syphilitic infants. These figures will be immediately recognized as again better than the anticipated expectancy of normal full term living infants as shown by the comparable non-syphilitic control group. Adequate treatment of the mother prior to conception is accordingly just as effective as specific therapy given during pregnancy in the prevention of congenital syphilis provided observation throughout the period of gestation is adequate and reinfection does not occur.

Discussion of Penicillin Treatment of the Syphilitic Pregnant Woman

a. Blood Serologic Test During Pregnancy and at the Time of Delivery

Since only a short time will intervene between the date of treatment and the date of termination of the pregnancy, in this group on an average three to four months, the majority of the syphilitic women will still be seropositive at delivery. In actuality 81.6 percent of the mothers treated with penicillin during pregnancy were seropositive at the time of birth of the child and 38.1 percent of the mothers treated prior to conception were seropositive. In evaluating the effect of treatment, repetition of the blood serologic test of the mother during preg-

nancy is of little value unless a titer is performed to determine quantitative response. Minor variations which may be indicative of activity of disease and at times predict infectious relapse may then be determined. A monthly examination for syphilis, including laboratory tests and an inspection for presence of lesions, from the time of treatment until termination of the pregnancy is essential to the ideal handling of such patients and formed a part of the routine management in this study.

Mothers seropositive at the time of delivery may give birth to seropositive non-syphilitic infants. In this group 46.1 percent of the normal (non-syphilitic) infant offspring of syphilitic mothers had positive blood serologic tests at the time of birth. Such normal infants develop negative blood tests in almost every instance by the time they are one month old. Only occasionally does a perceptible amount of syphilis reagin remain for as long as two to three months after birth. The presence of a substantial titer of reagin beyond the third or fourth week of life is usually indicative of prenatally acquired syphilis and must always be regarded with suspicion.

b. *Reasons for Failure of Treatment During Pregnancy*

Failure of treatment during pregnancy results from two principal causes. In the first place, the fetus may be diseased beyond all hope of survival at the time treatment is instituted. This occurs in some cases when the mother with active syphilis does not receive attention for her disease until the latter part of pregnancy, usually after the thirty-second week. The fetus may occasionally die during the course of treatment, in such instances or be stillborn shortly after its completion. This is a problem of general prenatal care. It is the reason why statistically, the stillbirth rate always has a tendency to be higher in the early syphilis group than in the normal control group. The disease and mortality rate from this cause cannot be reduced further as a result of treatment until the medication is given uniformly in the early months of the pregnancy (prior to the sixteenth week).

The second cause of failure, which usually results in the birth of a living syphilitic child, comes from recrudescence of activity of infection in the last weeks of the pregnancy in spite of treatment or occasionally from fresh infection. This was a problem in prepenicillin days as it is at the present time though for a slightly different reason. When arsenic and bismuth were used to prevent congenital syphilis, about ten weeks of therapy were essential prenatally to be reasonably certain that the fetus was protected. With active syphilis in late pregnancy it was not always possible from the practical standpoint to give this length of treatment course before the fetus was infected or the pregnancy terminated. With penicillin, total treatment may be given in a week or two, which is a great advantage. But, in the occasional case in which treatment is ineffectual in controlling the maternal infection and relapse occurs with or without the development of recognizable surface lesions, or when the woman is reinfected through some failure in epidemiologic procedure, then a diseased infant may result. Careful observation of the mother

through pregnancy will reduce these risks to a minimum, but even retreatment as indicated will probably not make possible the reduction of infantile syphilis to an incidence much below the one percent now obtained in the offspring of syphilitic mothers.

Among the women in this series who received presumably adequate amounts of penicillin 12 living syphilitic infants resulted (10 in mothers treated during pregnancy; 2 in mothers treated before pregnancy). The occurrence of each of these could be explained on the premises outlined above. All but one of these infants had positive blood serologic tests at birth. The sole seronegative infant became seropositive after the third week. A definite diagnosis of syphilis was established in six of these babies by the time they were one month old, in two instances during the third month and in two during the fourth month. In the other two infants medical follow-up-during the first four months was inadeaquate so that the positive diagnosis was not accomplished till the age of 5 months and 17 months respectively. All of these infants responded well to subsequent treatment for syphilis.

c. *Relation of Week of Pregnancy in which Treatment is Given to Unfavourable Outcome*

An analysis of the circumstances attendant on the birth of the living syphilitic infants among the mothers who receive more than 2.4 million Oxford units of penicillin during pregnancy will indicate the relative importance of the factors above mentioned in inducing failure. Of the ten mothers concerned, three of these women were treated after the thirty-second week of the pregnancy, but six were treated before the midpoint of pregnancy (only one was treated between the twentieth and the thirty-second week).

The reason for failure among those mothers treated after the thirty-second week is easy to understand. These are instances in which in all probability the fetus was already infected *in utero* and the amount of treatment given the mother was insufficient to complete the cure of the fetal syphilis prior to birth. That the majority of cases of fetal syphilis are cured in such circumstances, however, and only a few are not, is attested by the fact that in this series 148 (22.3%) of the mothers treated with penicillin during pregnancy received their medication after the thirty-second week. In such instances it would be anticipated that women with active early syphilis would have already transmitted the disease to the unborn child in a large percentage of cases.

The instances in which the mother was treated in early pregnancy (or even before pregnancy) and yet the infant was infected, can be explained usually only on the premise that the active maternal infection was not controlled. Since this occurred six times among 204 mothers treated before the twentieth week, it is apparent that the risk following a single course of treatment for active syphilis given *early* in pregnancy was somewhat greater in this series than if treatment was given in the latter months of the pregnancy. In these six failures among

mothers treated before the twentieth week in pregnancy, infectious relapse at or near term occurred in three cases, high sustained titer of the blood serologic test for syphilis throughout pregnancy in two cases and serologic relapse at about the termination of the pregnancy in the final instance. The majority of women (47%) were treated between the twentieth and the thirty-second week and yet only one failure in terms of birth of a living syphilitic infant developed in this group.

Even though the total number of failures is small, the differences in failure rate between the various periods of pregnancy is statistically significant (Table VI) and seems to indicate that the best time to protect the fetus with penicillin is

Table VI. *Syphilitic infants born of penicillin treated mothers referred to week in pregnancy that treatment was given*

Period of Pregnancy	Number of Mothers Treated with Penicillin	Percent Total	Number Living Syphilitic Infants	Failure Rate Per 1000
0 to 20	204	30.7	6	29
21 to 31	311	47.0	1	3
32 to term	148	22.3	3	20
Total	663	100.0	10	52

between the fifth and seventh months. The very occasional fetus which is infected during this period will usually be cured *in utero* and treatment at this time in pregnancy will hold the maternal infection in abeyance in almost every instance for a long enough interval to make infectious relapse prior to term unlikely. This is, of course, a tentative observation only on limited case material an is not to be construed as a recommendation for treating the syphilitic woman at any other time in pregnancy than as close as possible to the date of the first prenatal visit.

It is interesting to note that Cole, Plotke, Thomas and Jenkins (1949) also found the greatest number of confirmed syphilitic outcomes in mothers treated in the *first* trimester of pregnancy and the least when treatment was given during the middle trimester. In addition, both of the living syphilitic infants in the report (1950) with Bundesen as senior author were in mothers treated with 2.4 million Oxford units total dose of penicillin *prior* to the sixteenth week of pregnancy. Some clinical research workers have advocated retreating late in pregnancy all women with early syphilis who received their initial therapy before the sixteenth week. Considering the small risk to the fetus, however, even with the failures as described above, this can hardly be advocated as a routine procedure.

d. *Response of Pregnant Woman to Treatment and Question of Retreatment in Subsequent Pregnancies*

The value of arsenic and bismuth therapy given prior to pregnancy in preventing congenital syphilis has been answered even more conclusively than in the present study with a larger series of cases (570 pregnancies in 363 women) by Goodwin and Faber (1948). Their results are similar to those described by us in that none of the living infants were shown to have syphilis. This type of material is not strictly comparable to that compiled from the study of syphilitic women treated with penicillin prior to conception as shown in the present report and in that of Tucker (1949), because the latter groups deal with recently acquired infections and the arsenic and bismuth group largely with late syphilis. Because of the prolonged period necessary to administer arsenic and bismuth as compared to penicillin and the frequent failure to detect the disease at its inception, relatively few of the women who were treated prior to conception with the older remedies had syphilis of short duration when pregnancy resulted. To such a group the element of time has been added to that of treatment. This, as shown by reference to the control group of untreated syphilis in the present study, would be expected to greatly improve the outcome of pregnancy.

The question of retreatment of the syphilitic woman in subsequent pregnancies is intimately bound to the question of her response to initial penicillin therapy. In an unselected series of 285 syphilitic pregnant women from the University of Pennsylvania, 192 with early syphilis and 93 with late syphilis, we have endeavoured to obtain some impressions on this point (Tables VII, VIII) (Fig. 1) In the early syphilis group, which numbered 74 patients with primary and secondary syphilis and 118 patients with early latent syphilis, maximum serologic response was apparently not obtained from the single course of treatment until about the third year and then leveled off at between fifty and

Table VII. *Response of syphilitic pregnant woman to penicillin therapy alone; results of blood serologic test and number of patients retreated for progression of disease over five year period; mother originally treated for early syphilis*

Cases Observations Retreatment	Total	Period of Observation in Years					
		less than ½	½ to 1	1 to 2	2 to 3	3 to 4	4 to 5 or more
Number Cases	192	192	165	138	103	58	38
Number Observations	2537	1078	483	504	287	123	62
Number Seropositive	1803	913	321	304	153	52	32
Percent Seropositive	—	84.9	66.4	60.3	53.3	42.3	51.6
Number Retreated	7	4	1	1	1	0	0
Cumulative Percent Retreated*	4.7	2.1	2.7	3.4	4.3	4.3	4.3

*Based upon percentage patients observed in each time period and calculated by the life table method described by Iskrant, Bowman and Donahue (1948).

Table VIII. *Response of syphilitic pregnant woman to penicillin therapy alone; results of blood serologic test and number of patients retreated for progression of disease over five year period; mother originally treated for late syphilis*

Case Observations Retreatment	Total	Period of Observation in Years					
		less than ½	½ to 1	1 to 2	2 to 3	3 to 4	4 to 5
Number Cases	93	93	68	57	35	11	8
Number Observations	732	290	152	177	78	24	11
Number Seropositive	627	245	120	162	71	20	9
Percent Seropositive	—	84.5	78.9	91.5	91.0	83.3	81.8
Number Retreated	1	0	0	1	0	0	0

SYPHILITIC PREGNANT WOMEN TREATED WITH PENICILLIN
RESPONSE OF BLOOD SEROLOGIC TEST AND CUMULATIVE RETREATMENT RATE EARLY COMPARED TO LATE SYPHILIS

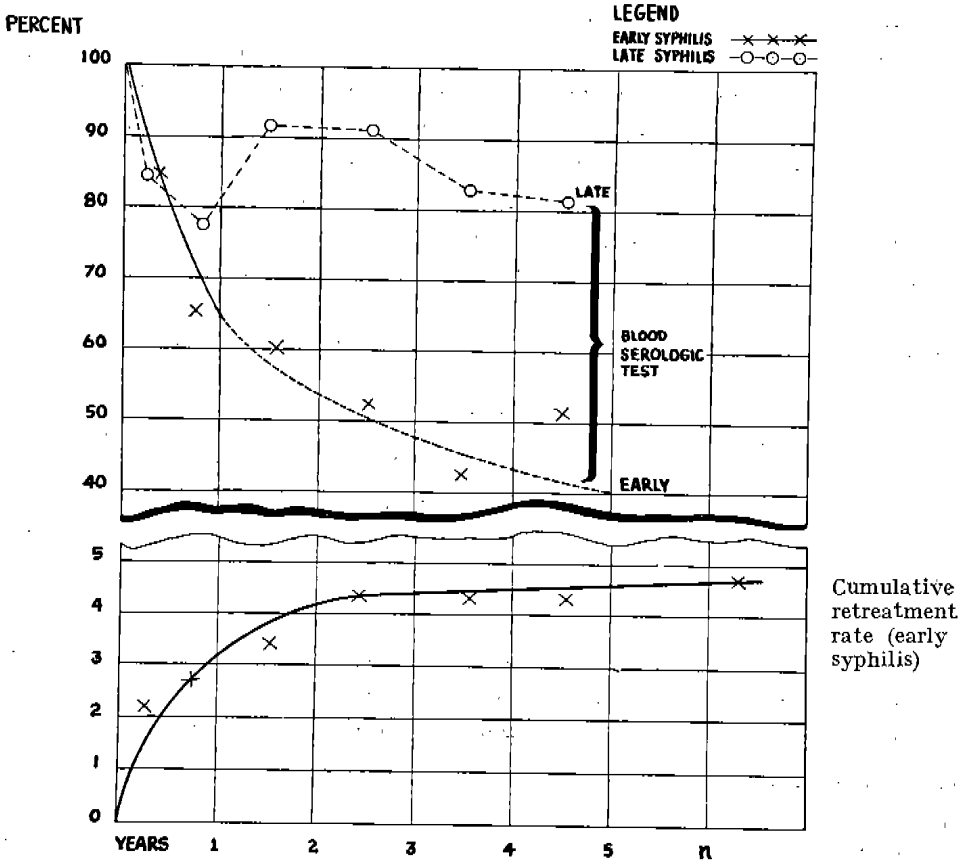

Figure 1. Prepared from data in Tables VII and VIII

sixty percent seronegative. This is certainly no better response, if as good, as has been obtained with non-pregnant patients, though problems concerning age, race, sex and stage of disease, which are difficult to correct for from available information make true comparisons difficult. With symptomatic early syphilis and comparable types of treatment courses in the non-pregnant patient, the percentage seronegative vary from 65 to 80 at 21 to 24 months after penicillin [Bauer, Usilton and Price (1950)]. One point of interest among these pregnant women is the low retreatment rate: only seven retreated in 192 cases of early syphilis observed for periods up to five years, the majority of retreatments occurring within the first year. This represents a retreatment rate of only 3.4 percent at 24 months (Table VII, Fig. 1). In contrast, the available statistics on non-pregnant patients with symptomatic early syphilis and comparable treatment schedules show retreatment rates at 21 to 24 months of from 16 to 25 percent [Bauer and Price (1949)].

In arriving at some conclusion with regard to the serologic and clinical response in *late* syphilis (largely latent) in the pregnant woman, there are little or no similar data for comparison in non-pregnant groups. It is realized, moreover, that short periods of observation (up to five years) may be less significant in this type of material. Nonetheless, among 93 pregnant women treated with penicillin for late syphilis there was very little indication of any favorable effect on the blood serologic test (Table VIII, Fig. 1). About one-fifth of the patients became seronegative within the first year of post treatment observation after which there was no evidence of continued favourable response. There was, however, clinical evidence of progression of the disease in these seropositive cases necessitating retreatment in only one pregnant patient with late syphilis during this period.

The continued positive serologic test for syphilis in spite of treatment imposes a number of practical considerations for the woman in the child-bearing age. Without any true attempt to evaluate the efficacy of penicillin therapy in curing maternal syphilis, which is beyond the scope of this paper, two observations are pertinent. The first is that, if we use the response of the blood serologic test as the criterion for cure or for retreatment in subsequent pregnancies, many mothers who have received standard courses of penicillin and who are capable of giving birth to perfectly normal infants, retain their positive blood serologic test. The second point to be stressed is that the decision as to retreatment of the pregnant woman with latent syphilis, and this includes most cases of syphilis and pregnancy, must be largely founded on more or less arbitrary criteria [such as have been outlined by Wammock, Carrozzino, Ingraham and Clair (1950)], based upon clinical experience with large numbers of patients. Of women who have received penicillin for symptomatic or latent *early* syphilis as many as 50 percent will remain seropositive in subsequent pregnancies up to five years after treatment and when we are concerned with symptomatic or latent *late* syphilis, some 80 percent may be expected to remain seropositive in the same period of observation.

Table IX. *Summary of value of treatment in prevention of congenital syphilis. Treatment given before or during pregnancy compared with untreated control group*

Outcome of Pregnancy	Treatment Status of the Syphilitic Woman											
	Untreated				Treated During Pregnancy				Treated Before Pregnancy Only			
	Early Syphilis		Late Syphilis		As and Bi		Penicillin		As and Bi		Penicillin	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Living Infant ..	40	18.2	61	74.4	244	91.4	613	92.5	106	92.2	345	91.0
Living Syphilitic Infant	90	40.9	2	2.4	6	2.2	10	1.5	0	0.0	2	0.5
Premature Non-Syphilitic Infant	5	2.3	2	2.4	2	0.7	2	0.3	4	3.5	3	0.8
Neonatal Death												
Full term infant	4	1.8	1	1.2	5	1.9	2	0.3	1	0.8	2	0.5
Premature infant	26	11.8	6	7.4	0	0.0	8	1.2	4	3.5	9	2.4
Stillborn												
At full term ..	40	18.2	10	12.2	9	3.4	22	3.3	0	0.0	13	3.4
Premature	15	6.8	0	0.0	1	0.4	6	0.9	0	0.0	5	1.4
Total	220	100.0	82	100.0	267	100.0	663	100.0	115	100.0	379	100.0

Table X. *Summary of the literature in the prevention of congenital syphilis. Living syphilitic infants born following penicillin therapy of the syphilitic woman from principal previously published reports*

Author(s)	year publication	Total dose penicillin (million oxford units)	When treatment given in relation *to pregnancy*	Total Pregnancies *Observed*	Living Syphilitic Infants	
					No.	Per cent
Frazier	(1946)	0.6 to 1.2	during	9	none	0.0
Olansky and Beck ..	(1947)	2.4	during	21	none	0.0
Allen and Delp	(1949)	3.0 to 6.0	during	47	2	4.3
*Cole, Plotke, Thomas, Jenkins	(1949)	0.2 to 10.0	during	414	11	2.7
	(1950)	0.6 to 9.6	before	229	1	0.4
*Cross, McCain, Heyman	(1949)	4.8	during	39	2	5.1
*Tucker	(1949)	0.6 to more than 5.0	during	149	none	0.0
	(1949)	1.2 to 9.6	before	111	1	0.9
*Bundesen, Rodriquez, Aron, Korman	(1950)	2.4 to 4.8	during	130	1	0.8
			before	76	1	1.3
			Total	1225	19	1.6

*Previous reports from same institution not cited, since it is assumed that all cases are included in most recent publication.

SUMMARY OF VALUE OF TREATMENT GIVEN BEFORE OR DURING PREGNANCY IN PREVENTION OF CONGENITAL SYPHILIS COMPARED WITH CONTROL GROUPS

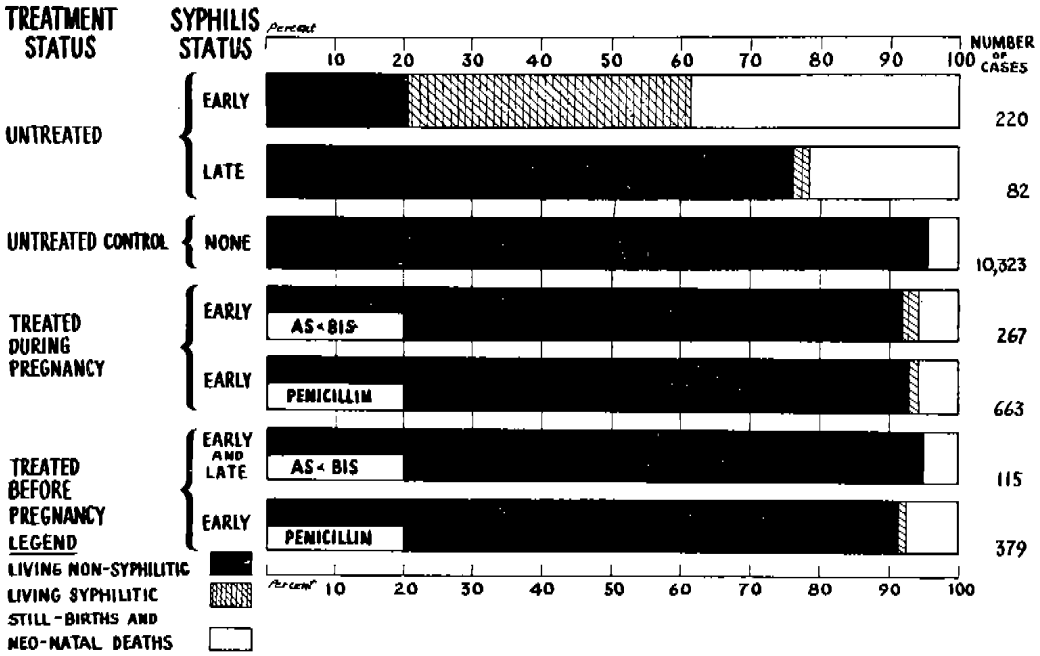

Figure 2. Prepared from data in Tables I and IX

e. *Recommended Treatment Schedule for the Pregnant Syphilitic Woman*

A summarization (Table IX, Fig. 2) comparing, one with the other, the relative values of the different types of treatment used in the prevention of congenital syphilis shows that adequate therapy administered either before or during pregnancy give identical results in fulfilling expectancy of full term living infants normal for the sample of the population surveyed, and in reducing the number of syphilitic births to the minimum (1 to 2 percent). The several major previous publications in this field from other clinics in the United States when combined show a failure rate following penicillin of 1.5 percent living syphilitic infants among 1225 pregnancies (Table X) which is a figure strictly comparable to that obtained in the presently reported studies. The greater value of penicillin, which makes it now the treatment of choice in this field is to be found not so much in its increased efficacy over arsenic and bismuth since both methods of treatment, ideally applied, give approximately equal results. It is to be found rather in ease of administration of penicillin, in its lack of toxicity, its ability to treat the fetus already infected *in utero*, and in the shorter time period necessary to produce the desired results. There are apparently almost no investigators, familiar with this subject, who express a contrary point of view as recent complete summaries of medical and public health thought show [Thomas (1949), Ingraham and Beerman (1950) and Goodwin (1950)].

The basic essential in treating the pregnant syphilitic woman to protect or cure the fetus is to maintain satisfactory penicillin concentrations over a period of seven to ten days. This, as we see it now, can best be accomplished by a total dosage of 6.0 million Oxford units of procaine penicillin in absorption delaying vehicle, such as a vegetable oil with 2% aluminum monostearate. Individual injections of 600,000 Oxford units once daily may be used, or perhaps a larger amount of antibiotic at longer intervals, provided the concentration of penicillin in the maternal blood is sufficient to permeate the fetal tissues in therapeutically effective amounts.

Congenital Syphilis

The story of penicillin treatment of congenital syphilis is, from the purely scientific standpoint, much less satisfactory and much less convincing than the material just presented on syphilis and pregnancy. This is inevitable since the increasingly effective antepartum syphilis care given in areas from which this material has been collected, is making congenital disease a less and less frequent occurrence. Most cases of congenital syphilis in Philadelphia currently arise from poor prenatal supervision among the some 10 to 12 percent of patients who do not report for medical observation until at or near the termination of pregnancy. Many of these are sexually promiscuous young women and unmarried mothers. The incidence and prevalence of syphilis and other venereal disease among them is high and in the magnitude of 200/1000. This is largely a problem in sociology, economics and public health education. The number of cases of congenital syphilis which occur among those mothers who have had adequate antepartum supervision is so small as to cause no concern. If good prenatal care occurred generally there would be no possibility of completing the remainder of this presentation.

As it is, we have been able to collect in the slightly less than seven year period of this study, from the combined services of the University of Pennsylvania and the Philadelphia General Hospital only 183 cases of congenital syphilis adequately observed after receiving penicillin therapy. Fifty-seven of these were infants less than four months of age when treatment was instituted, 23 were between the ages four months and two years, the remainder (103 cases) were late congenital syphilis classified as latent with stigmata, 40 cases; congenital neurosyphilis, 37 cases; active late syphilis of the skin and bone, 4 cases; interstitial keratitis, 22 cases. There were 79 (43 percent) males in the group and 104 (57 percent) females; 55 (30 percent) were White and 128 (70 percent) were non-White. A total of 1591 medical examinations including blood serologic tests and spinal fluid studies were carried out on these 183 patients (Table XI).

Response of Blood Serologic Test Following Penicillin

One of the most striking observations in the evaluation of congenital syphilis comes in the response of the blood serologic test in the penicillin treated material when analyzed by age at the beginning of therapy. (Table XII, Fig. 3). In in-

Table XI. *Early and late congenital syphilis. Analysis of number of cases observed during each time period following penicillin treatment*

Age When Penicillin Treatment Was Begun		Total	Period of Medical Post Treatment Follow-Up in Years							
			Up to ½	½ to 1	1 to 1½	1½ to 2	2 to 3	3 to 4	4 to 5	more than 5
Before 4 months	Number Patients	57	53	39	32	25	24	21	14	6
	Number Observations	496	209	100	48	37	39	35	19	9
	Number Died	10	10	0	0	0	0	0	0	0
4 months to 2 years	Number Patients	23	22	17	13	14	10	7	4	1
	Number Observations	217	88	35	28	22	20	16	6	2
	Number Died	0	0	0	0	0	0	0	0	0
more than 2 years	Number Patients	103	94	76	63	46	46	29	22	17
	Number Observations	878	307	207	106	71	83	48	32	24
	Number Died	0	0	0	0	0	0	0	0	0
Total	Number Patients	183								
	Number Observations	1591								

Table XII. *Early and late congenital syphilis. Response of blood serologic test to penicillin therapy analyzed according to age when treatment was given*

Age When Penicillin Treatment Was Given	Total Number Patients	Blood Serologic Test for Syphilis	Period of Medical Post Treatment Follow-Up in Years							
			At Start Treatment	up to ½	½ to 1	1 to 1½	1½ to 2	2 to 3	3 to 4	4 to 5	more than 5
Before 4 months (median 1.9 months)	57	Number Seronegative*	0	47	80	47	37	39	35	19	9
		Percent Seronegative	0	22	80	98	100	100	100	100	100
4 months to 2 years (median 8.6 months)	23	Number Seronegative*	0	9	10	7	9	14	6	4	2
		Percent Seronegative	0	10	28	25	41	70	38	66	100
more than 2 years (median 16.1 years)	103	Number Seronegative*	8	31	16	16	9	15	11	8	4
		Percent Seronegative	8	11	8	15	13	18	23	25	17

*For total number of observations in each time period see preceding table.

fants whose treatment was commenced prior to the age of four months (median age 1.9 months) not a single infant followed beyond the age of 18 months failed to become seronegative and clinically normal. One-fifth of the treated infants observed during the first six month post treatment interval were seronegative, four-fifths at 12 months were seronegative, 98 percent at 18 months and 100 per-

EARLY AND LATE CONGENITAL SYPHILIS; RESPONSE OF BLOOD SEROLOGIC TEST TO PENICILLIN THERAPY ACCORDING TO AGE WHEN TREATMENT BEGUN

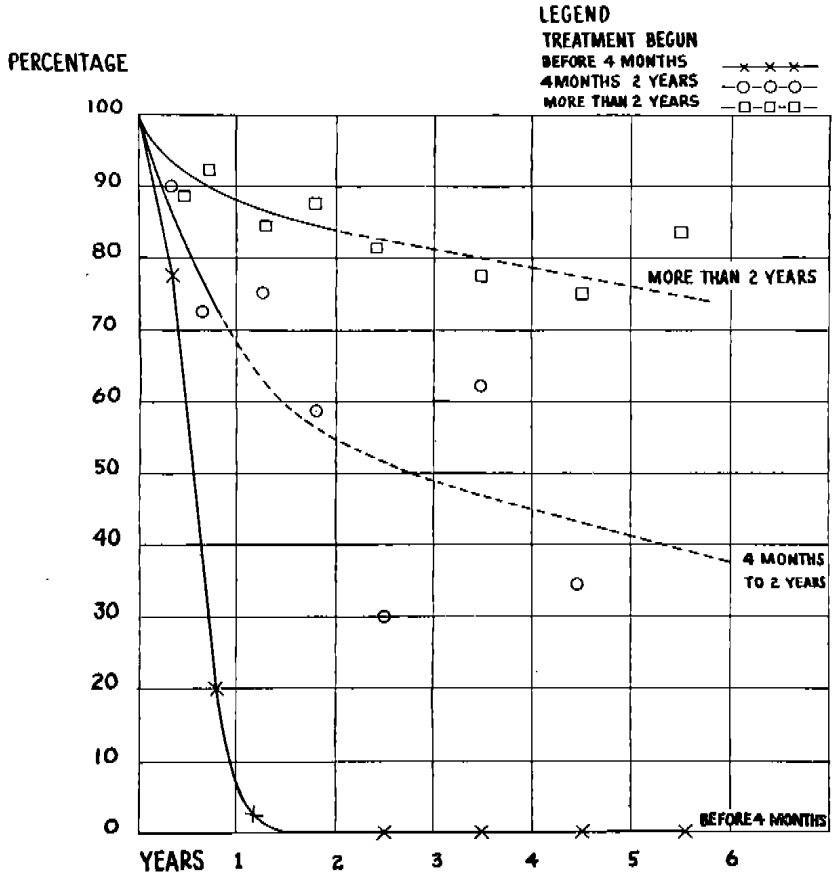

Figure 3. Prepared from data in Table XII

cent thereafter. This evidence of virtually complete response to penicillin treatment with almost total absence of clinical relapse or progression up to more than five years of observation is apparently peculiar to infantile congenital syphilis. It has been remarked upon by several other investigators.

With increasing age at the beginning of treatment the serologic response becomes less complete. In the group in whom treatment was started between the age of 4 months and 2 years (median age 8.6 months) about one-fourth had become seronegative at the end of one year and about one-half after 2 to 3 years of observation. In late congenital syphilis (median age at beginning of treatment 16.1 years) reversal of the blood serologic test following penicillin is hardly noticeable. One year after treatment there was no appreciable change in the blood serum reagin titer for syphilis and even into the fourth and fifth year after treatment no more than 20 to 25 percent of the cases had developed completely negative blood tests.

Treatment of Infantile Congenital Syphilis

In the management of infantile congenital syphilis the very considerable mortality rate has given rise to much discussion about the technique of treatment to be employed. In the present series it will be recognized that there were 10 deaths among 57 treated infants under 4 months of age: a rate of 17.5 per 100. These all occurred within a short period following institution of therapy and are the only deaths which resulted in the entire series of 183 patients many of whom were followed for several years (Table XI). There is a natural feeling that treatment may have caused the death of some of these infants, particularly when the fatality resulted during the course of therapy. It is difficult in the individual case always to be certain that the outcome would not have been different had some other approach been used.

It is recognized that the most important reason for death in all of these cases is the extreme debilitation caused by fetal and infantile syphilis. Irrespective of treatment some fatalities from syphilis occur. A partial answer to this point is obtained from the Philadelphia General Hospital material. In this group three deaths happened among 24 penicillin treated cases, a mortality rate of 12.5/100. In the same period (1946 to 1949), however, it was disclosed from the records that 10 infants with congenital syphilis were admitted to the wards and died without receiving specific therapy. In some of these cases diagnosis of the disease was made at autopsy, in other instances laboratory studies and roentgenograms which established the presence of the infection were not returned until after death of the infant. In actuality, therefore, among 13 infant deaths, known to have resulted from syphilis at the Philadelphia General Hospital during the period in question, three received penicillin and ten did not. Among the infants who received penicillin twenty-one survived and three died. It is not possible to draw definite conclusions from such a small number of cases, but they do serve to illustrate that many infants with syphilis are diseased beyond hope when first seen and that death in such cases cannot reasonably be attributed to the therapy.

Therapeutic shock (Jarisch-Herxheimer reaction) occurs in infantile syphilis following penicillin and may be severe. The most complete evaluation of this problem in the literature of the United States is that of P a r d o and T u c k e r (1949). The best chance of controlling the aftermath of such a reaction is through hospitalizing the infant and giving expert pediatric care directed toward restoring normal fluid, salt and protein balance and correcting anemia. Parenteral feedings, increased fluid intake and blood transfusions are sometimes essential. Almost all small infants with congenital syphilis are the victims of intercurrent infection and death results in the majority of cases, in our experience, from involvement of the respiratory tract culminating in bronchopneumonia, otitis media, septicemia or similar serious complication. The presence of other infectious disease which may also be helped by penicillin is a potent argument against reducing initial penicillin dosage. With limited experience and meager series of cases it is not certain that any final answer can be made to the question of the seriousness of

therapeutic shock in infantile syphilis. Clinical trial of alternative methods of approach which will stand critical analysis is, moreover, hardly feasible with small case material. The treatment for infantile congenital syphilis, capable of producing the results which have been described as approaching 100 percent in surviving infants treated under the age of four months, is accordingly somewhat arbitrarily suggested as follows:

Duration of Therapy: 12 to 15 days
Total dose: not less than 100,000 Oxford units penicillin per kg. of body weight.
Individual dose:

a. 1/120 of total dose, calculated in round numbers, of crystalline G penicillin sodium (or potassium) every three hours

or b. 150,000 to 300,000 Oxford units procaine G penicillin in absorption delaying vehicle once daily (less frequent administration of slowly absorbed penicillin has also been recommended but experience is very limited).

Method of Administration: by injection. There should be no reduction in dosage of initial treatment(s).

The recommendations just given are similar to those contained in the principal studies in the United States in this field [P l a t o u (1949); P l a t o u, H i l l, I n g r a h a m et al (1947)] based upon a somewhat larger series of cases, though on shorter periods of observation. Chief difference of opinion in the management of infantile congenital syphilis centers about the need for reducing the initial dose to avoid therapeutic shock and the question of supplementing penicillin with metal chemotherapy, on which subjects there is probably insufficient material available to come to a final opinion. N a b a r r o (1949), D e b r é (1949), B a t c h e l o r (1949), M o r g a n (1949) among others have recommended reduced initial dosage to avoid dangers of therapeutic shock. D e b a u c e n s (1948), D e b r é (1949), B a t c h e l o r (1949), E n k v i s t (1947) (1948), are some of the clinical investigators who feel that supplementing penicillin with arsenic or bismuth may be of some value in the treatment of infantile congenital syphilis.

The excellent results obtained with penicillin alone in infantile syphilis make use of adjunct metal chemotherapy (arsenical and bismuth) appear unnecessary. Penicillin therapy by mouth seems unwarranted under normal circumstances even with expert supervision because of gastrointestinal disturbances which often occur in the debilitated syphilitic infant and the uncertainties and irregularity of absorption. Relegation of such therapy to the even less experienced unsupervised parent would seem even less justifiable except for a total lack of other facilities. One matter for comment has been the infrequency of progression or relapse in infantile congenital syphilis, following penicillin therapy. This has occurred in only about one percent of cases. Satisfactory response has been induced uniformly in these infants by repetition of the penicillin course, usually with somewhat larger total dose of the antibiotic.

Late Congenital Syphilis

With late congenital syphilis evaluation of penicillin therapy is hampered not only by the meagerness of the case material but also by the prolonged period of observation which is necessary to reach conclusions on most points. In the patients in this series it has been customary to use what has been considered to be adult dosage of penicillin. Few patients received a total of less than 6.0 million Oxford units and many of the patients, particularly those with interstitial keratitis or involvement of the central nervous system, received 9.0 million Oxford units total dose or more. Patients with latent syphilis or benign symptomatic late syphilis (osseous, cutaneous) were treated on an ambulatory basis with 600,000 Oxford units penicillin in absorption delaying vehicle over a period of 10 days. Those with more serious manifestations of the disease were usually hospitalized and many received aqueous crystalline G sodium penicillin in dosage of 80,000 Oxford units every three hours for 15 days.

Gummatous *skin* and *bone involvement* as an accompaniment of late congenital syphilis heal promptly following penicillin therapy with scarring but with little tendency to relapse at least within the periods of observation.

The impossibility of evaluating the results of penicillin therapy in *late latent congenital syphilis* is manifest from the discussion on serologic response in the preceding section. The results with this material is similar to those presented by Hollström and Hård (1948) in the evaluation of this form of treatment in seroresistant patients with congenital syphilis. No recognizable response of the blood serologic test to penicillin was found. The thought with these patients has been to give an arbitrarily predetermined single course of penicillin as described above and then to await results of prolonged periods of observation.

Table XIII. *Late congenital neurosyphilis. Response of spinal fluid to penicillin therapy*

Number and Percentage of Cases Showing Each Type of Spinal Fluid	Before Treatment	Period of Medical Observation After Treatment in Years							
		up to ½	½ to 1	1 to 2	2 to 3	3 to 4	4 to 5	5 to 6	6 to 7
Total Number Cases	37	33	23	27	20	12	10	5	2
Total Number Observations	—	71	36	44	29	15	12	5	2
Percentage each *Type of Spinal Fluid**									
Type III	84	52	37	30	14	7	0	0	0
Type II	0	18	14	11	24	7	0	0	0
Type I	16	30	49	59	62	86	100	100	100
Normal									

*For spinal fluid types see Cooperative Clinical Group Classification (1937) as modified by Stokes, Beerman and Ingraham (1944).

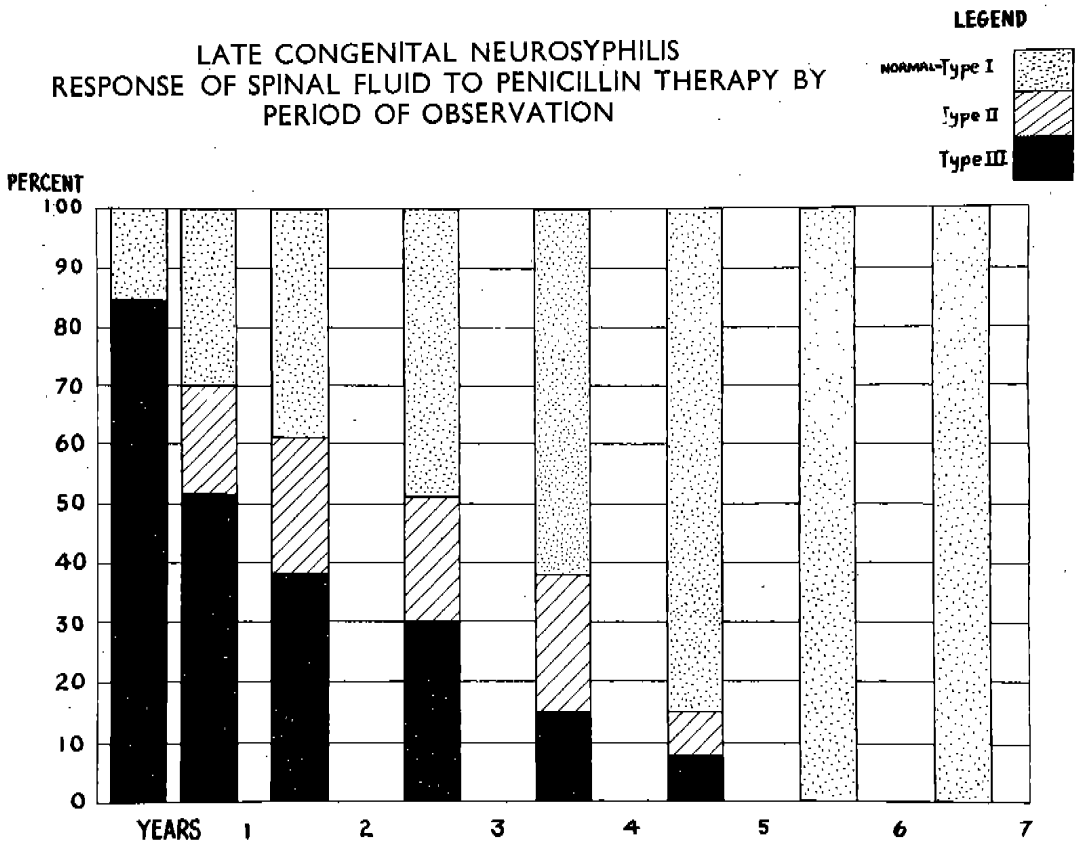

Figure 4. Prepared from data in Table XIII

The response of *late congenital neurosyphilis*[1] to penicillin is of interest even though the number of collected cases is small. The effect of treatment on the spinal fluid is summarized in Table XIII (cf. also fig. 4). Type III fluid is the most active and exhibits high cell count, definite increase in the total protein, strongly positive serologic reaction, and markedly positive colloidal mastic curve. This classification is the same as that used by the Cooperative Clinical Group in the United States (1937) as modified by Stokes, Beerman and Ingraham (1944). The spinal fluids negative at the commencement of treatment all occurred among the patients with eighth nerve deafness (3 cases) or meningovascular neurosyphilis (3 cases). There were four additional cases of meningovascular neurosyphilis, eleven cases of juvenile paresis, 6 cases of taboparesis, one case of tabes dorsalis and nine cases of asymptomatic neurosyphilis all with strongly positive spinal fluid reactions at the start of treatment.

Following treatment, all of the patients who were observed for the longest period of time (4 to 7 years) developed normal or near normal fluids. Almost

[1] Medical diagnosis, supervision and study of clinical progression in these cases was assisted by the Department of Neurology, University of Pennsylvania, George D. Gammon, M.D., Clinical Professor.

50 percent of those observed had reached this state by the end of the first year of post treatment observation, 62 percent by the third year and improvement seemed to continue without evidence of relapse beyond that period.

Since some of these cases had, prior to the institution of penicillin treatment, advanced degenerative changes of the nervous system which could not be expected to be restored, the symptomatic response was not as dramatic as the spinal fluid response, but further progression was averted and in the asymptomatic cases prevented. Similar experience has been reported by Calloway, Flower and Hirschmann (1950) in 17 cases of congenital neurosyphilis.

The results obtained in the 22 cases of *interstitial keratitis*[1] associated with late congenital syphilis in this series are similar to those discussed by Klauder (1947) and do not improve upon his observations. Among 94 involved eyes and periods of post treatment observation of from 9 to 33 months (mean 18.7 months) he obtained remission of acute symptoms following penicillin alone (dosage 0.5 to 7.8 million Oxford units) with final visual acuity between 6/6 and 6/21 in 84.5 percent of cases and with final visual acuity of less than 6/60 in 4.2 percent of cases. London and Noojin (1948) report similar results in nine patients.

Since the eye involvement does not represent an active syphilitic process in the sense that the causative organism is present in the lesion, the response to penicillin treatment is unpredictable and not always immediately favorable. The immediate outcome, insofar as it can be evaluated with small numbers of cases is as good but no better following penicillin than after metal chemotherapy. As with other forms of treatment, penicillin does not always prevent initial attack of interstitial keratitis, it does not stop involvement of the second eye when only one is involved and does not prevent recurrence of the disease in the previously affected eye. It is customary to use fever therapy in addition to maximal penicillin dose in this condition. Our experience with attempts to concentrate the penicillin in the active lesion by local instillation or injection of the antibiotic as has been advocated by some [eg. Sorsby (1949)] or by greatly increasing the dosage of the parenteral injections, has not seemed to modify the expected results, and considering what is known of the underlying process may actually be an illogical approach.

Congenital syphilis is rapidly ceasing to be a serious medical and public health problem where good control measures are possible. Still, it will continue to be a threat as long as syphilis is prevalent in any degree in the adult population. With modern public health practice and the effectiveness of penicillin during pregnancy the crippling, death dealing impact of infantile and late congenital infection results almost completely from neglect in application of our knowledge. The fact that an appreciable number of infants or children with prenatally acquired infection exist shows that, even in areas where general public health practice

[1] Medical supervision of these cases was under the supervision of William O. La Motte, M.D., Department of Ophthalmology, University of Pennsylvania.

is considered to be good, too many cases of syphilis are escaping detection in marriage and pregnancy. While this is not always the fault of the physician who handles the individual case and may often be attributed directly to the shortcomings of the patient, yet, it does represent a defect in social organization which *can* be remedied to the benefit of civilization and all mankind.

Summary and Conclusions

Experience at the University of Pennsylvania and the Philadelphia General Hospital over a seven year period, with the penicillin treatment of the syphilitic pregnant woman and of infantile and late congenital syphilis, is the subject of this report. One thousand and sixty-three pregnant women treated with penicillin for primary, secondary or latent early syphilis; 80 infants under 2 years of age with congenital syphilis, and 103 patients with symptomatic or latent late congenital syphilis are analyzed. As clinical controls, 10,323 pregnancies in a comparable group of women in whom syphilis was excluded by routine methods, 302 syphilitic women untreated during pregnancy and 594 pregnant women treated with arsenicals and bismuth are used.

The analysis reveals that, in the type of material reported upon, the probability of pregnancy, uncomplicated by syphilis, resulting in a normal full term living infant is about 86 percent. The most frequent complication is prematurity (12.75 percent). Stillbirths (2.6 percent) and neonatal deaths (2.2 percent) are of low frequency. Untreated early syphilis in an otherwise similar group of patients resulted in a dead or diseased infant in about 82 percent of cases, increased the possibility of neonatal death six times and of stillbirth at term 32 times over the normal control group.

Even a small amount of treatment with either arsenic and bismuth or penicillin was able to produce a markedly favorable effect on the outcome of pregnancy in the syphilitic woman. It is also revealed that the likelihood of favorable outcome of pregnancy increases with the duration of syphilis irrespective of treatment. In a group of 82 untreated women with late syphilis the likelihood of a normal full term living infant was three in four and of a living full term syphilitic infant only 2.4 percent, though the stillbirth rate at 12.2 percent continued to remain higher than that of the normal control group.

Effective dosage of penicillin given to 663 women with early syphilis during pregnancy resulted in 92.5 percent normal full term living infants and only 1.5 percent living syphilitic infants. In separate analyses of patients treated with penicillin in aqueous solution by frequent injection and with three schedules of slowly absorbed penicillin given by injection once daily or less frequently, it is shown that there is no statistical significance in the minor differences in the outcome depending on the type of preparation or course of therapy employed. The results attained, as measured by normal full term living infants with the adequately

treated syphilitic women, was in this series, at least equal to those exhibited by the non-syphilitic control group.

The exact method of treatment with penicillin is accordingly a matter of individual preference or expediency in meeting existing condition provided an adequate maternal (and if treatment is given in late pregnancy) fetal tissue level is maintained for from 7 to 10 days. The most practical tested course for average use would consist in 600,000 Oxford units procaine penicillin G in oil with 2% aluminum monostearate once daily for 10 days. Less frequent injection, for example 1.2 million Oxford units every other day to a total of six million Oxford units, has yielded similar results with smaller series of cases.

An analysis of 267 pregnant women treated for early syphilis with more than 10 weeks of arsenicals, with or without bismuth, in the period immediately preceding the introduction of penicillin yielded results not statistically different from the penicillin treated group. Nonetheless, ease of administration and short duration of therapy, the lack of toxicity and the ability to cure *in utero* the already infected fetus, makes penicillin alone the preferred treatment in the prevention of congenital syphilis.

Congenital syphilis case material is limited because of the widespread application of effective antepartum treatment for syphilis in the part of the world from which this study emanates. The infants with syphilis which do result are almost entirely from mothers who have had little or no prenatal care, rather than from failure of treatment as such.

It was possible to observe over varying periods up to five years 80 babies treated with penicillin alone. In surviving infants, the clinical and serologic response approaches perfection (in this group of cases the cure rate actually was 100 percent) when treatment is commenced prior to the fourth month of life. In older infants the clinical response has been good but the reversal of the blood serologic test to negativity is less satisfactory.

The mortality rate was 17.5 per 100 in the penicillin treated syphilitic infants less than four months of age. These deaths all occurred during the course of penicillin therapy or shortly thereafter. It is felt that death was the result of debility produced by syphilis and was not caused by treatment. Additional evidence is presented to show that the mortality rate from untreated infantile syphilis is high, in this same age group. No modification in the course of treatment to avoid therapeutic shock is suggested.

Since limited case material does not admit broad clinical trial of several methods of approach, the treatment course employed for infantile congenital syphilis is somewhat arbitrary. The suggested dosage which has been found to be effective consists in not less than 100,000 Oxford units of penicillin per kg. of body weight. This is given over a fifteen day period without additional specific treatment other than supportive pediatric care which is of extreme importance in debilitated infants. Specifically the total dose of penicillin crystalline G sodium (body weight in kg. $\times$ 100,000 Oxford units) in aqueous solution may be divided

into 120 individual doses to be given every three hours. Alternatively, 150,000 Oxford units procaine penicillin in oil with 2% aluminum monostearate may be given once daily (or in larger amounts less frequently) over a period of 15 days.

Patients with late congenital syphilis are given up to 9.0 million or more Oxford units of penicillin, if possible on an ambulatory basis, 600,000 Oxford units once daily (or larger dosage less frequently) of procaine penicillin in oil with 2% aluminum monostearate for 15 days.

The blood serologic test in latent or symptomatic late congenital syphilis (103 cases) is not markedly affected by such a course of treatment in periods of observation up to five years.

Late gummatous skin and bone syphilis heals promptly with such treatment without recurrence for the time period observed.

In congenital neurosyphilis (37 cases) response of spinal fluid following penicillin to normal or near normal is virtually complete in patients observed up to seven years, and relapse seldom occurs. Advanced irreparable damage to the nerve tissue in some symptomatic cases makes restitution of normal function impossible.

Interstitial keratitis associated with late congenital syphilis (22 cases) does not respond any better to penicillin than to other previously tried remedies and final results leave much to be desired. Penicillin should be supplemented by fever therapy routinely, if possible.

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A Follow-Up Study of the Results of Treatment in Children with Congenital Syphilis at the Welander Home, Stockholm, between 1900 and 1950

(Preliminary Report)

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In December of 1900 the Professor of Syphilology, Edward Welander opened the so-called Welander Home in Stockholm. He intended to create with his institution both a speciality hospital and a school and home for children with congenital syphilis. He himself called the hospital «The Little Home» (L.H.). Up to July 1, 1950, 500 children had been admitted.

Examination of the records reveals that 327 of these 500 presented definite signs of congenital syphilis, while 173 must be classed as uncertain or purely observation cases. None the less, 143 of those without demonstrable symptoms of syphilis have received specific therapy. The indications for treatment have thus been broad, and understandably so considering that the therapeutic agents formerly in use, especially at the beginning of the century, possessed neither the rapid action nor the efficacy of those at our disposal to-day. One finds that children of *untreated* syphilitic mothers in particular received the treatment, although no demonstrable symptoms of congenital syphilis were present. Edward Welander and his associate and successor, Karl Marcus, both eminent syphilologists, held the opinion that with regard to syphilis it was better to forestall than to be forestalled. They knew from experience that the earlier specific therapy is instituted, the sooner and better will be the results. In this respect it was considered of secondary importance if one or another non-syphilitic child received treatment. Moreover, the children of the Little Home often came from a bad environment, so that it was necessary for social reasons to take them in hand. An idea of this environment is conveyed by the fact that 354 of the children, or 70.8 per cent, were born of unmarried mothers.

On two occasions previously, follow-up investigations have been made with respect to the children treated at L.H.; namely, by Welander in 1915 and by Marcus in 1925. Welander found that only in one of 112 children had symptoms of syphilis redeveloped after discharge from the hospital. When Marcus conducted his investigation in 1925, 231 children had been admitted to L.H. If we deduct the 37 inmates at the time and the 20 children who had died of intercurrent diseases, 174 cases were followed up. Of this group 18 had died of non-syphilitic diseases and in 16 cases the patient could not be contacted. The remaining 140 cases Marcus divided into two groups, *successful* and *unsuccessful*. The second group consisted of 22 cases (15.7 per cent) in which more or less severe defects were found which could be definitely, probably, or possibly attributed to congenital syphilis. Only three patients showed definite syphilitic changes with positive Wassermann reactions. The remaining 19 had mental disorders of varying severity. Marcus classified 118 as successful; 71 of this group had had serologic control during the last year.

Twenty-five years have now elapsed since Marcus did his follow-up. I have therefore felt that it would be of value to conduct an all inclusive follow-up investigation of the congenital syphilitic children that have been treated at L.H., partly to elucidate their fate and partly in the hope that the results may be of future use as a comparative basis for evaluating the effect of modern antisyphilitic agents. Many of the former patients I have been unable to contact, for they are scattered throughout the country, their whereabouts being unknown. I have secured information about some through local or central authorities, or through parents and foster parents. Many have no knowledge of their past syphilitic infection, so that it was not possible to approach them directly without the risk of causing psychic trauma. In these cases, second-hand information has had to suffice.

The various forms of therapy at L.H. have kept pace with progress in the field of medicine. Early this century the treatment consisted almost solely in the use of mercury preparations, either in form of an ointment for inunction, or of the so-called «cloth-bag-treatment», which was preferred by Welander. As a rule the treatment was given in intermittent courses; a month of treatment followed by a month's rest. Even if the symptoms of syphilis disappeared immediately, the children were still treated for three years and generally held over for another year of observation. When arsenic preparations of different types came into use, they were employed in combination with the previous forms of therapy. It was not until salvarsan preparations for intramuscular administration, and bismuth preparations, were introduced that the mercury therapy was discarded. Even during this epoch the treatment was continued intermittently for three years, and in resistant cases for still a longer period, after which the children were usually kept under observation for one year. In general the children were treated for a minimum of one year after their Wassermann reaction had become negative. About 10 years ago the treatment was intensified, the doses being raised to the levels indicated in Table I.

Table I.

Weight kg	Solusalvarsan ml.	Iodine-Bismol ml.
5	1.0	0.25
10	1.5	0.5
15	2.0	0.75
20	2.5	1.0
25	3.0	1.25
30	3.5	1.5
35	4.0	1.5

The above doses of solusalvarsan and bismuth are not suited, however for constitutionally weak, cachectic children. Enkvist found at Hagahemmet in Helsinki, a counterpart of the Welander Home, that during the years immediately after the war the congenital syphilitic children, in general, were so severely undernourished that they could not withstand the doses commonly used in Stockholm.

In 1946 penicillin commenced to be used in the treatment of congenital syphilis at L.H., but almost invariably in combination with salvarsan and bismuth. In the beginning penicillin was given on a three-hour schedule with the total dose calculated on the basis of 50,000 units per kilogram of body weight. Later the total dose was raised to between 100,000 and 200,000 units per kilogram of body weight, with four intramuscular injections per 24 hours. At the present time procain penicillin is commonly used, with one injection a day for 8 or 10 days. Syphilis therapy at L.H. to-day is always initiated with a course of penicillin, followed by salvarsan-bismuth therapy. Courses of penicillin are often repeated one or more times, usually when intercurrent infections appear. Fever therapy has occasionally been resorted to in Wassermann-resistent cases, and previously in all cases with central nervous system involvement and in some with interstitial keratitis.

The *preliminary* results of treatment are shown in tables II—X. The follow-up is still proceeding, so that many points are not yet ready for detailed discussion. The observation time given in the tables is the interval between the last treatment and the last follow-up serologic examination.

Group I: Cases with manifest congenital syphilis.
» II: » » uncertain diagnosis of congenital syphilis.

Table II. *Children treated with mercury. (In 7 cases besides small amounts of KI).*

	Number	Died of intercurrent infection	Complications of treatment		Findings at follow-up-study[1]			
			Died	Not died				
	A	B	C	D	E	F	G	H
Gr. I	98	18	3	9	2	10	0	15
Gr. II	73	11	1	4	0	0	0	5

Observation Time.

Year:	½	1	2	3	4	5	6	7	8	9	10	11—15	16—20	21—25	26—30	31—40
Gr. I	4	9	9	0	5	5	3	1	1	2	2	9	3	4	1	1
Gr. II	3	7	7	2	5	3	2	1	2	1	2	9	3	3	0	1

[1] E = Pos. WaR; F = Eye changes; G = C. N. S. symptoms; H = Mental changes.

Table III. *Children treated with mercury and arsenic (in most cases, salvarsan).*

	A	B	C	D	E	F	G	H
Gr. I	25	4	0	2	1	1	0	4
Gr. II	6	0	0	0	0	0	0	1

Observation Time.

Year:	½	1	2	3	4	5	8	10	11—15	16—20	21—25	26—30
Gr. I ..	1	3	2	2	1	1	1	0	4	2	1	2
Gr. II ..	1	0	0	0	1	0	1	1	1	0	0	0

Table IV. *Children treated with mercury, bismuth, and arsenic (in most cases, salvarsan).*

	A	B	C	D	E	F	G	H
Gr. I	37	2	0	3	2	2	1	8
Gr. II	12	0	0	0	0	0	0	0

Observation Time.

Year:	½	1	2	3	4	5	6	7	11—15	21—25
Gr. I ..	5	11	2	1	1	2	1	2	3	2
Gr. II ..	4	6	1	0	0	0	0	0	0	0

Table V. *Children treated with mercury and bismuth.*

	A	B	C	D	E	F	G	H
Gr. I	7	1	0	0	0	1	0	1
Gr. II	4	1	0	0	0	0	0	0

Observation Time.

Year:	½	1	2	4	8	11—15	21—25
Gr. I	1	1	1	0	0	1	1
Gr. II	0	0	1	1	1	0	0

Table VI. *Children treated with only bismuth or arsenic.*

	A	B	C	D	E	F	G	H
Gr. I	4	0	0	0	0	0	0	2
Gr. II	17	0	0	1	0	0	0	1

Observation Time.

Year:	½	1	2	9	11—15	16—20
Gr. I	0	2	1	0	0	1
Gr. II	0	0	0	1	0	0

With arsenic alone only three children were treated. One died of intercurrent diseases. The rest were symptomfree after 9 years of observation.

Table VII. *Children treated with arsenic (salvarsan preparation) and bismuth.*

	A	B	C	D	E	F	G	H
Gr. I	76	2	1	8	5	7	3	14
Gr. II	24	2	0	0	0	0	0	6

Observation Time.

Year:	½	1	2	3	4	5	6	8	10	11—15	16—20
Gr. I	7	14	9	2	3	4	1	1	1	4	5
Gr. II	3	9	3	2	0	0	0	0	0	0	2

Table VIII. *Children treated with arsenic (salvarsan preparation), bismuth and penicillin.*

	A	B	C	D	E	F	G	H
Gr. I	42	1	0	10	3	3	2	5
Gr. II	2	0	0	0	0	0	0	0

Observation Time.

Year:	½	1	2	3
Gr. I	5	6	2	2
Gr. II	1	0	0	0

Table XI. *Children treated with penicillin only.*

	A	B	C	D	E	F	G	H
Gr. I	2	0	0	0	0	0	0	0
Gr. II	3	0	0	0	0	0	0	0

Observation Time.

Year:	1	2	3
Gr. I	1	0	1
Gr. II	0	1	0

Table X. *Children receiving fever therapy plus other forms.*

	A	B	C	D	E	F	G	H
Gr. I	21	0	0	4	8	6	1	8

Observation Time.

Year:	½	1	2	3	6	7	9	10	11—15
Gr. I	1	4	2	3	1	1	1	1	1

On studying the tables one is struck by the decrease in the number of cases with uncertain diagnosis of syphilis (Group II), which in the hospital charts have usually been designated as «symptom-less congenital syphilis». To-day the children without manifest symptoms, or with only a temporarily positive Wassermann reaction, are not treated.

The number of deaths from intercurrent diseases shows a conspicuous decline, which probably reflects the general trend toward a mounting incidence of cures in infections of various sorts. Most of the deaths were due to bronchopneumonia or other infectious pulmonary diseases (i.e. influenza epidemica) and diphtheria.

Complications following treatment led to death in five cases. Four children died following mercury intoxication (Table 2), one of toxic nephrosis and three of acute gastroenteritis. The fifth child developed a severe recalcitrant agranulocytosis resulting in death.

Complications after treatment but not resulting in death have not been uncommon. Of 171 treated with mercury alone, complications occurred in 13 cases (7.6 per cent). These toxic reactions consisted of acute gastroenteritis with or without sanguineous diarrhea in 9 cases, and nephrosis in 5 cases. One of the children had developed both complications. The complications indicated in table 3 consisted in dermatitis caused by sulfoxylated salvarsan and mercury respectively. Among those who received the combined Hg-As-Bi treatment, nephrosis occurred in one patient and stomatitis in another (table 5). Among those receiving bismuth alone, nephrosis developed in one (table VI).

When the first salvarsan preparations were introduced, attempts were made to administer them (Bayer 606, sulfoxylated salvarsan etc.) intramuscularly, but in nearly every case there developed slow-healing infiltrations, with or without subsequent necrosis. This form of treatment was therefore soon discarded, and the above-mentioned complications have not been included in the tables.

Treatment of 165 children with the salvarsan-bismuth combination (tab. 7, 8, 9, and 10) resulted in complications consisting of nephrosis (7 cases), hepatitis (1), agranulocytosis (1), salvarsan dermatitis (4), skin and mucosal extravasation (1), and gluteal infarction or infiltration with abscess formation (5): two of these patients had permanent anomalies of gait. Of the total number treated with the As-Bi combination, 13.5 per cent thus developed some complication.

Of all the children with manifest syphilis treated at L. H., excluding those who died at the hospital, 21 (15.3 per cent) showed a positive Wassermann reaction on the completion of treatment or at the follow-up examination. In 50 per cent of these cases the therapy had been initiated after the age of two years. Calculated as a percentage the best results, in regard to the Wassermann reaction, seem to have been obtained with mercury treatment. This is probably due largely to the fact that Table I comprises infants alone, while the late-treated children occur most in Tables IV—X. Of the 21 WaR positive, seven (5 per cent) seem to be real relapses. The children who received fever therapy were, in general, those who were WaR resistant despite intensive and protracted courses of As and Bi, as well as penicillin in five instances.

Persistent syphilitic changes of the eyes have occurred after all forms of therapy: Hg (table II) 10 per cent; Hg + As (table III) 4 per cent; Hg + As + Bi (table IV) 5.4 per cent; As + Bi (table VII) 9.2 per cent; As + Bi + Pc (table VIII) 7.1 per cent; fever, etc. (table X) 38 per cent. Only in three cases could definite

recrudescences of the eye affections be verified. However, relapses of WaR and eye symptoms during treatment were not rare.

Changes in the central nervous system were found after treatment in seven, of which five showed the manifestations of epilepsy, athetosis, etc., but only two a definite relapse of syphilis.

It is surprising to find such a large number of mentally defective children among those with manifest syphilis (Group I), compared with those in whom the diagnosis was uncertain but who were nevertheless treated (Group II), the figures being 20.3 and 10.3 per cent respectively. The most commonly occurring mental disorders have been varying degrees of intellectual deterioration, though psychopathia, psychasthenia, etc. have also been observed.

As stated previously, the statistical treatment of the series is not yet complete, so that I am unable to discuss here some points that are worthy of mention, i.e. the serologic relapses during treatment.

The stage we have now reached at L.H. is the transitional period between the As-Bi regime and treatment with penicillin alone. These forms of therapy are at present being combined, but it is becoming increasingly clear that penicillin is the drug of choice. I feel, therefore, that W e l a n d e r's creation, the Little Home, which has undoubtedly played a very necessary and important role in the care of these unfortunate children during the past fifty years, will soon be no onger required and in one or two years time may be closed down.

Round Table Discussion: Prenatal and congenital syphilis

I. Remarks of Discussion Leaders

Dr. Ole Enkvist (Helsinki): **The Severity of Congenital Syphilitic Infection in Offspring of Mothers, Treated or Untreated during Pregnancy.**

In this investigation were included 555 congenitally syphilitic children, aged 0—2 years. They were all treated as in-patients in the State hospital for congenital syphilis in Haga, Helsinki, Finland, during 1930—49. The diagnosis was based on obvious clinical symptoms and/or increasing positivity of serologic reactions.

The mothers of 102 children were insufficiently treated with bismuth and neoarsphenamine during pregnancy (group I); and the mothers of 453 were untreated during pregnancy (group II). The age of the children by onset of initial symptoms was the same in both groups. There were 5.9 per cent prematures born in group I, and 14.5 per cent in group II (birth-weight 2,500 grams or less). The death-rate of group I was 26.4 per cent, of group II 36.2 per cent. The death-rate among sick children was generally very high in Finland during the wars and the post-war period (1939—46).

Evidently arsenic-bismuth therapy during pregnancy had a slightly ameliorating effect on the children of syphilitic women, even in cases insufficiently treated, the intrauterine infection not being prevented or cured. The percentage of uncomplicated cases was 72.5 in group I, but 62.1 in group II. Visceral syphilis with enlarged spleen was less common in group I, 16.7 per cent, than in group II, 24.9 per cent. Clinically evident syphilis of the bones was also less often observed in group I (4.9 per cent) than in group II (7.9 per cent).

Neurosyphilis was, on the contrary, more common among children of mothers treated during pregnancy. Among the 102 children of group I we found five cases of neurosyphilis (4.9 per cent). In group II there were 13 cases among 453 patients (2.9 per cent). This fact seems to coincide with the old experience that inadequate treatment of syphilitic adults predisposes to involvement of the central nervous system. Unfortunately my material is too small to confirm this presumption.

Dr. Arvo Oksala (Turku): **The Duration of Syphilitic Stigmas and Signs in Patients with Keratitis Parenchymatosa and Lues Congenita.**

There have been many publications concerning the frequency of signs and stigmas in cases of lues congenita tarda and keratitis parenchymatosa, but relatively little has been written on the duration of these stigmas, although this is of considerable diagnostic importance, especially in older patients. According to Stokes, Beerman and Ingraham, the diagnosis of congenital syphilis after the age of twenty has to be established by clinical signs alone in more than 50 per cent of the cases. In the present study, which comprises 109 patients in whom the average age was 22.8 years, serologic tests were positive in 45 per cent, and in poorly treated or entirely untreated cases, 32 per cent. It is obvious that after the age of twenty years, the diagnosis of lues congenita is more reliably established by clinical signs than on the basis of serologic tests alone.

Wile and Mundt (1942) observed one or more signs of congenital syphilis in 86 per cent of cases of late congenital syphilis that were observed under hospital conditions. Igersheimer (1928) ascertained among his 165 patients with interstitial keratitis only 9 per cent that were entirely free from other stigmas of syphilis. In my own material (126 cases of keratitis parenchymatosa) I have observed only 9.4 per cent who were otherwise clinically negative. In Table I have presented the signs of congenital syphilis that were found in these 126 cases of keratitis parenchymatosa, and a comparison of the frequency of each with the reports of other investigators.

Table I.

	Carvill-Derby 145 patients	Klauder-Vandoren 532 patients	Oksala 126 patients
Hutchinsonian Incisors	76.0 per cent	40.0 per cent	57.1 per cent
Mulberry Molars	—	—	9.5 » »
Saddle Nose	2.7 » »	3.9 » »	8.7 » »
Rhagadic scars	11.7 » »	—	39.7 » »
Deafness	19.2 » »	10.0 » »	4.8 » »
Sequels of Periostitis	35.1 » »	16.5 » »	4.8 » »
Clutton's joints	12.3 » »	9.4 » »	12.7 » »
Frontal bosses	—	6.4 » »	19.8 » »
Facial Assymmetry	—	—	12.7 » »
Thickened clavicles	—	—	3.2 » »

It is to be expected that the figures of various investigators should differ considerably. There are conditions in the patient's environment that influence the signs; the age at which the patient was examined is a factor; and there also are subjective factors, since it often is extremely difficult to differentiate between normal variants and minor luetic stigmas. In my own experience there is no significant difference in the frequency of signs and stigmas between those patients with keratitis parenchymatosa and those without this complication.

In Table II, the patients are divided into two age groups, with the dividing line at twenty years, and the frequency of the various stigmas is compared in these two groups. The average age of the entire group was 22.8 years, that of the younger group 14.7 years and of the older group, 28.5 years.

Table II.

	Entire Material 126 patients	Under 20 Yrs. 52 patients	Above 20 Yrs. 74 patients
Hutchinsonian Incisors ..	57.1 per cent	65.4 per cent	51.4 per cent
Mulberry Molars	9.5 » »	15.4 » »	5.4 » »
Saddle Nose	8.7 » »	5.8 » »	10.8 » »
Rhagadic Scars	39.7 » »	32.7 » »	44.6 » »
Sequels of Periostitis	4.8 » »	1.9 » »	6.8 » »
Deafness	4.8 » »	3.8 » »	5.4 » »
Clutton's Joints	12.7 » »	7.7 » »	16.2 » »
Frontal Bosses	19.8 » »	34.6 » »	9.5 » »
Facial Asymmetry	12.7 » »	7.7 » »	16.2 » »
Thickened Clavicles	3.2 » »	1.9 » »	4.1 » »

From Table II can be drawn some interesting conclusions. Hutchinsonian incisors are observed with equal frequency in the two groups, and it is rather remarkable how little advancing age appears to affect this important sign. With mulberry molars on the other hand, there is a distinct age difference, since this sign was observed three times more frequently among the younger group of patients. It is clear that the process of deterioration affects the molars more than the upper central incisors. With regard to saddle nose and rhagadic scars there are no differences between the two groups, but the incidence of rhagadic scars in the present material is notably higher than in previously reported series. Sequelae of periostitis appear more frequently in the older group, perhaps because of chance, or possibly because some of these signs may not develop until later in life. In regard to Clutton's joints, the difference in favour of the older group may be explained partly by the fact that these also are late in developing. In 15 of my 16 cases, this condition appeared before or during active keratitis parenchymatosa, and in only one case did it appear one year later. The greater frequency of frontal bossing in the younger group perhaps shows that some of the bosses partly disappear as the patient grows older. Asymmetry of the face, which is not uncommonly seen, is, of course, more frequent in older persons, probably because of the smoothening effect of the soft tissues being less evident in older persons. This holds true especially in asthenic patients, who were in a clear majority among these patients. The congenital syphilitic facies is twice as common in the older group, which I believe to be due to psychological factors which affect facial expression. Patients without stigmas of any kind (with the exception of keratitis parenchymatosa) are also to be found twice as frequently among the older group. The youngest among the group without signs was eighteen years, and the oldest,

53 years. The average age of the group without signs was 30.2 years, which is considerably higher than the average age of the entire material (22.8 years), suggesting that the signs tend to disappear as patients grow older. In the entire material there were only five patients who had only one stigma that might have been questionable, such as the facies or rhagadic scars. Clavicular enlargement was found so seldom that no conclusion can be drawn as to differences between age groups.

Keratitis parenchymatosa is the most important sign of lues congenita tarda. Opinions as to its frequency differ greatly. In the literature there are reports that range from five to ninety per cent, but the most often mentioned frequency is 30—40 per cent. These striking differences seem to depend partly on the age at which the patients are examined, partly also on diagnostic difficulties. The disease may appear in a very mild or abortive form, that impares the patient's vision hardly at all. There were about six per cent of such cases in my material. Moreover, certain other ocular diseases (keratitis tuberculosa, keratoconjunctivitis phlyctaenulosa and iritis luetica) sometimes cause great difficulties in differential diagnosis.

Keratitis parenchymatosa usually leaves permanent changes in the cornea and iris. In the cornea can be found scars in the deeper layers, in this series in 95.5 per cent of the corneae examined by slitlamp. Dalsgaard-Nielsen (1938) observed such scars in 86 per cent of his cases. Generally the scars of congenital luetic keratitis parenchymatosa are in no way typical. More important from the diagnostic point of view are the residuals of deep corneal vascularization of the cornea, stressed especially by Klauder and Cowan (1939), who mentioned that these may be the only persistent signs of congenital syphilis. In 178 corneas examined, I have found deep vascularization in 84.8 per cent. Dalsgaard-Nielsen's corresponding figure was 88 per cent. A change in the eye that is quite characteristic and not uncommon in association with keratitis parenchymatosa and some diseases of the central nervous system is atrophy of the iris, one variety of which is known as Lemoine's sign. In the present material, atrophy of the iris was present in 64.6 per cent, of which the Lemoine's sign represents 20 per cent.

In this short report I have tried to emphasize the importance of a thorough knowledge of the clinical signs and stigmas of congenital syphilis from a diagnostic point of view, not only at the active stage of the disease but also decades later. Especially I have tried to stress the importance of the ocular signs, particularly those in the cornea and iris, since these can readily be identified, even by physicians who are not ophthalmologists.

Dr. Ole Enkvist (Helsinki): **Penicillin Treatment of Congenital Syphilis.**

In the State Hospital for syphilitic children in Haga, Helsinki, Finland, 199 infants under two years of age were treated with penicillin during the period 1 January 1946—1 May 1950. 157 suffered from congenital syphilis, one from acquired syphilis, and 41 received prophylactic treatment since their mothers

were syphilitic and had been inadequately treated during pregnancy. The diagnosis of congenital syphilis was based on obvious clinical symptoms and/or increasing positivity of serologic reactions.

There were 101 congenital-syphilitic infants admitted at an age of four months os less, 38 were four months to one year old; and 18 were aged one to two years.

Among the patients under one year of age suffering from congenital syphilis the death-rate has decreased continually from 32.2 per cent in 1946 to 10.0 per cent in 1949—1950. In these figures all known deaths are included, even those depending on other sources than syphilis.

The children younger than four months received penicillin only, the older ones penicillin combined with arsenic and bismuth. In both groups therapy was initiated with 200,000—300,000 Oxford units of penicillin per kg. body weight. In the group «penicillin plus other treatment» the patients subsequently received bismuth and neoarsphenamine continually.

No clinical relapses occured. Superficial mucocutaneous symptoms were cured in a week. Sixteen cases of Parrot's syndrome required 10—15 days, deeper bone-lesions 3—4 months, for healing.

Two serological relapses were observed, one of them in the group of children aged four months — one year, the other by a patient over one year of age. Both were rapidly restored to seronegativity by a repeated penicillin treatment.

Quite young infants respond to therapy better than children some months older. We emphasize the importance of *early* penicillin treatment of patients with congenital syphilis.

Dr. Th. M. Vogelsang (Bergen): **Serological Syphilis Control in Pregnancy in Bergen, Norway.**

During and after World War I, there was a marked rise in the number of cases of acquired syphilis in Bergen. However, the 1930 decade witnessed a gradual and considerable decline in the number of notified new cases of acquired syphilis. Congenital syphilis became at the same time so rare that the Welander Home came to be regarded as superfluous and was closed down in 1940.

The German occupation of Bergen in 1940 led to a marked rise in the number of cases of syphilis from 1942 onwards. On account of this considerable rise in the number of notifications of acquired syphilis, particularly in women, a simultaneous rise in the number of cases of congenital syphilis was to be feared. In 1944 a system of wholesale serological examinations for syphilis during pregnancy was therefore started in Bergen. A report of the results of these serological examinations during the period 1944—1948 has been given by Idsøe and myself (Brit. J. Vener. Dis. *26:* 63, 1950).

All the specimens of blood were examined by the WaR with a crude antigen and from 1946 also with cardiolipin antigen, by Kahn's standard reaction and by Meinicke's clarification test. In addition other flocculation reactions have also been employed from time to time.

The specimens were handled, and the results communicated to the doctors by the Venereal Disease Department of the Bergen Public Health Service, which saw that doubtful specimens were revised and that pregnant women found to be syphilitic were given specific treatment either by the Public Health Service or by doctors in private practice. Prior to 1946 the standard neosalvarsan-bismuth treatment was given. Since that date and after penicillin became available, most of the patients were treated with it, in a few cases in combination with arsenic and bismuth. The babies were examined directly after birth and thereafter at 2, 4, 6, 9 and 12 months. After this age an attempt has been made to carry out yearly examinations, both clinical and serological, for at least three years.

The report does not deal with women already under treatment and supervision for syphilis who had been found to be syphilitic in some other way and had meanwhile become pregnant. Incidentally, it is not such women who transmit their syphilis to the foetus, but the undetected cases of syphilis, usually latent which present the real danger during pregnancy. It is these undetected cases which mass examinations are designed to disclose.

Altogether 4,961 pregnant women were serologically examined during the years 1944—1948. In the same period there were 10,647 confinements in Bergen. About 10,000 women were confined in hospitals where serological tests for syphilis were also undertaken.

The examinations led to the discovery of syphilis in 44 women or 8.9 per thousand of those examined. As a result of prenatal treatment the final result was the birth of 35 healthy infants who have been kept under observation for periods up to three years. This result entirely justified the mass examinations undertaken, and we have every reason for continuing these serological examinations of pregnant women and for the extension of this system to include all pregnant women, whether married or unmarried, primiparae or pluriparae.

Dr. Else Vogt (Oslo): **Serological Examination of Pregnant Woman for Syphilis.**

From 1 May 1948 to 1 May 1950, the serodiagnostic department, State Institute of Public Health, Oslo, Norway, examined blood specimens from about 64,500 pregnant women. About 1% showed a positive reaction to syphilis tests. The data show:

1. A decrease in frequency of pregnant women with seropositive syphilis tests — about 1.23% in 1948—49, as compared with 0.81% in 1949—50.
2. The younger age groups still have the highest frequency.
3. The specimens are taken from a greater number of subjects than last year, but still too late in pregnancy. Only about 39% are taken during the first five months.

Conclusions:

Prenatal blood testing is indicated to prevent congenital syphilis.

Premarital blood testing of both husband and wife should be required.

Dr. Tauno Putkonen, (Helsinki): **Serological Tests for Syphilis in Pregnant Women in Finland 1946—1949; Results Compared with the Incidence of Congenital Syphilis and Acquired Fresh Syphilis.**

Dr. Vogt gave us some interesting information relating to serological examination of pregnant women in Norway. Therefore I will present here some data on corresponding examinations in Finland and compare the results with the incidence of congenital syphilis and of acquired fresh syphilis.

Examination of Pregnant Women

There is no prenatal law in Finland making a serological test for syphilis compulsory for pregnant women, but they come for medical examination because of our Maternity Benefit Act which demands a certificate of pregnancy (signed by a physician or midwife) for the benefit. At present such an examination must be made before the end of the fourth month of pregnancy. In connection with it a blood specimen is taken in cases in which the examined do not object.

Pregnant women are examined free of charge at the Maternity Centres of which there were already 1,246 throughout the country in 1947. As many as 86 per cent of all pregnant women called at these Centres that year. Data concerning the serological tests for syphilis at the Maternity Centres are collected in Table I.

Table I. *Serological Examinations of Pregnant Women for Syphilis at Maternity Centres in Finland 1946—1949.*

Year	Pregnant Women Tested		Wassermann Positive		Only Kahn Positive		Total STS Positive	
	Number	%	Number	%	Number	%	Number	%
1946	43,231	41					437	1.01
1947	54,558	50	308	0.56	165	0.30	473	0.86
1948	63,073	58	364	0.58	233	0.37	597	0.95
1949	74,655	72	411	0.55	314	0.42	725	0.97

The table shows that 41 per cent of the pregnant women in Finland were subjected to a serological examination at the Maternity Centres in 1946. This figure has since soared to reach 72 per cent in 1949. To this are to be added the examinations made by private practitioners.

This result was achieved by means of powerful propaganda among the general public, midwives and physicians. The support received from the United Nations Children's Emergency Fund (UNICEF) has been particularly valuable. This organization has supplied Finland with sorely needed laboratory and hospital equipment and with penicillin for the prevention of congenital syphilis. Of no less importance was the moral support of this international organization which lent strength to the educational work and stimulated our actions. Yet this foreign assistance was not fully effective until the latter half of 1949 and its results will therefore be clearly shown for the first time in the percentages for 1950. The

number of serological examinations will be further increased by the competition announced by the Society for the Prevention of Venereal Diseases: the number of pregnant women tested in the different localities will be published and the localities with the best results will receive prizes.

Results of Serological Examinations for Syphilis

Facilities for serological examination of blood specimens are available in six laboratories in Finland. They all use the same tests, i.e., the Wassermann reaction, the cholesterol Wassermann reaction, and the Kahn test. Neither of the complement fixation tests is particularly sensitive, but the Kahn test is on an international level. This was found out at the end of 1949: our results were compared with those obtained at the Venereal Disease Research Laboratory, Staten Island, when specimens were sent by air mail across the Atlantic.

Table I shows that about one per cent of the pregnant women were seropositive and this percentage remained about the same in the years 1946—1949, in spite of the fact that the number of fresh cases of syphilis at the same time decreased abruptly (Fig. 1). This disparity indicates clearly that syphilitic infection in the

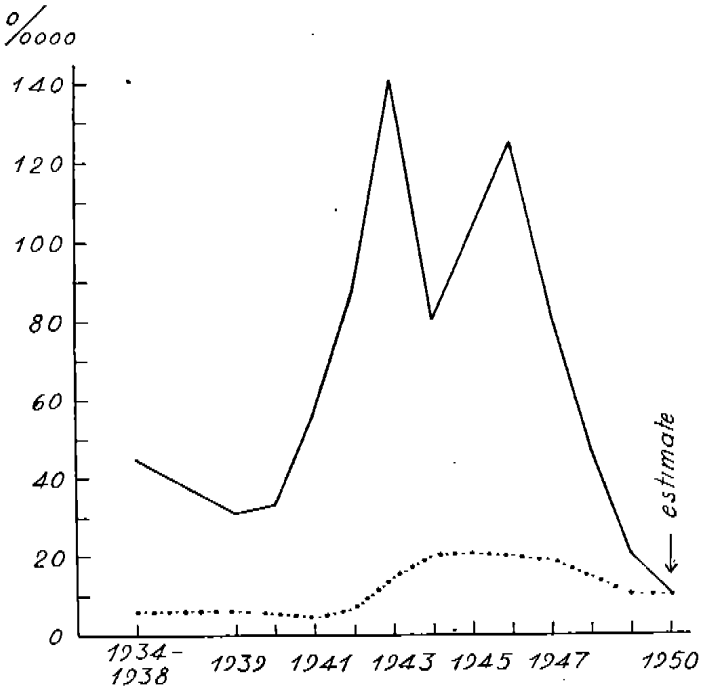

Fig. 1 Cases of primary and secondary syphilis reported in Finland and Sweden during and after World War II per 100,000 population

Finland ——— *Sweden* ·····

pregnant women for the most part was of earlier origin. The only change that appeared in the reactions of the pregnant women during 1947—1949 was the increase in the number of cases in which the Kahn test alone was positive. The natural explanation of this development is probably that the syphilitic women partially recovered, either as a result of treatment or spontaneously with the progress of time; this also brought about a weakening of the serological reactions.

Incidence of Congenital Syphilis in Finland

The figures for recorded cases of congenital syphilis (Table II) are very high considering the population — 4 millions. No clear falling trend appears during the last five years. This may be due to the fact that the statistics include all previously untreated cases, regardless of age. The changes in the incidence of congenital syphilis would, of course, appear most rapidly in the age group of infants.

Table II. *Recorded cases of congenital syphilis in Finland 1943—1949.*

Year	1943	1944	1945	1946	1947	1948	1949
Cases of Congenital Syphilis	182	165	125	137	115	131	106

But this cannot be separated in our present statistics, in which the youngest age group consists of the 0 to 4 years old. These numbered 59 in 1947, 78 in 1948, and 53 in 1949. Even these figures show no distinct reduction, perhaps because the decrease in congenital syphilis had not yet properly started in 1949. It is more probable, however, that the figure for 1949 is increased by the syphilitic children discovered when also the older children of syphilitic pregnant women have been more extensively examined.

Acquired Syphilis and Congenital Syphilis

The prevalence of acquired syphilis in Finland is responsible for the high incidence of congenital syphilis. Fig. 1 compares the incidence of primary and secondary syphilis in Finland with that of Sweden. It appears that before World War II there was seven times as much acquired fresh syphilis in Finland as in Sweden, in relation to the population. The figure also shows the great increase in fresh syphilis in Finland resulting from the war. From these years there still remain a great number of undiscovered and untreated cases of syphilis, especially among women, and they are continually a source of congenital syphilis.

Since 1946 the curve of fresh syphilis has fallen so sharply that this year it will reach the same low level as Sweden's judging from the figures for the first seven months. Thus in four years we shall have caught up with Sweden whose figures were in 1946 less than one-sixth of ours. Though this fall in fresh syphilis will, of course, in time result in a great reduction of congenital syphilis, the un-

treated old cases are still a potential source; consequently control measures must be intensified rather than relaxed.

Dr. N. Danbolt (Oslo): **Combined Penicillin and Metal Chemotherapy in Syphilis during Pregnancy.**

I should like to report briefly on our schedule of therapy utilizing 5.0—6.0 million units of penicillin together with seven injections of arsenoxide and twelve injections of bismuth.

The series includes 45 women observed in 48 pregnancies. Six of the 48 pregnancies were complicated by early syphilis: of these, there were five children born without syphilis and one miscarriage at three months that was not due to syphilis. Twelve pregnancies occured in women who had previously received antisyphilitic treatment; there were three stillbirths (none due to syphilis); all of the others gave birth to normal children. Thirty women had latent syphilis: in all these, the outcome of pregnancy was non-syphilitic children.

II Discussion

Q: *If penicillin therapy is given early in pregnancy, should it be repeated later?*

Dr. Ingraham. It depends somewhat upon the ability to follow the patient throughout the remainder of her pregnancy, and also upon the facilities for quantitative blood testing. Ordinarily if a woman has had adequate treatment during the early months of pregnancy, the possibility of the child being syphilitic is very slight; hence if the additional therapy were given routinely, we would be treating many who did not require it.

Ideally the patient after receiving treatment early in pregnancy should be observed once a month until delivery, and the examination should include a quantitative serologic test. If the woman originally was treated for early syphilis, we would expect a decreasing titer as a result of therapy. If this is not observed. retreatment during the later months of pregnancy would be advisable. Unfortunately as we all realize, the majority of the pregnant women we see have latent syphilis, usually of unknown duration. Perhaps the best general rule is not to retreat unless we have evidence that the earlier treatment was not effective.

Every case we have seen that was a treatment failure had either a clinical or serologic relapse or there was a sustained high titer following treatment for early syphilis. From a practical standpoint, it would be unadvisable to retreat routinely in late pregnancy since there is so little likelihood that the child will be diseased.

Q: *What evidence is there as to the time at which the fetus is infected?*

Dr. Danbolt. There have been done several studies of miscarriages occuring in women with syphilis, but usually no syphilitic manifestations are

found before the sexteenth week. Therefore the general opinion is that fetus is not infected before that time.

Dr. Ingraham. There are also other ways of determining when the fetus becomes infected in utero. One has to do with the roentgenologic examination of the long bones soon after birth, since the depth of the syphilitic process in the bone at birth is a reasonably accurate index of its duration. These studies also indicate that the fetus is not infected before the sixteenth or twentieth week. More than that, these studies suggest that in many instances the fetus is not infected until very late in pregnancy. Perhaps as many as 60—75% of the infants are not infected until the last two months.

Some infants have negative STS at birth. These, I believe are those infected late in pregnancy. Children who at birth have strongly positive STS probably were infected earlier.

Q: *Is it possible to have third generation syphilis without stigmas, i.e., with only a positive serologic test?*

Dr. Perdrup. Having seen only two cases of probable third generation syphilis, it is difficult for me to suggest an answer.

Dr. Putkonen. This question was discussed at the Zurich Meeting of the International Union against Venereal Diseases. The concensus there was that if this occurs it is very rare indeed and not susceptible of definitive proof.

Dr. Hollström. We have studied the question of third generation syphilis and have two and perhaps three cases that are definitely established. Whether the condition occurs with no clinical signs or stigmas would be extremely difficult to establish incontrovertably.

Q: *What is the treatment of choice for interstitial keratitis?*

Dr. Enkvist. When I visited Philadelphia some time ago I heard that ACTH was being tried for interstitial keratitis. What was the outcome?

Dr. Ingraham. This work was done by Dr. Klauder at Wills Hospital, who presented his findings at the last syphilis symposium in Washington. There was evidence indicating endocrinologic abnormalities in many patients with interstitial keratitis, but ACTH proved to be not particularly helpful.

We have used large doses of penicillin — 9—10 million units, plus fever therapy, usually with typhoid vaccine.

Dr. Enkvist. We recently combined penicillin therapy with fever produced with intravenous pertussis vaccine, and had good results.

Dr. Dattner. The results of treatment in interstitial keratitis are still disappointing. It is not uncommon to have the second eye become involved during active therapy. We tend to use everything — penicillin, fever, arsenic and bismuth, and still the results are none too satisfactory.

Dr. H o l l s t r ö m. In our Welander Home we too have used at most everything. We think malarial therapy is the best, but even with this there have been relapses.

Dr. O k s a l a. Our routine treatment consists of penicillin plus fever produced by injections of sterile milk plus vitamin E, but it is not always satisfactory.

Q: *Is procaine penicillin G in oil with aluminum monostearate as efficacious as other forms of penicillin in the treatment of prenatal syphilis?*

Dr. E n k v i s t. There is reason to believe that if properly administered, the effect of comparable dosages would be the same.

Dr. I n g r a h a m. Yes, the important thing is that therapeutically effective concentrations reach the fetal tissues, especially if treatment is given late in pregnancy. All the evidence we have indicates no superiority of one type of penicillin over another.

Q: *Why is the Wassermann more frequently positive than are flocculation tests in non-syphilitic children born of mothers with treated syphilis?*

Dr. R e i n. The work of Wiener on the Rh factor has stimulated interest in the study of multiple antibodies in syphilis. He has shown that two antibodies are produced in the Rh-sensitized mother: the bivalent antibody (agglutinin), which is retained by the intact placenta, and the univalent antibody (glutinin), which passes through the intact placenta and is responsible for erythroblastosis in the fetus. The latter antibody has the capacity to fix complement.

In the comparison of titers of reagin antibody in adequately treated syphilitic mothers and in their normal fetuses, it has been observed that a similar separation of univalent and bivalent antibodies seems to be effected. In the complement-fixation tests for syphilis (detecting univalent antibodies) similar titers of reagin are found in the mother and in the fetus. In the flocculation tests (detecting bivalent antibodies) the level of reagin antibody titers in the infant is minimal as compared with that in the mother.

Thus it is apparent that two varieties of antibodies, the univalent and the bivalent, may be produced in syphilitic infection. In syphilotoxemia (the passive transfer of reagin antibody to nonsyphilitic offspring of syphilitic mothers), the univalent antibodies predominate. In true prenatal syphilis both varieties of antibodies may be found in similar amounts. Furthermore, this observation serves to explain why maternal reagin in the infant's blood has always been more readily detected by complement-fixation than by flocculation technics. In his textbook on the treatment of syphilis, M o o r e was unable to account for the fact that 113 of 292 normal offspring of syphilitic mothers gave positive complement-fixation tests for syphilis, whereas only eight of a similar group of 158 infants gave positive flocculation reactions. These facts are explainable on the basis of

these newer concepts of two antibodies — the univalent complement-fixing antibody, which readily passes through the intact placenta, and the bivalent flocculation antibody, which does not.

Dr. P e r d r u p. This suggests that if the infant at birth has a high titer flocculation test, he probably has syphilis.

Dr. R e y n. We can confirm the fact that the Wassermann is more frequently positive in new-born children. These data will appear subsequently in the *Acta.*

Q: *To what extent does penicillin enter the fetal circulation when the mother is being treated with it?*

Dr. K i t c h e n. We have recently made a study of this at Bellevue Hospital, following a suggestion from Dr. R e i n. Two hundred women in labour were given 300,000 units of penicillin in oil with 2% aluminum monostearate, and following delivery, simultaneous penicillin assays were made on the maternal and cord blood. It is obvious that the period of time from injection to delivery would vary greatly; yet we found that in practically every case we could demonstrate a theoretically effective concentration of penicillin in the cord blood. The pattern was remarkably constant, with the concentration of penicillin in the cord blood only slightly below that of the maternal circulation. To be sure penicillin had not previously been administered, we made pre-injection penicillin assays of the mother's blood in each case.

Q: *If serologic tests are performed simultaneously on both mother and newly-born child and the child's titer is the higher, does this mean the child has congenital syphilis?*

Dr. R e i n. Theoretically it is impossible for the mother to pass to the fetus a higher concentration of reagin than she herself has. To adjudge accurately this situation, we would have to be assured of the technician's accuracy by repeating the tests. If confirmed, it would be presumptive evidence of syphilis in the child.

Dr. R e y n. We have seen cases where at birth the titers of the mother and child were the same. Later the child became seronegative only to relapse into seropositivity with clinical evidences of congenital syphilis.

Dr. I n g r a h a m. I have been interested in trying to collect cases in which the serologic test of the infant is higher in titer than that of the mother. It must be extremely rare, for in our cases this situation obtained was in only 0.5% of the cases.

Q: *Is it possible for a child born with congenital syphilis to acquire syphilis in adult life?*

Dr. S a l m i n e n. In the cases I have analyzed, there was the one patient who had been treated with mercury early in life, and who upon reaching adult life contracted primary syphilis.

Dr. Reynolds. It is, as Dr. Salminen has observed, quite possible for a patient with congenital syphilis also to have an acquired infection upon growing into adult life. We now are entering an era during which patients who as infants received effective antisyphilitic treatment for congenital syphilis, now as adults are exposed to the possibility of the acquired disease. Indisputable cases have been reported by Hahn and by Allison, and Dr. Salminen's case now adds to the number recorded. The interesting thing is that all of the cases of which I am aware, have received considerable antisyphilitic therapy in infancy and in most of the cases are known to have become seronegative prior to the exposure that caused their second infection. I think more and more cases of this kind will be encountered in the future, and that we should be on the lookout for them.

Q: *The «paradox» that it is easier to cure syphilis in the unborn child than in the mother: what is the explanation for this?*

Dr. Rein. This observation seems to support the group that is willing to admit to more reinfections after penicillin.

Dr. Ingraham. It certainly is true that infantile congenital syphilis responds better to treatment than does adult syphilis, and I agree with Dr. Rein that this fact may be something of an argument in favour of more reinfections in the adult disease. It is a very interesting observation.

Dr. Reynolds. I should think that the information we already have considered regarding the time of infection of the fetus also applies to this question. We know that the fetus is not infected until pregnancy is fairly well advanced; hence in quite a few cases we are treating not the infected fetus but rather the mother in order to prevent fetal infection.

Another consideration is that the response to penicillin therapy is directly related to the duration of the infection. In most cases the infection of the mother will be considerably longer than the infection of the fetus, hence one might logically expect it to respond more readily. Perhaps there is less of a paradox here than has been presumed.

Q: *Please discuss the Herxheimer reaction in infants with congenital syphilis who are being treated with penicillin.*

Dr. Putkonen. The Herxheimer reaction in children with congenital syphilis treated with penicillin was studied by Pardo and Tucker. Of previously untreated children under 2 years of age, 48 per cent had a febrile Herxheimer reaction, which often recurred after repeated injection. These workers are not afraid of beginning the treatment of the disease with large doses of penicillin.

This question has been studied at the Kumpula Hospital and a paper concerning it has recently been sent to Dermatologica. The series comprised 16 infants under 6 months of age, 15 of whom gave a febrile Herxheimer reaction. Of the previously untreated children who were over 1 year of age, 2 out of a total of 26 gave a febrile reaction. One of them had juvenile paralysis, the other a severe bone syphilis. According to our observation, thus, congenital syphilis resembles acquired syphilis in that it gives regularly a febrile Herxheimer reaction at the beginning of the disease; later, however, this reaction becomes rare in congenital syphilis.

We were also able to corroborate the observation of PARDO and TUCKER that a febrile Herxheimer reaction repeats itself in infants after the second injection of penicillin, even if the first dose has been large. In this respect congenital syphilis differs from acquired syphilis. In our series there were no dangerous reactions when the treatment of children was started with large doses of penicillin.

Dr. E n k v i s t. We do not fear the Herxheimer reaction very much in treating infants with penicillin. I have only once seen a really dangerous reaction of this kind. Dangerous complications occur usually later on, about 2—3 weeks after starting of therapy.

Q: *Why do we still see cases of congenital syphilis in Finland?*

Dr. E n k v i s t. I think there are several important factors: 1) in rural districts, patients may be far removed from the Maternal Health Centres. To attend means loss of work and considerable expense to the patient for travel; 2) we still see cases in which the mother's prenatal serologic test is negative and when the child is born it has congenital syphilis. Of 77 women with congenitally syphilitic children, 40 were seronegative on the one test that was done; 3) we treat the mother and we treat the children, but sometimes we neglect to treat the father and thus occasionally have cases due to «ping-pong» infection.

Section III: Neurosyphilis

Chairman Martti Kaila

Diagnostic and therapeutic problems in neurosyphilis

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Neurosyphilis comprises a variety of clinical syndromes. It is customary to classify them according to the prevalent involvement of specific tissues of the central nervous system. If the meninges are affected we speak of syphilitic meningitis. If the cerebral vessels alone are implicated we designate this form of syphilis as vascular neurosyphilis. If both, meninges and vessels bear the brunt of the inflammation, we name it meningovascular syphilis. It is obvious that these diagnostic categories refer primarily to the pathologic anatomic changes in the brain or spinal cord. Any clinical classification based on such changes is assuming first, that the syphilitic process is limited to only one kind of structure, and second and still more important, that there is a close parallelism between anatomical alterations in the central nervous system and clinical syndromes. The first assumption is easily disproved by the neuropathologist who frequently finds the meninges and vessels simultaneously involved and sometimes in addition even the parenchyma itself. I wish to quote only one author, Adams from Harvard. He states, «Clinical syndromes such as syphilitic meningitis, meningovascular syphilis, general paresis, tabes dorsalis, optic atrophy, etc. are abstractions which at autopsy seldom exist in pure form. More often, since all of them have a common origin in a meningitis there is a combination of two or more syndromes, i.e. meningeal and vascular syphilis, tabes and paresis, etc.» The second hypothesis that there is a close parallelism between anatomical changes and the clinical syndromes is also refuted by the fact that the syphilologist had to create a special diagnostic category, i.e. asymptomatic neurosyphilis. By definition, asymptomatic neurosyphilis implies a syphilitic process in the central nervous system which does not manifest itself by clinical signs or symptoms. In other words, pathologic changes may take place in the central nervous system without revealing themselves to the examining physician. Therefore, the clinician is forced to surrender his prerogative to the laboratory which establishes the presence or absence of a pathologic process.

If this holds true for asymptomatic neurosyphilis, then there is no reason why it should not apply to the other diagnostic categories mentioned before, especially to the syndrome of meningovascular and vascular neurosyphilis. If a closer analy-

sis of the concept of these diagnostic entities is attempted one becomes aware that asymptomatic and symptomatic neurosyphilis are caused by identically the same processes looked upon at one time from the clinical point of view, at another time from a pathologic-anatomic standpoint. The discriminating factor between asymptomatic and symptomatic neurosyphilis is the appearance of clinical signs and symptoms. What, then, constitutes a clinical sign? An anomaly which has been found by keen and reliable observers as significant in revealing a specific pathologic process. As an example, let us take the Argyll Robertson pupil and Westphal's sign. It is clear, that a sign must be known to the examiner either by personal experience or by textbook information because otherwise it will be missed even by the most conscientious physician. That is what happened to all experts examining syphilitic patients before 1869 and 1875 when Argyll Robertson and Westphal had not yet described their respective signs. But even if a «sign» is already known and the medical profession is familiar with it, its detection is still dependent on the thoroughness of examination. Furthermore, as long as clinical signs are taken as a guide for diagnosis, one has to register even the slightest deviation from the norm as an indication of a pathologic condition. To detect them, one ought, therefore, to utilize the most refined aids, e.g. in the case of Argyll Robertson pupils the cinematographic registration of movements of the iris, the audiometer in testing the acoustic nerve or in studies of visual function the Bjerrum screen, etc. Since a syphilologist rarely, if ever, will be able to use these tools, many of his patients will be considered as patients with asymptomatic neurosyphilis, whereas in fact they may be patients with early manifestations of meningovascular or parenchymatous neurosyphilis.

Still more difficult is the task of evaluating the «symptoms» of our patients. Irritability, nervousness, insomnia, lack of initiative, and memory impairment may be present, but not volunteered by the patient. Quite frequently some of our patients state after termination of treatment that they feel much better than ever before and often they become conscious of their former shortcomings. Since the initial personality changes in general paresis, for example, are often insidious, they remain unnoticed by the patient, his family and friends and even the physician, especially if the latter has not known the patient before. The patient, therefore, will be labelled as asymptomatic whereas he may already be affected with parenchymatous neurosyphilis.

These are only a few of the arguments which militate against any attempt to classify neurosyphilis according to clinical signs and symptoms. Since, as pointed out before, there is no difference in the nature of the underlying processes in asymptomatic and symptomatic neurosyphilis — the appearance of clinical signs and symptoms depending partly on the alertness of the physician and partly on the localization and extension of the pathologic involvement — one should not place too much reliance on a clinical differentiation which only confuses the real issue, namely the presence or absence of a syphilitic infection of the central nervous system.

But even if clinical signs and symptoms are apparent they do not necessarily incriminate syphilis as their principal cause, since none is exclusively characteristic. For example, the Argyll Robertson pupil, generally considered one of the most specific stigmata of neurosyphilis, has been observed in neurologic complications of diabetes mellitus, in lethargic encephalitis, in alcoholism, in brain tumors, following head injuries etc. The Adie pupil, seemingly a harmless anomaly, has frequently been mistaken for an Argyll Robertson pupil. Westphal's sign, i.e. absent knee and ankle jerks, can be found associated with so many pathologic conditions other than syphilis that we must abstain from enumerating them. The hypotonia and ataxia of the tabetic are encountered with cerebellar disorders. Painless fractures and Charcot joints can be associated with diabetes, syringomyelia or Morvan's disease. Primary optic atrophy may be due to pressure upon the optic nerves or to toxic agents. Mental changes resembling those frequently encountered in general paresis may be manifestations of chronic alcoholism, abuse of the barbiturates, presenile involution of the brain, etc. The term pseudoparesis has been coined for this condition. Even the entire clinical syndromes of tabes and paresis can be closely, simulated by pathologic processes other than syphilis so that often great effort and the aid of physical means like X-rays, myelograms, electro- and airencephalograms are required to establish a correct diagnosis. We have seen numerous patients suspected of having neurosyphilis who by further studies were found to have brain or spinal cord tumors, metabolic disorders, like diabetes, blood dyscrasias, including pernicious anemia, and often obscure diseases of undetermined etiology. I do not doubt that many of you have had similar experiences.

How, then, can neurosyphilis be diagnosed? The answer is that we must depend on laboratory tests of the spinal fluid. No one will challenge this statement with regard to asymptomatic neurosyphilis. Since, as mentioned before, asymptomatic neurosyphilis differs from symptomatic only by the absence of observed signs and symptoms and since the cause of both is identical there is no reason why the spinal fluid examination should not be used the same way for both, symptomatic and asymptomatic neurosyphilis. What are the essential changes of the spinal fluid in syphilis and what does each signify?

The first important test is an accurate cell count. It is a clinically well established fact that most infectious processes involving the central nervous system give rise to a pleocytosis. Inasmuch as the meninges may be invaded by spirochetes in the early stages of syphilis, abnormal cell counts are often the first sign of syphilitic involvement of the central nervous system. In early neurosyphilis pleocytosis quite frequently is the only sign of the syphilitic infection. It is also generally accepted that with the arrest of the syphilitic process the abnormal cell count returns to normal. For this reason, correct cell counts should be obtained first.

The second obligatory test of a spinal fluid is the total protein determination. Increase of total protein is encountered in many inflammatory or degenerative

processes of the central nervous system. With the use of an electrophotometer, measurements of the protein content of the spinal fluid can be performed with a high degree of precision. Values so obtained can be duplicated without difficulty. It is, therefore, possible to observe changes in the pathologic process in the central nervous system by comparing total protein values over periods of time. As with the cell count, the total protein closely follows the intensity of the inflammatory-degenerative alterations of the nervous tissues.

A third desirable test is one of the colloidal reactions. They were originally designed for the determination of the various globulins and albumins constituting the total protein. Lange, the author of the colloidal gold test, assumed that by its application it would be possible to differentiate between interstitial and parenchymatous neurosyphilis. Many difficulties are encountered in the preparation and proper standardization of colloidal sols, especially the gold sol, with the effect that the curves obtained cannot always be duplicated and, therefore, reliable comparisons cannot be made in the follow up of patients. Some 6 years ago Lange devised a new technic for the colloidal gold which affords not only dependable qualitative but also quantitative results. By adding the figures for the color values in each tube the sum total affords quantitative information.

The last, and the only so called specific test for syphilis of the central nervous system are the serologic procedures (the complement fixation and flocculation tests). Assays of the syphilitic reagin have been greatly refined in the past decade. Cardiolipin was recently introduced as an antigen. It constitutes chemically known substances which have rendered the test more accurate. At the same time procedures for a more exact quantitative determination of reagin in blood and spinal fluid have been made available.

The four just mentioned are obligatory examinations of the spinal fluid in neurosyphilis. They form a syndrome which must be interpreted as a whole. No single item will give adequate information. If all four are positive neurosyphilis is present and if all are negative the diagnosis of neurosyphilis must be looked upon with great doubt.

Since the spinal fluid examination has to serve as an aid for the diagnosis, the question arises to what extent the spinal fluid syndromes correlate with the signs and symptoms of the different clinical entities of neurosyphilis. It is quite obvious that, inasmuch as there is no strict parallelism between structural changes in brain and spinal cord and clinical symptoms, as illustrated by asymptomatic neurosyphilis, there can also be no correlation between spinal fluid findings and clinical signs and symptoms. This rule works both ways. There may be no clinical evidence of neurosyphilis and the spinal fluid may reveal a very active syphilitic process in the central nervous system, and on the other hand a completely negative spinal fluid may be associated with signs and symptoms of healed neurosyphilis of any type. The term burned-out tabes may serve as illustration. It must therefore, be concluded that there is neither a constant parallelism between the clinical

status and the pathologic process, nor one between the clinical status and the spinal fluid syndromes. This fact is clearly indicated by the failure of all syphilologists and neuropsychiatrists to establish typical spinal fluid syndromes for the different diagnostic categories of neurosyphilis. Although it is true that almost all untreated paretics demonstrate what has been called a group III spinal fluid formula, i.e. high cell counts and protein, a first zone colloidal gold curve and a positive complement fixation test in high dilutions, there are numerous patients with asymptomatic and meningovascular neurosyphilis who exhibit the same syndrome. On the other hand, patients, in whom the diagnosis of general paresis might be justifiable from their clinical status may have a Group II spinal fluid syndrome which has often been considered characteristic for meningovascular syphilis. These may be the cases alluded to by Adams where one wonders if the results of the spinal fluid tests should not have precedence over the clinical judgement. From these observations it is evident that a spinal fluid examination per se does not always provide a diagnostic clue to the type of neurosyphilis we are dealing with. It does, however, minimize mistakes with regard to the syphilitic or non-syphilitic nature of a neuropsychiatric disorder and in addition, as will be discussed later, it gives us information about the activity, subsidence or arrest of the syphilitic process.

Let us now turn to the second part of the paper, that is the therapeutic problems in neurosyphilis. In dealing with diagnostic problems of neurosyphilis we have learned to accept the spinal fluid tests as an essential aid. A similar approach will be necessary if we wish to understand the potentialities and limitations of therapy for neurosyphilis. It is easily understood that the primary goal of treating neurosyphilis is to eliminate the etiologic agent and thereby stop the progress of the syphilitic infection. It is also desirable to efface the clinical signs and symptoms which may have resulted from the inflammatory process. The ideal aim of the syphilologist, therefore, is first, to kill the spirochetes and second to dispose of their deleterious effects. Consequently, in evaluating success or failure of therapy we must consider both, the status of the inflammatory and/or degenerative process, and the clinical status. Since both, as discussed before, do not correlate, it will be necessary to discuss them separately.

Starting with so called asymptomatic neurosyphilis, the therapeutic problem resolves itself very easily. Since there are no apparent clinical signs and symptoms, the optimus results are obtained with the permanent return of the pathologic spinal fluid to the normal state. It is a generally accepted view that once a normal spinal fluid has been achieved and maintained there is no danger of subsequent appearance of clinical manifestations. I would like to stress at this point that when we speak of normal or abnormal spinal fluids we do not mean to imply that the spinal fluid is diseased but that the spinal fluid findings reflect normal or abnormal conditions of the central nervous system. If following therapy we secure a normal spinal fluid we have reason to assume that the diseased central nervous system has been favorably influenced by the therapy..

From the laboratory point of view, the same situation prevails in symptomatic neurosyphilis with regard to the arrest of the process. As mentioned before, there is adequate evidence to warrant the statement that a normal spinal fluid indicates inactivation of the syphilitic infection. If, therefore, therapy reverses a pathologic spinal fluid to one that is normal the optimum result has been obtained.

Many difficulties arise if we try to evaluate therapeutic success from the clinical point of view only. It is common knowledge that many signs of neurosyphilis are irreversible. The Argyll Robertson pupil provides a good example. Once the reaction of the pupil to light has been abolished by the syphilitic process — no one knows when and how it occurs — there is no restoration of normal function possible by any means now at our commant. Once the knee and ankle jerks have disappeared in tabes, they remain absent forever. One can enumerate many other types of such permanent damage as a result of syphilitic infection. How, then, do we know, whether or not our treatment has been successful, if we are faced with these constant changes? On the other hand it should be pointed out that some clinical signs and symptoms disappear quite rapidly with or without treatment. How can we be sure, that the reversal when it occurs is due to the therapeutic agent? It is obvious that no amount of neuropsychiatric acumen and experience enables the physician to express an opinion as to the effect of treatment in such cases. Keeping these facts in mind we are reluctant to rely solely on a clinical evaluation of the patient's condition after any type of therapy.

Many more reasons can be given for this attitude. In the instance of general paresis it is well known that spontaneous remissions may occur lasting for many months, later to be followed by a relapse which may result in the death of the patient. It also happens quite frequently that the patient does not show any clinical improvement and still has been benefited by the treatment as evidenced by his unexpected long survival. In meningovascular syphilis there may be disappearance of a hemiplegia or an aphasia and the syphilitic process may continue unchecked. Conversely, nerve deafness, Bell's palsy or a squint may persist although the syphilitic meningitis has been cured. The tabetic Charcot joint may remain unchanged although the infection has been arrested, etc. The situation becomes still more complicated when there are symptoms the pathogenesis of which is totally obscure. To them belong the phenomena of lightning pains and gastric crises in tabes, paranoid-hallucinatory states in paresis, etc. Shall we assume that the persistence of these manifestations is proof of treatment failure? There is good evidence against any such assumption.

What then is the solution of our problem? Let us go back to our discussion of the importance and significance of spinal fluid examinations. We have stated that the spinal fluid syndromes best reveal the syphilitic nature of a neuropsychiatric disorder. We have also briefly alluded to the fact that there is a constant and close interrelationship between the spinal fluid spectrum and the trend of the infectious or degenerative involvement of the central nervous system. As mentioned before pleocytosis appears very early in the history of neurosyphilis.

Occasionally, there is also a slight increase in protein at the same time. Only with the very sensitive colloidal gold test of Lange can changes in the gold sol be observed in the earliest stages of syphilitic central nervous system involvement. If the infectious process continues, then the cell count remains high, the total protein increases and the colloidal gold and serologic reactions show pathologic values. In the most severe form of neurosyphilis, in general paresis, the so-called group III spinal fluid formula becomes established. On the other hand, if the process subsides, then the spinal fluid eventually returns to normal.

Is there any further evidence supporting our concept that the spinal fluid findings best mirror the pathologic-anatomic involvement of the central nervous system and its resolution? Here, a brief review of our past experiences may be justified. When malaria therapy of general paresis was introduced by Wagner-Jauregg very little was known about the reversal of positive spinal fluid findings in neurosyphilis. Since the previous methods of treatment rarely if ever had success and the patients died within a few years there was little opportunity to study this problem. Soon, however, it became obvious that malaria fever was a potent weapon in controlling this fateful disease and more and more of the patients treated surpassed their short life-expectancy. It, therefore, occurred to me that it might be advantageous to examine the spinal fluids of the patients simultaneously with their clinical follow up to learn what if any effect treatment had on the spinal fluid. Such an undertaking seemed the more desirable because all attempts to classify the results of treatment by clinical methods proved unsatisfactory. Some patients, who showed a definite improvement of their mental status and should have been considered as successfully treated, were regarded as treatment failures because they were unable to attain their former social status. Other patients who did not show the expected remission remained alive for long years which seemed to indicate the arrest of the progressive disease. Early in our studies it was found that the complement fixation test stood in the foreground. Very little was known at that time about the significance of the cell count and the protein content. Since the Wassermann reaction remained positive in patients with clinical improvement and the colloidal gold curve, whenever such a test was done, likewise did not become normal, many authors — among them even Wagner-Jauregg — attached no importance to a spinal fluid examination. There was, however, a definite modification observed in the two other components of the spinal fluid, if the treatment resulted in clinical remission. The cell count became normal within a few months and the total protein showed declining values. Then in the course of some years the results of the Wassermann reaction and the colloidal gold tests tended toward the normal and it finally became apparent that there was a slow retrogression of all the pathologic findings in the spinal fluid, the pleocytosis disappearing first, the total protein diminishing next and the Wassermann and the colloidal gold reactions lagging behind for a considerable period of time. On the other hand, patients who were clinically progressive, maintained a highly abnormal positive spinal fluid syndrome. It is noteworthy that each

of the four tests we have mentioned, represents a totally different and independent approach to the study of the pathologic processes in the central nervous system. Each, with the possible exception of the Wassermann reaction, may be the only one registering abnormal values in the presence of various diseases of the central nervous system. Thus, in benign lymphocytic choriomeningitis there may be no abnormal findings except a pleocytosis; in infectious polyneuronitis (Guillain-Barré-Strohl syndrome) only the total protein is high; in disseminated sclerosis, we may find nothing more than a «first zone» gold curve. If then, in neurosyphilis, all these tests form a composite picture of progression or regression, one is justified in assuming that this represents activity, recession or arrest of the pathologic process.

Based on my experience in Vienna and more recently on observations at Bellevue Hospital in New York, Thomas and I have determined that following successful treatment of all types of neurosyphilis the cell count drops to 3 or less cells per mm^3 within approximately 6 months and, that, therefore, a normal cell count is the most sensitive index of the arrest of the syphilitic process. The total protein values show a more gradual but still a relatively prompt decrease and for this reason in conjunction with a normal cell count can be accepted as evidence of the inactivation of the disease. The serologic tests for syphilis and the colloidal gold reactions in their *qualitative* aspects do not as a rule contribute to the prognosis. If, however, the *quantitative* values of the complement fixation test and the colloidal gold reaction are taken into consideration, then it becomes apparent that these as well help to differentiate between activity and inacsivity. We, therefore, feel that all four tests of the spinal fluid give us definite information as to whether the syphilitic process in the central nervous system is progressing, regressing or has been definitely checked, and we regard them as obligatory in the treatment of neurosyphilis.

No one, therefore, should be surprised that we so consistently stress repeated spinal fluid examinations. That does not mean that we are not eager as are all workers to evaluate all the available clinical data. We believe, however, that for the intelligent interpretation of therapeutic results in neurosyphilis the spinal fluid syndrome takes first rank. If clinical improvement parallels the trend of the spinal fluid findings in cases in which the syphilitic process has been arrested, we are content, as Earle Moore states it, with «the patient, his family, or his physician». If, however, the patient does not recover normal function because of injured or destroyed tissues and there is a divergence between the clinical and spinal fluid findings, we rely largely on the latter in gauging results. We are certainly not sanguine when a treated paretic continues to have signs of activity as demonstrated by the *spinal fluid*, even though the patient has improved clinically. On the other hand, we cannot attribute failure to the treatment if the patient continues to exhibit clinical signs and symptoms provided the spinal fluid spectrum gravitates towards normal. It appears to us that our concept of the spinal fluid serving as a mirror image of the pathologic processes in the central nervous system will finally

lead to a better understanding of the dynamics of clinical signs and symptoms. Lightning pains and gastric crises may exemplify what we have in mind. As is well known, tabetic patients often continue to suffer from these painful phenomena, even though the spinal fluid is inactive or entirely negative, indicating a burned-out process. Since these pains are by no means constant but attack the patient periodically and with varying intensity, is it not likely that they are caused by factors other than the spirochetes? Or, if a paretic patient continues to exhibit a psychotic behavior for many years, sometimes even for decades, in the presence of an inactive or even a negative spinal fluid, should we not believe that he suffers from the sequelae of his disease rather than from a continuation of the infection itself? Unquestionably many different mechanisms may influence a permanently damaged central nervous system resulting in clinical phenomena in spite of the evident arrest of the infection. Their exact nature is not known and I am afraid that it will require long future research before they can be fully understood.

Summarizing our analysis of the diagnostic and therapeutic problems in neurosyphilis, we have to stress again that no syphilologist is able to deal with his patients successfully without a proper understanding and evaluation of the spinal fluid syndromes. It is my conviction that much confusion about the best methods of treatment could be cleared and occasionally much harm to the patients could be prevented, if physicians dealing with neurosyphilis were aware of the fact that clinical signs and symptoms are by no means reliable guides to the effectiveness of therapy and that further attempts to kill spirochetes are useless when the infection has already been arrested or cured.

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Febrile Herxheimer Reaction in Neurosyphilis

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In neurosyphilis, as in other types of syphilis, penicillin treatment has been found to produce the so-called Herxheimer reaction (HR) which may appear as an exacerbation of local signs and as a rise in temperature. Much attention has been directed to the dangers which the symptomatic reaction may involve [(Barksdale (1), Gammon, Stokes and others (7), Shaffer and Shenkin (20), Stokes and others (22), Tucker and Robinson (23)]. Yet further experience has shown that severe exacerbation of the symptoms and signs is rare and not of great importance. On the other hand, the febrile HR has received increasing attention in recent years [Callaway and others (2), Hoekenga and Farmer (8)]. Since the end 1947 we have studied this reaction, which is of great theoretical interest, and also apparently of diagnostic importance. Our results will be reported below.

Material and Methods

Our material comprises 229 patients with neurosyphilis*). Of these 142 were from the Kumpula Hospital, 52 from the Neurologic Department of the Kivelä Hospital, 21 from Nikkilä Mental Hospital, and 14 from Lapinlahti Mental Hospital. Men numbered 87, women 138, and children 4. The unusually marked female predominance is due to the fact that the Kumpula Hospital has until recently admitted almost exclusively women patients.

The diagnosis was dementia paralytica in 49 cases, tabes dorsalis in 38, meningovascular neurosyphilis in 48, and asymptomatic neurosyphilis in 94 cases.

A psychiatrist was consulted in borderline cases of dementia paralytica. Cases of taboparalysis were classified as dementia paralytica. For the diagnosis tabes it was required that the patients had at least two of the symptoms or signs of this disease; one of these was usually Argyll Robertson pupils. This group also included 5 patients with primary optic atrophy in addition to the other signs of tabes,

* Some of the results (in 57 of these cases) have been previously reported in another connexion (17).

and 3 patients who had Charcot's disease; one case in which primary optic atrophy was the only manifestation was also regarded as tabes.

The cases of manifest neurosyphilis which could be placed in neither of these two groups, also those showing no other signs than pupillary changes, were included in meningovascular neurosyphilis. The patients with no neurological signs but with abnormalities in the cerebrospinal fluid were put in the group of asymptomatic neurosyphilis. All patients with primary or secondary syphilitic lesions were intentionally excluded.

Table I. *Age Classification and Average Age of Patients in Various Diagnostic Types of Neurosyphilis.*

Age in Years		Asymptomatic	Meningovascular	Dementia paralytica	Tabes dorsalis	Total Number of Cases
0—10		2*	—	1*	—	3
11—20		3	—	2*	—	5
21—30		33	9 (1**)	2 (1**)	—	44
31—40		28	15	12 (1**)	5	60
41—50		19 (1**)	16	15 (6**)	19	69
51—60		7	4	14 (10**)	11 (1**)	36
Above 60		2	4	3 (3**)	3	12
Total		94	48	49	38	229
Average age***	Men	38	45	45	49	
	Women	34	38	39	48	
	Both	35	40	43	49	

*Congenital neurosyphilis.
**Number of patients with previous malarial therapy.
***Average age of all patients excluding those marked * and **.

Table I shows the age classification and the average age of the patients with different diagnostic types of neurosyphilis. It will be seen that the average age of the patients increases gradually while passing from the group of asymptomatic neurosyphilis to that of meningovascular neurosyphilis, and then to dementia paralytica and tabes dorsalis. In our series the average age of the women was lower than that of men. Data regarding the duration of syphilitic infection were mostly so indefinite that it was impossible to classify the cases according to it.

As regards previous treatment our cases were distributed as follows: 92 had never previously been treated for syphilis, and 94 had received As- and/or Bi-treatment (chemotherapy); in 25 of this latter group treatment had been stopped within the last half year, in all others 1 to 10 years previously. Therapeutic malaria had been induced in 35 patients. None of the patients had had penicillin treatment for early syphilis, only 4 had had it for neurosyphilis, and 4 patients knew that they had received penicillin for some other disease than syphilis. Here it must be taken into account that penicillin was regulated in Finland until the beginning of 1949.

The cell count of the cerebrospinal fluid was determined in Fuchs-Rosenthal's counting chamber, and the total protein content with photometric absorptiometer (Hilger) using sulfosalicylic acid. The Wassermann test on the cerebrospinal fluid was made in two dilutions [Sievers (21)], but only the negative and positive reactions are differentiated in our paper. The mastic test was made according to Emanuel, Jacobstahl and Kafka (5), using 0.5 cc. of cerebrospinal fluid and serial dilutions of 10 tubes.

The pathological spinal fluids were classified according to Moore (14) into grades I, II and III as follows: the fluids in which the cell count and/or the protein content were increased, but the mastic test and the Wassermann reaction normal, were considered as grade I. We have arbitrarily regarded a cell count of 5 and a protein content of 40 mg per 100 ml. as the highest normal values*). Of grade III were the fluids in which all four findings were abnormal and the mastic test was of paretic type. Spinal fluids of an intermediate type belonged to grade II.

For the purpose of studying the Herxheimer reaction the patients were given at least 100,000 units of penicillin by one injection before initiation of treatment. The axillary temperature was recorded immediately before the injection and after it at hourly intervals for at least 24 hours, the patients being kept in bed all this time; in 52 cases temperatures were recorded at two-hour intervals.

Results

We have not paid attention systematically to the intensification of the neurologic signs. However, no alarming reactions appeared. In a few patients with dementia paralytica increased confusion was noted during the febrile response. In addition, a child of 12 who had earlier had epileptiform attacks due to juvenile paralysis and lasting 5 to 10 min., now in connexion with the fever peak had a convulsive seizure which lasted about one hour.

The pattern of the febrile reaction in neurosyphilis

The earliest elevations of temperature appeared 3 to 10 hours after the penicillin injection. In a few hours a peak was reached and the patients were again afebrile 24 hours after injection. The maximal elevation, which in patients with primary or secondary syphilis usually appears 6 to 10 hours after penicillin administration [Farmer (6), Putkonen and Rehtijärvi (17, 18)], appeared considerably later in the patients with neurosyphilis. Among the 43 patients, in whom the maximal response was at least 37.6° C., it occurred in only 7 within 10 hours of the injection; in all others the maximum was recorded later, and in 22 patients (50 per cent) 12 to 16 hours after injection. These results of ours support the observations of Hoekenga and Farmer (8) as to the febrile response being slower in neurosyphilis than in early syphilis. In their series, too, the maxi-

* In our investigation the total protein values are too high and their importance is only relative.

mal elevation occurred in about 50 per cent of the cases 12 to 16 hours after injection.

We regarded the maximal elevation of the temperature as an index of the intensity of the febrile reaction. According to the intensity of the response, the cases were grouped as follows: a temperature of 37° C. or less was defined as HRO and the following groups, always increasing by 0.5° C., as HR1, HR2, etc. The bottom row of Table II shows the result in all cases by this classification. It appears that in about 50 per cent of the patients the maximal temperature was 37° C. or less (HRO), in over 30 per cent it ranged from 37.1° C. to 37.5° C. (HR1), and in only 43 patients, about 19 per cent, it was 37.6° C. or over. This latter was regarded as the lowest positive reaction and is here referred to as the threshold level. In 40 patients with this reaction the fever curve was of typical pattern. In the HR1 group, on the other hand, typical fever curves were seen in only 30 per cent of the cases, the others having only incidental elevations entirely unrelated to real febrile reactions.

Febrile response in the different diagnostic types of neurosyphilis

Table II shows the incidence of febrile reactions in the different types of neurosyphilis in relation to previous treatment.

In patients with *dementia paralytica* febrile reactions were frequent. In 22 of 49 patients the maximal response was 37.6° C. or more, in 18 over 38° C., and in one 41.1° C.

Studying the relationship of the febrile reactions to previous treatment it is observed that all 12 patients with dementia paralytica never previously treated had reactions of at least 37.6° C. In 9 of 10 patients who had received only chemotherapy the response exceeded this limit, and in only one it was lower, 37.4° C., but the pattern of fever was so typical even in this case that the reaction can be regarded as definitely positive. Nine years previously this patient had had a course of 10 neoarsphenamine and 10 Bi-injections and then interrupted the treatment. His only signs were syllable stumbling and impaired memory. In the cerebrospinal fluid the Pandy and Nonne reactions were positive, the cell count was 13, the mastic test 4443221100, and the Wassermann reaction positive.

One of the patients with dementia paralytica had been given 20 million units of penicillin because of febrile abortion 3 months previously. Mentally she was confused but the spinal fluid, which had also been examined one month earlier, had improved much; the cell count had fallen from 75 to 6 and the Wassermann reaction had become negative. Another patient of this group had also been given penicillin about 6 months earlier and the cell count of the spinal fluid had fallen from 110 to 4. In neither of these patients did a febrile response occur.

Therapeutic malaria had been induced in 25 of the patients with dementia paralytica. The reactions to penicillin were as follows: in 19 HRO, in 5 HR1, and in only one case a real febrile response. In this last case malaria had been induced one year previously but it resulted in only three paroxysms. This patient

Table II. *Type of Neurosyphilis and the Maximal Elevation of the Febrile Herxheimer Reaction (HR).*

Type of Neurosyphilis and Previous Treatment		HR0 —37°	HR1 37.1—37.5°	HR2 37.6—38°	HR3 38.1—38.5°	HR4 38.6—39°	HR5 39.1—39.5°	HR6 39.6—40°	HR7 40.1—40.5°	HR8 40.6—41°	HR9 41.1—41.5°	Total Number of Cases
Dementia paralytica	Untreated	—	—	3	3	2	3	1	—	—	—	12
	Chemotherapy	—	1	1	3	4	—	—	—	—	1	10
	Penicillin	1	1	—	—	—	—	—	—	—	—	2
	Malaria	19	5	—	—	1	—	—	—	—	—	25
	Total	20	7	4	6	7	3	1	—	—	1	49
Tabes dorsalis	Untreated	6	7	—	—	—	—	—	—	—	—	13
	Chemotherapy	10	7	3	—	—	—	—	—	—	—	20
	Penicillin	2	1	—	—	—	—	—	—	—	—	3
	Malaria	1	1	—	—	—	—	—	—	—	—	2
	Total	19	16	3	—	—	—	—	—	—	—	38
Meningo-vascular	Untreated	7	8	1	1	1	1	—	—	—	—	19
	Chemotherapy	13	9	3	—	—	—	—	—	—	—	25
	Penicillin	—	—	—	—	—	—	—	—	—	—	—
	Malaria	4	—	—	—	—	—	—	—	—	—	4
	Total	24	17	4	1	1	1	—	—	—	—	48
Asympto-matic	Untreated	23	19	2	1	2	—	1	—	—	—	48
	Chemotherapy	20	15	4	—	—	—	—	—	—	—	39
	Penicillin	2	1	—	—	—	—	—	—	—	—	3
	Malaria	2	1	1	—	—	—	—	—	—	—	4
	Total	47	36	7	1	2	—	1	—	—	—	94
Total number of cases		110	76	18	8	10	4	2	—	—	1	229

was the only one among those given malarial therapy who still had an increased cell count (15 cells) in the spinal fluid. All abnormalities of the fluid had disappeared in 10 patients in whom therapeutic malaria had been induced, in 4 the Wassermann reaction was still positive and in 11 the mastic test was abnormal. The blood tests for syphilis were negative in 16 patients, in 3 the Kahn test was still positive, and in 5 both the Wassermann and the Kahn tests were positive.

Our cases show clearly that a febrile HR is characteristic of dementia paralytica. It occurred regularly in the case of previously untreated patients or such as had earlier received only chemotherapy. Induced malaria, on the other hand, had suppressed the capacity of reacting to penicillin by fever. The same effect was produced by penicillin in the two cases previously thus treated.

The group *tabes dorsalis* included 38 patients; in 19 of these the reaction was HR0, in 16 HR1, and in 3 HR2. More strongly positive reactions failed to appear in this group in spite of the fact that only two of the patients had previously received malaria and only three penicillin. The abnormalities in the spinal fluid were also less in the patients with tabes than in the others: in only 12 cases was

the cell count over 10, and only 18 had a positive Wassermann reaction. Although the number of cases is small it shows that a febrile Herxheimer reaction is not usually a feature in tabes dorsalis.

In *meningovascular neurosyphilis* HRO was observed in 24 and HR1 in 17 patients. Seven patients of 48 (15 per cent) had higher elevations; of these 4 occurred in cases never previously treated for syphilis and 3 in patients who had earlier had chemotherapy.

Of the patients with *asymptomatic* neurosyphilis, totalling 94, the majority failed to react: HRO occurred in 47 patients and HR1 in 36. Real febrile responses were observed in 11 patients, or 12 per cent. Six of these were previously untreated, four had had chemotherapy, and in one therapeutic malaria had been induced.

The few patients with asymptomatic or meningovascular neurosyphilis in whom febrile responses occurred, generally showed marked abnormalities in the cerebrospinal fluid; 16 had a positive Wassermann reaction, and in 10 of the 15 patients on whom the mastic test was made it was of paretic type and the spinal fluid of grade III. It is therefore probable that at least in part of the cases there was a parenchymatous process but it was not yet far advanced enough to cause symptoms of dementia paralytica. The same observation has been made by Callaway (3) who states that some of the asymptomatic neurosyphilis patients who showed a febrile response would have been classified as pre-paresis or early paresis if these patients had had careful psychometric examinations.

We have pointed out earlier that there were a number of reactions below 37.6° C. but with a fever pattern typical of a positive reaction. This appears also from the relationship between the groups HR1 and HRO in the different diagnostic types of neurosyphilis. For instance among the paralytics previously treated with malaria the group HR1 was small in relation to HRO (5: 19). But this ratio was considerably higher (27: 30) among the patients with untreated meningovascular or asymptomatic neurosyphilis.

Relationship of febrile reactions to abnormalities of the cerebrospinal fluid

Table III shows the relationship of the febrile HR to the cell count, total protein, Wassermann reaction and mastic test in the cerebrospinal fluid and to these findings as a whole, according to Moore's classification.

The *cell count* ranged from 0 to 5 in 78 cases, from 6 to 10 in 21, and exceeded 10 in 129 cases. In the first group (less than 6 cells), fever occurred in only one patient (1.3 per cent) and it was as low as 37.6° C. In the second group (6 to 10 cells) there were 3 febrile reactions which were almost as low. However, the patients with a cell count more than 10 included 39 (30 per cent) with febrile reactions and all elevations above 38° C. occurred in this group. It should also be noted that the ratio of HR1 to HRO was 48: 42 among the patients with a cell count of more than 10, but only 31: 64 among those with counts of 0 to 10. This,

Table III. *Cerebrospinal Fluid Findings and the Maximal Elevation of the Febrile Herxheimer Reaction (HR).*

Cerebrospinal Fluid Findings		HR0 —37°	HR1 37.1—37.5°	HR2 37.6—38°	HR3 38.1—38.5°	HR4 38.6—39°	HR5 39.1—39.5°	HR6 39.6—40°	HR7 40.1—40.5°	HR8 40.6—41°	HR9 41.0—41.5°	Total Number of Cases
Cell count	0—5	51	26	1	—	—	—	—	—	—	—	78
	6—10	13	5	3	—	—	—	—	—	—	—	21
	11—	42	48	14	8	10	4	2	—	—	1	129
Total protein	—30 mg%	26	14	2	—	—	—	—	—	—	—	42
	31—40 mg%	19	17	4	—	2	—	—	—	—	—	42
	41—50 mg%	15	9	1	1	1	—	1	—	—	—	28
	51— mg%	21	13	1	3	4	2	—	—	—	—	44
Wassermann reaction	negative	34	20	3	—	1	—	—	—	—	—	58
	positive	75	57	15	8	9	4	2	—	—	1	171
Mastic test	normal	37	19	1	—	—	—	—	—	—	—	57
	luetic or meningitic	26	22	2	1	2	1	—	—	—	—	54
	paretic	32	24	11	5	5	3	2	—	—	—	82
CSF	normal	11	5	—	—	—	—	—	—	—	—	16
	grade I	10	6	1	—	—	—	—	—	—	—	17
	» II	52	38	2	—	2	1	—	—	—	—	95
	» III	22	17	11	6	4	3	2	—	—	—	65

again, indicates that an elevation of 37.1° to 37.5° C. may be a real Herxheimer reaction.

The *total protein content* was determined in 156 patients*. In 42 it was 30 mg. per 100 ml. or less; in this group only two patients had a low febrile response. In 42 patients the protein content was 31 to 40 mg per 100 cc. and in 6 of them fever occurred. The remaining 14 febrile reactions appeared in the 72 patients in whom the total protein content was higher. These findings clearly show that febrile reactions increase with the increasing protein content.

The *Wassermann reaction* in the spinal fluid was negative in 58 patients of whom only 4 (7 per cent) had a febrile HR. In the remaining 171 the Wassermann reaction was positive and in 39 of these cases (23 per cent) fever occurred.

The *mastic test* was made on 193 patients. It was normal in 57 and only one of them had fever, 37.6°C., but not a typical temperature curve. The test was of luetic or meningitic type in 54 patients; in 6 of these (11 per cent) a febrile response was observed. All other febrile reactions occurred among patients in whom the mastic test was of paretic type. Such patients numbered 82 and 26 of them (32 per cent) showed a febrile HR.

*Cf. footnote on p. 122.

The cerebrospinal fluid was entirely normal in 16 cases. In none of these did a febrile HR appear. A low reaction appeared in one of 17 patients whose spinal fluid was of grade I. The reaction was observed in 5 of the 95 patients (5 per cent) of grade II, and in 26 of 65 patients (40 per cent) of grade III.

These results indicate that the incidence of febrile responses increases with that of abnormalities of the cerebrospinal fluid. Yet this correlation is not definite; for instance among the patients with asymptomatic or meningovascular neurosyphilis there were 14 with a cell count of more than 100, and only 5 of these showed a febrile HR.

Discussion

The cases here studied support the results of previous observers but our results nevertheless differ in some important details which call for a closer consideration.

The incidence of febrile Herxheimer reactions in neurosyphilis varies in reports published by different investigators. This is evident from Table IV, in which our results are also included.

Table IV. *Incidence of Febrile Reactions According to Different Observers.*

Observer	Total Number of Neurosyphilis Cases	Incidence of Febrile Reactions		Threshold of Febrile Reaction
		Number	%	
Callaway and others	100	47	47	37.4°
Koteen and others	111	17	15	38.0°
Hoekenga and Farmer	349	119	34	37.9° (rectal)
Putkonen and Rehtijärvi	229	43	19	37.6°

The last column in the table shows that the lowest temperature defined as a febrile reaction is not the same in all the reports. This «threshold» is lowest in the studies of Callaway and others and Hoekenga and Farmer (37.9° C. rectal = 37.4° C. axill.) and highest in the study of Koteen and others (12). The frequency of the HR clearly increases the lower this threshold is. If, in our material, the threshold is lowered from 37.6° to 37.4° C., the incidence of reactions increases from 43 to 66, or from 19 per cent to 29 per cent. But in only about one-half of the cases thus added was the fever pattern typical of HR.

The variability of the results depends also upon other factors. Such are for instance previous treatment, the diagnostic type of neurosyphilis, and abnormalities of the cerebrospinal fluid. The relationship of previous treatment to the incidence of febrile responses is shown in Table V which compares the results obtained by Hoekenga and Farmer with ours. The results show consistently that previously induced therapeutic malaria makes the patients with neurosyphilis much less liable to react to penicillin by fever. Hoekenga and Farmer observed febrile reactions in only one such patient of 14, and in

our series they were observed in 2 of 35; in one of these two the reaction was low and the other occurred in a patient who had previously had only three paroxysms during induced therapeutic malaria.

Table V. *Relationship of Previous Treatment to Frequency of Febrile Herxheimer Reaction in Neurosyphilis.*

Observer	Untreated			Chemo-therapy			Malaria			Penicillin		
	Number of Cases	Incidence of Febrile Reactions		Number of Cases	Incidence of Febrile Reactions		Number of Cases	Incidence of Febrile Reactions		Number of Cases	Incidence of Febrile Reactions	
		No.	%		No.	%		No.	%		No.	%
Hoekenga and Farmer	107	41	38	87	28	32	14	1	7	9	2	
Putkonen and Rehtijärvi	92	22	24	94	15	17	35	2	6	8	0	

Previous penicillin treatment seems to influence the incidence of febrile reactions in the same way as malaria. True, the figures in Table V are low but they are supported by the fact that repetition of the febrile response was not observed in our material after the second injection of penicillin.

Hoekenga and Farmer stress that the incidence of reactions was similar in patients recently given chemotherapy and in previously untreated patients. In our series the incidence of febrile responses was somewhat lower among the patients given chemotherapy than among those never previously treated, in spite of the fact that at least one year had in most cases (71 of 92) passed since such treatment. However, the difference between the two groups is not statistically significant ($\chi^2 = 0.97$, $P = 0.33$).

In Table VI we have compiled the data from the literature concerning the frequency of the febrile HR in different diagnostic types of neurosyphilis. Of our cases we included only those not previously given malaria or penicillin treatment. Jones and Perk's six cases are also previously untreated. Exact data about the previous treatment are not given in the other materials, but at least three of them include also patients given malarial therapy or penicillin.

Accordingly it may be concluded that in dementia paralytica practically all the previously untreated cases show a febrile response. Evidence of this are Jones and Perk's 6 patients — all reactors — and our 22 cases in only one of which the reaction was as low as 37.4° C., even that showing a typical pattern of fever. It seems probable that in the other series, in most cases at least, the HR was absent in previously treated patients. We feel that the absence of a febrile reaction actually argues against the diagnosis dementia paralytica, if therapeutic malaria or penicillin have not been used earlier. In other types of neurosyphilis the incidence of febrile reactions is lower than in dementia paralytica, according to all observers. This difference is least in the cases reported by Calla-

Table VI. *Febrile Reactions in Different Diagnostic Types of Neurosyphilis*

Observer	Dementia paralytica and Taboparesis			Tabes dorsalis			Meningovascular			Asymptomatic		
	Number of Cases	Febrile Reactions		Number of Cases	Febrile Reactions		Number of Cases	Febrile Reactions		Number of Cases	Febrile Reactions	
		No.	%		No.	%		No.	%		No.	%
Callaway and others (2)	39	24	62	11	4	36	6	3	50	37	12	33
Reynolds and others (19)	24	19	79									
Jones and Perk (16)	6	6	100									
Hoekenga and Farmer (8) ..	55	41	74	40	9	23	78	28	36	136	33	24
Chesney and Reynolds (4)				33	4	12						
Putkonen and Rehtijärvi	22	21	95	33	3	9	44	7	16	87	10	12

way and others, and greatest in our cases which included only three weak reactions among 33 cases of tabes, the incidence of HR being as low as 16 per cent in meningovascular neurosyphilis and 12 per cent in asymptomatic neurosyphilis. The higher percentages in these types in the material of Callaway and others and of Hoekenga and Farmer can probably be explained by the lower threshold level for a positive reaction. In order to show how our results would be affected by the use of a lower threshold we include in Table VII the incidence of febrile reactions when defined as a rise to at least 37.4° C. and 37.2° C.

Table VII. *Variations in the Percentage of Febrile Reactions in Different Types of Untreated Neurosyphilis with Different Tresholds of Fever.*

Type of Neurosyphilis, Untreated	Lowest Treshold of Febrile Reaction			Total Number of Cases
	37.6°	37.4°	37.2°	
Dementia paralytica	95 %	100 %	100 %	22
Tabes dorsalis	9 %	24 %	45 %	33
Meningovascular	16 %	32 %	55 %	44
Asymptomatic	12 %	19 %	49 %	87

Table VII shows that such a lower threshold does not appreciably affect the results in the group dementia paralytica which as it is includes 95 per cent reactors. In the other types of neurosyphilis, however, the incidence of febrile responses increases when the threshold 37.4° C. is substituted for 37.6° C. But about 50 per cent of the cases thus added do not show a typical fever pattern. If a still lower rise (37.2° C.) is defined as a reaction the percentages become even higher

and an increasing number of fever curves do not show the typical pattern of the HR. These unspecific rises reduce unduly the differences between the groups.

In early neurosyphilis the incidence of reactions may increase because of other factors. We (17, 18) have previously demonstrated that a febrile HR begins to appear in patients during the seronegative primary stage, is regularly present in seropositive primary syphilis, and is most intense in the late primary or early secondary phase. Then the reaction becomes weaker and often disappears during the late secondary stage when the practically HR-negative latent phase is approached. In early neurosyphilis reactions may then be observed which are in no way related to the localization of the disease to the central nervous system. Because of this we excluded from our series all cases with primary or secondary manifestations. If such cases occur among those studied by C a l l a w a y and others and by H o e k e n g a and F a r m e r, they may partly contribute to the high incidence of febrile responses in early neurosyphilis.

A third important factor influencing the incidence of febrile reactions is the cerebrospinal fluid finding. H o e k e n g a and F a r m e r have demonstrated that this incidence increases with the cell count and total protein, and with the degree of positivity of the complement fixation reaction in the spinal fluid. Our results support this opinion. However, a close comparison in this respect has not been possible because H o e k e n g a and F a r m e r in their study combine the cell count and the protein content and include the weakly positive Wassermann reactions with the negative. It may be mentioned that they obtained a 93 per cent incidence of febrile reactions in cases of dementia paralytica with increased protein content and cell count. This observation lends strength to our statement that in untreated dementia paralytica the incidence of reactors is nearly 100 per cent.

The cerebrospinal fluid findings also explain why the cases studied by C a l l a w a y and others include an exceptionally great proportion of reactors; the cases were selected so that all showed an increased cell count and/or total protein content, in addition to a positive Wassermann reaction.

Finally we wish to stress the peculiar similarity between dementia paralytica and late primary or early secondary syphilis. At these two phases of the disease a febrile Herxheimer reaction is obtained in almost 100 per cent of the cases, but in all other phases of acquired syphilis it is rare (18).

If — as is generally believed — the febrile HR is caused by destruction products of spirochetes, then its frequency in dementia paralytica proves that a marked spirochetosis is present at this stage, as in the initial stage of the disease. The spirochetes are only localized to different areas. In early syphilis they are most numerous in the perivascular tissue, in dementia paralytica in the brain substance. Their different localization also perhaps explains the fact that the maximal elevation of temperature occurs many hours later in dementia paralytica than in early syphilis. Penicillin possibly does not penetrate into the brain substance so

rapidly as into foci of spirochetes concentrated in the perivascular tissue during the early stages of syphilis.

Noguchi and Moore (16) were the first to find spirochetes by the method of Levaditi in the brain of paralytics. Later Noguchi (15) found them in 24 per cent of 200 cases studied. Valente (24) demonstrated spirochetes in 70 per cent of his dark-field examined cases, and Levaditi, Marie and Bankowski (13) in all of their 8 patients who died in convulsive seizures. It has also been noted that very great numbers of spirochetes may occur in the brain of paralytics, occasionally even more than in the organs of patients suffering from early congenital syphilis (9). In tabes dorsalis, on the other hand, spirochetes are not usually demonstrated in the spinal cord (15, 9), neither will they be easily discovered in the brain of paralytics in whom therapeutic malaria has been induced. These observations are also in harmony with the opinion that marked spirochetosis is a prerequisite for a febrile Herxheimer reaction.

Summary

The febrile Herxheimer reaction has been studied in 229 patients with neurosyphilis by administering an initial therapeutic dose of at least 100,000 units penicillin and recording the temperature of the patients at hourly intervals.

All 22 patients with dementia paralytica without previous malarial or penicillin treatment showed a febrile response. In asymptomatic neurosyphilis this reaction occurred in only 12 per cent, in meningovascular neurosyphilis in 16 per cent and in tabes in 9 per cent of the cases. Previous chemotherapy (As- and/or Bi-treatment) may perhaps reduce the incidence of febrile responses to some extent and previous malarial or penicillin treatment generally make a febrile reaction impossible.

Increased abnormality of the cerebrospinal fluid caused an increase in the incidence of febrile responses. When the cell count rose to over 10 the incidence of febrile reactions increased eightfold, and when the Wassermann reaction turned positive, threefold. This incidence also increased when the protein content became higher and the mastic test became abnormal. When the spinal fluid was of grade III, 40 per cent of the patients showed a reaction, whereas those of grade II included only about 5 per cent reactors.

The maximal elevation of temperature occurred a few hours later in neurosyphilis than in primary and secondary syphilis, mostly 12 to 16 hours after injection of penicillin. This delay may be due to the fact that penicillin penetrates into the perivascular foci of spirochetes of early syphilis more rapidly than into the spirochetes present in brain substance.

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Round Table Discussion: Neurosyphilis

I Remarks of Discussion Leader

Dr. C. H. Flodén (Stockholm): **Summary of Questions to be Raised.**

I Are there any objective signs of «activity» of the neurosyphilitic process, and is the so-called Dattner-Thomas concept of neurosyphilis justified?

The clinical picture alone is misleading in many instances as it does not identify asymptomatic cases and may give an impression of activity in burnt-out cases. Spinal fluid findings on the other hand can now claim to reflect the activity of the neurosyphilitic process, fairly accurately, the diagnostic measures having attained a high degree of reliability.

II Is it possible to make the spinal fluid examination still more exact?

Protein determination with the methods hitherto generally employed is lacking in exactness. With a more accurate determination of total protein globulin, albumin and globulin/albumin ratio, there would be a greater chance for comparison of punctures with short intervals in the same patient as well as in different patients, enabling us for instance to evaluate more rapidly the results of treatment. I think the method evolved by Izikowitz offers the advantage of an exactness as great as the Kjelldahl method. We have made it the standard procedure for protein determinations in the dermatologic clinic at Karolinska Sjukhuset and have found it very reliable and not too difficult to carry out.

III Is penicillin the best antisyphilitic agent?

Penicillin is to-day a most effective antisyphilitic agent with few ill effects, but we still do not know the full extent of its possibilities and limitations.

1) What is the optimal time-dosage relationship?
2) To avoid Herxheimer effect and therapeutic paradox it seems advisable to give some treatment with iodide or bismuth prior to penicillin therapy especially in cases with vascular involvement and/or myocardial damage.
3) To make results of penicillin therapy more lasting a course of bismuth and arsenic may be valuable following penicillin therapy.
4) Is it possible that the institution of penicillin alone can lessen chances of a good result in certain cases through loss of time or through making the infection more resistant towards therapy.

5) Is it advantageous to directly institute malaria therapy, alone, or in combination with penicillin, for instance in cases of general paresis with a psychotic trend and in primary optic atrophy?
6) What is to be done in cases where penicillin fails?

IV Could we lay down some general rules for the management of neurosyphilis? The scheme followed at the dermatologic clinic at Karolinska Sjukhuset is:

1. Management of neurosyphilis can only be carried out in conjunction with spinal fluid examinations.
2. Neurosyphilitic involvement in early syphilis generally is reversible and does not require special treatment. If there should still be abnormal spinal fluid findings 6 months after institution of therapy those cases are treated as late neurosyphilis.
3. In neurosyphilis after primary or secondary stage 600,000 units of procaine penicillin are given daily for 15 days, preceded by iodides by mouth and bismuth injections for some time depending on the state of heart and vessel.
4. In cases where a more rapid effect is desired, i.e., paralyses of psychotic type and primary optic atrophy, malaria is given in combination with penicillin.
5. Penicillin treatment is followed by a course of bismuth and arsenic.
6. Results are evaluated through spinal fluid examinations after 3—6—9 etc. months. As long as the tendency is towards a normal state no more treatment is given. Should the amelioration cease or change into a trend to the worse another course of penicillin with or without fever is given.
7. When the cerebrospinal fluid has been normal for a year after treatment there is considered to be no risk of a flare-up of the neurosyphilis process.

II Discussion

Q: *If patients with early syphilis were to receive no treatment at all, how many of them would develop neurosyphilis?*

Dr. D a n b o l t. I believe we now have additional information on this point. You will recall that in Norway, Professor B o e c k (1890—1910) considered mercury treatment to be harmful and his patients with early syphilis were hospitalized without treatment until all evidence of early syphilis had disappeared. Twenty years ago, B r u u s g a a r d reported on the fate of these patients, having been able to obtain follow-up observations on about 23% of them. We are now restudying this important material, and hope to obtain follow-up information on approximately 80% of B o e c k's original patients. We find, from a preliminary sample of the group, that approximately 5% of the untreated patients developed neurosyphilis.

Q: *In early syphilis, does pleocytosis in the spinal fluid indicate neurosyphilis if the Wassermann reaction is negative?*

Dr. F l o d é n. We believe the first abnormalities to appear in the cerebrospinal fluid are alterations in the globulin/albumen ratio and an increase in lymphocytes. The positive Wassermann develops later. The Wassermann reaction assumes greater importance in late cases. In cases of tabes dorsalis, for example, if there is an increase in cells and an increase in protein associated with a negative Wassermann, it would be desirable to repeat the spinal fluid examination. In general, we should consider the entire spinal fluid picture, although occasionally isolated parts of it are of some importance.

Dr. D a t t n e r. We recently have been using a new and more sensitive colloidal gold test. With this we are seeing more and more cases where changes in the protein components are the first abnormality to appear. It certainly is true that active neurosyphilis may occur without a positive spinal fluid Wassermann.

Q: *How frequent is asymptomatic neurosyphilis?*

Dr. P u t k o n e n. When routine spinal fluid studies are made, asymptomatic neurosyphilis is not infrequent. About 13% of more than 400 STS positive pregnant women at Kumpula Hospital had spinal fluid abnormalities. Only 3% had symptoms or signs of neurosyphilis, and 10% were asymptomatic.

Q: *When should the spinal fluid first be examined? How frequently?*

Dr. F l o d é n. If we could be sure of our follow-up examinations, it would be advisable to do the spinal puncture early and repeat it several times. If only one examination can be made, it would be better to defer it for 3—5 years after the infection. In cases of late syphilis, of course, the examination should be made without delay.

Dr. D a t t n e r. As to the frequency of spinal fluid examinations, I have never seen a patient whose initial spinal fluid examination was negative develop neurosyphilis, unless a reinfection occurred. Were the spinal fluid tests negative one year following the course of therapy, I think we can safely assume that neurological relapse will not occur.

Dr. K a i l a. This is an important consideration in Finland, since it frequently is difficult to obtain repeated spinal fluid examinations for control purpose.

Q: *Can we estimate the amount of penicillin required from the spinal fluid findings?*

Dr. D a n b o l t. In Oslo we have used routinely 6.0 million units for asymptomatic neurosyphilis, but with symptomatic neurosyphilis, especially general paresis, we give more, usualy 10.0 million units.

Dr. Dattner. If it were possible to assay the sensitivity of the spirochetes in cases of paresis as we do with bacterial endocarditis, we could readily estimate the amount of penicillin required. Since we cannot, it is difficult to forecast how much penicillin will be required in any particular case. We have cases that failed to respond to six, nine or even fifteen million units of penicillin, but who did respond to thirty million units. With the amount of penicillin given routinely, we have approximately 4% failures, but if we knew in advance about the sensitivity of the organism, I am confident we should have hardly any.

Q: *Is antisyphilitic treatment effective if the spinal fluid of patients with neurosyphilis is normal?*

Dr. Danbolt. If the cerebrospinal fluid is negative, there is probably no benefit to be derived from further antisyphilitic therapy. It is reasonable to give additional treatment, but we should not expect much in the way of results.

Dr. Flodén. I agree with Professor Danbolt that in the absence of spinal fluid changes, little can be expected from additional therapy. I have seen a few cases of urinary incontinence associated with a normal spinal fluid in which the patient appeared to improve after penicillin treatment, although the effect may not have been on the syphilitic infection.

Dr. Dattner. I have never seen neurosyphilis improve further once the spinal fluid is normal. There no doubt are cases where an intercurrent infection that is causing symptoms may benefit from additional treatment with penicillin, but this effect is not on the neurosyphilitic process itself. I should suspect that Dr. Flodén's patients with incontinence will not remain continent, but will develop further urinary difficulties.

We must carefully interpret «progression» of the disease in neurosyphilis. The development of a Charcot's joint, for example, is not true progression, but rather the ultimate outcome of a disease process long since dormant.

Dr. Kaila. Then you are of the opinion that it is useless to treat with penicillin a patient with severe lightning pains if the spinal fluid is normal?

Dr. Dattner. That is my opinion, qualified by the comment that at times lightning pains are associated with some infection which may be favourably affected by penicillin. There also is another factor, the tonic action of penicillin upon patients who although not aware of any disability feel generally better after a course of treatment.

Q: *How can one interpret a bloody spinalfluid tap?*

Dr. Putkonen. The tap should be repeated if possible. Some information, however, can be obtained from a comparison of the numbers of RBC and the WBC that are present in the spinal fluid. We have some data which suggest that a small

amount of blood does little harm. If one adds Wassermann positive whole blood to spinal fluid it takes a surprisingly large amount to cause a significant change in the spinal fluid titre.

Dr. F l o d é n. I agree that a small amount of blood in the spinal fluid makes little difference, but it is important that the examination be cause promptly, and that the presence of blood be recorded in the report.

Dr. D a n b o l t. I am very reluctant to accept reports of spinal fluid tests when even a small amount of blood is present.

Q: *Is it possible to have a false positive spinal fluid Wassermann?*

Dr. R e y n o l d s. Some years ago, Dr. V i r g i l S c o t t, Dr. C h a r l e s M o h r and I studied this question. We were able to collect seven cases of confirmed false positive spinal fluid Wassermann reactions in nonsyphilitic persons and other cases in which we suspected there had been a passive transfer of reagin from the blood to the spinal fluid. These were mostly cases of meningitis-tuberculous, meningococcal and lymphocytic choriomeningitis.

This is not a common occurrence, but false positive spinal fluid Wassermann tests may occur and a diagnosis of neurosyphilis based on the Wassermann reaction alone is not justified in patients with meningitis and perhaps other inflammatory conditions of the central nervous system.

Q: *Do patients with early syphilis who have spinal fluid changes require more intensive therapy than those whose spinal fluids are normal?*

Dr. F l o d é n. We have no precise data on this point, but I have a clinical impression that the early spinal fluid changes respond readily to antisyphilitic therapy and that treatment in these cases need not be intensified.

Dr. D a t t n e r. We can answer this question only indirectly. It seems practically certain that these are the patients who if untreated would develop neurosyphilis later in life. Whether they need more intensive therapy with penicillin is difficult to prove, since this has been used for too short a time to be sure.

Q: *In a patient who received antisyphilitic therapy during the early stages of the disease, there is observed an Argyll Robertson pupil. The spinal fluid is normal, but the blood is positive. Does this patient have central nervous system syphilis?*

Dr. D a t t n e r. An Argyll Robertson pupil is presumptive evidence of neurosyphilis, although it is well established that this may be «burnt out». There is no strict correlation between the serologic findings in the blood and in the spinal fluid, but it seems highly probable that this patient had involvement of the nervous system which left its mark but which burned out before more serious involvement occurred.

Q: *How frequent are clinical Herxheimer reactions in patients with neurosyphilis? Is there ever permanent damage to the nervous system that might be considered a therapeutic paradox?*

Dr. Putkonen. For minor transient intensifications of the clinical syndrome we usually are dependent upon the observations of the attending nurses. In our series of cases there were 43 patients who developed a marked febrile reaction. Three of these appeared to have some increase in clinical signs. It has been reported that some cases of general paresis have become unmanageable on open wards but we have not observed this.

Dr. Kaila. We had one such case.

Q: *Are there clinically active cases of neurosyphilis in which the only spinal fluid abnormality is an increase in the spinal fluid protein?*

Dr. Flodén. The answer to this question depends on what methods are used in the spinal fluid protein determinations. With usual methods, it is not infrequent to have active neurosyphilis with a normal total protein. With the Izicovitz's method, more subtile changes are detected. It is not common, but with sensitive procedures, we do see cases in which alterations in the spinal fluid protein constitute the only spinal fluid abnormality. More often there is an accompanying pleocytosis.

Dr. Kaila. Perhaps protein determinations are more helpful in post-treatment observations, because following treatment the cell count may respond rapidly but changes in the protein content persist for a far longer time.

Q: *Should pentavalent arsenicals be used following penicillin treatment of patients with neurosyphilis?*

Dr. Dattner. We have completely abandoned the use of tryparsamide and other pentavalent arsenicals in the treatment of neurosyphilis. These are toxic drugs of limited value therapeutically and now that we have penicillin there is no reason for their continued use.

Q: *Do certain types of paretic psychoses respond better to therapy than others?*

Dr. Donner. In our experience paretics who are maniacal respond most satisfactorily as a rule.

Dr. Reynolds. One might think that paretics whose type of psychosis would bring them promptly to medical attention would respond better than those whose mental deterioration comes about gradually. The duration of the psychosis prior to treatment is an important consideration.

Dr. Donner. The duration of the cerebral inflammation is an important factor, but there are quite a few exceptions to the general rule.

Q: *Is pleocytosis of the spinal fluid a more sensitive index of activity within the central nervous system than, for example, leucocytosis is of a systemic infection?*

Dr. Dattner. I can only say that the presence or absence of cells in the spinal fluid is a very sensitive index of the activity of the neurosyphilitic process.

Q: *Should penicillin alone be used in patients with progressive primary optic atrophy?*

Dr. Dattner. All too often by the time we see the patient, his optic atrophy has progressed very far indeed. As Dr. Klauder has pointed out, if routine and very careful perimetric studies are made, the diagnosis can be established much earlier.

I recall that when malaria therapy was introduced, there was considerable opposition to it because in some cases the patients became completely blind while being treated. Thus it is surprising that some now advocate treatment with malaria and penicillin rather than with penicillin alone. As you know, there is an incubation period of about three weeks with therapeutic malaria, and this means the loss of valuable time. With penicillin, treatment can be started the day the patient comes to our attention.

I have thus far treated 37 patients with primary optic atrophy by the use of penicillin alone, and the results have been very satisfactory. There are patients who become blind, but these are the ones whose atrophy was far advanced. We have patients in whom the condition has remained arrested for as long as four years. I see no reason from the past experiences with malaria and the present experiences with penicillin to use fever in primary optic atrophy.

Dr. Danbolt. It seems likely that some of the unfavourable results from penicillin therapy are due to the use of large doses of penicillin at the start. It might be better to initiate treatment with smaller doses.

Dr. Dattner. We have given full therapeutic doses of penicillin to all patients, even to those with cardiovascular syphilis. Perhaps there is an occasional one who reacts unfavourably, but we do not like to deprive the others of treatment which is fairly often dramatic in its effectiveness.

Q: *Do post-mortem examinations of penicillin-treated paretics indicate complete absence of inflammatory changes in the brain tissues?*

Dr. Dattner. There are now altogether eleven cases in the literature in which penicillin-treated patients have been examined post-mortem. Cases reported in which the autopsy was performed 30—108 days after penicillin was started revealed distinctly less inflammation than in the average case of untreated general paresis, and were comparable pathologically with the changes found after malaria. A recent report from Bruetsch, a very careful and competent worker, also states that penicillin arrests the signs of cerebral damage as effectively as

does malaria. There is the same reduction in perivascular infiltration and the same reduction in iron pigment. In one of four brains, B r u e t s c h found a single spirochete. On the basis of this he recommends 15 million units of penicillin in the treatment of general paresis. B r u e t s c h concludes that penicillin is equal to malaria therapy in effectiveness and may even surpass it by a small margin. I might mention that he did not favour penicillin alone some time back, but that he has convinced himself by histopathologic studies that penicillin is as effective as malaria.

Dr. K a i l a There are patients whom penicillin alone does not help. Should we not give them the benefit of malaria?

Dr. D a t t n e r. I should certainly give them malaria in combination with additional penicillin, because our first function is to do everything possible to help the patient. For the sake of our research studies, we have restricted therapy to penicillin alone, and retreatment with larger and larger amounts of penicillin has always been successful.

Dr. K a i l a. I agree and should also advise malaria and penicillin. I am inclined to believe that a neurosyphilitic process is not completely inactive until the spinal fluid is entirely negative, except for the persistently positive Wassermann reaction.

Section IV: Serodiagnosis of Syphilis and Laboratory aspects

Chairman K. O. Renkonen

Problems in the Serodiagnosis of Syphilis

By

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Physicians have often been confronted with the problem of how to evaluate or interpret serologic reports obtained from the laboratory in determining the presence or absence of a syphilitic infection. Most physicians have probably had patients with clinical syphilis in whom the routine serologic tests gave negative reactions, as well as nonsyphilitic patients with unexplained positive serologic reactions. Such discrepancies are to be expected, since it is well known that there are no true specific tests for syphilis, with the possible exception of the Nelson treponemal immobilizing test (1). When Wassermann, Neisser and Bruck (2) developed the first serologic test for syphilis nearly half a century ago, they felt that they had devised a specific and a sensitive laboratory procedure for the diagnosis of syphilis. They considered their test specific because they employed a saline extract of *syphilitic* liver for the antigen. They thought it was adequately sensitive because positive reactions were obtained with the blood of many individuals with active clinical syphilis. It was, however, soon discovered that not only were these antigens nonspecific, but that alcoholic lipoid extracts obtained from normal tissue were more «specific» and more sensitive than the aqueous extracts of syphilitic tissues. Fortunately the combined efforts of research-minded serologists and clinicians have done much to improve those procedures which are employed today in the serodiagnosis of syphilis. The following is a brief description of some of the improvements made in laboratory techniques and in materials employed in serologic tests for syphilis.

Collecting Tubes. The use of wet and non-sterile syringes in the collection of blood specimens rendered many of them unsatisfactory for serologic testing. The development of inexpensive dry and clean vacuum tubes for the collection and mailing of blood specimens has done a great deal to decrease the number of unsatisfactory specimens received by the laboratory. Sterility is not an absolute necessity when clotted bloods are shipped, since the clot seems to exert a bacteriostatic effect on the serum. It is important, however, that the collecting and mailing tubes be clean and dry.

Serum Preservatives. In warm climates, clotted blood specimens become hemolyzed and may therefore become unsatisfactory for testing. Army facilities found it necessary to separate the serums from the clots to eliminate hemolysis. Frequently it was necessary to ship these serum specimens to distant laboratories, and it was sometimes difficult and often impossible to ensure sterility in the collection and preparation of serum. During the several days required for the specimens to reach the laboratory they became badly contaminated and unsatisfactory for testing. It was necessary to find a suitable substance which would prevent this contamination and not interfere with serologic testing. Merthiolate answered this need. Merthiolate (sodium ethyl mercuri thiosalicylate) is an excellent bacteriostatic and bactericidal agent for the preservation of serums, and for the past several years has been employed by the United States Public Health Service, United States Army and other agencies for the preservation of serum and spinal fluid specimens intended for shipment over considerable distances. In the Division of Serology at the Army Medical School (3), sera preserved with one mg. of merthiolate per millimeter have been used routinely with excellent results. The use of merthiolate as a preservative has markedly decreased the number of specimens rendered unsatisfactory for serologic testing because of bacterial contamination. In a series of more than 20,000 merthiolated specimens received in a central laboratory for special serologic studies, less than 0.1 per cent were unsatisfactory for testing because of bacterial contamination.

Inactivation of Serum. For many years it was believed that it was not necessary to heat or «inactivate» serums prior to testing with the various flocculation tests for syphilis, and that such «inactivation» was only necessary to destroy the native complement present in fresh serums when tested with the complement-fixation proceduras. Investigations by Rein and Pillimer (4) have indicated that fresh syphilitic serums contain a thermolabile substance which inhibits or retards the aggregation of lipoidal antigens in flocculation reactions. Strongly positive serums would often give negative reactions when tested in the raw or unheated state. It was found that all serums had to be heated (5) before testing with complement-fixation or flocculation procedures. Serums heated for ten minutes at 56° C., for one minute at 69.5° C., and seven seconds at 100° C. (in boiling water) gave results that were practically identical with those obtained with serums heated for the routine thirty minutes at 56° C. It was also found that the unnecessary prolongation of the heating period tends to destroy some of the reagin in the serum. The rapid «inactivation» of serum is especially valuable as a time-saving factor where the rapid flocculation tests are used for the detection of syphilis in donors just prior to transfusion.

Antigens. Considerable progress has been made in the improvement of the various lipoidal antigens. The isolation by Pangborn (6, 7 and 8) of the substance cardiolipin from beef heart and the development of methods for the purification of lecithin (9) prepared from both heart and egg yolk, has been the greatest contribution for the improvement of the serodiagnosis of syphilis in

recent years. Several investigators, Harris and Portnoy (10), Harris Rosenberg and Reidel (11), Kline (12), Brown (13), the Maltaners (14), Kahn (15), Kolmer (16) and Mazzini (17) have described the preparation of cardiolipin antigens for use in various complement-fixation, macro and microflocculation tests. At the Army Medical School, a cardiolipin antigen (18) was successfully adapted for use in a microflocculation slide test for the serodiagnosis of syphilis. The sensitivity of this test was higher than that obtained with the Kline diagnostic, Mazzini, Kahn, Hinton, Eagle, Boerner-Jones-Lukens and Kolmer tests. It was of interest to note that this increased sensitivity was obtained without any apparent increase in nonspecificity. In fact, the extraordinary specificity of the cardiolipin antigen in the presence of malarial infection was repeatedly demonstrated (19).

Preserved Sheep Blood. One of the difficulties encountered in the performance of complement-fixation tests is in obtaining satisfactory sheep blood. The smaller hospital laboratories with no facilities for the raising of sheep have to obtain their supply from the slaughter house. Many times the red blood cell suspensions prepared from such sheep blood prove to be unsatisfactory. A preservation technique for maintaining uniformity in the properties of sheep cells would be a great laboratory convenience. It would be advantageous to employ preserving fluids which would maintain the properties of sheep blood over long periods and particularly during periods of transportation. Quantitative studies (20) indicate that aseptic collection of sheep blood in modified Alsevers' solution at ordinary temperatures and subsequent refrigeration permit the preservation of the blood for several months without the development of appreciable hemolysis or change in susceptibility to lysis by guinea pig complement and rabbit amboceptor. Blood collected in this fashion by the United States Army Laboratory has been used for the past five years with excellent results. Preserved sheep cells are now commercially available.

Spectrophotometer. Accurate standardization of the hemolytic system in the complement-fixation tests has become of paramount importance in maintaining a constant level of sensitivity. To this end the spectrophotometer has been adapted (21), not only for quantitative titration of complement and amboceptor, and for the standardization of sheep cell suspensions, but also for the final readings of the tests themselves. The use of this instrument has been adapted for the complement-fixation test for syphilis as well as for complement-fixation tests employed in the serodiagnosis of other diseases, such as malaria (22) and amebiasis (23).

Amboceptor. The preparation of antisheep amboceptor with the elimination of rabbit shock has also proved advantageous to laboratories performing complement-fixation tests. The chief difficulty in preparing amboceptor has been the heavy loss of rabbits by shock, particularly following the injection of the second dose of cells. Furthermore, when whole cells are employed, the finished amboceptor may contain relatively large amounts of agglutinogens or precipitins, rendering it unsatisfactory for use. A method (24) was developed at the Army Medi-

cal School for the preparation of antisheep amboceptor utilizing the cell stroma instead of the packed washed cells. The stroma is prepared by specifically hemolyzing washed sheep cells with amboceptor and complement. Satisfactory amboceptor has been produced in about ten days, and the titers are higher than those usually obtained by other methods.

Complement. The majority of small laboratories do not have facilities for maintaining their own colony of guinea pigs which are necessary for their supply of guinea pig complement. Dried or lyophilized guinea pig serum has been used at the Army Medical School in various types of complement-fixation tests with excellent results. Dried guinea pig complement supplied to the Army Medical School had to meet the following requirements:

1. *Titer:* The exact hemolytic unit should be contained in no more than 0.45 ml. of a 1: 30 dilution when titrated by the Kolmer method.
2. *Moisture Content:* Should not exceed 1 per cent by weight.
3. *Homoglobin Content:* Should be minimal.
4. *Source of Guinea Pigs:* The serum should be obtained from normal healthy guinea pigs which have never been used for any other purpose.
5. *Preserving Fluid:* Supplied with the dried products should contain 6 per cent sodium acetate and 2 per cent boric acid.

Several commercial concerns prepare dried guinea pig complement which meet the above requirements and give satisfactory results.

Serum Controls. A positive and negative serum control should be included every time serologic examinations are made. This helps to ensure the sensitivity and specificity of the test employed and tends to minimize the occurrence of technical errors. Unfortunately, many laboratories select a strongly positive serum for their control. Such controls are unsatisfactory for detecting a decrease or increase in the sensitivity of a serologic procedure, for if the sensitivity has been reduced or increased as much as 50 per cent, a strongly positive serum might still give a four-plus reaction. The use of weakly positive or partially positive serums would more readily detect a change in sensitivity due to technical error or to deterioration of materials employed. If strongly positive serums are utilized, they should be subjected to serial dilutions and the test performed on each dilution. A reduction or increase in *titer* would indicate a change in sensitivity. The routine utilization of a strongly positive serum (quantitative control) or weakly positive serums (qualitative controls) is of utmost importance in controlling the sensitivity level of a serologic procedure.

There have been many more improvements such as the use of recalcified plasma (25) instead of serums for serologic testing; the use of the 50 per cent hemolytic unit (26) instead of 100 per cent end point of hemolysis in determining the degree of fixation of complement by specific antigen-antibody complex; the introduction of the new wetting agents for the proper washing of serologic glassware; the use of buffered solutions in preparing the antigen emulsions, comple-

ment and amboceptor dilutions and for diluting strongly positive serums for the various quantitative tests; and the prevention of non-specific and prezone reactions in the complement-fixation test with spinal fluid by the addition of egg albumen or normal serum to the complement. Suffice to say that all of these advances have helped considerably in the improvement of our serodiagnostic procedures.

Quantitative serologic tests for syphilis

The demand for quantitative serologic testing by the practicing physician has shown a marked increase since the introduction of rapid therapeutic measures for the treatment of syphilis with penicillin. These requests for quantitative serologic reports will become more numerous as the recently advocated schedules of penicillin therapy are more generally adopted. It must be pointed out, however, that a quantitative serum test is not necessarily an aid to diagnosis, but merely determines the maximum dilution in which that particular serum still gives a positive reaction. A patient whose serum is positive in a 1: 16 dilution is no less syphilitic than the individual whose serum is positive in a dilution of 1: 256. Too much emphasis has been placed on the pseudoquantitative method of reporting weakly positive reactions as 1 plus, 2 plus, 3 plus and 4 plus in the routine qualitative tests. The physician is often lulled into a sense of false security on serologic recheck, if the laboratory reports a reduction in titer from 3 plus to 1 plus, and again he and the patient may be unduly concerned if the titer rises from a 1 plus to a 3 plus reaction. Furthermore, a 4 plus reaction does not necessarily indicate a »strongly» positive reaction since some «4 plus» serums may only be positive in a dilution of 1: 2 whereas another 4 plus serum may continue to give positive reactions in a dilution of 1: 256. Obviously the latter serum is 128 times more positive than the first serum, yet both were reported as 4 plus or «strongly» positive by the routine qualitative method. The value and importance of carefully performed and properly interpreted quantitative tests cannot be overemphasized. Unfortunately, there has been a great deal of confusion regarding the present status of quantitative procedures because of the dissimilar methods of performance, interpretation, and reporting of the tests.

The chief value of quantitative tests lies in the fact that the physician can more adequately evaluate the serologic response of his patient to a particular treatment schedule from the very onset of therapy throughout the period of clinical and serologic follow-up. A reduction in serologic titer may be of great value and is often the only clue to the success of the previously administered anti-syphilitic therapy.

The following are a few instances where carefully performed and properly interpreted quantitative tests may be of value to the practicing physician.

1. As a guide of response to treatment.

Short intensive methods of therapy, especially with penicillin, are completed

or terminated while the patient is still seropositive. If the serologic tests are to be of any value in determining the efficacy of the therapy, quantitative procedures performed at regular (monthly) intervals to indicate the degree of positivity are necessary. If the quantitative tests remain strongly positive long after a reversal to seronegativity is anticipated, one may consider that patient as treatment failure. There are, however, several factors which may influence the length of time required to attain seronegativity, and they will be discussed later on.

2. As a means of differentiating between serologic relapse and re-infection.

3. Differentiate between prenatal syphilis and syphilotoxemia.

4. To determine reagin fastness or seroresistance.

5. To differentiate between true and false positive serologic reactions for syphilis.

Carefully performed and interpreted quantitative serologic tests under uniform and standard conditions are of definite value to the practicing physician.

Antibodies

On the basis of experiments with «palligen», Eagle and Hogan (27) demonstrated the presence of two antibodies in syphilitic serum: an antilipidal antibody and an antitreponemal antibody. When syphilitic serum was adsorbed with an excess of beef heart lipidal antigen, all reagin antibody was removed. The reagin-free filtrate still gave agglutination and complement-fixation reactions with spirochetal suspensions in the same titer as in the original serum. However, when the same serum was adsorbed with spirochetal suspensions, its reactivity with both lipidal and spirochetal antigen was removed.

Recent studies by a group of other investigators confirmed the presence of multiple antibodies in syphilitic serum. D'Alessandre (28), in working with «palligen», demonstrated the presence of three distinct antibodies in syphilitic serum: antilipidal, antitreponemal (thermolabile) and antitreponemal thermostable). He expressed the belief that in early primary syphilis the antitreponemal antibodies manifest themselves before the antilipidal antibodies. In secondary and tertiary syphilis both types run a parallel course. In cases of prenatal syphilis the antilipidal antibody often exists alone.

The work of D'Alessandre was confirmed by Puccinelli and Oddo (29), who described the technic of demonstrating the three antibodies.

The most convincing evidence to date of the existence of a specific antitreponemal antibody in syphilitic serum stems from the work of Nelson and Mayer (30). These workers demonstrated the presence of immobilizing antitreponemal antibodies. Employing the virulent Nichols strain of T. pallidum, kept alive on a special basal medium, they showed that these actively motile spirochetes lost their motility when incubated at 35° C. for sixteen hours in the presence of syphilitic serum. No such immobilizing effect was observed with normal and with false positive control serum. In addition, these workers demonstrated

that this immobilizing antibody was distinct and separate from the antilipidal antibody. On the adsorption of all the reagin of syphilitic serum with lipidal antigens until the filtrate gave negative flocculation and complement-fixation reactions, the immobilizing effect of the serum remained unaltered. The same specific immobilizing antibody has been demonstrated by these workers in the spinal fluids of patients with untreated syphilis of the central nervous system.

Because a truly virulent T. pallidum was employed in this work, these workers have made a distinct contribution to the immunology of syphilis by demonstrating what appear to be a truly specific antitreponemal antibody.

Serologic response in penicillin treated syphilis

Some physicians are often disappointed when serologic tests remain positive for several months or longer following penicillin therapy for syphilis. There are, however, several factors (31) which influence the length of time required to attain sero-negativity.

State of Disease. The older the disease, the longer the spirochetes are present and the longer it takes for the body cells to stop forming antibodies. As a rule patients with secondary syphilis require more time to acquire sero-negativity than patients with sero-positive primary lesions.

Immunologic Response of Individual Patients. Some patients with syphilis develop more antibodies than do others after the same type of stimulus. The former patients usually require more time to attain sero-negativity.

Serologic Titer. As a rule, patients with high serologic titers at the onset of therapy may require more time than those with relatively low titers to attain sero-negativity.

Sensitivity of the Serologic Procedure. The more sensitive the serologic test, the longer it will take to attain sero-negativity. When a serologic battery consisting of tests with varying sensitivities is employed, negative reactions may be obtained with the less sensitive tests long before the more sensitive tests become negative.

Type of Test. Certain *types* of tests may remain positive long after other tests have become negative, even though they may be of the same relative range of sensitivity.

Treatment Schedule. The amount, duration and type of therapy may also affect the length of time required to attain sero-negativity. As a rule, the higher the total dosage of penicillin and the longer the period of time during which the treatment is administered, the shorter the time to attain sero-negativity.

It must be pointed out, however, that there are many variations to the above factors, and no set rules can be made to determine or anticipate the length of time required to attain sero-negativity. It is generally agreed that the persistance of serologic reactions does not necessarily indicate the persistance of a syphilitic infection. Therefore, it should not be necessary to retreat patients if they do not revert to sero-negativity soon after completion of therapy.

Limitations of serodiagnostic procedures for syphilis

While it is true that most positive serologic reactions obtained with our current nonspecific lipoid antigens are due to syphilis and perhaps represent some type of immunologic response, it is no less true that some positive results are unrelated to syphilis and represent a general biologic phenomenon. Such *false positive* or nonspecific reactions may be caused by a variety of infectious diseases, immunizations and metabolic disturbances. It has also been shown that similar nonspecific (nonsyphilitic) reactions may occur in individuals who show no evidence of any pathologic state. Since false positive reactions may occur in the absence of syphilis, unquestionably many persons have been stigmatized and have been given treatment solely on the basis of positive reactions disclosed by routine serologic examinations, in the course of, or immediately following, a nonsyphilitic disease. Compulsory preinduction, prenatal, premarital serologic examination, and the increasing widespread use of routine blood testing in medical practice, industry, and on separation from the armed forces, have undoubtedly increased the number of individuals needlessly subjected to antisyphilitic treatment.

Since serodiagnostic tests are not truly specific for syphilis, the physician must be aware of those conditions, other than syphilis, which may produce nonspecific (nonsyphilitic) reactions. False positive reactions may be either technical or biologic. Technical false positives may occur in serum containing no antibodies and may be due to: 1. technical errors in the collection and labelling of specimens; 2. the use of unsatisfactory blood specimens (contaminated or hemolyzed); 3. errors in the performance of the serologic tests; 4. the use of faulty materials and reagents in the test or; 5. errors in recording or reporting the final results. With the improvement of serologic technics and the use of improved materials, especially purified antigens of the cardiolipin type, there has been marked reduction in the incidence of technical false positives.

Biologic false positives may be due to: 1. the presence of antibody-like substances similar to the antibodies produced in syphilitic diseases; 2. an increase or alteration of the sero-globulin fraction or; 3. an increase or alterations of some chemical substance or substances in the blood.

As a result of a series of studies at the Army Medical School, it was found that there are a number of factors involved in the incidence of false positive reactions for syphilis (32). Time does not permit a discussion of all of these factors, but it was found that almost any condition or nonsyphilitic disease may evoke a nonspecific reaction in a susceptible individual (serologic reactor). Since the majority of these false positive reactions are of the transient type and revert to sero-negativity within a short period of time, it is suggested that all individuals with positive serologic reactions for syphilis, unconfirmed by history or clinical evidence, should be followed serologically and without treatment for a period of three months, serologic tests being performed at two to four-week intervals. At he end of that time the patient should be completely reappraised to ascertain whether or not syphilis may be present. A continuing drop in serologic titer in a

relatively short period of time, without the administration of antisyphilitic treatment, is strong evidence in favour of nonspecific serologic reactions. Irreparable harm has been done by an ill-considered or hasty diagnosis. If treatment is started prematurely, the evidence which could finally lead to an accurate diagnosis is often obscured. Serologic tests may become negative with a few injections, and one is at a loss to know whether the sero-negativity represents response to therapy or merely reflects the fact that the patient never had syphilis.

Another serious limitation of our serodiagnostic procedures is the occurrence of *false negative* reactions. When the serum of a patient with clinical syphilis gives a negative reaction, that patient is said to have sero-negative syphilis, and the reaction is considered as falsely negative. Actually the serum contains so little reagin that the particular test used is unable to detect its presence. Yet, if that same serum is rechecked by a more sensitive test, it would frequently yield a positive reaction. Such discrepancies are often observed in patients with primary syphilis. After the development of the primary lesion, the serum may give negative reactions with the insensitive tests for a week or longer, while with the more sensitive tests, a positive reaction may be obtained within a few days after the appearance of the chancre. In an unpublished study (33) of experimental syphilis in rabbits, it was possible to detect the evidence of syphilis by means of a sensitive serologic test as much as five days before the clinical appearance of the chancre. This suggests, at least, that antibodies begin to appear in the blood serum soon after inoculation with the Treponema pallidum, but the routine tests are not sufficiently sensitive to detect their presence. Therefore, the incidence of sero-negative primary syphilis depends not only on the time which has elapsed since inoculation, but more so on the sensitivity of the tests employed.

The same holds true in sero-negative late syphilis. It is not uncommon to find that patients with syphilis of the aorta may have negative blood tests. In the literature there are reports that the incidence of sero-negative cardio-vascular syphilis and neurosyphilis is as high as 40 per cent. This high incidence is based on the fact that the tests used in these investigations were relatively insensitive. When the more sensitive tests are used, the incidence of negative reactions is markedly decreased. Therefore the number of cases of sero-negative late syphilis does not depend entirely on the clinical manifestations of syphilis, but rather on the sensitivity of the particular tests. Yet even with the most sensitive tests available today, one may obtain a negative reaction in a patient with clinical syphilis. The clinician, therefore, must be careful in the interpretation of serologic reports because syphilitic patients may give negative reactions.

Sero-negative syphilis may be due to a number of factors, as 1. the amount of antibody as minimal and cannot be detected by tests with ordinary sensitivity; 2. the presence of too much antibody so that false negative zone reactions occur; 3. the use of serologic tests with low levels of sensitivity; 4. the use of fresh serum containing considerable amounts of thermolabile-inhibiting substances, and 5. the presence of a thermostabile-inhibiting substance in the albumin fraction of the serum.

Conclusions

1. Modern serodiagnostic tests for syphilis, employing purified antigens, are extremely valuable to the physician in establishing or excluding a syphilitic infection.

2. With improvement in techniques and materials employed, the specificity and sensitivity of the serodiagnostic procedure has been appreciably increased.

3. There are certain limitations (false negative and false positive reactions) inherent in the currently employed tests. The physician must be aware of these limitations, for otherwise serious errors of omission and commission will be made.

4. There is a great need for the development of a procedure which would consistently differentiate between true and false positive reactions.

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Problems in the Preparation and use of Cardiolipin Antigens

By

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The history of the use of alcoholic extracts of beef-heart tissue as antigens for the serodiagnosis of syphilis is too familiar to all of you to need review. The difficulties in preparing and standardizing such antigens have always been considerable since the extracts contain a very complex mixture of lipides. It had long been evident that purification of the active ingredient of the antigenic extracts would simplify this problem, and the work of many investigators directed toward this end had established the fact that the serologic activity was associated with the phospholipide fraction, in particular with the lecithin. It was logical to assume, therefore, that by careful purification of the crude lecithin and examination of the fractions removed during purification one could expect to find in such fractions the substance responsible for the serologic activity of the extracts.

When this was attempted, however, it soon became evident that the problem of the antigen was not merely that of identifying a single active substance. Purified lecithin was inactive, but all the fractions separated from it were also inactive, provided they had been adequately freed of lecithin. Only when such fractions were recombined with purified inactive lecithin could the serologic activity characteristic of the original extract be demonstrated. Thus it was certain, even before any new compound was isolated, that not one but two substances, one of them lecithin, were necessary for the serologic activity. The second substance, a previously unknown phospholipide, was finally isolated and purified and was given the name cardiolipin (1, 2, 3).

Now the fact that two substances are involved makes it necessary to study more than one kind of problem before we can make practical use of a purified antigen. We must first secure both substances in a satisfactorily pure state, and then study how they should be combined and how the mixtures can be used as diagnostic reagents. I should like to divide today's discussion into these two topics and consider first the actual production of cardiolipin and lecithin and

then some of the problems involved in the standardization and serologic use of these substances.

In most of the antigen mixtures now in use there is a third ingredient, cholesterol, since the sensitizing effect of cholesterol that had already been observed with extract antigens has proved notably useful in the purified antigens also. However, cholesterol is crystalline and its purification is not very difficult. The two problems in producing the antigen are the purification of cardiolipin and of lecithin. We shall consider first the simpler half: the purification of cardiolipin.

Cardiolipin is a complex phosphatidic acid: that is, a phospholipide containing no nitrogenous base but having certain acid valences of the phosphoric acid groups free. It therefore forms true salts, and it evidently exists in tissue extracts in the form of salts. The method of purification outlined in Figure 1 is base don the formation of salts of different solubility in organic solvents. Although this looks like a complicated chart with numerous steps, the method is not particularly difficult or tedious in actual operation. A modification of the method, employing in part the free acid form of cardiolipin, has been successfully used by F a u r e and C o u l o n (4). I have preferred to work exclusively with salts because the free acid is unstable.

Fig. 1. Preparation of cardiolipin

I

(1) CH_3OH extract precipitated with $BaCl_2$
(2) Crude Ba salts converted to Na salts
(3) CH_3OH soluble portion of Na salts reprecipitated with $BaCl_2$
(4) Ba salts from (3) reprecipitated several times from ether with acetone
(5) *Ba precipitate from (4) is nearly pure cardiolipin.* Converted to Na salt and dissolved in absolute alcohol.

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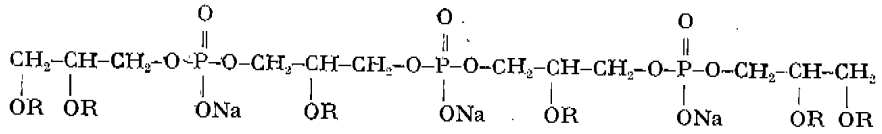
(6) Na salt from (5) precipitated with $CdCl_2$
(7) Cd salt reprecipitated from ether with acetone
(8) Purified Cd salt converted to Na salt
(9) Purified Na salt from (8) dissolved in absolute alcohol.

Most of the known lipides are not simple chemical individuals but mixtures of closely related homologues. It is evidently quite pertinent to inquire whether cardiolipin is also such a mixture and if so, whether this introduces an element of uncertainty in its use in antigens. We shall need to consider the chemical structure in order to discuss this point.

The formula tentatively suggested on the basis of a study of the hydrolysis products (5) is illustrated in figure 2. It must be emphasized that this *is* tentative and is offered only as the simplest type of structure that would fit the known facts. These facts were: that the products found on mild hydrolysis were fatty acids and a peculiar polyglycerophosphate complex, breaking down rather easily to glycerophosphoric acid and glycerol. The proportions of the isolated components were in rather close agreement with the composition of the molecule as illustrated. The actual spatial configuration and the position of the various linkages are, however, not known.

Fig. 2. Probable composition of cardiolipin



Let us use the illustrated formula as a starting point to see how many variations on this theme might also fit the facts. For example, there might be β-ester linkages instead of the α-linkages shown, or there might be a branching structure. Isomers of this sort would probably be so much alike in solubility and chemical properties that they would be all but impossible to separate. Hence, even if absolutely constant analytical data were obtained, we could not assert that cardiolipin was necessarily a single chemical species. A second type of variation might be the occurrence of different combinations of fatty acids. This would be reflected in variations in the iodine number. The actually observed variations in iodine number are not great, and it is always difficult to be sure that a low iodine number is not due to partial oxidation during preparation. The only fatty acids that have been demonstrated in samples studied by hydrolysis are linoleic and oleic. However, the possibility of this type of variation is not excluded.

Finally, we might have two or more molecular species conforming to the same general type structure but differing somewhat in molecular size, possibly having longer or shorter polyglycerophosphate chains or different numbers of fatty acid radicals. Such molecules would be very similar in all chemical properties but would probably be separable, though only with difficulty, and their composition as determined by chemical analysis would be different.

Now the experimental evidence does suggest that this last supposition is probably true: that there are in fact at least two cardiolipins of slightly different composition. The variations in results of chemical analysis, though not great, are outside the limits of experimental error and are not readily accounted for by assuming the presence of «impurities.» Our attempts to fractionate cardiolopin by means of various salts have given some evidence of separation into fractions of different carbon content. Surface film studies by Shulman and his colleagues at Cambridge (6) have indicated the presence of two components, one of which spreads less readily on aqueous solutions than the other. Faure and Coulon (4) reported that paper chromatography showed two components, and Rice and Osler (7) stated that they had succeeded in separating two components by chromatographic adsorption. As a working hypothesis, it can be assumed that cardiolipin is a mixture of two very closely related compounds.

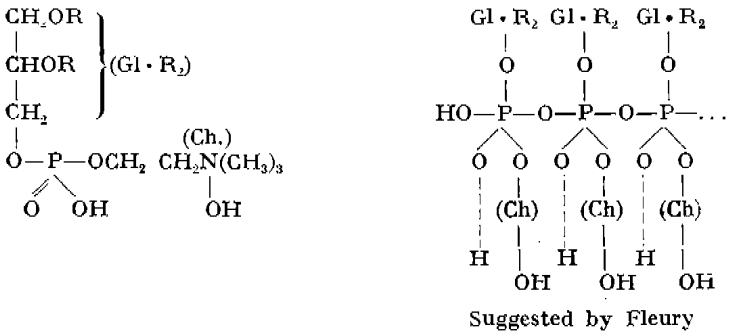
But if we now inquire what is the practical aspect of this — what bearing does it have on our attempts to make a constant antigen — it appears that we really do not need to worry about it. In our laboratory, experience in testing cardiolipin antigens has now extended over a number of years during which we have tested many samples prepared in other laboratories as well as our own, and we have observed a remarkable constancy in the serologic activity of different lots,

even though the ratios of phosphorus to carbon might vary enough to indicate significant differences in the proportions of the postulated two components. Rice and Osler (7) stated that the two components they separated by chromatography both gave satisfactory antigens, though no quantitative details were given. It seems fairly safe, therefore, to include in our working hypothesis the assumption that the two components of cardiolipin have the same activity in serologic tests for syphilis. Obviously the best way to study this would be to separate the two components in a pure state on a large enough scale so that thorough chemical and serologic studies could be made of both. This is a problem for the future. In the meanwhile the recognition that cardiolipin is a mixture does not need to introduce any uncertainties into the work of preparing standard antigens, since it is not difficult by present methods to produce a «mixed» cardiolipin of constant serologic activity. I will come back to this question of constant activity a little later in discussing standardization.

The second ingredient in the antigen mixture is lecithin. Although this substance has been known and studied for a long time, it has presented much greater difficulties in purification than the recently discovered cardiolipin. As soon as a thoroughly satisfactory method of preparing uniformly pure lecithin is developed, the practical problem of producing a standard antigen will be solved. We are now reasonably close to this goal. I am sure, however, that everyone who has become interested in cardiolipin antigens is aware that lecithin has been rather a stumbling block, and I should, therefore, like to discuss certain aspects of this problem in some detail.

The commonly accepted structure of lecithin is shown in Figure 3. This structure has recently been questioned by Fleury (8) who discovered interesting evidence that lecithin may actually be a polymer. The structure suggested by Fleury is illustrated. In any case it is recognized that naturally occurring lecithins are not chemical individuals but are mixtures of homologues containing different combinations of fatty acids. In speaking of purification of lecithin we therefore do not imply the preparation of a single compound but rather the removal from the mixture of all substances not having the composition indicated by the illustrated formulas.

Fig. 3. — Lecithin



Suggested by Fleury

Such removal of substances other than lecithin is rendered particularly difficult by two facts.

In the first place, lecithin does not form a variety of derivatives usable in purification. It is a neutral compound, not combining significantly with either acids or bases. This is presumably due to internal neutralization of the basic group of choline by the acid group of phosphoric acid. Lecithin does form one well-known derivative, the double salt or complex with $CdCl_2$, and for purification we are practically limited to this; we cannot prepare a variety of true salts as with cardiolipin. Most of the methods that have been used for purifying lecithin are based on treatment of the $CdCl_2$ complex with various organic solvents.

In the second place, separation of impurities from lecithin is rendered very difficult by the marked ability of lecithin to hold other substances in solution. Thus, such substances as »cephalin» or sphingomyelin are only sparingly soluble in absolute alcohol yet they dissolve to an appreciable extent in alcoholic solutions of lecithin. Water-soluble substances such as urea, sugar, etc., may also be held in solution in organic solvents by lecithin (9, 10). Therefore a marked difference in solubility between two substances, such as lecithin and sphingomyelin, does not mean that these two can be sharply separated by treatment with solvents. Moreover, the similarity in analytical composition of the various lipides means that chemical analysis is not a very sensitive method for detecting small quantities of one in the presence of another.

Now, since lecithin is found in practically all types of animal and plant cells, there is a wide choice of sources from which it might be made, and lecithins from different sources can be expected to differ chemically in two ways. First, they may contain different combinations of fatty acids; and second, they may be accompanied in the crude state by quite different kinds and amounts of other lipides, so the methods necessary for purification may vary greatly with the source of the lecithin. This is a point of great practical importance, and we shall return to it in a moment.

In a word, then, we have to consider two possible reasons for the occasionally observed variations in the properties of different lots of purified lecithin. On the one hand, even if we succeed in removing every trace of substance other than lecithin, we should still expect some variation in chemical composition due to the presence of different fatty acids. On the other hand, because of the difficulty in removing every trace of «impurities» we may have two lots that differ in their content of residual substances other than lecithin; in particular, lecithins from different sources may be expected to differ in the amount and nature of these residual impurities. These are two separate problems and by treating them separately, we shall reach the soundest basis for decisions on standardization of our antigens.

Let us look first at the question of variable fatty acid composition because this has been used by some workers as an argument for the necessity of restandardizing each lot of lecithin. If we confine our work to lecithin from a single source, such as beef heart, this variation will be kept to a minimum, though not elimi-

nated. If we study lecithins from different sources, however, we shall find that the iodine numbers differ considerably and therefore we know that the proportions of saturated and unsaturated acids are different. We may also compare hydrogenated or partly hydrogenated lecithins (11) or a natural or synthetic hydrolecithin (12, 13) with the ordinary mixed lecithins from various sources. The experimental evidence on this point is not very copious as yet, but as far as it goes, it supports the idea that fairly marked differences in fatty acid composition do not significantly alter the serologic properties. For example, the iodine number of beef-heart lecithin is usually between 75 and 85 while that of egg lecithin is about 55, showing that there is a higher percentage of saturated fatty acids in egg lecithin. Serologic comparison of carefully purified egg and beef-heart lecithins have recently proved that these two can be used interchangeably in the previously determined formulas for the complement-fixation antigen and also for certain slide flocculation tests; no differences were observed either in sensitivity or specificity.

Now these facts simplify the problem of standardization very greatly; for if we can work on the assumption that the inevitable variation in fatty acid content is not an important factor, we are left with only one problem, logically simple if technically rather difficult. This is, to employ means of purification which will remove all traces of substances other than lecithin, or, more precisely, will reduce these trace impurities to such low levels that they produce no detectable differences either in chemical analysis or serologic activity. To a considerable degree this has already been done. Both in our laboratory and others, there have been prepared and used many lots of purified lecithin which did check each other within the limits of precision of serologic testing. However, there have also been an annoyingly large number of unsatisfactory preparations, and the methods are rather tedious. There is a need, therefore, for ways of accomplishing the required purification more easily and with more consistent success. The methods now in use for purification of beef-heart lecithin are outlined in Figure 4.

Fig. 4. Beef-heart lecithin

(1) Cd salt three times precipitated from $CHCl_3$ into C_2H_5OH
(2) Cd removed, free lecithin dissolved in ether. Ether solution chilled and precipitate discarded
(3) Lecithin in C_2H_5OH + $Ba(OH)_2$ and CO_2. Discard precipitate
(4) Solution from (3) reprecipitated with $CdCl_2$
(5) Cd precipitate from (4) two times precipitated from $CHCl_3$ into C_2H_5OH
(6) Cd precipitate from (5) treated once with petroleum ether and 80% alcohol. Concentration of alcoholic layer → precipitate of Cd lecithin
(7) Cd removed and cold-ether treatment repeated
(8) Purified free lecithin dissolved in absolute alcohol.

One suggestion that keeps coming up in discussions of this problem is that we ought to use a synthetic lecithin in antigens rather than a natural product. This would not necessarily simplify matters; the use of a synthetic product does not eliminate the problem of purification but merely introduces a different set of such problems, concerned with the removal of by-products and reagents em-

ployed in the synthesis. At present, moreover, there is no easy and practical synthesis available by which synthetic lecithin could be made in quantity. However, this suggestion introduces a related one which deserves further study.

The lecithins so far synthesized have contained only the saturated fatty acids. Now hydrolecithin can be easily prepared by direct hydrogenation of the ordinary mixed lecithins and such a product would have the advantage of stability to oxidation and lesser chemical complexity. Some preliminary studies of hydrolecithins in antigen mixtures have been reported by Faure (11) and by Rosenberg (12), but much more work would be needed before we could judge whether this method of attacking the lecithin problem is a useful one.

Another approach is simply to continue the study of purification methods in the hope that we can make them still better. A great deal of effort has already been expended on this, but it is always possible that more can be done. Progress is very likely to come through the application of new procedures such as chromatography. Rice and Osler (7) have reported separating lecithin by chromatographic adsorption into three fractions, only one of which could be used in antigens. These authors have not yet described their results in sufficient detail to permit evaluation of them, but this line of study evidently should be pursued further.

Now I should like to offer a third suggestion, very simple and unexciting, which I think is the easiest immediate solution for the practical problem of preparing a uniform standard lecithin. Much of the difficulty in making such standards has been due to the unfortunate historical accident that we used beef-heart lecithin for the first studies on cardiolipin antigens. This was done because all the emphasis of previous serologic studies was on the use of beef-heart extracts, and because beef-heart lecithin was available from the same extracts that yielded cardiolipin. We can see now, however, that this was an unwise choice. Beef-heart lecithin has proved very difficult to purify adequately because of the complexity of the lipide mixture extracted with it, and this would be equally true of lecithin from other adult animal tissues. In egg yolk, however, we have a much simpler and more easily handled source material. Comparison of the two charts on preparation methods (Figure 5) graphically shows the difference in ease of purification.

Fig. 5. Egg lecithin

(1) Cd salt four times precipitated from $CHCl_3$ into C_2H_5OH
(2) Precipitate from (1) treated once with petroleum ether and 80% alcohol
(3) Cd removed, free lecithin dissolved in ether. Ether solution chilled and precipitate discarded
(4) Purified free lecithin dissolved in absolute alcohol.

Since the impurities characteristic of beef-heart lecithin are either absent or present in much smaller amounts in egg yolk, the purification can not only be accomplished with a smaller number of steps but also with a much more satisfactory degree of uniformity in successive lots. Our recent studies have shown that egg lecithin can be directly substituted for beef-heart lecithin in at least two of the antigen mixtures in current use without changing the formula of the antigen or any of the test conditions. My own opinion, therefore, is that we should discon-

tinue the use of beef-heart lecithin altogether and prepare our cardiolipin antigens with purified lecithin from fresh egg yolks.

This discussion of the problem of producing cardiolipin antigens may be summed up as follows. While it is certainly true that more remains to be learned by fractionation and purification studies on both cardiolipin and lecithin, it can be confidently asserted that our present knowledge and experience is sufficient for the production of both these substances in such a state of purity that their serologic properties are constant within the limits of accuracy of serologic technics. We may therefore turn next to a consideration of the use of these substances in antigens.

The labours of many serologists have now made it clear that any type of serologic test for which beef-heart extracts had been used can be carried out with suitably adjusted cardiolipin antigens. Emphasis is on the qualification «suitably adjusted»: since these antigens are three-component mixtures, careful studies of the effects of varying the proportions of the three were needed. As an example of the systematic type of study that is necessary, let us consider the work on the complement-fixation antigen.

The relationships of cardiolipin, lecithin, and cholesterol in the complement-fixation test were very carefully studied by Doctor and Mrs. Maltaner (14). Cardiolipin and lecithin were first tested separately. Neither substance alone had any significant activity; nor was any activity shown by mixtures of cardiolipin and cholesterol or lecithin and cholesterol, Mixtures of cardiolipin and lecithin, however, were active antigens. Cardiolipin alone was anticomplementary; but the optimally active mixtures of cardiolipin and lecithin were not.

The method of study was, therefore, first to determine the optimum proportions of cardiolipin and lecithin and then to study the effect of adding varying amounts of cholesterol. A fairly definite optimum ratio lecithin: cardiolipin = 5: 1 was found. This *ratio* was still found optimal in cholesterolized mixtures; the effect of adding cholesterol was to make it possible to detect a given serum reaction with a much smaller amount of cardiolipin and lecithin. As a result of this work, the antigen formula illustrated in figure 6 was adopted and this antigen has been officially used in our regular diagnostic service since January 1945.

These studies were all carried out by means of the quantitative complement-fixation test developed by Wadsworth, Maltaner, and Maltaner (15). Under the conditions of this test, a linear relationship exists between

Fig. 6. Complement-fixation antigen

	Percentage composition			Ratios	
	Cardiolipin	Lecithin	Cholesterol	*Lecithin* Cardiolipin	*Cholesterol* Lecithin
Optimal formula	.0175	.0875	.3	5: 1	3.4: 1
Hypersensitive formula	.035	.05	.3	1.43: 1	6: 1

the reagents employed; both antigen and complement may be accurately titrated and the amounts used in tests adjusted to any degree of serum reactivity, so that the maximum reactivity of the serum is brought out. The reaction is measured in terms of the amount of complement required to give 50 per cent hemolysis which is much more accurate than estimations based on complete hemolysis. Although this method in all its refinements is not used as widely as it deserves, the conclusions reached in this study have been found directly applicable to the simpler and better known variants of the «Wassermann» test. Thus Kent, Boyd, and Sanders (16) showed conclusively that the same antigen formula as that used by the Maltaners was also optimal in the Kolmer complement-fixation test. In one modification or another the complement-fixation test is very widely used, and in all modifications the basic conditions for combination of antigen and reagin are the same: the evidence is that the antigen formula developed by the very thorough studies of the Maltaners is the best to use in any of the varieties of complement-fixation tests.

Now this formula was actually not the one which showed the highest apparent sensitivity, and this point illustrates some of the pitfalls of work with the three-component antigen. When the ratio lecithin/cardiolipin was decreased below 5, it was necessary to increase the cholesterol/lecithin ratio in order to bring out maximum reactivity; that is, addition of cholesterol could be made to compensate for lack of lecithin. Shifting the proportions in this direction gradually produced mixtures that appeared *more* active than those containing the optimal lecithin/cardiolipin ratio of 5: 1; maximum sensitivity was found at about lecithin/cardiolipin = 1.5 and cholesterol/lecithin = 6. Such a mixture has actually received considerable trial and has been recommended by certain authors (17, 18). However, the weight of experience is definitely against its use. The Maltaners considered it probably unsuitable on logical grounds because the amount of lecithin in this mixture was known to be insufficient to overcome the non-specific anticomplementary effect of cardiolipin, and low dilutions of the cholesterolized mixture were somewhat anticomplementary. Prior to these findings, the mixture had been given experimental trial in our routine diagnostic service, and it gave occasional reactions that were considered non-specific. The same tendency for this mixture to give non-specific reactions was noted by Kent, Boyd, and Sanders (16).

This experience illustrates a general principle which can hardly be overemphasized in discussion of cardiolipin antigens. Mere purification of the antigen, no matter how perfectly it might be done, will never be enough, because both the sensitivity and specificity depend on the proper balance of the three components used. This is very noticeable in the various flocculation tests where the situation is much more confused than in complement fixation.

The number of flocculation tests has now multiplied so greatly that to do justice to this topic will require separate discussion at another point on our program. Here it is enough to point out that several different types of floccul-

ation reactions with cardiolipin have been developed: tests to be read on a microscopic slide, as in the Mazzini or Kline type of technic; or to be read in a tube as in the Kahn test; and the end is not yet. It is apparently possible to adjust the sensitivity of these tests at practically any level by varying the antigen formula and the conditions of the test. The large number of competing and only slightly dissimilar tests is becoming embarrassing, and it is highly desirable that a concerted attempt be made to evaluate these tests so that practices in different laboratories can be made more uniform.

From these remarks it is evident that the actual results obtained by the use of cardiolipin antigens will depend greatly on the type of test and the antigen formula employed, so that it is meaningless to make any general statement about the sensitivity and specificity of cardiolipin antigens as such. Such statements can be made only with reference to particular tests. With this qualification it can be stated that where well-adjusted tests have been used, it has proved possible to attain highly satisfactory levels of sensitivity and specificity. In certain types of cases the purification of the antigen has evidently increased its specificity. Thus the early work in our laboratory indicated that the cardiolipin antigen would prove somewhat more specific in patients with malaria and in vaccinated persons, cases in which false positive results are often encountered. Later experience has confirmed this. Similar conclusions were reported by Rein and Bossak (19), Rein and Kent (20), and Kline (21), who found cardiolipin antigens much more specific than crude antigens in cases of malaria. But there seems to be no logical basis for supposing that all non-specific reactions are due to characteristics of the antigen, and it should therefore not be expected that the use of cardiolipin antigens will solve all these problems.

The great advantages that can be confidently claimed are the uniformity and reproducibility of the purified antigens and the far greater ease of standardization. It would now be possible to set up an international standardization for cardiolipin and lecithin which would ensure that identical antigen materials would be available to serologists in all countries. Our present knowledge of these substances, in spite of the gaps in it that I have mentioned, is adequate for this purpose. Much collaboration and organization would, of course, be necessary to work out the best way of doing this: here I would like merely to say something about the principles on which such standardization can be based.

The practice which has been found satisfactory in our laboratory is as follows. Each new lot of cardiolipin or lecithin is first analyzed chemically; N, P and iodine number are the determinations usually made, and in the case of lecithin we usually determine amino-nitrogen also. On account of the difficulty of determining an accurate dry weight on lipide samples, the concentration of the solution is usually calculated from the phosphorus. If the purification methods have been properly carried out, there is little likelihood that a sample will be rejected on the basis of chemical analysis. As examples of possible rejection at this point, it could

be mentioned that an iodine number lower than 110 would cause rejection of a cardiolipin sample, or N greater than 0.1 per cent in cardiolipin would require repurification.

But we cannot rely on chemical analysis alone, partly because the available analyses are not sensitive enough and partly because we do not know exactly what we should look for: we do not know just what trace impurities are responsible for the occasional unsatisfactory samples. We therefore submit all samples to serologic testing as a final check on their acceptability. If I spend some time on this apparently simple point, it is because there is a deep-seated disagreement about how this should be done and this disagreement would have to be resolved before any international standardization could be set up.

Our practice is as follows: Each new lot of cardiolipin or lecithin is used to compound an antigen in which the other ingredients have been previously tested and found satisfactory — a new cardiolipin with previously tested lecithin, for example. In compounding this antigen, the formula previously found satisfactory is followed *exactly*. We do *not* attempt to repeat the original standardization experiment by making up solutions containing the ingredients in varying proportions. A new sample is preferably tested in more than one type of antigen: that is, in complement fixation and in one of the flocculation tests. The new solution is then compared with previously tested antigen by making a series of parallel tests with the two antigens on both reacting and nonreacting sera. Suppose we are testing a new lecithin sample; we thus compare two solutions of identical percentage composition, differing only in that they are made with different lots of lecithin. If the new lecithin is satisfactory, the readings of the tests with the two antigens will agree as closely as duplicate tests done under the same conditions with the same antigen. This, of course, does not mean that the readings will always be identical; it is essential in evaluating antigens in this way to know what degree of precision in duplicating readings can actually be expected from the serologic test in question. This may require more careful statistical studies than are usually thought necessary in serologic testing.

Now, suppose the two solutions show discrepancies greater than could reasonably be expected in duplicate readings. What shall we do?

According to our practice, the new sample which failed to check would not be accepted for use in antigens. The decision whether to discard it altogether or to try reclaiming it by further purification would depend on several factors — the history of the preparation, the chemical data, the quantity of the total lot, and so on. If repurified, it would have to be retested as a new sample.

In our laboratory, we thought this procedure seemed not only logical but obvious; but certain serologists approach the question in a totally different way. Kahn (22), and Harris (23) for example, have preferred to redetermine the optimum amount of lecithin *de novo* for each new lot. The constancy of activity of cardiolipin is such that the question hardly arises in this case, but with lecithin it has been a real practical problem. The argument seems to be that it is better to

expend the labour necessary to restandardize each lot separately than to waste the occasional batches of lecithin that fail to check. This seems to me very shortsighted economy. In the first place, if this principle is generally accepted, it will postpone indefinitely the day when antigens composed of genuinely standard materials can be made available. As long as these lots that fail to check are considered acceptable, it will be impossible to secure the necessary cooperation of serologists on the *real* problem which is to prepare and distribute antigen materials of uniform activity. In the second place, the excuse for this restandardization of unsatisfactory lots is rapidly vanishing because, as I have pointed out above, there is a very good prospect that preparation of uniform lecithins can be made much easier and the waste involved in discarding occasional poor preparations can be made negligible. It is negligible in any case, I think, compared to the disadvantages of a failure to put this matter on the soundest possible basis by insisting on the use of antigens of constant composition.

I should like to summarize this problem of standardization somewhat as follows: New lots of cardiolipin and lecithin must be checked by serologic as well as chemical methods because the available chemical methods are not sufficiently sensitive to detect all traces of impurities that might affect the serologic properties. But the serologic tests should be regarded as an *additional check on the uniformity of the sample*, a hypersensitive test for chemical purity if you will, *not* as a basis for restandardizing the antigen formula. Only those samples which do in fact pass this uniformity test should be used. I would go further, in fact, and offer as my personal opinion that no cardiolipin test should be accepted for study as an internationally acceptable standard procedure until it has been standardized on the basis of a constant antigen formula.

We have seen from this discussion that in two respects the problem of a purified antigen for the serodiagnosis of syphilis has been reasonably well solved. We know how to produce and standardize cardiolipin and lecithin in a sufficient state of purity so that their serologic properties will be uniform. We know that by appropriate combination of these substances with cholesterol, we can prepare antigens that have definite advantages over the crude extracts formerly used, and we have accumulated considerable experience in the use of such antigens. But we now have on our hands a third problem for which no solution is in sight as yet. This is the increasing multiplicity of cardiolipin tests. The situation at present seems to be that everyone who has had a sample of cardiolipin to work with has developed his own favorite test. This is obviously a problem on which a mere chemist has nothing to offer; it will have to be settled somehow by agreement among serologists — if such a phenomenon is possible.

Jesting aside, I should like to recapitulate in closing how the very nature of this antigen has placed a new and heavy responsibility on the serologist. We do not have a single substance which requires only adequate purification to provide us with a good antigen. We have instead a complex and delicately balanced colloidal system, very sensitive not only to variations in the proportions of the

components but also to such technical factors as methods of dilution and heating of antigen suspensions. By variations in such details sensitivity and specificity may be greatly altered. This is not altogether new, of course, since the crude extract antigens were also prepared at different sensitivity levels by various adjustments, but such adjustments can evidently be made with much greater precision and in greater variety by the use of the pure components. To determine what sensitivity levels are safe and desirable and which of the many suggested tests can best supply the information needed by the physician is a problem still needing much thought and collaboration between serologist and clinician. Such an international meeting of minds as this which the World Health Organization has made possible will surely make it easier to solve such problems as this.

Summary

Cardiolipin antigens are mixtures of cardiolipin, lecithin, and cholesterol. The problem of producing purified antigen is to secure adequate purification of the two phospholipide components, cardiolipin and lecithin. *Cardiolipin* is probably a mixture of two closely related compounds not yet separated for study. The evidence suggests, however, that these two have essentially identical properties in reactions with syphilitic sera; and the experience of several years in preparing cardiolipin by present methods has yielded many lots of constant serologic activity. The chemical and physical properties of *lecithin* render its purification a more difficult problem, although preparations of satisfactory constancy have actually been made and used on a large scale. It is probable that the differences occasionally observed in the serologic properties of lecithin are not due to the variations in fatty acid composition but to residual traces of impurities. Hence a purification method that would remove all substances other than lecithin could be expected to yield a satisfactory product even if the chemical composition of the mixed lecithin varied somewhat. This might be accomplished (1) by using a *saturated* lecithin; (2) by continued modification of purification methods; or (3) by employing the most easily purified natural lecithin, that from egg yolks, as the standard in all cardiolipin antigens. It is suggested that the latter course is the most practical at present and should be adopted.

In order to utilize cardiolipin antigen for a particular serologic technic, the proportions of the three components must be carefully adjusted. Methods for studying these proportions are illustrated by discussion of the standardization of the complement-fixation antigen. Cardiolipin is not active alone or mixed with cholesterol, but mixtures of cardiolipin and lecithin are active; addition of cholesterol makes it possible to detect a given serum reaction with smaller amounts of cardiolipin and lecithin. Both sensitivity and specificity depend not only on purity but on proper balance of the three components; certain ratios yield hypersensitive antigens which tend to give non-specific reactions. The same principles

apply to flocculation tests; each serologic technic requires special study for adjustment of the antigen. When well-adjusted antigens have been used, highly satisfactory levels of sensitivity and specificity have been obtained in various types of serologic technic; in particular, the incidence of false positive reactions due to malaria is less with cardiolipin than with crude antigens.

New lots of cardiolipin and lecithin must be tested by serologic as well as chemical methods because chemical analysis may not detect all factors that might affect the serologic reaction. It is recommended that this be done on the basis of a constant antigen formula and not by restandardizing the antigen formula to allow for lack of constancy in the phospholipides.

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The Wassermann Reaction carried out with Cardiolipin and Crude Antigens

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1. *Introduction*

In a paper read before the Eighth Scandinavian Pathological Congress in Uppsala on 8 July 1947, a preliminary report was given of experiences with Wassermann's reaction (WaR.) carried out with cardiolipin-lecithin-cholesterol antigen (V o g e l s a n g, 1948). The material consisted of 5,630 sera examined. Among them were 700 sera from persons known to be syphilitic. The following three parallel tests, used as a matter of routine at Gade's Institute, were compared with each other: WaR. carried out with a cholesterolinized extract of ox heart, the Kahn standard test, and the Meinicke clarification test. The investigations confirmed that with the aid of chemically pure substances it is possible to produce an antigen which is satisfactorily sensitive and so reliably specific that it can be employed in the complement fixation test for syphilis. WaR. carried out with the cardiolipin antigen gave fewer false positive results than the three other tests.

There is already considerable literature on the subject of the employment of the cardiolipin antigen not only in complement fixation tests, but also in macroflocculation and microflocculation tests. The various observers have agreed that the cardiolipin antigens are very valuable in the serological diagnosis of syphilis, being more specific than the older lipoidal antigens. K l i n e (1949) maintained that Pangborn's discovery is the most brilliant contribution to the serological diagnosis of syphilis since the introduction of the WaR.

Among the complement fixation tests it is particularly Kolmer's, and here in Scandinavia M ø r c h's method which have been employed in connexion with the new antigenic component. The technique employed for the WaR. at Gade's Institute is in the main the same as that described by E a g l e (1937). The differences between this method and the two others mentioned include not only the preparation and the properties of the antigen suspension, but concern also the doses, the fixation time and the reading of results.

In 1947, an opportunity presented itself, with the aid of a small material

consisting of some 1000 sera, to compare the Bergen test with the Copenhagen test (Mørch's method). It was shown that the sensitivity of the Bergen test was greater than that of the Copenhagen test. While the latter had a sensitivity of 2.9% and the Kahn standard test a sensitivity of 4.1%, the Bergen test showed a sensitivity of 5%. The material was not large enough to prove that the Bergen test gave more non-specific reactions than the Copenhagen test. Meanwhile, among a total of 16 non-specific sera there were 13 giving positive results with the Bergen test and 12 with the Kahn standard test, while there were only six giving positive results with the Copenhagen test (K r a g & V o g e l s a n g, 1948).

This comparison seems to confirm that the Bergen test is exceedingly sensitive. But it confirms the experience that the most sensitive reactions are, as a rule, liable to give more non-specific results than the less sensitive reactions. It is this Bergen test which was also used when the cardiolipin antigen was employed. This test should be well suited to an evaluation of the specificity of this antigen in relation to the crude antigen. It is for this reason that I feel justified in presenting as a contribution to this international syphilis symposium the results of our further investigations with the cardiolipin antigen.

2. *Technique*

The antigen employed for WaR. is prepared at Gade's Institute from ox heart muscle which is first given preliminary treatment with acetone, and after it has been dried and pulverized has been treated with ether for the removal of undesirable substances. The antigen itself is an alcoholic ox heart extract to which 1% of cholesterol is added. During the test it is used in a dilution of 1: 120—1: 140. A detailed account of the preparation of the antigen and of the carrying out of the test has been given in an earlier publication (V o g e l s a n g, 1940).

To 0.20 ml inactivated serum or dilutions thereof are added 0.20 ml 10% complement without previous titration and 0.20 ml antigen. After fixation overnight at a temperature of + 2—4° C, followed by incubation for half-an-hour at a temperature of 37°C in a water-bath, add 0.40 ml of a mixture of equal parts of 3% sheeps' blood corpuscles and amboceptor, 2½—3 times stronger than the titre obtained on each occasion. Read off when the controls in the glasses to which no antigen has been added are dissolved.

The cardiolipin antigen used in the comparative investigations has been kindly provided us by Dr. M a r y C. P a n g b o r n. It has had the following composition:

Cardiolipin	0.0175%
Lecithin	0.0875%
Cholesterol	0.3%

It will thus be seen that the antigen contains five times more lecithin than cardiolipin, and about 3.4 times more cholesterol than lecithin.

In the complement fixation test, the crude antigen has been replaced by cardiolipin antigen, but in other respects the procedure has been exactly the same. An addition of 0.20 ml cardiolipin antigen has been made in a dilution of 1: 130. An antigen prepared by ourselves has been used for the Kahn standard test, but for the Meinicke clarification test the Swedish Astra antigen has been employed.

3. *Material*

The comparative investigations were carried out at Gade's Institute on current material, the sera received being examined by the following four tests:

1. WaR. carried out with cardiolipin antigen
2. WaR. carried out with crude antigen
3. The Kahn standard test
4. The Meinicke clarification test

The cases in which there was not enough serum for carrying out all the four tests are not included in this study. The sera which were not too obviously damaged were included in the routine examinations, but when the sera showed marked anti-complementary action, they were excluded from this study.

Altogether this study deals with 30,000 sera which were classified in two main groups according to anamnestic or clinical evidence pointing to the presence or absence of syphilis. Included among the sera classed as syphilitic in this study are those from cases in which at the time of the serological examination there was no information indicative of syphilis, but in which subsequent clinical examinations showed the presence of this disease.

4. *Results*

Table I shows the WaR. results obtained with cardiolipin antigen and with crude antigen.

The 4,651 syphilitic sera were classified in different sub-groups. Either they were examined with a view to the diagnosis of syphilis before specific treatment had been instituted, or they were examined in the course of such treatment or after its completion for the purpose of supervision during the following four years. The sera from patients who had not received specific treatment during the

Table I

Sera from	Nr. of sera	Identical Results				Conflicting Results		
		Nr. of sera	%	+	+	Nr. of sera	Card. antigen	Crude antigen
Untreated Syphilis	1579	1510	95.6	1347	163	69	6	63
Treated Syphilis..	2226	2068	92.9	908	1160	158	42	116
Latent Syphilis ..	846	776	91.7	467	309	70	13	57
Syphilis + ...	4651	4354	93.6	2722	1632	297	61	236
Syphilis + ...	25349	25114	99.1	205	24909	235	39	196

last four years before the examination, or had not presented clinical evidence of syphilis during the same time, come under the heading of latent syphilis.

Among the patients with untreated syphilis, the WaR. results were concordant with the two antigens in more than 95% of the cases, whereas there was a greater number of conflicting results among the patients who had been treated and those whose syphilis was latent. Among the cases of untreated syphilis with conflicting results, it was notably the cardiolipin antigen which failed. Even though among the cases of latent and treated syphilis there were more positive results with crude antigen than with cardiolipin antigen, the difference in favour of the former was not so marked here.

On the whole, among the 4,651 sera from persons known to be syphilitic there were 4,354 or 93.6% giving concordant results. Of the remaining 297 sera, only about one-fifth gave a positive reaction with cardiolipin antigen while about four-fifths did so with crude antigen.

There was no evidence, clinical or anamnestic, of syphilis connected with 25,349 sera. Of these, 235, or 0.9% gave conflicting results. Here again we find the same state of affairs as with the syphilitic sera: the crude antigen gave the greatest number of positive results. But this finding was still more marked in connexion with the sera unaccompanied by information indicative of syphilis, for here more than four-fifths of the sera showing conflicting results gave a positive reaction only to the crude antigen.

Further, to form an opinion of the usefulness of the cardiolipin antigen, Table II was drafted so as to compare the results of the two different WaR. antigens and of the two flocculation tests carried out on the current material of Gade's Institute.

Table II

Sera from	Nr. of sera	Identical Results				Conflicting Results						
		Nr. of sera	%	+	+	Nr. of sera	Nr. of positive tests 3		2		1	
Untreated Syphilis ..	1579	1338	84.7	1215	123	241	123	(93)	90	(45)	28	
Treated Syphilis	2226	1574	70.7	654	920	652	231	(199)	209	(88)	212	(9)
Latent Syphilis	846	641	75.8	384	257	205	93	(72)	67	(22)	45	(2)
Syphilis + ...	4651	3553	76.4	2253	1300	1098	477	(364)	366	(155)	285	(11)
Syphilis + ...	25349	24557	96.8	47	24510	792	101	(81)	274	(105)	417	(11)

Number of positive results with cardiolipin antigen is given in brackets.

Here too, it will be seen that concordance is best among the untreated cases of syphilis, whereas among the treated cases there is a discrepancy of about 30%, and among the latent cases a discrepancy of about 25%. On the whole, the results were conflicting in 23.6% of the 4,651 syphilitic sera examined. When only one of the tests failed, this was so in less than one-fourth of such cases with the cardiolipin antigen. Less than half the number of the sera giving a positive result to

WaR. with cardiolipin antigen positive in 2,783 sera, i.e. in 59.8%
» » crude » » » 2,958 » 63.6%
The Kahn standard test » » » 2,532 » 54.4%
The Meinicke clarification test » » 3,097 » 66.6%

Among the 25,349 sera unaccompanied by any evidence of syphilis were 1,103 with no data concerning them. Here there may therefore have been some sera from patients with a history of syphilis and from others with definite clinical manifestations of this disease. In Table IV, in which the material without evidence of syphilis

Table IV

Sera from	Nr. of sera	Identical Results				Conflicting Results				
		Nr. of sera	%	+	+	Nr. of sera	Positive Tests Card.	Crude	Kahn	Meinicke
Various Diseases	14480	13916	96.1	26	13890	564	126	238	160	384
Control in Pregnancy	7010	6893	98.3	6	6887	117	43	68	20	58
Health Certificate	2756	2700	98.—	2	2698	56	12	14	10	44
No notes	1103	1048	95.—	13	1035	55	16	34	7	34
Syphilis + ...	25349	24557	96.8	47	24510	792	197	354	19	520

is classified in several sub-groups, it will be seen that among the above-mentioned sera there were 13 which gave concordant positive reactions to the four tests.

There were 14,480 sera accompanied by data concerning various diseases while there was nothing known about any infection with syphilis. Among these sera were 26 giving positive reactions to all the tests, while there were 564, or 3.9% giving conflicting results. Among the same sera were 1,230 from patients with diseases of the respiratory tract, mainly bronchitis, pneumonia and pulmonary tuberculosis. Among these again were 26 giving a positive reaction to three tests, 38 giving a positive reaction to two tests, and 52 to one test. Thirty-six of these sera gave a positive reaction to the cardiolipin antigen, whereas twice this number, 72, gave a positive reaction to the crude antigen.

In connexion with recent legislation in Norway, 7,010 sera of pregnant women were sent to the Institute for examination, and 2,756 sera were from healthy persons willing to serve as blood donors or requiring health certificates, etc. Among these sera were 8 giving a positive reaction to all four tests, 16 sera to three tests, 64 sera to two tests, and 93 to one test. Sixty-three of the sera gave a positive reaction to the cardiolipin antigen. Most of them were presumably false positive reactions, whereas in other cases there were doubts in the minds of the clinicians as to the existence of syphilis also after the serological control examination. As syphilis was not diagnosed in these cases, the corresponding sera were classed among the non-syphilitic sera.

two tests did so to the cardiolipin antigen, whereas most of the sera giving a positive reaction to only one test were negative to the cardiolipin antigen.

With regard to the sera from persons with no evidence of syphilis and giving a positive result with three of the four tests, the result with the cardiolipin antigen was positive in four-fifths of the sera. Of the 417 sera giving a positive result with only one test, only 11 did so with the cardiolipin antigen.

Table III shows how many positive results were obtained with the different tests in the various groups of syphilis. The cases of untreated syphilis are classified in the various stages of the disease according to available information.

Table III

Sera from	Nr. of sera	Identical Results			Conflicting Results				
		Nr. of sera	+	+	Nr. of sera	Positive Tests			
						Card.	Crude	Kahn	Meinicke
Congenital syphilis	94	52	52		42	24	38	15	13
Primary »	199	127	59	68	72	31	53	26	54
Secondary »	222	221	221		1		1	1	1
Tertiary »	860	760	724	36	100	64	83	26	83
Cerebral »	204	178	159	19	26	19	20	4	21
Untreated »	1579	1338	1215	123	241	138	195	72	172
Treated »	2226	1574	654	920	652	296	370	158	499
Latent »	846	641	384	257	205	96	140	49	173
Syphilis + ...	4651	3553	2253	1300	1098	530	705	279	844

The Meinicke test gave the greatest number of positive reactions, and the Kahn test the fewest of the four. The two WaR.s hold an intermediate position in this respect, but with the crude antigen there were altogether 705 positive reactions among the cases with conflicting results as compared with 530 with the cardiolipin antigen. If we study the disease stage by stage, we find that it is only in cases of cerebral syphilis that the positive results with the cardiolipin antigen are as numerous as with the crude antigen. But the number of conflicting results under this heading is small.

In cases of secondary syphilis, the positive results were concordant in all but one case in which no importance can be attached to the failure of the cardiolipin antigen. The difference with regard to primary syphilis is noteworthy. Here WaR. was positive in 25 cases with the crude antigen and negative with the cardiolipin antigen, whereas the reverse was the case with only three sera. It may also be noted that among the sera giving positive results with both WaR.s there were several which gave a stronger reaction with the crude antigen than with the cardiolipin antigen.

Altogether, among the 4,651 sera from persons with evidence of syphilis the results were as follows:

the proper proportions of the three chemically pure components, cardiolipin, lecithin and cholesterol, to ethyl alcohol. The sensitivity and the specificity of the antigen depend not only on the quantitative relationship of these three components, but also on how the saline solution is added to the alcoholic solution in the preparation of the colloidal suspension.

At the present time various laboratories carry out the complement fixation test according to widely different methods. This means that the results may be most divergent, not only with regard to sensitivity, but also with regard to specificity. It would therefore be a great advance in the serology of syphilis if a standard method could be agreed on and if the various laboratories were obliged to adopt it. The increase of specificity achieved with the cardiolipin antigen seems at the present time to justify the use of this antigen in the standard method till more specific reagents are evolved.

It is therefore important to supply with sufficiently chemically pure substances the various laboratories in which different methods are employed in a search for the most convenient composition and preparation of the cardiolipin antigen with a view to achieving the optimal level of sensitivity. When this objective has been reached, the various methods should be compared in respect of their specificity and sensitivity. For this reason the World Health Organisation is to be congratulated on having taken the initiative in calling a serological conference a year or two hence. We have every reason to hope that such a conference will provide a useful contribution to the solution of the problem: the use of recognized standard procedures.

6. *Conclusion*

It is with regard to its specificity that the cardiolipin antigen first and foremost is of great value and really constitutes a decisive advance in the serology of syphilis. With the aid of the three chemically pure component parts of this antigen it seems possible to arrive at a standard method which the various laboratories must be obliged to adopt.

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Among the 25,349 sera from persons without evidence of syphilis there were altogether the following:

WaR. with cardiolipin antigen positive in	244,	i.e.	1%
» » crude » » »	401	»	1.6%
The Kahn test » »	244	»	1%
The Meinicke clarification test » »	567	»	2.2%

Among the pregnant and healthy persons were:

WaR. with cardiolipin antigen positive in	63,	i.e.	0.6%
» » crude » » »	90	»	0.9%
The Kahn standard test » »	38	»	0.4%
The Meinicke clarification test » »	100	»	1.1%

5. *Discussion*

These comparative investigations, concerned with a material of 30,000 sera, show that WaR. carried out with cardiolipin antigen revealed a sensitivity inferior to that of the Meinicke clarification test and that of WaR. carried out with a crude antigen. But on the other hand, its sensitivity was considerably greater than that of the Kahn standard test. This state of affairs was demonstrable not only with regard to certain definite forms of syphilis, but also with regard to treated, and latent syphilis. In particular it should be emphasized that, in early syphilis, WaR., carried out with the crude antigen in a series of cases, not only reacted earlier, but also more strongly than when this test was carried out with the cardiolipin antigen. The same observation has recently been made in another Scandinavian laboratory (L u n d b ä c k, 1949).

When, however, the specificity of the cardiolipin antigen is considered, the evidence in favour of it is by contrast quite strong. Even though several reactions which must be regarded as falsely positive were observed in response to this antigen also, their number was considerably smaller than was the case with either the Meinicke test or WaR. carried out with the crude antigen. It is therefore first and foremost by virtue of its specificity that the cardiolipin antigen is to be recommended and is to be regarded as a definite advance in the serology of syphilis.

It should be pointed out that in these investigations a comparison is made with a definite WaR. technique between a definite crude antigen cholesterolinized ad maximum and a cardiolipin antigen of definite composition. The crude antigen was found to be very sensitive, but it seems to be so at the expense of its specificity to a certain extent. Attempts are therefore being made to improve the specificity of this antigen by changing its cholesterol content. Conversely, it is conceivable that the cardiolipin antigen may possibly be rendered more sensitive without impairing its specificity. The complete antigen is prepared by adding

Round Table Discussion: Serology

I Remarks of Discussion Leaders

Dr. K. O. Renkonen (Helsinki) **Serology and Syphilis**

There are many good reactions used mainly for the diagnosis of syphilis. When comparing them, constancy of the reaction, its sensitivity and specificity must be taken into consideration.

Most of the commonly used reactions are fairly constant. For instance, the Kahn test gives practically the same results in New York and Helsinki, if both laboratories perform the tests with antigens which they themselves consider to be good. A comparatively simple method with a simple antigen is easier to keep constant than is a complicated one.

According to the general rule, increased sensitivity is frequently accompanied by decreased specificity. That is the fact we have to keep in mind when selecting our test for the mass examination of, for instance, pregnant women, especially if the incidence of true syphilis is low among this group. Increased sensitivity without a significant decrease in the specificity has been the purpose of almost all improvements in the tests. We know, however, from many investigators that the highest occurrence of discrepant results is to be found among the lues medicata group. Vogelsang, for instances, gives the following figures:

	Number of samples:	Positive results in per cent obtained with:			
		B.W.	*Kahn*	*Meinicke*	*Müller*
Lues non medicata	1,513	92.8	93.4	94.4	93.0
Lues latens	888	29.6	33.7	38.3	31.8
Lues medicata	2,150	48.7	54.1	60.3	54.4

The difference between the results obtained with the most sensitive and those obtained with the least sensitive tests was in the group lues non medicata 2.6%, but in the group lues medicata 11.6%.

Apparently a possible increase in the sensitivity of «ideal» future tests can be expected to be due to an increasing number of positive reactions from the group of lues medicata. But do we need that, do we have much use for a test to which all syphilitics react, however well they have been treated? Physicians ascribe

frequently all the signs and symptoms of an illness to syphilis and treat the patient accordingly even if only the most sensitive test is positive. That is certainly wrong. We have use for a test to diagnose cases of active syphilitic infection, but the commonly used tests, however, do this. We have use for a test indicating a possible reactivation of temporarily latent infection. This is done either by titration of the degree of reaction or by using a parallel and distinctly less sensitive test as we have done for 20 years in Finland.

Even now it is extremely difficult to evaluate and interpret the significance of a weak Kahn or VDRL reaction if the patient has received «adequate» treatment. Perhaps a weak Kahn reaction after bismuth and salvarsan treatment has a different significance from a similar reaction after penicillin treatment. With still more sensitive tests a proper evaluation would be almost impossible. The clinical analysis of the serological findings is most essential. We still have many unsolved problems with our present tests.

Dr. Alice Reyn (Copenhagen): **The Specificity and Sensitivity of Cardiolipin-lecithin Antigens with Special Reference to the Problem of Biologic False Positive Reactions**

I think it is agreed that cardiolipin-lecithin antigens are generally more specific and more sensitive than most of the older antigens that have been used for the serodiagnosis of syphilis. However, both specificity and sensitivity depend on the material examined. Non-specific reactions, even with the same technique, are found to a highly variable extent in different parts of the world, partly according to the frequency of diseases which can cause non-specific reactions, and as reported recently, partly because of unknown factors (Guthe, 1949). The sensitivity of the antigens depends in addition to the technique on the *origin* of the syphilitic sera.

Lundbäck (1949) found that the *Moerch-WR was significantly more sensitive than the cardiolipin-WR in cases of primary lues*, and this result has recently been confirmed in our own laboratory (Henning Schmidt, 1950), and also in Professor Vogelsang's laboratory in Bergen, Norway.

If the main purpose of a given serological examination is to diagnose fresh cases as early as possible, then the Moerch-WR serves this purpose better than the cardiolipin-WR, but the greater sensitivity is gained at the expense of an increased number of non-specific reactions. If the incidence of fresh syphilis is high and routine serological examinations not very commonly used, a sensitive test like this at least as a screening procedure is of great value; but when the fresh cases are few and the routine use of serological examination in hospitals and maternal clinics is great, the non-specific reactions will cause much trouble to both doctors and patients.

According to the Act of Pregnancy, which took effect on 1 October 1945, all pregnant women in Denmark are entitled to free examination by their physician, including serological examinations for syphilis. Among the first 30,000 pregnant women examined, there were 49 syphilitics and in addition 64 with presumably

biologic false reactions (K r a g and R ø j e l, 1947). As about 80,000 specimens of this nature from pregnant women are examined yearly, one may expect about 150—200 false positive reactions among such people alone.

Furthermore, it was found by W i i n g a a r d (1948) that the incidence of false positive sero-reactions in specimens examined in the State Serum Institute was about 0.24%, i.e. 1,000 of the 400,000 yearly examinations. Most of these reactions were weak and were found in patients suffering from diseases with a known tendency to cause non-specific reactions, but about one fifth of them were from pregnant women. These reactions may cause diagnostic difficulties and the responsibility of the physician is great.

On the other hand, the incidence of notified fresh cases is rapidly decreasing, and this again means that the non-specific reactions will play a relatively greater and greater role, and therefore the procedures by which we are able to distinguish between true and false reactions grow more and more important. I d s ø e and V o g e l s a n g (1950) recently have discussed this problem, pointing out the difficulties in determining whether doubtful sero-reactions in pregnancy should lead to treatment or not.

Speaking about the need for a specific and sensitive reaction, I shall here point out that the *Meinicke antigen*, although only partially purified, has proved in our hands to be nearly as sensitive, and in some instances more specific, as the cardiolipin-lecithin antigen used in the «VDRL» slide test.

Since the purification of cardiolipin and lecithin was made possible by Dr. P a n g b o r n's excellent work, one has more hope than before that some standardization of the serological reagents in syphilis might be possible and many serologists already have turned their attention to this matter. The chemical problems of cardiolipin and lecithin are yet far from solved; I am here thinking of the various attempts to replace cardiolipin and lecithin made from beef heart by similar substances made from other sources.

Lipoids from cabbages, beets, carrots, soya beans, peas and wheat have for instance been used to replace the cardiolipin and dipalmityl-lecithin (R o s e n b e r g) and egg-lecithin to replace the lecithin from beef hearts. It is very remarkable that S t e v e n s o n (1950) found that Kahn antigen made with soya bean flour gave hypersensitive results when stored for four weeks.

In this connexion I will also mention the work done by Mlle F a u r e (1948 and 1949) who hydrogenized the unsaturated fatty acids and facilitated the production of cardiolipin by omitting the many laborious distillations.

The properties of cardiolipin and cholesterol are fairly constant, but there seems to be most variation in the lecithin (P a n g b o r n, K a h n and D e r m o t t) from different batches. Furthermore, it seems that the ratio between cardiolipin and lecithin in a successful production is not constant. Our own experiences with only 4 successful productions have shown that the cardiolipin-lecithin ratio in the output was about 1—7 in the first three, but only 1—20 in the last.

The main difference between the last production and the others was that the

hearts in the last portion originated from younger animals than usual. This problem is not so important now when we have heard from Dr. P a n g b o r n about the very easy production of egg lecithin. To come back to the problem of standardization I think that we must be clear to what degree standardization is possible. The antigens here mentioned might in the future be synthesised or nearly so, but then we still have the sera, and they are very individual, indeed, as they originate from animals and human beings. Serum is not a chemically well-defined or constant substance. On the contrary, it is a relatively labile mixture of water, salts, proteins, lipoids and many other substances.

It would then be necessary to have available standard sera which were serologically as constant as possible. If stored deeply frozen most sera keep for many months, but better results might perhaps be obtained if the antibodies were isolated and dried in vacuo (C a n n e f a x, 1949), (N. B. H e i d e l b e r g e r and D i l a p i, 1949) — or perhaps preserved with merthiolate. The work done by N e l s o n and collaborators (1948—1949) and later confirmed by M a g n u s s o n and T h o m p s o n (1949) on the spirochaetal immobilization test has shown that it *may* not be long until we are able to cultivate the *Treponema pallidum,* and that the reagents which are thought to combine with the cardiolipin-lecithin antigen in either complement-fixation tests or flocculation tests are not identical with the immobilizing antibodies.

Even if we were able to cultivate spirochaetes and thus prepare our antigens from syphilitic organisms, we should still have no guarantee that false positive reactions would be eliminated. At present, the N e l s o n test is the most specific test, but unfortunately it cannot be used on a large scale, especially in smaller laboratories.

It will therefore be necessary to continue to use various extracts, but during the past ten years, we fortunately have seen the advent of the cardiolipin-lecithin-antigens and the discovery by N e u r a t h and V o l k i n of the significance of serum-lecithin as an important factor in disclosing biologic false positive sero-reactions. N e u r a t h and V o l k i n attacked the problem systematically by fractionating sera and one of their most interesting findings was that weakly positive sera from fresh cases of syphilis were of the biologic false type. N e u r a t h ascribes this either to the presence of syphilitic antibodies of altered serologic specificity or to the presence of antibodies of the genuinely biologic false positive type.

The Neurath test is believed to depend on the inhibiting or competing effect of serum-lecithin in relation to, for instance, a cardiolipin-lecithin antigen. In mixtures of euglobulin fractions of syphilitic and false positive sera inhibition is exclusively directed to the latter.

Some cross-reactions found by several investigators [K n o t t et al. (1943); D u l a n e y and P a c k e r (1947)] in patients suffering from lymphogranuloma venereum and fresh syphilis may to some extent be explained by the formation of less differentiated antibodies. Furthermore, we have the finding that the

cardiolipin-lecithin antigen used in the complement-fixation reaction is relatively less sensitive in sera from fresh cases of syphilis than from older ones — suggesting a resemblance between the non-specific antibodies and the «fresh made» specific antibodies.

Another fact worthy of mention is that the reaction with «lygranum control» (Squibb) antigen is generally only found in sera from fresh cases of syphilis.

I may here mention that I have found (not yet published) a high incidence of positive sero-reactions (especially complement-fixation) with both syphilitic antigens and with Lygranum-antigen in primary atypical pneumonia, the cardiolipin-lecithin antigen here forming an exception.

In this connexion there are at least two points of special interest: 1) the findings by Brown (1948) that a decreasing lecithin-cardiolipin ratio enhanced the prozone phenomenon and (2) the discovery by Ahrens and Kunkel (1949) that lecithin in serum acts as a stabilizer, so that when the ratio between the phosphor lipoids and the total lipoids is ≥ 0.29, the lipoids will form a suspension of very small drops, and the serum will appear as a clear translucent liquid, but when the ratio is below 0.29 the serum will appear more or less turbid. The somewhat obscure findings by Kahn of reactions which he calls the «universal» serological type may also be explained by the aid of these lipoid-chemical examinations.

Many investigators have dealt with problems touching the facts mentioned. Malmgren (1946) found that false positive sera were more liable to react with cholesterinated WR-antigen than specific sera, and that absorption with Kahn-antigen did not remove the antibodies from the false positive sera. Penttinen (1946) found that an increased cholesterol percentage gave more false positive among non-syphilitic pregnant women. Hecht (1947) found by extracting placental, decidual and foetal tissues, beef-hearts or bile, a water-soluble antigenic substance which reacted positively with presumably false positive sera and negatively with syphilitic sera; furthermore, Widelock et al. (1950) isolated by prolonged extraction an acetone-soluble antigen from beef-heart powder, which reacted strongly with false positive sera, but not at all or only slightly with specific sera; this was most striking in a series of sera from a pregnant woman. Widelock et al. were inspired by Mackie and Anderson's studies in 1937, who found that both normal and syphilitic sera reacted with an acetone-soluble part of beef-heart antigen, and that the reaction often was of a bi-zonal character indicating that more than one substance was active.

Sievers (1947) observed that at least some of the biologic false positive complement-fixation-reactions in sera from patients with liver diseases, malaria and primary atypical pneumonia are due to increased anti-complementary power. This effect was in some cases only revealed by making a serum-control of double strength or by making a complement-titration in the presence of serum. I may mention here that I have observed something similar with sera from patients suffering from *mononucleosis* (not published).

In connection with this, it is interesting that Marner (1948) found the thymol-reaction positive in more than 50% of 34 patients with mononucleosis, the thymol-reaction being regularly positive in acute and chronic hepatitis. Other investigators (Cohen and Thompson, 1947), consider, on the basis of electrophoretic examinations, that a positive thymol-reaction might be due to abnormalities associated with the globulins. It is also important to recollect the findings of Davis and his collaborators (1944) which were supported by electrophoretic and serological studies. They found a fraction of gamma globulin in both syphilitic and normal sera, which was highly anti-complementary, and this anti-complementary effect could be counteracted by heating or by the addition of small amounts of beta globulin or albumin. The recent finding by Rein and Kostant (1950) of a very high percentage of anti-complementary sera in patients suffering from lupus erythematosus is interesting, as this disease is known to cause biologic false reactions.

At the risk of going too far in my attempt to collate the various experiences collected by different investigators, I shall mention that Ensbruner and Wendlberger (1933) found non-specific complement-fixation reactions and some anti-complementary tendency in sera from patients suffering from different allergic conditions such as salvarsan-dermatitis and mercury-dermatitis. They demonstrated a correlation between a fall in the number of the white blood cells and the degree of complement-fixation reaction by stimulating so called «hämoklastische Krise» in the hypersensitive patients. This finding brings up the much debated theory of Abraham White in which he claims that antibodies are formed in the lymph-nodes and that they are released from the lymphocytes when the latter are destroyed. I shall later briefly refer to this and to the term »anamnestic reaction».

Malthe-Jacobsen (1949) tried by means of different serological and biological methods, including complement-fixation, to demonstrate antibodies in rabbits, guinea-pigs and human-beings treated with sulfa-drugs, and succeeded by causing anaphylactic reactions in guinea-pigs injected intravenously with sulfa-drugs. As an additional result he found some doubtful positive complement-fixation reactions and a strikingly high percentage of anti-complementary sera in rabbits «immunized» with pure sulfa-drugs.

Dougherty, Chase and White (1945) have thrown a new light on the old term «anamnestic reaction» by reporting the great response to a single injection of adrenal cortical extract or pituitary adrenotrophic hormone. Rabbits were immunized by repeated injections of red sheep cells for nine weeks; after a rest of three months the rabbit sera were reacting negatively, when tested for hemolytic power. The rabbits now received 5 ml of an oily solution of adrenal cortical steroids and were bled after 3, 9 and 25 hours; after 9 hours the authors observed an increase in titre to about the same level as the titre obtained at the end of the initial immunization period The authors' explanation is the release of antibodies from the lymphocytes. I dare to suggest, partly in order to stimu-

late discussion, that at least some of the biologic false reactions may be due to processes resembling this.

I have just mentioned that Ensbrunner and Wendlberger (1933) found a correlation between the non-specific complement-fixation reactions in allergic patients injected with salvarsan and a decrease in the number of *leucocytes* without any differentiation between the different sorts of white cells. Rottmann and Teichmann (1950) have recently tried to explain the many positive sero-reactions found in Hamburg (Führer) 1949, during the last world war on the basis of an increasing destruction of lymphocytes due to starvation. It is in favour of this theory that a great number of different conditions, especially *infectious diseases*, are reported as a cause of biologic false reactions; in many of them we find an increased destruction of white blood cells, especially in mononucleosis and presumable lymphogranuloma venereum too.

The high percentage of biologic false positive reactions found in primary atypical pneumonia may also be due to an increased destruction of white blood cells.

This theory does not explain all the known causes of false positives; in malaria and leprosy it seems more natural to explain the reactions on the basis of a destruction of erythrocytes thus liberating lipoids and also on lipoids originating from the leprosy-bacilli.

Time does not allow me to discuss in detail the interesting problems concerning the effect of di-valent cations on antigens and antibodies (Pierce and Breazeale 1942, Maltaner and d'Almeida 1949, Rein and Kostant 1949) and the very remarkable observation that only the so-called «univalent» syphilitic antibodies may pass through the intact placenta. (Rein Weiner and Speiser — unpublished, Nørgaard 1950, unpublished)

Summary

The following points are suggested as a basis for further discussion:

1. The significance in the difference of sensitivity between cardiolipin-lecithin-antigens in fresh and old cases of syphilis, and in this connexion, the greater sensitivity of the Moerch-WR in fresh cases.
2. The advantage of the greater specificity of cardiolipinantigens in syphilitic tests, especially of pregnant women.
3. The standardization of cardiolipin-lecithinantigens.
4. The use of phosphor-lipoids from vegetable sources as antigens in syphilitic sero-reactions; and the probable variation of the phospholipoid-antigens according to the source of the vegetables, and the different methods of production. The effect of race, sex age and nutrition of animals from which the hearts for the antigenpreparation are obtained.

5. The findings of Neurath and collaborators that serum-lecithin is an important factor in disclosing biologic false positive reactions, thus apparently forming a link between the significance of the cardiolipin-lecithin ratio for specificity and the sensitivity of the various reactions, and at the same time, emphasizing the importance of the stability of serum-lipoids. The similarity between false positive reactions and fresh specific reactions should be remembered.
6. A more or less hidden anti-complementary quality of sera responsible for at least some false positives.
7. The so-called «anamnestic reaction» in relation to some of the false positive reactions, and
8. The effect of di-valent cations on antigens and antibodies, and
9. The different behaviour of the so-called uni- and di-valent antibodies by passages through the intact maternal placenta.

It is very apparent that serological work is becoming more and more chemical or physico-chemical. This is only an evolutionary step, which implies that various investigators must be *à jour* in several different fields, which requirement is, I feel, very difficult to fulfil.

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Dr. Eero Uroma (Helsinki). **Sitolipin Antigens in the Serodiagnosis of Syphilis**

Many different antigens have been used and are used in the serodiagnosis of syphilis, and the same is the case with the various serological reactions which have been used and developed over the past decades. The reason for this complexity in respect to antigens and reactions is that we have thus far been unable to develop a serological reaction which would yield absolutely certain results, which circumstance is due chiefly to the fact that it has not been possible to develop an antigen specific to syphilis. All antigens and reactions presently used in different parts of the world defend their place well and we cannot state that any one is definitely better than the other. With present antigens and reactions we obtain in the Scandinavian countries (where no spirochetal disease other than syphilis occurs) relatively satisfactory results, whereas in tropical countries sero-diagnosis often meets with great difficulties.

The most frequently used antigens throughout the world are alcohol extracts obtained from different organs, of which the best have proved to be cow heart extracts, the preparation of which on a large scale is not particularly difficult, albeit a rather laborious and time-consuming procedure. In addition to the mentioned antigens of animal origin, attempts have been made to isolate from plants substances with antigenic qualities as regards syphilis. Experiments with plant substances yielded no mentionable results until last year, when it was found that satisfactory alcohol extracts could be obtained from soya bean. In the beginning these antigens were unstable and destroyed and became useless in a few days. In later research this drawback has with all probability been eliminated, and the extracts have thus attained a practical value.

Despite the fact that antigens presently in use yield relatively specific reactions, they are chemically impure; i.e. the amount of inactive substances is rather large as compared with the amount of active substances. It may be that the impurities mentioned cause the so-called non-specific reaction and that by development of an antigen containing only one active substance we might be able to obtain more specific reactions than earlier, which in turn may bring us to the solution of the rather difficult problem of exact standardization of the syphilis reaction by either chemical or physical means, which at present is impossible.

In order to solve these problems, Pangborn embarked on a lengthy and difficult task: to purify the heart alcohol extract and to isolate the pure active substance. The result of her work was the so-called cardiolipin, a glycerophosphate containing approximately 4% phosphorus. However, cardiolipin has not completely met the hopes attached to it, because despite its purity it has not proved to be entirely specific as regards syphilis. Nor is standardization of cardiolipin antigen possible by either chemical or physical means. Also in this case serological methods must be resorted to chiefly because of the lecithin used in addition to the cardiolipin.

At the end of last year at the State Serum Institute we isolated from wheat embryos a substance which greatly resembled cardiolipin chemically and with app-

roximately similar biological properties. We have named this substance sitolipin. Sitolipin is a practically colourless substance, containing 4% phosphorus as does cardiolipin, and a very small quantity of nitrogen, which latter is in all probability due to some minor impurity. Although sitolipin differs somewhat chemically from cardiolipin, it forms salts with certain metallic compounds in the same manner as the latter, for example, with cadmium chloride, being then insoluble in alcohol but soluble in chloroform. Sitolipin is a stable substance: it endures temperatures of 60°C in alcohol solution for long periods without becoming oxidised, but on the other hand, it is oxidised relatively easily when dry, then changing its colour to orange and losing practically all of its antigenic qualities. As an alcohol solution, sitolipin can be kept at room temperature for months without any mentionable changes and it is thus easy to store.

The preparation of sitolipin, although much the same as the preparation of cardiolipin, is relatively simple on a large scale, particularly because the raw material can be obtained directly from a wheat mill in the shape of flour and thus requires no preliminary treatment, being as such suitable for extraction. As a rule, the wheat embryo flour should preferably be as fresh as possible and in no case older than three days. The basic extraction of sitolipin requires relatively less solvent than is the case with heart muscle, as the material is considerably drier and solvent is therefore not required for drying the raw material. The wheat embryo flour, which is a kind of mill waste, is very cheap as compared with the price of cow hearts, and we do not take it into consideration at all when preparing sitolipin because it forms only a small proportion of the total preparation cost of sitolipin.

The amount of sitolipin in one kilogram of wheat embryo flour is relatively great when it is considered that a quantity of antigen sufficient for 250,000—300,000 tube tests can be obtained from it. The amount of sitolipin required for the antigen is very small, about 0.03 per cent. Similar to cardiolipin, sitolipin is not ready for use without addition of cholesterol and lecithin. When using sitolipin in the VDRL test we reiceive the same type of reaction as with cardiolipin although the silken swirl which appears is slightly coarser and more granular. Sitolipin antigen can be used for both VDRL tube and slide tests and it is also useful in cerebrospinal fluid examinations.

The sensitivity of sitolipin antigen can be fixed at desired level by altering the proportions between sitolipin, cholesterol and lecithin. However, in preparation of sitolipin antigen we have kept the quantities of cholesterol and sitolipin constant and have varied only the amount of lecithin. We have prepared the lecithin from egg yolk in accordance with Pangborn's method and have in this manner obtained a usable product without great cost. In considering the expenses incurred in the preparation of sitolipin and lecithin we have found that our antigen, even when prepared on a laboratory scale, is one hundred times cheaper than the cardiolipin antigen sold on the market.

For the time being, we have used sitolipin antigen on a large scale only as a

VDRL tube test and have compared the results in part of the cases with the Kahn reaction and the VDRL tube tests obtained with cardiolipin and, in part of the cases, with the Wassermann and Kahn reactions.

The following results were obtained in the former part of cases: 78 positive cases with all reactions; sitolipin and cardiolipin positive, but Kahn negative, in 13 cases; sitolipin and Kahn positive, but cardiolipin negative, in one case; cardiolipin and Kahn positive, but sitolipin negative, in one case; solely sitolipin positive, in 7 cases; solely cardiolipin positive, in 3 cases; and solely Kahn positive, in 4 cases.

The results in the latter part of cases are given in Table I.

Table I

WaR	*Chol. WaR*	*Kahn*	*Sitol.*	*No. of cases.*
+	+	+	+	56
−	+	+	+	120
−	−	+	+	87
−	−	−	+	20
−	−	+	−	5
−	−	−	−	2,553
				2,841

All positive cases in Table I either suffered or had suffered from syphilis, except the solely Kahn positive cases, among which there were two in whom syphilis could not be demonstrated and in whom nothing suggesting syphilis was obtained by anamnesis.

The raw material of sitolipin, wheat embryo *flour*, is much more homogenous than heart muscle, it keeps better and is easier to handle, all of which qualities must be counted to the credit of preparation of sitolipin, and also *facilitate* its preparation in large quantities. To some extent the preparation of sitolipin is simpler and the amounts of solvents used are smaller. In our opinion, sitolipin fully corresponds to cardiolipin as an antigen by VDRL tube test, however, being no better, and it yields practically the same results. Sitolipin must be considered as having the same drawbacks as cardiolipin: for use as an antigen it requires supplement of lecithin, which means that the antigen cannot be standardized by other than serological means.

As an antigen, cardiolipin has proved capable of being used in more sensitized form than the other antigens in general use in syphilis diagnostics, without the non-specificity of its positive reactions being greater than that of other sensitive reactions presently in use.

We have observed in using sitolipin as a syphilis antigen, that it generally yields positive results in all cases where the WaR and Kahn reactions are positive and, in addition, in a number of cases where the WaR and Kahn reactions have

been negative. To what extent are the latter positive results specific or non-specific? This question we have endeavoured to answer by studying a series of samples obtained from maternity health centres and group examinations conducted in different parts of the country, chiefly among industrial workers.

We have performed the VDRL tube test using sitolipin and have compared the results with those obtained using the Kahn reaction. It deserves to be mentioned that the sensitivity of the Kahn reaction used by us has been compared with the Kahn reaction used at the Venereal Disease Research Laboratory at the Marine Hospital in New York, and that they proved to be almost equal in this respect.

In this manner we have studied a total of 2,338 samples, of which 2,270 were negative and 68 positive. The positive cases are distributed as follows: Kahn and sitolipin positive, 45 cases; Kahn negative but sitolipin positive, 21 cases; Kahn positive but sitolipin negative, 2 cases.

Table II

Kahn	*Sitolipin*	*Number of Reactions*
–	–	2,270
+	+	45
–	+	21
+	–	2
	Total	2,338

The cases differing from one another serologically can be divided on the basis of information obtained from the patients, as follows: in 4 cases no answer was received, in 9 cases the patient suffered or had suffered from syphilis, in 4 cases syphilis was probable on the basis of history and physical examination, and 4 cases were such in which neither history nor physical examination indicated syphilis. Nothing indicating syphilis could be found in the two cases in which the Kahn reaction alone was positive.

If we consider all cases specific in which both the Kahn and the sitolipin reactions were positive or in which anamnesis and status indicated syphilis, there are at the most 4 non-specific sitolipin reactions in the series, or 1.8 per thousand, whereas the number of possible cases of syphilis obtained by the sitolipin reaction alone exceeded by 11 those obtained by the Kahn reaction, or by 8 per thousand.

The extent to which the mentioned solely sitolipin positive results are of any significance in the treatment of syphilis is difficult to state at this moment, but it is possible that in the mentioned cases relapses might occur and that therefore observation of the patient is advisable, although syphilis treatment may not be necessary.

Dr. M. Tuomioja (Helsinki): **Sitolipin Complement-Fixation Tests**

We have used sitolipin as an antigen in complement-fixation tests performed with sera and have compared the results with those obtained in complement-fixation tests performed with the common Wassermann antigen and cholesterolized Wassermann antigen, as well as with the Kahn test. The sitolipin complement-fixation (SCF) is performed in the same manner as the Wassermann tests, except that a dilution of sitolipin similar to the sitolipin dilution used in tube flocculation tests is used as the antigen.

The number of samples which were taken at random from routine investigation cases was 1,318. In 1,126 cases all the tests were negative; 192 cases were Kahn positive. In 119 cases the sitolipin complement-fixation test was positive; in 89 cases the cholesterolized Wassermann test was positive and in 62 cases the old Wassermann test was positive.

Table 1

WR	Chol.WR	SCF	Kahn	
+	+	+	+	62
−	+	+	+	25
−	+	−	+	2
−	−	+	+	32
−	−	−	+	71
−	−	−	−	1,126
62	89	119	192	1,318

The above demonstrates that the sensitivity of the sitolipin complement-fixation test is somewhat greater than that of the cholesterolized Wassermann performed with the same technique.

II Discussion

Q: *If field teams could use only one serologic test for syphilis, which one would be the best for them to use?*

Dr. Vogelsang: It would be a mistake to use only one serologic test, since there are few situations indeed where a confirmatory procedure is not feasible. Perhaps if only one test could be used it should be the Meinicke clarification test, because it is sensitive and reasonably specific.

Dr. Uroma: Would you recommend this test for areas where malaria is prevalent?

Dr. Rein: It seems to me that many factors would have to be taken into account. A great deal depends on what the test is expected to accomplish. The

ideal test would certainly be sensitive, specific and easy to perform. I think the increased specificity of cardiolipin would make it especially waluable in areas where malaria is a problem.

Dr. Renkonen: So many factors have to be considered that there can hardly be any one single answer to this question.

Q: *Are cardiolipin antigens better in flocculation tests or in complement-fixation tests? Sitolipin antigens?*

Dr. Rein: Cardiolipin can be adapted to either flocculation procedures or to complement-fixation tests, provided only that the serologist works out the optimal cardiolipin/lecithin/cholesterol ratio for the particular procedure. Within the past few years most author-serologists have been able to adapt cardiolipin to the test they have devised.

Dr. Uroma: We have used sitolipin mostly in flocculation tests, although complement-fixation procedures are readily adaptable to its use and the results have been equally satisfactory.

Q: *Is pregnancy the cause of biologic false positive tests for syphilis?*

Dr. Vogelsang: I don't know whether pregnancy causes false positive tests, but in pregnancy as in other conditions false positive reactions occur. When they do, they are particularly troublesome, because the physician frequently cannot defer treatment long enough to ascertain whether the positive result represents syphilis or some other condition.

Dr. Penttinen: Our studies have shown no evidence that pregnancy *per se* causes false positive reactions. Dr. Vogelsang's material seems to me to confirm this, for the percentages of conflicting results (which may at times suggest false positives) were lower in the pregnant women than among those tested prior to marriage.

Dr. Rein: Dr. Kline and I studied a large series of hospitalized patients in Cleveland. Among 20,000 or more sera from pregnant women the occurrence of positive reactions was no higher than in a comparable group of non-pregnant women.

Sera from pregnant women have been used in national serologic surveys in the United States and there has been no indication that false positive reactions occur. I should think that when a false positive occurs in a pregnant woman that it is due to a complication of the pregnancy rather than to the pregnancy itself.

Dr. Reyn: It has been our experience that when a positive reaction is first observed during pregnancy this reaction will remain positive long after the pregnancy.

Dr. K r a g: We have observed one interesting case in which there seemed no other cause for the positive reaction. This was a woman who during each of two pregnancies had a single strongly positive test that spontaneously became negative after the child was born. Both children are known to be non-syphilitic.

Q: *Are cardiolipin antigens more specific than other antigens?*

Dr. R e y n: There are many studies that suggest that cardiolipin antigens are more specific. There may, perhaps, be one exception, and that is the Meinicke antigen. We are studying this now.

Q: *In cases in which cardiolipin tests are positive and other tests negative, does this not most often represent syphilis that has been treated?*

Dr R e i n: Dr. R e y n mentioned earlier that in the earliest stages of syphilis, the Moerch test becomes positive before cardiolipin tests. This, it seems to me, confirms other studies — by N e u r a t h, K a h n and N e l s o n — which show that the first antibody to be developed is a non-specific one, that does not inhibit euglobulin, that does not immobilize spirochetes. Later true antibody develops. This may be additional evidence that cardiolipin is more specific. The reason why cardiolipin is more sensitive in treated cases of syphilis is because it is more specific and will detect minute traces of specific antibody longer than other tests. Thus, by virtue of being more specific and more sensitive, cardiolipin tests become positive somewhat later than ordinary antigens and remain positive longer following treatment.

Dr. R e n k o n e n: How essential is it to have a test that will detect a treated case?

Dr. R e i n: It is not too important, of course. But there are cases of active syphilis with positive reactions to cardiolipin and negative reactions to other antigens. It depends upon what we expect of a serologic test. If its purpose is to detect all serologic reactors, the test must be very sensitive.

Dr. R e n k o n e n: Of course persistent reactors and persistent infection are two different things. I think that by keeping our tests too sensitive we encourage physicians to treat patients who do not have syphilis or to tread syphilitics who are not in head of treatment.

Dr. R e i n: This may happen occasionally. Nevertheless, a positive test does not necessarily mean syphilis; it means simply that the serum is from a positive reactor. Whether the patient should or should not receive treatment should be left to the judgement of the clinician rather than to the serologist. It would be better to educate physicians to the proper interpretation of serologic tests than to lower the sensitivity to meet their present understanding of the tests.

Dr. R e n k o n e n: One wonders, however, about the importance of detecting weakly positive reactors.

Dr. R e i n: I think it is highly important. Dr. R o s a h n has made a careful autopsy study of patients with histories of syphilis. Approximately one half of these persons had positive serologic tests at the time of their death whereas the others were seronegative. Yet there was no more evidence of pathologic changes in the seropositive group than in the seronegative group.

A second point — patients who remain seropositive (after treatment for early syphilis) are in more danger than those whose tests become and remain negative. This was shown recently in a report from Dr. S h a m b e r g from Philadelphia.

There are three kinds of cure in syphilis: clinical, serologic and biologic. It is the last of these that is important. In early syphilis, clinical cure can be accomplished readily with penicillin, but this by no means guarantees biologic cure. Serologic cure may, provided we use sensitive tests and these tests not only become but remain negative.

Dr. R e y n: There is of course the problem of the patients whose serum has remained negative for years with older techniques and who appears to «become» seropositive because a more sensitive test is introduced. These patients must be carefully examined, and the question of further therapy decided on clinical rather than serological grounds.

Q: *Why does not the thermolabile inhibitor interfere with the Meinicke test, in which the serum is not inactivated by heat?*

Dr. R e i n: The inhibitor (fraction C prime 1) can be removed chemically as well as by heat. In the Meinicke test it is the high salt content that removes it.

Dr. R e y n: In our laboratory we have found the Meinicke test to be more sensitive with heat inactivated serum, so perhaps the inhibiting substance does interfere with the test to some degree at least.

Q: *Has sitolipin been used in testing sera from patients with atypical pneumonia, leprosy, infectious mononucleosis and other conditions known to cause false positive reactions?*

Dr. U r o m a: We are not prepared to report on this matter as yet. We require more tests to be sure.

Q: *If parallel quantitative tests are performed with cardiolipin and sitolipin antigens, which gives the higher titer?*

Dr. U r o m a: We have made parallel studies of this kind. The titer will be about the same. Comparisons with the Kahn test were presented earlier.

Q: *What is the value of so-called «screen tests»?*

Dr. K r a g: We have already touched on this subject in the discussions of reactions that should be used by field teams. In considering screen tests, we must first understand clearly what the purpose of the procedure is to be. If it is proposed to find as rapidly as possible as many infectious cases as possible and if a certain amount of unnecessary therapy is of secondary importance, a very sensitive screen test may be used. On the other hand, it may be desirable to have as specific a test as possible. The choice may depend upon the conditions under which the work is being done. Another consideration in deciding for or against screen tests would be the facilities that are available to check positive screen reactors and the ease with which this can be done.

I might mention the experience of a WHO team in Northern India. Here a double screening procedure (with VDRL slide and Meinicke tests) has been used in over 10,000 cases. The results of these were in agreement in a high proportion of the patients tested. In most areas there were a slightly higher number of positive Meinicke tests than VDRL, but the difference was a small one. In one area, where a certain number of leprosy cases were found, the VDRL test was more frequently positive than the Meinicke.

Dr. R e i n: This again raises the issue of the sensitive test. We are seeing an interesting phenomenon in America that bears on the question. Some patients will not be convinced that their serologic test is negative until they have been accepted as a donor by the Red Cross blood bank (where very sensitive screening tests are used). Hence it is important that sensitive tests be used in institutions where the physicians are competent to interpret them properly.

Another reason for the sensitive test is in the case of prostitutes, who frequently can be detained only long enough to have one blood test. Still another situation is in prospective blood donors. I have seen two cases of transfusion syphilis developing in recipients of transfusions from donors whose chancre did not appear until after the donation of blood. I believe the answer lies in the use of cardiolipin antigen that has been adjusted to a high degree of sensitivity.

Q: *What is the present status of verification tests?*

Dr. P e n t t i n e n: None of the so-called verification tests is entirely satisfactory. I believe the euglobulin inhibition procedure of Neurath is the best. We have tried the verification tests proposed by Kahn and can report that these have not been helpful.

Dr. R e i n: We too have had no success with the Kahn «verification» tests. I agree with Dr. P e n t t i n e n that the Neurath technique is the best available. In our laboratory this has given 95 per cent correct results. At the present time

the treponema immobilizing test of Nelson is being watched with great interest. This test, of course, is not one for the serologist, but rather for the bacteriologist to perform. It is none too practicable for most laboratories.

Dr. K r a g: We have tried to calculate whether it might be feasible to use the Nelson test at the State Serum Institute in Copenhagen. If we assume 1,500 samples per day and that 10 per cent of these are positive, this gives 150 positive sera per day. Most of these are treatment controls, but there are perhaps 10 sera per day in which the diagnosis depends largely on the outcome of the serologic tests. These should be rechecked by repeating the conventional tests, but if still positive, the Nelson test might be helpful. If the test were done twice a week it might be feasible in large central laboratories.

Q: *Can cardiolipin be adapted to a test in which serum inactivation is not required?*

Dr. V o g e l s a n g: Yes, this is theoretically possible. Sera for complement-fixation tests must always be inactivated, but flocculation tests may be performed on non-inactivated specimens and here cardiolipin can be used.

Q: *How frequently are darkfield-positive chancres associated with negative serologic tests?*

Dr. R e i n: The association is not at all infrequent. There is even an interesting group of patients who have developed a biologic false positive reaction during the incubation period of syphilis, which tends toward seronegativity only to revert to strong seropositivity as the syphilitic infection develops.

It is also possible for a person whose blood test remains positive following treatment (for early syphilis) to be reinfected (or superinfected, if one prefers).

Q: *Does the serum of non-syphilitic persons ever contain reagin?*

Dr. R e y n: There are a few such persons, but they are not responsible for many of the false positive reactions that occur.

Dr. R e i n: I believe that many persons have a very minute quantity of reagin in their blood. The more of this natural reagin a person has, the more readily will he develop a biologic false positive under a variety of stimuli. It is possible to detect the «ready reactors» by means of the Neurath technique.

Dr. R e y n: This suggests also the question of the anamnestic reaction. We see positive serologic tests developing in 40 per cent of our blood donors. The giving of blood actually is a good «provocative» procedure.

Dr. R e n k o n e n: We avoid this difficulty by not having such extremely sensitive tests!

Q: *When merthiolate is added to sera non-specific reactions are more likely to disappear than are specific reactions. What test was used to determine this?*

Dr. R e i n: We have studied only a few cases and the data have not been published, but this effect was observed in each of six tests — Kline, Mazzini, Rein-Bossack cardiolipin, VDRL cardiolipin, cardiolipin complement-fixation and Kolmer complement-fixation. A similar effect has been reported following storage of serum in the refrigerator, although we have seldom observed the latter. Perhaps there are a few sera in which the reacting substance is unusually labile.

Dr. R e y n: We have compared the titers of 10 strongly positive biologic false positive sera that were divided into two parts, with half stored in the ice box and the other half frozen. There was no difference.

Dr. K r a g: Some years ago, we tested the effect of drying the sera on reactivity. We found that syphilitic sera kept well when dessicated, but that the reactivity of false positive sera was not retained quite as well.

Q: *What ratios of lecithin and cholesterol are best with sitolipin?*

Dr. U r o m a: We have used an antigen with 0.03% sitolipin, 0.9% cholesterol and 0.20—0.40% lecithin.

Q: *Is there any influence of the antecedent diet on the composition of cardiolipin obtained from beef heart?*

Dr. P a n g b o r n: We have no precise data on this, but only a series of impressions from people working in different parts of the country. Our own cardiolipin has been quite constant, but there is some indication that the yield varies with the nutritional status of the cattle. This information is difficult to obtain because seldom can we determine accurately the diet of the cattle whose hearts are used.

Q: *What steps might be taken toward international standardization of cardiolipin?*

Dr. P a n g b o r n: That is a broad question, but an important one. One of the most useful things that could be done here would be to have an expression of opinion as to what needs to be done, what would be acceptable, and how it could be managed.

There are several things that could be done:

1. Reference standards for both cardiolipin and lecithin might be made available through WHO, preferably in such a way that materials produced in all countries could be checked against the standard.

2. Agreement should be reached as to the most practical way of setting up the tests. This should be done on the basis of a *constant antigen formula* and refusal to

accept preparations that fail to measure up to this formula. It is not reasonable to compare one antigen used in 0.3% dilution with one used in 0.25% dilution.

How many centres should there be for testing preparations? Where should they be located? How many serologic tests should be used in comparing new preparations with the standard? These all are controversial issues.

The main difficulty is not with the substances themselves, but with the multiciplicity of tests in which they are used. Were there only 3—4 tests, standardization would be much simpler.

Dr. K r a g: The question of cardiolipin standardization will be discussed at the next meeting of the WHO Subcommittee on Serology and we look forward to having Dr. P a n g b o r n discuss the matter with this group. One problem is whether new lots of cardiolipin and lecithin should be tested by the commercial producer or by a central reference laboratory. Perhaps the producers should test new lots prior to the final check by an outside laboratory. Dr. Pangborn's laboratory has checked samples from many different parts of the world, but now as more and more groups are producing cardiolipin, it is becoming very difficult.

Dr. P a n g b o r n: It makes a difference whether cardiolipin is produced by a commercial firm, or, for example, by the State Serum Institute in Copenhagen, where all the facilities for serology exist. I think we will need 3—4 centres that will check the products of the different manufacturers.

It is pertinent to mention the more recently developed substances. It is clear that there is a family of chemically related substances — the sitolipin on which Dr. U r o m a is working, preparations derived from soya beans, etc., with some degree of common antigenic activity. The relation between the chemical composition of the purified substances and their serologic specificity is pure speculation.

In our serologic standardization of cardiolipin we have been using a slide test developed by Dr. R a c h e l B r o w n and the Maltaner complement fixation test. Both are used to evaluate each new sample of cardiolipin or lecithin, and we do not accept the sample unless it proves to be satisfactory in both types of test.

Dr. K r a g: Would you mind discussing stability of the antigen as compared to standard antigens?

Dr. P a n g b o r n: We are not as much concerned with stability as we were formerly. We really need new and more strictly physical-chemical means for testing colloid stability and chemical uniformity of the lecithin. I think there is some hope of getting chemical tests for this purpose. There is, for instance, the chromatographic test, in which lecithin is passed through an absorption column and the number of zones determined. This might be a substitute for some of the tests we have been using.

Q: *What is the nature of antigens that detect false positives?*

Dr. Pangborn. It would be very helpful if we knew more about this interesting problem. There is a recent paper by Widclock and his collaborators describing the use of an acetone-soluble fraction which ordinarily is discarded during the purification of antigens. He suggested that this might be of some use in the verification of tests, since the acetone-soluble material, when used in the Mazzini test, reacted with certain sera that apparently were false positives, whereas it might or might not react with syphilitic sera. The report was a short one, and the chemical nature of the fraction is not known. We found that the acetone-soluble fractions that we usually discard during purification were highly anticomplementary and therefore undesirable substances. The cephalin fraction which is also a discard is known to be anticomplementary as well.

Q: *In various communities, is there a correlation between the incidence of early syphilis and the occurrence of weakly positive serologic tests?*

Dr. Krag. Thus far there has been no study of different areas in this respect. I should think that in towns with a high incidence of early syphilis there would also be a high incidence of weakly positive serologic reactions and that the same ratio would be seen in areas of low incidence.

Q: *The present status of the plans for the International Serologic Conference?*

Dr. Krag. Although I have been concerned with the proposed Serologic Conference for one and a half years, I am still learning more and more about the many difficulties that are involved. Through the National Health Administrations we have invited outstanding author serologists to send in preliminary applications, and to date have received 27 such applications from different parts of the world. All three types of reactions, complement-fixation tests, tube tests and slide tests are represented, but there are more slide tests than any other type. Then we have sought to find a suitable place to hold the conference. It has been impossible to find a building in which each serologist could have an individual room, and the only possibility is to utilize large classrooms and give each participant 4—5 square meters of desk space.

We must decide how many participants we can invite; how many days the conference should last; whether the serologist can bring a technician; how many serum specimens and what kinds should be used in order to evaluate the results properly; and many other details. We are awaiting further information from the prospective participants, and have sought the advice of statisticians so that the results may be valid. Of course we want as many different kinds of tests represented as is possible, also tests that can be used under different conditions. We certainly would not be able to solve all of the problems with this conference, but we hope to be able to solve some of them.