and T.N.O. on each other's boards. And, of course, many other interrelations have been created to ensure perfect cooperation.

Two and a half million guilders ought to be available in 1951. Under the circumstances, while manpower is still the limiting factor in nearly every branch of science, this seems to be adequate for the present. Many plans are, however, being made, for which far larger sums may be needed. Among them an extensive fellowship program is anticipated to find and develop promising talent. The financial situation of the country makes it uncertain if these funds will be found. The present government has an open mind toward science and has done what it could without too many ill-effects on the budgetary balance, which was in view before devaluation but which now again seems a long way off. E.C.A. has already been approached on the question of whether Marshall-aid funds can be directed toward T.N.O. and Z.W.O. It seems certain that only with this help can Z.W.O. reach its more immediate goals.

The financial structure of the organization is such that money appropriated on one year's budget, contrary to governmental practice, can be transferred to the next year or later. This is based on the necessity to assure scientists beforehand that grants for work that will take more than one year will not be withdrawn solely on the grounds of nonavailability of next year's funds. Even though shortage of money has made this an empty gesture thus far, it deserves mention as a legal novelty.

It may be interesting to end this résumé with a few details on expenditures. Of the four million spent up to September 1950, 50 per cent was granted for research in physics and chemistry, mostly in fairly large amounts for well-coordinated work of (often interuniversity) teams. Mathematics got 13 per cent, nearly all of which went to the Amsterdam Mathematical Centre (which is looked on as a possible nucleus of the international mathematical institute that Unesco is planning). Astronomy, geology, and biology were given a total of 11 per cent. Medicine got 13 per cent, divided over a large number of mostly individual research grants. The social sciences had only a few projects, which took, however, 7 per cent of total expenditures; and, finally, 6 per cent went to the humanities in a large number of grants. In this last category falls nearly all the 3.5 per cent made available for publication of books and papers.

Grants vary from 250 guilders for visiting a foreign country to study some geomorphological structures, to a few hundreds or thousands to invite foreign scientists to demonstrate or participate in research from some weeks to several months; to five to ten thousand for publishing studies of history, archaeology, linguistics, ethnology, etc.; to twenty or thirty thousand for analyzing and interpreting results of psychological examinations of draftees for military service; to fifty thousand or more for crystal-structure research with electron rays; to about 150,000 a year for mathematical research and apparatus; to a total of more than a million for highly coordinated work of a large group of physicists. In 1946 two grants were made; this number has steadily risen and reached 119 in 1950. Altogether 275 yearly subsidies were directed toward 179 separate research projects.

Technical Papers

The Colloid Osmotic Pressure of Serum

George Scatchard

Department of Chemistry, Massachusetts Institute of Technology, Cambridge

The paper "A Rational Method for Calculating Colloid Osmotic Pressure of Serum" (*1*) contains several statements that may be misleading.

One that concerns me particularly is "Scatchard attempted a theoretical derivation, but made an erroneous substitution invalidating his result." Dr. Kesselman informs me that it is our footnote 5 (*2*) that he criticizes. The equations in this footnote are correct except that the indication of a continued series (+ . . .) is omitted in two of the intermediate equations. This footnote makes no attempt at a theoretical derivation. It is merely a restatement of the well-known Donnan equilibrium relations for an ideal solution and their application to real solutions. The last equation in the main paper contains a typographical error, and should read

$$P/c = 268/[1 - (0.4 + 0.9\,\mathrm{pH})c].$$

It should, however, be replaced by the equations of our later papers (*3, 4*). The equation for the osmotic pressure of plasma in footnote 10, which contains the same error, has been found too limited in application to be recommended.

In the last paragraph Kesselman says, "It is to be noted then that, with all other factors remaining constant, a fall in serum sodium produces a rise in serum colloid osmotic pressure. . . . It is interesting in this connection that oral administration of isotonic sodium chloride has been shown to produce a fall in serum colloid osmotic pressure" (*5*). In this reference, the authors say, "In the present investigation, salt solution was administered in order to effect hemodilution and decrease of the colloid osmotic pressure." It is not impossible that this treatment leads to an increase in the concentration of serum sodium, but

it is certain that the principal cause for the decrease in osmotic pressure is the decrease in the concentration of serum protein.

Perhaps the most dangerous error in Kesselman's paper is the implication that the osmotic pressure at one pH can be calculated from that at another pH by the use of the Donnan equation *for ideal electrolytes*. It has been shown (*2, 4*) that the variation of pressure with pH for albumin is less than one third the value indicated by this equation, so that it is actually more accurate to assume that the variation is zero than to use this equation.

It is true that the osmotic pressure of normal serum under physiological conditions may be calculated by Kesselman's equations, but it may be measured more easily than the quantities from which he calculates it.

The plasma proteins cannot be characterized merely by the albumin-globulin ratio. Oncley, Scatchard and Brown (*6*) report the physical properties of ten of the globulins of normal human plasma, with contributions to the osmotic pressure varying from 5% to more than 75% that of albumin. In pathological sera the quantity of each of these does not change in the same ratio, so the character of the globulin changes as well as its quantity.

References

1. KESSELMAN, R. H. *Science*, **112**, 255 (1950).
2. SCATCHARD, G., BATCHELDER, A. C. and BROWN, A. *J. Clin. Invest.*, **23**, 458 (1944).
3. ———. *J. Am. Chem. Soc.*, **68**, 2320 (1946).
4. SCATCHARD, G., *et al. Ibid.*, 2610.
5. MANKIN, H., and LOWELL, A. *J. Clin. Invest.*, **27**, 145 (1948).
6. ONCLEY, J. L., SCATCHARD, G., and BROWN, A. *J. Phys. & Colloid Chem.*, **51**, 184 (1947).

Fumagillin (H-3), a New Antibiotic with Amebicidal Properties[1, 2, 3]

Max C. McCowen, Maurice E. Callender, and John F. Lawlis, Jr.

The Lilly Research Laboratories, Indianapolis, Indiana

A new crystalline antibiotic, designated as H-3, with antiphage activity, has been isolated from cultures of a species of *Aspergillus* sp. Hanson and Eble (*1*) first isolated the active concentrates that were capable of inhibiting *Staphylococcus aureus* 209 bacteriophage.

Little antibacterial and antifungal activity was demonstrated, and no antiviral activity was exhibited *in vivo* when tested against MM virus and influenza (PR8A) infections in mice.

We have found this antibiotic to be an extremely potent amebicide, producing inhibitory effects *in vitro* against a strain of *Endamoeba histolytica* (NIH200) with mixed bacterial flora at dilutions as high as 1:131,072,000. The present paper reports preliminary tests designed to investigate the amebicidal potentialities of this antibiotic.

The initial tests showed a crude concentrate (Lot 109-TEE-1) to be effective at dilutions of 1:8,192,000 to 1:16,384,000 in cultures of *E. histolytica* with mixed bacterial flora as shown in Table 1.

TABLE 1

EFFECT OF H-3 ON *E. histolytica* (NIH200) *in Vitro*

Preparation No.	Multiplying bacteria	Minimum effective dilution*
109-TEE-1	Present†	1: 8,192,000
	"	1: 16,384,000
	Absent‡	1: 4,096,000
41-TEE-4 (crystalline)	Present	1: 131,072,000
77-TEE-4 (")	"	1: 65,536,000

* Control tubes with untreated amebae gave heavy growth at 37.5° C for 48 hr.
† Balamuth egg yolk infusion media.
‡ Shaffer-Frye media.

This crude concentrate of the antibiotic when tested in cultures of *E. histolytica* in the absence of multiplying bacteria modified (*2*) after the technique described by Shaffer *et al.* (*3*) was effective at dilutions of 1:4,096,000. Since no associated bacterial growth influenced the growth of the amebae in these cultures, the activity of antibiotic H-3 is interpreted as being direct upon the amebae. H-3 is the first antibiotic or amebicide that has demonstrated such effective amebicidal properties in our laboratories.

Two lots of crystalline H-3 (41-TEE-4 and 77-TEE-4), reported to be five times more active against *S. aureus* phage than the crude concentrate, were approximately as effective against *E. histolytica* and demonstrated activity at dilutions of 1:131,062,000.

The amebicidal properties of H-3 were further tested *in vivo* using young rats experimentally infected with cysts of *E. histolytica* (NIH200) (*4*). The crude concentrate (Lot 109-TEE-1) was found to clear rats of cecal infections of *E. histolytica* when four divided doses were administered orally for 2 days. The total dosage was 36 mg/kg as shown in Table 2. Crystalline preparations (Lots 41-TEE-4 and 77-TEE-4) cleared rats of amebae when four divided doses were administered orally for 2 days. The total dosage was approximately 11 mg/kg. No antibacterial activity has been observed against the intestinal flora in rats.

Further tests were made using the crystalline antibiotic H-3 (Lot 77-TEE-4) against experimental amebiasis in young rabbits infected by the technique described by Tobie (*5*). The antibiotic was found to clear the animals of *E. histolytica* when 4 divided doses were administered orally for 2 days as shown in Table 2. A total dosage of 100 mg/kg was given during this period of treatment.

Additional tests are being conducted in experimental animals to establish an amebicidal end point.

[1] A preliminary report.
[2] Fumagillin, generic name given antibiotic H-3 by the Upjohn Company.

[3] We wish to thank the Upjohn Company which generously supplied us with samples of crude and crystalline H-3.