lating K^{42}-labeled cells was also determined. The K^{42} and P^{32} (14.3-day half-life) were obtained from Oak Ridge. Each isotope was prepared for human injection in neutral sterile isotonic saline solution.

Ten ml of heparinized blood was incubated with about 50 μc carrier-free P^{32}, and a similar volume was incubated with 100–200 μc K^{42} contained in about 50 mg of stable potassium carrier. With this carrier level, the presence of serum potassium had no effect on the uptake of potassium by the cells. The method of incubation and preparation of the blood for injection was a modification of the method described by Reeve and Veall (*5*).

The percentage of K^{42} taken up by the red blood cells ranged from 2% to 6% under varying conditions in which approximately the same amount of carrier potassium was used. The factors determining the rate of uptake are at present under study.

A weighed volume of the saline-suspended K^{42}-labeled cells was injected, and heparinized blood samples were withdrawn about 5 and 15 min later. This procedure was then repeated with the P^{32}-labeled cells. The radioactivity of the K^{42} in the injected and withdrawn samples of blood was determined immediately. The radioactivity of the P^{32} in the injected and withdrawn samples was determined 5 days later, at which time the K^{42} in the withdrawn blood was no longer detectable. The blood volume in each case was calculated in the usual manner. For the determinations of the biological half-life of the K^{42}-labeled cells, multiple specimens were taken for a 12- to 15-hr period.

The results of the almost simultaneous blood volume studies are given in Table 1. These two determinations

TABLE 1

Blood volumes

Patient	K^{42} (ml)	P^{32} (ml)	Av (ml)	Difference from av (%)
F. S.	5,940	6,400	6,170	3.7
J. R.	7,655	7,800	7,727	0.9
J. P.	4,945	4,820	4,882	1.3
O. H.	4,170	4,080	4,125	1.1
R. F.	4,750	4,870	4,810	1.3
J. B.	5,950	5,300	5,625	5.7

give essentially the same values within the errors inherent in the methods.

The biological half-life of the K^{42}-labeled cells *in vivo* ranged from 28 to 35 hr. This is consistent with studies on the *in vitro* rate of potassium uptake in red blood cells (*6*) and with studies that we will report elsewhere on the *in vivo* uptake of K^{42} by the RBC after plasma specific activity has reached a constant.

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The Metabolism of *Blastomyces dermatitidis*, Antagonists to the Growth-inhibiting Effect of Trimeton Maleate[1]

Frederick Reiss and Leona Caroline

Department of Dermatology and Syphilology, New York University Post-Graduate Medical School, and Service of Dermatology and Syphilology, Bellevue Hospital, New York

Previous reports from this laboratory (*1, 2*) presented evidence that trimeton maleate[2] (1-phenyl-1-α-pyridyl-3-dimethylaminopropane maleate, Schering) could completely inhibit the growth of *Blastomyces dermatitidis*[3] and to a lesser extent the growth of other fungi, which results are similar to those reported by Carson and Campbell (*3*) using different antihistaminics. In our series (*2*) partial inhibition of *B. dermatitidis* was evident with 0.0003 *M* trimeton maleate, with complete suppression of growth of the fungus at 0.015 *M* concentration.

For investigation of the therapeutic implications of these findings, mice were infected with *B. dermatitidis* and treated with trimeton maleate. Twenty-eight albino mice of the Swiss strain (18–20 g) were infected by the intraperitoneal route with a heavy suspension of the yeast phase of *B. dermatitidis* suspended in 4% maltose, 1% peptone water. The organisms used for the mouse inoculations had been grown on blood agar in the incubator at 37° C for 2 weeks. The animals were divided into 2 groups for therapy, with paired controls receiving no treatment. Therapy was administered by subcutaneous injection of trimeton maleate, with a daily dosage of 40 mg/kg, divided into 2 injections/day. One group of the treated mice received therapy from the day of infection; in the other group therapy was initiated on the tenth day after the date of infection. For the prophylactic trial, 20 mice were divided into 2 groups. One group received 40 mg/kg trimeton maleate daily for 5 days preceding infection with *B. dermatitidis*; the other group received no pretreatment, and treatment was instituted at the time of experimental infection.

All animals were sacrificed on the twenty-first day after infection, since in the experience of Spring (*4*), infection with *B. dermatitidis* is at a maximum in mice at this time. At autopsy, infection could be readily demonstrated by the presence of widespread nodules and partly necrotic masses affecting the mesentery, the retrosplenic and retrohepatic regions. Infection was determined by positive wet mounts, positive cultures, and by demonstrating the microorganism in histological sections.

These experiments indicated that trimeton maleate,

[1] Preliminary report.

[2] For generous supplies of trimeton maleate, we wish to express our gratitude to Edward Henderson, director of clinical research, Schering Corp., Bloomfield, N. J.

[3] We are indebted to Harry Seneca for his kindness in supplying the strain of *Blastomyces dermatitidis* used in this study.

TABLE 1

COMPARISON OF EXTENT OF GROWTH OF *Blastomyces dermatitidis* ON TRIMETON MALEATE TREATED MEDIUM* IN THE PRESENCE OF ADDED NEOPEPTONE AND ASHED NEOPEPTONE

Addition of neopeptone			Addition of ashed neopeptone		
Amt neopeptone added (mg)	Colony diam (mm) Tube 1	Colony diam (mm) Tube 2	Amt ashed neopeptone added† (mg)	Colony diam (mm) Tube 1	Colony diam (mm) Tube 2
200	6	7	7.8	6	7
400	17	12	15.6	11	10
600	17	19	23.4	19	20

Control Cultures Run Simultaneously‡

Additions	Observations
No addition	Good growth covering entire slant
0.03 *M* trimeton maleate (final concentration)	No growth
400 mg neopeptone	Enhanced growth covering entire slant
15.6 mg ashed neopeptone	Enhanced growth covering entire slant

* Medium: 4% glucose, 1% neopeptone agar, with a final concentration of 0.03 *M* trimeton maleate. Standard amount of medium used was 20 ml/tube.

† 7.8 mg ashed neopeptone is equivalent to 200 mg neopeptone.

‡ Medium: 4% glucose, 1% neopeptone agar used; amount, 20 ml.

under the conditions of the experiment, failed to prevent the infection, and furthermore the infected animals did not respond favorably to the therapy with trimeton maleate.

In order to elucidate the mechanism of the *in vitro* inhibitory effect of trimeton maleate on the growth of *B. dermatitidis,* a series of experiments was conducted to determine a means of reversing this inhibition and to search for an explanation of the mechanism. For that purpose the following substances were incorporated in an 0.03 *M* trimeton maleate, 4% glucose, 1% neopeptone agar: (1) neopeptone (Difco); (2) ashed mineral residue of neopeptone (Difco); (3) histamine dihydrochloride; (4) l-histidine monohydrochloride (Tables 1 and 2). Before incorporation of the added substances, the pH in each instance was adjusted to the pH level of the medium. Experimental tubes were inoculated at one point from a fresh culture of *B. dermatitidis* and incubated at room temperature for one month, when the extent of growth was determined by inspection.

Reversal of the inhibitory effect by additions of neopeptone (200–600 mg neopeptone added per 20 ml culture medium) induced us to investigate whether the mineral content or the organic part of the neopeptone was involved in this mechanism. After adding ashed neopeptone (ashed residue of 200–600 mg neopeptone per 20 ml culture medium) to the trimeton-containing glucose medium, growth of *B. dermatitidis* was obtained that was equal in each case to the growth with the corresponding amount of neopeptone. Thus the ashed residue evidently caused a marked reversal of the inhibitory effect of trimeton maleate. Growth with the largest amount of ashed residue added (equivalent of 600 mg neopeptone) was not quite equal to the growth in the untreated control, but the extent of growth in the experimental tubes varied directly with the concentration of added ashed residue (Table 1).

Subsequent trials with the following cations were and are being performed: Mg, Na, K, Ca, Li, Ba, Ni, Sr, and Fe. With the exception of nickel and lithium, the remaining metals (added in molar concentrations equal to the concentration of trimeton maleate in the medium as well as in twice that amount) showed appreciable reversal of the growth inhibition by trimeton maleate. The effect of the addition of several anions on the suppression of growth of *B. dermatitidis* by trimeton maleate is being studied.

Although actually we have no proof to offer that the cations tested are part of an enzyme system of *B. dermatitidis,* in the light of our experiments such a possibility can be considered. Similar investigations were conducted by Abelson and Aldous (*5*), who demonstrated that the toxicity of Ni, Co, Cd, Zn, and Mn for *Escherichia coli* could be lowered by adding large amounts of magnesium. In a similar way the toxicity of Ni and Co could be diminished in the presence of magnesium in the case of three other organisms tested: *Aerobacter aerogenes, Torulopsis utilis,* and *Aspergillus niger.* It is of additional interest to mention that Utter and Werkman (*6*) have demonstrated that Mg activated an important enzyme converting phosphoglycerate to phosphopyruvate. This enzyme acts partially without the addition of the divalent metal. The addition of small amounts of Ni

TABLE 2

ADDITIONS OF HISTAMINE AND HISTIDINE TO TRIMETON MALEATE TREATED MEDIUM, INOCULATED WITH *Blastomyces dermatitidis*

Tube No.	Molar concentration of trimeton maleate	Molar concentration of histamine	Molar concentration of histidine	Observations
1	0	0	0	Good growth*
2	0.03	0	0	No growth
3	0.03	0.03	0	" "
4	0.03	0.06	0	" "
5	0.03	0.09	0	" "
6	0	0.06	0	Enhanced growth
7	0	0.09	0	" "
8	0.03	0	0.03	No growth
9	0.03	0	0.06	" "
10	0.03	0	0.09	" "
11	0	0	0.06	Enhanced growth
12	0	0	0.09	" "

* Results reported represent 6 replicate tubes for each condition with uniform findings.

to the medium, however actually reduces the activity of the enzyme and at a higher concentration stops it completely. It thus appears possible that the cations Mg, Na, K, Ca, Ba, Sr, and Fe play a certain role in the enzyme systems of *B. dermatitidis* which may be bound by the addition of trimeton maleate and can be overcome by a certain concentration of the above-mentioned cations.

From a pharmacological point of view it was deemed of interest to determine whether added histamine and/or histidine could neutralize the growth inhibition by trimeton maleate in a way similar to the neutralization of the histamine effect by this agent in human and animal experiments. Histamine and histidine, singly and combined, were added to trimeton-treated culture medium in amounts ranging from one half to three times the molar equivalent of the combined trimeton. Results of the trials revealed that addition of histamine and/or histidine failed to overcome the growth inhibition of *B. dermatitidis* by trimeton maleate under the conditions of the experiments.

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Visual Acuity and the Normal Tremor of the Eyes[1]

Lorrin A. Riggs and Floyd Ratliff

Psychological Laboratory,
Brown University, Providence, Rhode Island

Recent measurements have demonstrated that the "grain," or mosaic structure, of the retina does not set a limit to the resolution of fine detail. For example, it has been shown that a dark line is visible against a bright field if its width subtends a minimum angle of 0.5″ at the eye of the observer (*1, 2*). Vernier displacements of slightly under 2″ are now reliably reported (*3, 4*). Stereoscopic and real depth thresholds of about 2″ have consistently been obtained (*4–9*). Since the subtense of a single cone receptor is not less than 15″–30″ at the center of the human fovea (*10, 11*), it appears that human visual resolution is 10–20 times better than one might anticipate on the basis of "local signs" from individual receptor cells.

The various hypotheses that have been suggested to account for resolution share the central idea that discreteness in the spatial arrangement of the receptor cells is somehow compensated for by continuity in time. That is, the relatively large receptor cells may "scan" the image and convey to the brain a temporal and spatial pattern of nerve impulses which signal the presence and relative position of the corresponding objects in space. In short, the most sensitive local signs from the retina are "mean local signs" (*6*) and not "cone receptor local signs." A mean local sign is derived from a temporal summation of graded responses of a number of receptor cells, so that its spatial position is not restricted to the discrete position of any one cone receptor.

It is not our purpose to summarize or evaluate here the "dynamic" theories of visual acuity. The reviews by Walls (*9*) and Senders (*12*) may be consulted in this connection. Rather, we wish to describe some experiments that appear to demonstrate the role of mean local signs in binocular vision. Our conclusion from these experiments is that the "corresponding points" of binocular vision represent corresponding mean locations on the retina, rather than a one-to-one correspondence between cone receptors in the two eyes.

The basic system of recording eye movements by the use of a contact lens has been described elsewhere (*13*). The diagram in Fig. 1 shows the manner in which this system has been modified for binocular measurements. Plane, first-surface mirrors at M_1 and

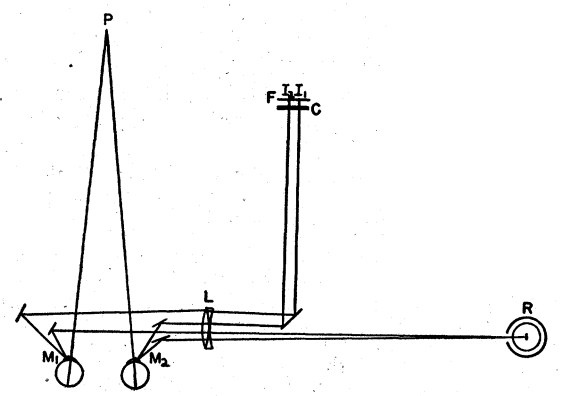

FIG. 1. Diagram of apparatus for recording the horizontal component of binocular eye movements (not drawn to scale).

M_2 are mounted on plastic contact lenses that have been fitted to the eyes of the subject. Any rotation of the eyes in the horizontal plane will displace the images at I_1 and I_2, formed by lens L of a vertical ribbon filament R. A cylindrical lens C serves to concentrate the vertical line images as points on the recording film F. The film, moving at a constant speed, registers the horizontal component of the movements of each eye during attempted steady fixation on a point P.

Binocular records have been obtained for two of the five subjects who took part in the original investigations (*13*). Fig. 2 contains samples of records from one subject. The relatively large involuntary drifts and jerky motions, described in earlier investigations (*13–15*) are in general rather closely synchronized. They appear to be coordinated in the achievement of convergence and lateral fixation on the target point. Note, however, that the relatively small involuntary tremor movements are independent for the two eyes.

[1] These experiments were done under Contract N7onr-358, Task Order II, Project NR-140-359, between Brown University and the Office of Naval Research.