280 (9.9), and 312 nm. (11.1) at pH 7 and 13. Calc. for $C_{13}H_{19}N_3O_2$: C, 62.62; H, 7.68; N, 16.86. Found: C, 62.78; H, 7.92; N, 17.15. Compound VII, R_1 = *n*-C_4H_9, R_2 = CH_3: oil, n_D^{25} 1.5799. Calc. for $C_{14}H_{21}N_3O_2$: C, 63.85; H, 8.04; N, 15.96. Found: C, 63.64; H, 7.92; N, 15.99.

Benzamidines—Compound VIII, R_1 = R_2 = CH_3: m.p. 113° dec. (hexane–chloroform); $UV_{max.}$ ($\epsilon \times 10^{-3}$) at 226 (10.9) and 327 nm. (22.4) at pH 7. Calc. for $C_9H_{13}N_5$: C, 56.52; H, 6.85; N, 36.63. Found: C, 56.32; H, 6.59; N, 36.53. Compound VIII, R_1 = methyl, R_2 = cyclohexyl: m.p. (hydrochloride) 235° dec. (ethanol–ethyl acetate); $UV_{max.}$ ($\epsilon \times 10^{-3}$) at 228 (12.0) and 333 nm. (25.0) at pH 7. Calc. for $C_{14}H_{21}N_5 \cdot HCl$: C, 56.84; H, 7.50; N, 23.68; Cl, 12.00. Found: C, 56.64; H, 7.43; N, 23.59; Cl, 12.0.

In standard tests against mouse lymphoid leukemia L-1210, *o*-(3,3-dimethyl-1-triazeno)benzamide, the analogous *o*-(3-butyl-3-methyl-1-triazeno) derivative, and *p*-(3,3-dimethyl-1-triazeno)benzamide increased lifespan by 40–60%. Dosages of these compounds that prolonged survival time are summarized in Table I; additional data in Table I indicate that a benzoic acid hydrazide, a benzoate ester, and a benzamidine also cause modest increases in lifespan. Although additional testing is required to delineate the degree and scope of activity of Compounds II–VIII, the available biological data indicate that at least some of the derivatives represented by Structures II–VIII can cause significant increases in average survival time of mice bearing leukemia L-1210. Previously, it was reported (18) that certain benzenoid triazenes, which lack the amide or carboxyl-type groups and which are inhibitory to certain experimental tumors (18–20), are not active against lymphatic leukemia L-1210.

The stability to sunlight of the benzamide analog (II, R_1 = R_2 = CH_3) of I*a* and of *p*-(3,3-dimethyl-1-triazeno)benzamide (V, R_1 = R_2 = CH_3) is a point of additional interest. In a prior study (11), it was shown that I*a* decomposes more rapidly in direct sunlight than does its pyrazole analog, 3-(3,3-dimethyl-1-triazeno)pyrazole-4-carboxamide. Solutions (4×10^{-5} *M*) of the two dimethyltriazenobenzamides and of the pyrazole analog in 50% aqueous ethanol were placed side-by-side in direct sunlight which passed through window glass and through the Pyrex glass of the containers. Under the prevailing exposure conditions, the UV absorbance of the pyrazole analog decreased by 40% within 3 hr. and by 85% within 10 hr., whereas the UV spectra of the two benzamide derivatives were unchanged during the same periods.

(1) Y. F. Shealy, J. A. Montgomery, and W. R. Laster, Jr., *Biochem. Pharmacol.*, **11**, 674(1962).

(2) Y. F. Shealy, C. A. Krauth, and J. A. Montgomery, *J. Org. Chem.*, **27**, 2150(1962).

(3) Y. F. Shealy and C. A. Krauth, *J. Med. Chem.*, **9**, 34(1966).

(4) Y. F. Shealy and C. A. Krauth, *Nature*, **210**, 208(1966).

(5) Y. F. Shealy, C. A. Krauth, S. J. Clayton, A. T. Shortnacy, and W. R. Laster, Jr., *J. Pharm. Sci.*, **57**, 1562(1968).

(6) K. Hano, A. Akashi, I. Yamamoto, S. Narumi, and H. Iwata, *Gann*, **59**, 207(1968).

(7) Y. F. Shealy, C. A. Krauth, R. F. Pittillo, and D. E. Hunt, *J. Pharm. Sci.*, **56**, 147(1967).

(8) Y. F. Shealy and C. A. O'Dell, *J. Med. Chem.*, **9**, 733(1966).

(9) C. W. Noell and C. C. Cheng, *ibid.*, **12**, 545(1969).

(10) Y. F. Shealy and C. A. O'Dell, *J. Pharm. Sci.*, **59**, 1358 (1970).

(11) *Ibid.*, **60**, 554(1971).

(12) Y. F. Shealy, C. A. Krauth, C. E. Opliger, H. W. Guin, and W. R. Laster, Jr., *J. Pharm. Sci.*, **60**, 1192(1971).

(13) J. K. Luce, W. G. Thurman, B. L. Isaacs, and R. W. Talley, *Cancer Chemother. Rep., Part 1*, **54**, 119(1970).

(14) J. G. Erickson, P. F. Wiley, and V. P. Wystrach, in "The Chemistry of Heterocyclic Compounds," vol. 10, A. Weissberger, Ed., Interscience, New York, N. Y., 1956, chap. 1.

(15) J. Elks and D. H. Hey, *J. Chem. Soc.*, **1943**, 441.

(16) J. Nakayama, O. Simamura, and M. Yoshida, *Chem. Commun.*, **1970**, 1222.

(17) Cancer Chemotherapy National Service Center, *Cancer Chemother. Rep.*, **25**, 1(1962).

(18) J. H. Burchenal, M. K. Dagg, M. Beyer, and C. C. Stock, *Proc. Soc. Exp. Biol. Med.*, **91**, 398(1956).

(19) D. A. Clarke, R. K. Barclay, C. C. Stock, and C. S. Rondestvedt, Jr., *ibid.*, **90**, 484(1955).

(20) K. Sugiura, *Gann*, **50**, 251(1959).

Y. Fulmer Shealy
C. Allen O'Dell
Joe D. Clayton
Charles A. Krauth

Kettering-Meyer Laboratories
Southern Research Institute
Birmingham, AL 35205

Received April 9, 1971.

Accepted for publication June 11, 1971.

This work was supported by Chemotherapy, National Cancer Institute, National Institutes of Health, U. S. Public Health Service, Contract PH43-64-51; biological testing was performed under the terms of Contract PH43-65-594 and under the supervision of Dr. F. M. Schabel, Jr., and Dr. W. R. Laster, Jr.

Assessment of Compression Characteristics of Powders

Keyphrases ☐ Powders—compression characteristics ☐ Tablets—compression characteristics ☐ Compression properties—powders, tablets

Sir:

The characterization of the compression properties of powders by the "modulus of pressing," *i.e.*, the slope of the log of the applied pressure against the log of the relative density of the compact, has been criticized by Jones (1). As an alternative, he suggested that a plot of the power expended in pressing a powder against the volume displacement would show differences in the pressing qualities of various powders (1). Rather than using the power in forming the tablet, *i.e.*, the energy expended in unit time, we consider that the work done in forming the tablet, *i.e.*, the force times the distance moved by the punch, would be a more useful characterization.

Varsano and Lachman (2) described how the work done in forming a tablet can be obtained from the area under the load/displacement curves when powders are compressed at a constant rate on an Instron physical

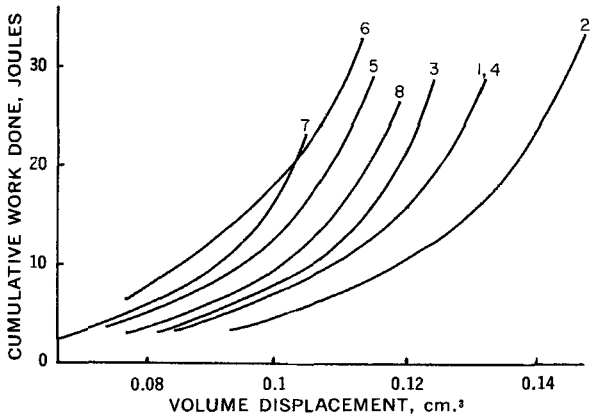

Figure 1—*Relationship between work done and the displacement of the powder bed. Key: 0–32-μ size fraction, 1 = crystalline and 2 = spray dried; 75–104-μ size fraction, 3 = crystalline and 4 = spray dried; 210–295-μ size fraction, 5 = crystalline and 6 = spray dried; and unfractionated, 7 = crystalline and 8 = spray dried.*

testing instrument. This method of determining work done has applied when known particle-size fractions of crystalline and spray-dried lactose were compressed, as described by Fell and Newton (3). These two materials were chosen because they have different direct compression characteristics (4). The modulus of pressing is given in Table I; the work done, calculated from the area under the load/displacement curve, for loads greater than 200 kg. is shown in Fig. 1. The former treatment shows slight differences between the two materials, the spray-dried lactose being more compressible. The latter treatment, however, shows clearly that, for a given value of work, there is a greater displacement of spray-dried lactose than crystalline lactose. Similarly, the differences between the various size fractions are clearly distinguishable by the latter treatment of results.

The ability of a powder mass to reduce in volume when compressed does not ensure the formation of a tablet. It is essential that the powder cohere into a suitable form after removal of the applied load. The tensile strength of the various tablets, as determined by the diametral compression test (3), provides a

Table I—Modulus of Pressing of Crystalline and Spray-Dried Lactose

Particle-Size Fraction, μ	Modulus of Pressing	
	Crystalline Lactose	Spray-Dried Lactose
0–32	0.11	0.13
75–104	0.11	0.12
295–410	0.10	0.11
Unfractionated	0.09	0.10

measure of the utilization of the work done in forming the tablet. The results presented in Fig. 2 show that there is a linear relationship between the work done and the tensile strength of the tablet for both forms of lactose and all the particle-size fractions tested. Although crystalline lactose is less compressible, it forms stronger tablets for an equal amount of work, except the 0–32-μ size fraction. For spray-dried lactose, the tablet strength increases as the particle size decreases for the same amount of work expended. For crystalline lactose this is not the case; the tablets prepared from the 75–104-μ size fraction are the strongest of the three size fractions. Thus, the work done in compressing a powder mass is not necessarily utilized in the same manner for volume reduction and particle bonding.

The application of these concepts can provide useful characterization of the compression properties of pharmaceutical materials.

(1) W. D. Jones, "Fundamental Principles of Powder Metallurgy," Edward Arnold, London, England, 1961.
(2) J. Varsano and L. Lachman, *J. Pharm. Sci.*, **55**, 1128(1966).
(3) J. T. Fell and J. M. Newton, *ibid.*, **59**, 688(1970).
(4) W. C. Gunsel and L. Lachman, *ibid.*, **52**, 178(1963).

J. T. Fell
Pharmacy Department
The University
Manchester 13, England
J. M. Newton
Lilly Research Centre Ltd.
Erl Wood Manor
Windlesham
Surrey, England

Received October 29, 1970.
Accepted for publication June 11, 1971.

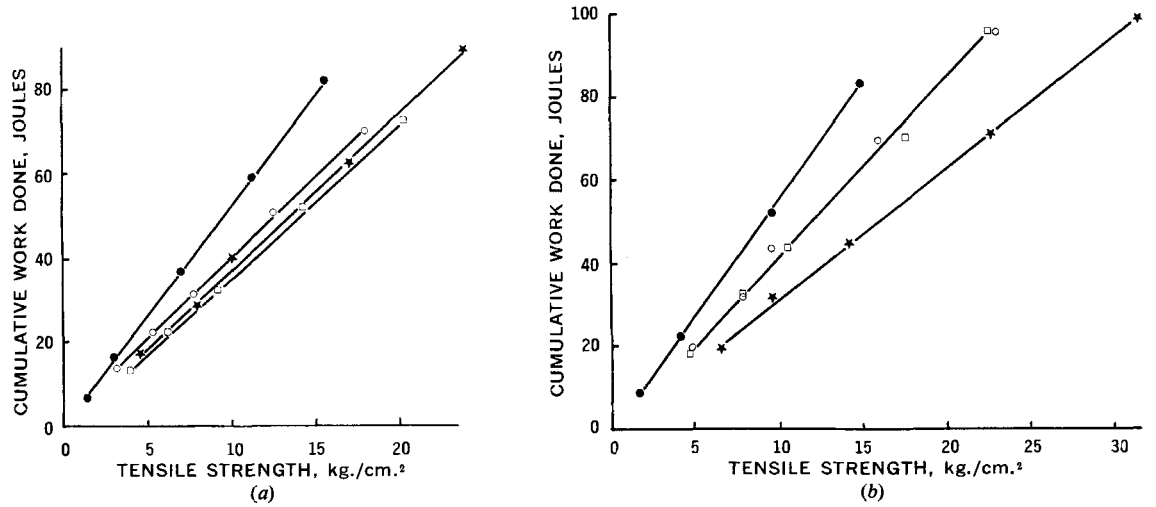

Figure 2—*Relationship between work done and the tensile strength of tablets:* a = *crystalline lactose and* b = *spray-dried lactose. Key:* ●, *210–295 μ;* □, *75–104 μ;* ∗, *0–32 μ; and* ○, *unfractionated.*