The described concept of the disintegration-dissolution analysis can be rather general, but several restrictions were employed to study a simple system and to demonstrate the use of the method. First, the tablet was prepared by direct compaction, which permits disintegration directly into primary particles. A granulation may introduce a more complex disintegration pattern and may also modify somewhat the primary particles. Second, the Hixson–Crowell equation (5) was employed. Alternative theories for powder dissolution exist, but the resulting mathematical equations do not describe the experimental dissolution process as well as the cube-root law (12).

Third, the drug powder was of a uniform particle size. If a powder with a wide size distribution were used, an additional feature would have to be included to account for the change in size distribution over time for each fraction disintegrated. Fourth, it was assumed that the compression force did not alter the primary particles, *i.e.*, that K for the pure powder represented K for the disintegrated powder. Although compression can fracture particles, the relatively low force used apparently did not have a significant effect because the experimentally observed disintegration time was in close agreement with the time for complete disintegration on the disintegration profile determined by Eqs. 4 and 5.

Finally, because the disintegration profile for the acetaminophen tablet was zero order, the discussion regarding the linearity of the dissolution profile vis-á-vis the disintegration-controlled release and the significance of the inflection points are restricted to this case. As further studies indicate other disintegration profiles, *e.g.*, with negative curvature or sigmoidal, model simulations can be employed to explore these effects.

The described method for determining the time course of disintegration can provide a means to study tablet disintegration under idealized conditions. Work is being continued to extend the model so that regular tablet formulations, *i.e.*, not idealized, can be evaluated.

REFERENCES

(1) "The United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., 1975, p. 650.

(2) H. Nogami, J. Hasegawa, and Y. Nakai, *Chem. Pharm. Bull.*, **7**, 331 (1959).

(3) M. H. Rubinstein, J. I. Wells, and C. A. Holland, *J. Pharm. Pharmacol. Suppl.*, **27**, 54 (1975).

(4) W. Lowenthal, *J. Pharm. Sci.*, **61**, 1695 (1972).

(5) A. Hixson and J. Crowell, *Ind. Eng. Chem.*, **23**, 923 (1931).

(6) W. I. Higuchi and E. N. Hiestand, *J. Pharm. Sci.*, **52**, 67 (1963).

(7) K. G. Nelson and A. C. Shah, *ibid.*, **64**, 610 (1975).

(8) L. J. Leeson and J. T. Carstensen, "Dissolution Technology," Academy of Pharmaceutical Sciences, American Pharmaceutical Association, Washington, D.C., 1974.

(9) J. G. Wagner, *J. Pharm. Sci.*, **58**, 1253 (1969).

(10) F. Langenbucher, *J. Pharm. Pharmacol.*, **24**, 979 (1972).

(11) A. C. Shah, C. B. Poet, and J. F. Ochs, *J. Pharm Sci.*, **62**, 671 (1973).

(12) P. V. Pedersen and K. F. Brown, *ibid.*, **65**, 1442 (1976).

ACKNOWLEDGMENTS AND ADDRESSES

Received November 22, 1976, from the *College of Pharmacy, University of Minnesota, Minneapolis, MN 55455.*

Accepted for publication March 11, 1977.

Supported by a grant from the Pharmacy Research Unit, The Upjohn Co., Kalamazoo, Mich.

[x] To whom inquiries should be directed.

Bioavailability of Three Isoniazid Formulations

S. SVED [x], I. J. McGILVERAY, and N. BEAUDOIN

Abstract □ The bioavailability of three isoniazid formulations was assessed using a procedure specific for the free drug. Nine human volunteers, all slow acetylators, were each given 4 × 100 mg of isoniazid of three different tablet formulations at weekly intervals; the plasma drug levels were measured at different times during the first 24 hr. No significant differences ($p > 0.05$) were detected among the three products as to relative bioavailability, peak plasma concentrations, C_{max}, and the time of C_{max}, t_{max}. Analysis of variance of the pharmacokinetic parameters obtained according to a one-compartment open model did not demonstrate any significant formulation or time effect but revealed a significant intersubject variation in all parameters involved.

Keyphrases □ Isoniazid—bioavailability of three commercial formulations compared □ Bioavailability—isoniazid, three commercial formulations compared □ Tuberculostatic antibacterials—isoniazid, bioavailability of three commercial formulations compared

Isoniazid has been used since the early 1950's for the treatment of tuberculosis and has been largely responsible for the virtual eradication of this disease in certain parts of the world. It is widely used in preventive therapy in the United States and Canada. Its clinical efficacy and bioavailability assessment are complicated by methodological and metabolic problems. First, the presence of slow and fast acetylator genotypes in the population has been demonstrated (1–5), and the inclusion of both types in a study could lead to increased variability and difficulties in design. Second, isoniazid tends to form relatively stable, probably less active, hydrazones with either physiological (sugars and pyruvate) or excipient (lactose and glucose) aldehydes and ketones (6–9), thus necessitating an assay that can distinguish between the free drug and its hydrazones.

Earlier studies (10) on isoniazid bioavailability did not demonstrate any difference between six commercial preparations available in the United States. The method used, however, could not distinguish between free isoniazid and its hydrazones. This study was initiated to compare the bioavailability of three Canadian isoniazid preparations using a homogeneous group and an assay that measures only free isoniazid in the plasma.

EXPERIMENTAL

Materials—Isoniazid tablets, 100 mg, were supplied[1] from current production lots. Evacuated heparinized blood collection tubes were obtained locally[2]. Extractions were done in glass tubes with polytef-lined screw caps[3]. 2,4-Pentanedione (practical), diethanolamine, ethylene glycol, potassium carbonate, zinc acetate (all reagent grade)[4], methyl

[1] See "Quad Review 4," Health Protection Branch, Health and Welfare Canada, Ottawa, Canada, 1975, p. 44.

[2] Vacutainers, Becton-Dickinson; obtained through Canlab, Ottawa, Canada.

[3] Catalog No. T 1356-1, Canlab, Ottawa, Canada.

[4] Baker; obtained through Canlab, Ottawa, Canada.

Table I—Specificity of Assay Used for Isoniazid

Substance	Amount Added, nmoles	Amount Found[a], nmoles	Recovery, %
Isoniazid	72.9	74.4	102
I	55.5	0	0
II	48.3	2.9	6
III	37.7	1.5	4

[a] Estimated by the method of Lever (13) as described under *Experimental*. (Means of duplicate determinations.)

isobutyl ketone[5], and chloramine-T[6] were used without further purification. Ether[7] was freshly distilled before use.

Solutions—Acetylisoniazid (I) and isoniazid hydrazones of pyruvate (II) and α-ketoglutarate (III)[8] were dissolved in water containing excess sodium bicarbonate to keep the solution pH above 7.

***In Vitro* Testing**—Potency, content uniformity, and disintegration time were tested according to the USP XVIII (11) requirements for isoniazid tablets. Dissolution time, $\bar{t}_{60}$, was measured using the USP rotating-basket method (11) with 900 ml of distilled water at 37° as the dissolution medium. The basket was rotated at 100 rpm, and the dissolved drug was measured by following the absorbance of the filtered dissolution medium at 262 nm in a suitable spectrophotometric system[9].

Subjects—Nine normal, healthy, male volunteers, all slow acetylators, 26–44 years old and 66–86 kg, were selected on the basis of a complete medical and biochemical examination. Isoniazid acetylator phenotype was determined according to the test described by Hodgkin *et al.* (12).

Bioavailability Trial—The three isoniazid preparations were administered to each subject at a dose of 400 mg (4 × 100-mg tablets), at intervals of 1 week, according to a design incorporating three replicate 3 × 3 Latin squares. The subjects, having fasted overnight, ingested the drug with 50 ml of water (0 time), took a light, xanthine-free beverage at 1.5 hr, and had food and water *ad libitum* from 3 hr on. Blood was obtained by venipuncture using heparinized collection tubes[2] at 0, 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 7.5, and 24 hr; the plasma was separated by centrifugation and kept frozen at −20° for not more than 5 days before analysis.

Assay—Plasma isoniazid was estimated by a minor modification of the fluorometric procedure of Lever (13). Plasma, 1 ml, was incubated in a polytef-lined screw-capped tube[3] with 0.6 ml of 7% 2,4-pentanedione in 1 *M* Na_2HPO_4 for 20 min at 45°. After the addition of 0.4 ml of 5 *M* K_2CO_3 and 5 ml of methyl isobutyl ketone, the mixture was extracted[10]

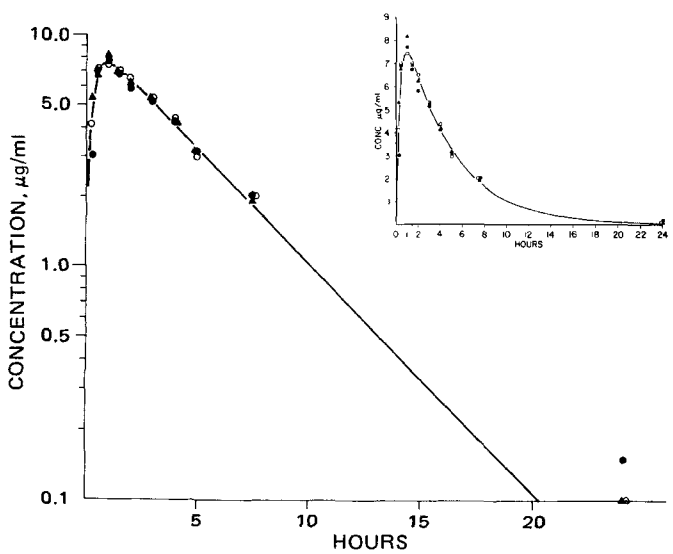

Figure 1—*Plasma profile of isoniazid following the administration of 400 mg to human volunteers. The points represent the mean plasma isoniazid concentration for each formulation. Key: ●, Formulation R; ▲, Formulation 1; and ○, Formulation 2. The solid line is the curve fitted to the overall means of concentrations. The inset is the linear plot.*

[5] Certified, Fisher Scientific, Ottawa, Canada.
[6] Eastman; obtained through Fisher Scientific.
[7] Anhydrous, Mallinckrodt Chemicals, Montreal, Canada.
[8] Gift of Dr. L. Eidus, Ottawa, Canada.
[9] Beckman DB-GT, Beckman Instruments, Fullerton, Calif.
[10] Roto Rack, Fisher Scientific, Ottawa, Canada.

Table II—*In Vitro* Test Results of the Isoniazid Formulations[a]

Formulation	Potency[b], mg/Tablet	Content Uniformity[c]	Disintegration Time[d], min	Dissolution Time[e], min
R	103.7	Pass	—	3
1	101.1	—	0.5	1
2	99.3	Pass	5.5	11

[a] Specifications according to USP XVIII (11). [b] From 93 to 107% of label claim. [c] Minimum of nine tablets out of 10 within 15% of label claim. [d] A 30-min maximum. [e] Test not required by the USP XVIII.

for 15 min and centrifuged for 10 min. The organic phase (4 ml) was extracted as already described with 1.2 ml of a solution of 2.5 *M* diethanolamine and 2 *M* zinc acetate in ethylene glycol and centrifuged.

The ethylene glycol layer was washed with 1 ml of ether and placed under vacuum for 10 min to remove the dissolved ether, and its fluorescence was measured on a fluorometer[11] using as excitation the mercury line at 436 nm and an emission wavelength of 540 nm. Readings were made against blanks prepared identically using pooled plasma of normal blood donors. All 0-hr samples of the bioavailability trial gave consistently zero readings within instrumental error.

Calculations—The areas under the plasma isoniazid concentration–time curve, *AUC*, were estimated by the trapezoidal method; the analyses of variance on the *AUC* and on the maximum observed plasma concentration, C_{max}, were done using the logarithmic transform of the raw data adjusted for potency. The pharmacokinetic parameters for each individual treatment were obtained by a nonlinear regression program[12] according to:

$$C_p = C_0 \frac{k_a}{k_a - k_e} (e^{-k_e t} - e^{-k_a t}) \qquad \text{(Eq. 1)}$$

where C_p is the plasma concentration at time t, C_0 is the dose absorbed divided by the volume of distribution, and k_a and k_e are the rate constants for absorption and elimination, respectively. The starting parameters for the program were obtained using the graphic method of Rescigno and Segré (14).

RESULTS AND DISCUSSION

Isoniazid Assay—Two problems were encountered when evaluating suitable procedures for plasma isoniazid: the specificity of the procedure and the stability of the drug in plasma stored in the frozen state. Specificity has been a problem since isoniazid therapy was introduced, as witnessed by the plethora of published procedures (*cf.*, 15, also 13, 16–19). The ease with which isoniazid forms derivatives with ketones and aldehydes and the controversy as to the therapeutic efficacy of the resulting hydrazones were described previously (6–9). Observations in this laboratory with rabbits suggest that at least some hydrazones of isoniazid remain intact and are rapidly eliminated when injected. The method selected was, therefore, chosen without acid treatment during extraction or deproteinization to avoid possible hydrolysis of any isoniazid hydrazones present.

The second problem, loss of isoniazid during frozen storage of plasma, has been reviewed (20). It appears to be minimal when the chromogenic reaction is performed in the presence of plasma proteins within a few days of storage, as in the present study.

To verify the specificity of the method, isoniazid and I–III were added to plasma and assayed for isoniazid. Table I shows the recoveries as isoniazid. Physiological hydrazones did not interfere to any appreciable extent when the temperature was kept below 50°, although considerable interference was noted at higher temperatures (up to 80% at 100°). The final ether wash and drying were found advisable to avoid development of turbidity, caused by residual methyl isobutyl ketone, on cooling of the final solution.

***In Vitro* Tests**—The results of the test performed on the isoniazid formulations are summarized in Table II. All parameters studied were within the specifications of USP XVIII (11). Two of the three formulations contained lactose as excipient, but the amount of isoniazid bound as hydrazone was too small (4.2% or less[13]) to vitiate the estimation of bioavailability.

Bioavailability—The plasma isoniazid concentrations following the

[11] Aminco-Bowman SPF-125, American Instrument Co., Silver Spring, Md.
[12] The program used was a modification of the Bio-medical Statistical Program, BMD-X-85 package.
[13] Dr. K. McErlane of these Laboratories, personal communication.

Table III—Plasma Profiles for Isoniazid (Formulation Means)

Formulation	*AUC*, μg hr/ml	Plasma Concentration[a], μg/ml, at 0.25 hr	0.5 hr	1 hr	1.5 hr	2 hr	3 hr	4 hr	5 hr	7.5 hr	24 hr
R	50.29	3.03	6.92	7.72	6.75	5.82	5.16	4.15	3.12	2.03	0.15
(*CV*)	(14.53)	(69.14)	(38.33)	(26.89)	(16.72)	(14.69)	(16.36)	(17.18)	(14.92)	(17.92)	(50.31)
1	49.87	5.32	6.76	8.20	6.93	6.22	5.27	4.18	3.08	1.91	0.10
(*CV*)	(16.59)	(78.53)	(39.77)	(19.17)	(17.29)	(18.93)	(19.81)	(18.28)	(23.12)	(19.49)	(62.45)
2	50.63	4.14	7.00	7.44	6.99	6.50	5.31	4.38	2.97	2.02	0.10
(*CV*)	(17.20)	(74.49)	(52.63)	(33.36)	(22.27)	(20.28)	(12.53)	(16.40)	(15.73)	(22.02)	(42.13)

[a] Arithmetic means, $n = 9$ for each formulation.

Table IV—Bioavailability Parameters of Isoniazid Formulations

Formulation	Potency[a], %	*AUC*[b], μg hr/ml	RBA[c], %	C_{max}, μg/ml	T_{max}, hr
R	103.7	50.3	100	7.86	0.83
1	99.3	49.9	101.4	9.15	0.75
2	101.1	50.6	105.0	8.27	1.03
CV	—	—	11	17.5	60

[a] Percent of label claim. [b] Area under the 0–24-hr plasma concentration–time curve (arithmetic means of uncorrected data). [c] Relative bioavailability: *AUC* relative to the reference formulation (*R*) (geometric mean of data corrected for potency).

ingestion of 400 mg each of three different formulations are given in Table III. The *AUC* and mean plasma concentrations at each time were very similar to each other, and the coefficient of variation (*CV*) between 1.5 and 7.5 hr was 22% or less. The high values for the coefficient of variation at 24 hr were probably due to the very low concentrations, which were near the detection limit, while those during the first 30–60 min (up to 78% at 0.25 hr) may have been indicative of person-dependent irregularities in absorption. However, since this time interval represented a small fraction of the total area (typically ~15%; *cf.*, Fig 1, inset), it had only a minor effect on the overall variability of the area under the curve (*CV* = 14–17%). In fast acetylators, where the elimination phase is several times shorter (1), irregularities during absorption would probably be more marked.

The results of the analysis of variance are summarized in Table IV. The bioavailabilities of Formulations 1 and 2 relative to the reference formulation (*R*) were 101.4 and 105%, respectively (values corrected for potency), and the coefficient of variation was 11%. None of these values was significantly different from the others at the 95% confidence level. These results are similar to those obtained by Gelber *et al.* (10) who found no differences in the bioavailability of six different isoniazid formulations.

Table IV also gives the geometric means for maximum plasma concentrations, C_{max}, observed with the formulations. These ranged from 7.86 to 9.15 μg/ml, with an overall coefficient of variation of 17.5%, and gave no significant difference ($p > 0.05$). The times, t_{max}, at which C_{max} was observed ranged from 0.25 to 2 hr (arithmetic means of 0.75–1.03, $CV = 60\%$). An apparent rank correlation between t_{max} and dissolution time could not be considered significant with the small number of formulations tested.

Pharmacokinetic Considerations—The mean plasma concentrations obtained for each formulation are compared in Fig. 1 with the theoretical curve fitted by a nonlinear regression to the overall means. The parameters obtained in fitting this curve gave half-lives of absorption and elimination of 0.25 and 3.01 hr, respectively. The C_{max}, 7.5 μg/ml, occurred at 0.98 hr ("mean fit," Table V). All points were close to the theoretical curve, except the 24-hr values which were near the lower limit of the assay method used and appeared to fit poorly on the semilogarithmic plot. However, this discrepancy had a minor effect on the *AUC* (Fig. 1, inset).

The trapezoidal method appeared to overestimate the 0–24-hr *AUC* by about 20% compared to the theoretical value. The major part of this error was due to the lack of points between 7.5 and 24 hr. However, similar relative bioavailabilities were obtained by using either the theoretical 0–∞ *AUC* (C^0/k_e) or the truncated 0–7.5- or 0–24-hr *AUC*, in agreement with findings of Lovering *et al.* (21).

To examine the pharmacokinetic behavior of isoniazid, data points from each individual treatment were used to fit individual theoretical curves by means of the nonlinear regression program. The data for 19 out of the total 27 treatments, as well as the mean data, demonstrated a good fit to the theoretical equation. The remaining eight treatments (mostly with 0.25-hr values in the upper or lower extremes) did not fit the equation and could not be used.

The pharmacokinetic parameters derived are summarized in Table V. The overall mean of the parameters gave a C_0 of 9.94 μg/ml, an ab-

Table V—Formulation Means of Parameters Derived from the Fitting of Plasma Isoniazid Concentration Data to a One-Compartment Open Model

Formulation	Number of Observations	C_0	k_a	k_e	Theoretical C_{max}	Theoretical[a] T_{max}
1	5	10.35	2.35	0.26	7.66	1.13
2	6	10.10	2.98	0.26	7.78	1.00
R	8	9.40	3.30	0.24	7.60	0.88
All combined	19	9.94	2.85	0.25	7.58	1.00
CV, %		10.02	30.6	12.0	9.4	20.6
Mean fit[b]	27	9.37	2.78	0.23	7.50	0.98

[a] Means for theoretical T_{max} are arithmetic; all others are geometric means. [b] Parameters of the curve fitted to the arithmetic means of all observed plasma concentrations ($n = 27$ for each point, $r^2 = 0.998$).

Table VI—Analysis of Variance of All Parameters Derived from the Fitting of Plasma Isoniazid Concentration Data to a One-Compartment Open Model[a]

Parameter	Factor: Subject, Value of *F* Test	Subject, Significance[b]	Period, Value of *F* Test	Period, Significance	Formulation, Value of *F* Test	Formulation, Significance
C_0	7.44	*	0.12	n.s.	1.29	n.s.
K_a	7.32	*	1.08	n.s.	1.23	n.s.
K_e	4.59	*	0.80	n.s.	1.61	n.s.
C_{max}	6.75	*	1.18	n.s.	0.09	n.s.
T_{max}	5.95	*	2.11	n.s.	1.58	n.s.
Degrees of freedom	8,6		2,6		2,6	

[a] Only values of the *F* test and its significance and the degrees of freedom are given for each factor for each parameter. [b] * = significant at $\alpha = 0.05$; n.s. = not significant at $\alpha = 0.05$.

sorption rate constant of 2.85 hr^{-1}, and an elimination rate constant of 0.25 hr^{-1} (half-life ~3 hr). The theoretical C_{max}, reached at 1 hr, was 7.58 μg/ml. A similar set of parameters was obtained when the equation was applied to the means of all 27 treatments, which gave an excellent fit (r^2 = 0.998).

The results of an analysis of variance of the parameters are shown in Table VI. Of the three parameters, as well as C_{max} and t_{max}, none showed any significant formulation or time effect. However, analysis of variance revealed a statistically significant between-subject variation ($p < 0.05$) for all parameters studied, including k_e. Since all subjects were of the slow inactivator phenotype, the finding with this small sample lends support to the proposed existence of additional minor genes involved in the elimination of isoniazid (2), although other mechanisms, *e.g.*, multiphasic absorption, cannot be ruled out entirely.

In conclusion, no significant differences in the relative rate or extent of bioavailability could be demonstrated in three Canadian isoniazid formulations. In slow acetylator subjects, the drug was absorbed rapidly from the gut and was eliminated with a half-life of approximately 3 hr.

REFERENCES

(1) J. H. Peters, *Am. Rev. Resp. Dis.*, **81**, 485 (1960).

(2) D. A. Price Evans, *Ann. N.Y. Acad. Sci.*, **151** (Art. 2), 723 (1968).

(3) L. Eidus, M. M. Hodgkin, and A. H. E. Hsu, *Int. J. Clin. Pharmacol.*, **8**, 154 (1973).

(4) C. W. L. Jeanes, O. Schaefer, and L. Eidus, *Can. Med. Assoc. J.*, **109**, 483 (1973).

(5) G. Raghupati Sarma, S. Kailasam, D. A. Mitchison, N. G. K. Nair, S. Radhakrishna, and S. P. Tripathy, *Tubercle*, **56**, 314 (1975).

(6) J. H. Peters and V. E. Hayes, *Arch. Int. Pharmacodyn. Ther.*, **159**, 328 (1966).

(7) K. Kakemi, T. Arita, H. Sezaki, and N. Takasugi, *Chem. Pharm. Bull.*, **13**, 551 (1965).

(8) K. V. N. Rao, S. Kailasam, N. K. Menon, and S. Radhakrishna, *Indian J. Med. Res.*, **59**, 1343 (1971).

(9) W.-H. Wu, T.-F. Chin, and J. L. Lach, *J. Pharm. Sci.*, **59**, 1234 (1970).

(10) R. Gelber, P. Jacobsen, and L. Levy, *Clin. Pharmacol. Ther.*, **10**, 841 (1969).

(11) "The United States Pharmacopeia," 18th rev., Mack Publishing Co, Easton, Pa., 1970.

(12) M. M. Hodgkin, A. H. E. Hsu, P. Varughese, and L. Eidus, *Int. J. Clin. Pharmacol.*, **7**, 355 (1973).

(13) M. Lever, *Biochem. Med.*, **6**, 65 (1972).

(14) A. Rescigno and G. Segré, in "Drug Tracer Kinetics," Blaisdell, Waltham, Mass., 1966, p. 20.

(15) J. N. Miceli, W. A. Olson, and W. W. Weber, *Biochem. Med.*, **12**, 348 (1975).

(16) H. Bartels and P. Spring, *Chemotherapy*, **21**, 1 (1975).

(17) J. T. Stewart and D. A. Settle, *J. Pharm. Sci.*, **64**, 1403 (1975).

(18) J. T. Stewart, I. L. Honigberg, J. P. Brant, W. A. Murray, J. L. Webb, and J. B. Smith, "Abstracts of the 19th National Meeting of the APhA Academy of Pharmaceutical Sciences," vol. 5, American Pharmaceutical Association, Washington, D.C., 1975, p. 163.

(19) D. W. Russell, *Clin. Chim. Acta*, **41**, 163 (1972).

(20) T. O. O'Barr, D. J. Keith, and E. B. Blair, *Am. Rev. Resp. Dis.*, **107**, 472 (1973).

(21) E. G. Lovering, I. J. McGilveray, I. McMillan, and W. Tostowaryk, *J. Pharm. Sci.*, **64**, 1521 (1975).

ACKNOWLEDGMENTS AND ADDRESSES

Received October 14, 1976, from the *Drug Research Laboratories, Health Protection Branch, Ottawa, Ontario, K1A 0L2, Canada.*

Accepted for publication March 11, 1977.

The authors thank Dr. L. Eidus for valuable discussions, Dr. W. Tostowaryk for the statistical analyses of the results, and Dr. J. C. K. Loo and Mr. P. Fitzsimmons for setting up the computer program.

[x] To whom inquiries should be directed.

NOTES

Influence of Human Skin Surface Lipids on Protection Time of Topical Mosquito Repellent

W. A. SKINNER [x], H. C. TONG, H. JOHNSON, R. M. PARKHURST, D. THOMAS, T. SPENCER [*], W. AKERS [*], D. SKIDMORE [‡], and H. MAIBACH [‡]

Abstract □ Skin surface lipids were extracted from volunteers who had been ranked according to the duration of protection from mosquitoes by diethyltoluamide. These lipids were analyzed by GLC–mass spectrometry for their fatty acid contents. Correlations were found between total skin lipid content and protection time of diethyltoluamide and between certain fatty acid concentrations in the skin lipids and the protection time of diethyltoluamide.

Keyphrases □ Lipids, skin surface—effect on protection time of diethyltoluamide, humans □ Diethyltoluamide—protection time, effect of skin surface lipids, humans □ Repellents, insect—diethyltoluamide, protection time, effect of skin surface lipids, humans

Topical mosquito repellents protect some individuals longer than others. In studies of repellents applied to forearms, the repellency duration with diethyltoluamide (I) against female *Aedes aegypti* (yellow fever) mosquitoes varied in a reproducible way among the volunteers[1]. This report investigated the role of skin surface lipids in affecting the protection time of I toward mosquitoes.

Surface lipids contain certain components that are repellent to *A. aegypti* mosquitoes when evaluated in a dual-port olfactometer (1, 2). The primary repellency of these lipids is derived from the volatile fatty acids, whereas the hydrocarbon fraction exhibits a degree of repellency, primarily due to the unsaturated components present (3).

[1] W. Akers, unpublished data.