amidine is removed by washing the cells with Tyrode's solution after 30 minutes before storing overnight in Tyrode's.

The observation on basophilic staining, fluorescence and marked absorption at the wave-lengths characteristic for nucleic acid and stilbamidine of the cytoplasmic granules induced in ascites tumor cells indicate that these granules, like those described by SNAPPER and coworkers in myeloma cells, consist of stilbamidine ribonucleate. That most of the cytoplasmic RNA is also affected by stilbamidine but without the production of granular precipitates is indicated by the observation that whereas a few minutes of UV irradiation in the KÖHLER microscope at 257 mμ reduced the originally high cytoplasmic absorption at 257 mμ of untreated ascites tumor cells to practically zero, stilbamidinized cells show no appreciable change in absorption on prolonged UV irradiation. However, the combination of the cytoplasmic RNA with stilbamidine appears to be without immediate effect on the virulence of the tumor. A delayed effect is noted in that cells allowed to remain *in vitro* after stilbamidine treatment show a much more rapid loss in virulence then untreated cells. It may be that the noxious effect of stilbamidine on the cells can be manifest only in the presence of additional unfavourable conditions which exist on *in vitro* storage, which it has been observed results in much more gradual loss of RNA and virulence in untreated cells[1].

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Zusammenfassung

In *in-vitro*- und *in-vivo*-Versuchen wurde die Wirkung von Stilbamidin auf die Tumorasziteszellen der Maus untersucht. Intrazytoplasmatische körnige Präzipitate konnten durch die Behandlung hervorgerufen werden, die wahrscheinlich aus Stilbamidinribonukleat aufgebaut sind. Das Auftreten der Präzipitate hat keinen unmittelbaren Effekt auf die Virulenz des Tumors.

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[2] This work was done in part (N. B. KURNICK) under a fellowship granted by the American Cancer Society on the recommendation of the National Research Council, Committee on Growth.

"Potentiating" Effect of Repeated Penicillin Treatments in *B. novyi* Infection

Analysing the factors which could account for the excellent clinical[1] and experimental[2] therapeutic results obtained without the continuous presence of penicillin in the host organism, we expressed the opinion[3] that the *additive effect* of repeated treatments probably plays an important role in this picture. In order to test this assumption, an infection was required which would allow us to follow the fate of the infective organism—as well as that of the drug—in each phase of the therapy. We found the experimental *Borrelia novyi* infection of mice, which is very sensitive to penicillin dosage variations[1], applicable for this purpose.

Experimental. The infection used in these experiments is similar to that described by R. J. SCHNITZER and coworkers[1], to whom we are indebted for the strain of *Borrelia novyi*. Material for infection was prepared by suspending a few drops of blood from an infected mouse in heparinized tryptose broth and diluting to obtain 3–6 spirochætes per dark field (x 900). Intraperitoneal injection of 0·4 cc. of this suspension into albino mice weighing 16–22 grams produces an infection with 1–4 parasites per dark field in the blood after 18–22 hours.

All treatments were by the subcutaneous route. Mice were observed repeatedly the first day of treatment, then daily, for a period of 3 weeks; most of them were reinfected after this time and the take of this reinfection considered further circumstantial evidence of cure. Groups of 3 to 10 mice for each dosage or treatment schedule were used in these experiments.

Table I

Effect of pretreatment with "ineffective" doses of penicillin in *B. novyi* infection of mice.

Schedule		Hours after treatment	Ineffective (50-100%)[1]	Slight eff. (25–40%)	Signif. red. (0–15%)
24 hours after infection	48 hours after infection		in number of mice		
Pretreatment: 150 μ/20 g (ineffective)	Treatment: 300–400 μ/20 g	3½	1	2	7
		6	1	1	8
		10	1	1	8
Pretreatment: none	Treatment: 300–400 μ/20 g	3½	5	2	3
		6	1	4	5
		10	3	2	5

[1] Percentage of the initial spirochæte count.

Results. The minimal subcutaneous dose administered the day after initial infection, which *significantly* reduces the parasite count within 3 to 5 hours, is 500 μ/20 g. Fractions of this dose varying from 75 to 150 μ, which had no immediate effect on the parasite count, were used for "pretreatment". (A) *One pretreatment with ineffective doses.* In one set of experiments pretreatment with these fractions was made the first day and was followed, the next day, by the determination of the minimal clearing dose. In one experiment, No. 50, one pretreatment with 100 μ, followed by 300 μ the next day, resulted in significant reduction (80 and 98%) in the parasite count in $^2/_3$ mice and complete clearance in the third. The 3 non-pretreated mice injected with the 300 μ showed no response. A somewhat similar experiment (No. 55) is presented in more detail in Table I. (B) *Repeated pretreatments with ineffective doses.* A number of pretreatment schedules were used. In Experiment 48, 2 pretreatments with 100 μ, on the first and second days after infection, had no effect on the parasite count. The subsequent treatment was given the third day following the infection. 400 and 800 μ cleared 3 out of 6 mice, while in 2 other mice significant reduction took place. In contrast, in the non-pretreated group 800 μ were

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Table II
Effect of 350 μ/20 g penicillin 48 hours after infection on the *Borrelia novyi* in mice

Group	No. of mice	Initial count	Average change of spirochætes after treatment	Effect on the spirochætes 3 and 6 hours after treatment – Number of mice			% mice cleared in 48 hours
				Ineffective (0–50%)	Slight effect (60–80%)	Signific. reduction (85–100%)	
Controls:							
Untreated	15	4,925	Increased 17%	15	0	0	6·6%
"Pretreated" only .	15	3,850	Increased 30%	15	0	0	6·6%
Treatment:							
Non-pretreated group.	55	4,643	Decreased 57%	25	21	9	21%
"Pretreated" group	53	3,262	Decreased 90%	1	5	47	54%

completely ineffective, while 1,600 μ gave partial reduction of the parasite count. This reduction, however, appeared as late as 10 hours after treatment, while in the pretreated group half of this dose—800 μ—gave reduction within 5 hours. In Experiment No. 49 the same pretreatment schedule (100 μ for 2 days) was used. The third day, 200 μ cleared $^2/_5$ mice, 400 μ cleared $^4/_5$ mice within 3 hours and all 5 mice within 6 hours. In the non-pretreated group 200 μ were ineffective; 400 μ cleared only $^1/_6$ mice, with a marked reduction in another 3 mice which occurred, however, after 6 hours.

(C) *Experiments on larger groups.* In these experiments carried out during the years 1948–1949, using small number of mice in the single experiments, it was noticed that, under a number of conditions, *per se* ineffective penicillin dosages improve the outcome of successive treatments. In order to obtain statistically significant figures, more recently (November, 1949) we carried out two large experiments, each involving 63 and 75 mice respectively, under identical conditions. For "pretreatment" 150 μ/20 g penicillin was given subcutaneously, 24 hours after infection. This dosage was ineffective since the number of spirochætes in the animals treated did not decrease (initial count, 203; count 5 hours after treatment, 174; count 22 hours after treatment, 3571/100 dark fields). Subcutaneous treatment with 350 μ/20 g followed 24 hours after previous treatment, respectively 48 hours after infection. While this dosage, as it appears from Table II, gave significant reduction in only 9 out of 55 mice, in the pretreated group it was effective in the majority of the animals (47/53). This dosage might also be considered as the average (54%) clearing dose for the pretreated group and as ineffective for the non-pretreated controls (21% clearing).

Discussion. It has been shown that one or two penicillin injections of doses which *per se* give no therapeutic response increase the sensitivity of the *B. novyi* infection to later therapy. The interval between successive treatments was such as to exclude any possible accumulation of the antibiotic in the host organism: a 24 hour interval between injections compared to a maximum 3 hour duration of the penicillin in the organism. (In this experimental infection which clears spontaneously, we could not establish the effect of more frequent repetition of treatment which, from a clinical standpoint, presents greater interest.)

On the basis of the experimental evidence it can be concluded that in relapsing fever infection successive penicillin treatments induce a synergistic effect greater than the sum of the effects which each treatment would have by itself. According to pharmacological terminology this synergism represents a potentiation phenomenon. This potentiation is perhaps only the final apparent consequence of the chemotherapeutic effect on a certain number of spirochætes of doses which do not visibly influence the bacterial population as a whole. This limited, invisible effect of "non-effective doses" might well change, however, through some immunological mechanism the responsiveness of the infection to successive therapy. That the chemotherapeutic responsiveness to penicillin is influenced by immunological phenomena has been definitely proven[1]. Possibly supporting this interpretation is the observation that even after doses which have no effect on the *rapidly increasing* parasite count, the progressive infection counted the next day was frequently not as heavy (5–40/field) as that of the untreated controls (30–90/field). Since this delayed influence on the heaviness of the infection is noted long after the disappearance of the antibiotic from the organism, it could hardly be caused by a direct action of the drug, while it could be interpreted as induced through immunological mechanism following the effect on some spirochætes. Another possibility to be considered is that the pretreatment with subtherapeutic doses might change the *sensitivity* of the microorganism itself to penicillin. Suggestive of such a possibility is the recent finding of GRUNBERG, UNGER, and ELDRIDGE: hemolytic streptococci exposed *in vivo* to penicillin acquired a higher sensitivity[2].

On the basis of our present and previous findings, we might express the view that the therapeutic response cannot be successfully interpreted in numerical terms related to the drug (blood concentration, duration, etc.) or to the sensitivity established *in vitro*. Presumably, the sensitivity of the infection in the host is continuously changing as a result of the previous phases of therapy (e. g. reduction of bacterial population) and intercurrent immunological reactions. The variations in sensitivity of the microorganism itself to the drug should be considered a possible contributing factor in such a changing condition.

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Department of Pharmacology and Chemotherapy Warner Institute for Therapeutic Research, New York, January 15, 1950.

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Riassunto

In topi infettati sperimentalmente con *Borrellia novyi*, l'iniezione di una o più dosi di penicillina per sé senza effetto apprezzabile sull'andamento dell'infezione («*pretrattamento*») determina un aumento della sensibilità dell'infezione verso una successiva iniezione di penicillina («*trattamento*»). Questo effetto additivo del pretrattamento con dosi ineffettive e del trattamento è dimostrato: 1) dal fatto che dopo 3 e 6 ore dall'iniezione di 350 μ/20 g di penicillina il numero delle spirochete nel sangue è notevolmente diminuito negli animali pretrattati e poi trattati, mentre questo non avviene nei controlli semplicemente trattati; 2) dal fatto che negli animali pretrattati la dose di 350 μ/20 g, somministrata 48 ore dopo l'infezione assume il valore della dose terapeutica media, in quanto le spirochete scompaiono completamente, entro due giorni, dal sangue nel 54% dei topi, mentre negli animali non pretrattati la scomparsa si ha solo nel 21%, per cui questa dose è da considerarsi inefficace.

A spiegazione di questo fenomeno di potenziamento si può supporre o che il pretrattamento con dosi subterapeutiche modifichi la sensibilità del germe verso la penicillina, o che l'azione delle dosi subterapeutiche *su alcune* spirochete influenzi lo stato di difesa immunitaria dell'animale nel senso di renderne più valido l'intervento in occasione di iniezioni successive di penicillina.

Questi dati fanno ritenere che la sensibilità dell'infezione verso certi trattamenti chemoterapici non dipenda solamente dalla durata del trattamento, dalla concentrazione del farmaco nel sangue, ecc. ma si modifichi di continuo in conseguenza delle singole introduzioni del medicamento.

Nouveaux livres - Buchbesprechungen - Recensioni - Reviews

Science and its Background

By H. D. ANTHONY. 304 pp., 74 figs.

(Macmillan & Co. Ltd., London, 1948) (sh. 10/6)

Mit «Hintergrund» ist in diesem flott geschriebenen Werk der kulturgeschichtliche Rahmen gemeint, in welchem sich die Entwicklung der exakten Wissenschaften vollzieht. Der Autor, Lecturer in Mathematics am Westminster Training College und während des zweiten Weltkriegs Chief Inspector of Army Education, hat es fertiggebracht, auf nur 300 Seiten die geistige Entwicklung der Menschheit von der Steinzeit bis zum Atomzeitalter in ihren charakteristischen Zügen zu skizzieren, ohne dabei die wichtigen Einzelheiten im Fortschritt der Fachwissenschaften zu vergessen. In jeder Kulturperiode – der Verfasser unterscheidet die Flußperiode (Ägypter und Babylonier), die Mittelmeerperiode (Antike und Mittelalter, d. h. Griechen, Römer, Araber, Westgermanen), die atlantische Periode (Renaissance und Neuzeit) und die kommende «Weltperiode» des Atomzeitalters von planetarischem Ausmaß – wird die Zivilisation durch Action (Politik), Knowledge (Wissenschaft und Technik) und Vision (Zeitgefühl in Kunst und Ideologie) bestimmt. Mit zahlreichen schematischen Skizzen gibt der Autor eine instruktive Darstellung seiner historischen Klassifikation. Wenn auch die historische Analyse nicht in die Tiefe geht und vor allem die philosophische Entwicklung des naturwissenschaftlichen Erkenntnisproblems ganz unterlassen wird, so ist das Werk als ein Beitrag zu dem Versuch, die Geschichtsschreibung der exakten Wissenschaften aus dem Staub des biographischen und bibliographischen Details zu befreien, um die ideengeschichtlichen Zusammenhänge hervortreten zu lassen, nur zu begrüßen.

J. O. FLECKENSTEIN

A Mathematician's Apology

By G. H. HARDY. 93 pp.

(Cambridge University Press) Neudruck 1948

Dieses kleine Buch des vor zwei Jahren verstorbenen englischen Mathematikers liegt jetzt in zweiter Auflage vor. In leicht verständlicher und anregender Weise stellt uns HARDY vor die Frage nach dem Sinn des mathematischen Schaffens. Die Mathematik findet ihre Rechtfertigung nicht oder nur zum kleinsten Teil in dem Nutzen, den sie für andere Wissenschaften und die Technik bedeutet. Es sind die geistigen Werte, welche der Verfasser obenanstellt. Aber auch ein «Spiel» ist die Mathematik nicht. Ihre Sätze sind durch Allgemeinheit, Schönheit und Tiefe ausgezeichnet. Reizend ist die kleine Selbstbiographie, die uns der Verfasser im letzten Kapitel gibt. Mit der Leichtigkeit, die nur der englische Stil erlaubt, werden wir an sehr tiefe menschliche Probleme, wie solche des schöpferisch Tätigen, herangeführt.

E. BATSCHELET

Higher Algebra for the Undergraduate

By MARIE J. WEISS. 165 pp.

(John Wiley & Sons, New York, 1949) ($3.75)

Das Buch ist eine Einleitung in die Grundbegriffe der modernen Algebra und bringt in sehr klarer Form die Einführung der negativen, gebrochenen und komplexen Zahlen, die Begriffe Gruppe, Körper, Ring, die Polynome über einem Körper, die Äquivalenztheorie der Matrizen und ihre Anwendung auf die linearen Gleichungen, die Determinanten, und schließt mit einem Abschnitt über Faktorgruppe, Restklassenring und Idealbegriff. Zahlreiche Beispiele und Aufgaben ergänzen das didaktisch gut durchdachte Buch.

G. KÖTHE