# Serum lipids and serum uric acid in human twins

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SUMMARY This report describes a study of serum total cholesterol, free cholesterol, glyceride glycerol, total phospholipids, and uric acid in human twins and is presented in three sections.

Section 1 presents evidence that interpair variance of free cholesterol, total cholesterol, total phospholipids, glyceride glycerol, and uric acid are significantly greater in dizygotic than monozygotic twins. Twins living apart have greater variance than twins living together; interpair variance is greater than intrapair variance for all variates. These results provide more conclusive evidence for genetic control of blood lipids and uric acid in normal man than has been available previously.

Section 2 presents interrelations of total cholesterol, glyceride glycerol, and uric acid. Glyceride glycerol and total cholesterol show significant regression coefficients in women but not in men.

Section 3 presents evidence that monozygotic twins show significant evidence of heterogeneity with respect to intrapair differences of total cholesterol, free cholesterol, glyceride glycerol, and uric acid. This argument is supported by two parallel lines of reasoning; a new approach to twin data which we have devised, and a method for studying the concept of zygosity in twins developed by Fisher before the introduction of blood typing for determination of zygosity. Demonstration that monozygotic twins do not form a homogeneous population focuses attention upon an unanswered question regarding the resemblance between twins which is deeply ingrained in twin studies but has received little recent attention.

KEY WORDS serum levels · free cholesterol · total cholesterol · uric acid · phospholipids · glyceride glycerol · human twins · monozygotic twins · dizygotic twins · intrapair variance · interpair variance · discordant · concordant · homogeneity

THIS REPORT is of a study of blood lipids and uric acid in human twins. Following a description of methods, the material is presented in three sections. Section 1 is an analysis of variance comparing monozygotic (MZ) and dizygotic (DZ) twins who live together and apart. A simultaneous study of serum total cholesterol, free cholesterol, total phospholipids, glyceride glycerol, and uric acid is presented. The lipid data augment and extend several previous studies. The data on uric acid are the first to be published.

Section 2 is a comparison of serum uric acid, glyceride glycerol, and total cholesterol levels. In addition to genetic information, the data used in section 1 provide the opportunity to study the interrelation of these variates in healthy individuals. Several recent reports indicate that total cholesterol, glyceride glycerol, and uric acid may be correlated in certain disease states, but little has been published about their interrelation in health.

Section 3 is an analysis of differences between MZ twins of the same pair. Our data indicate that MZ twins do not form a normally distributed population with respect to differences between twins of the same pair of total cholesterol, glyceride glycerol, free cholesterol, and uric acid. These results focus attention upon an unanswered question about twins, longstanding, but rarely discussed: can a continuously distributed characteristic transmitted by polygenic inheritance exhibit the phenomenon of concordance and discordance in MZ twins?

## MATERIALS AND METHODS

Sixty-seven pairs of twins were studied. These responded to a call for volunteers in a daily newspaper.[1] Twins were examined over a period of 6 months in the order in which they volunteered. They came from Los Angeles middle class families and were in good health. The younger twins were high school and college students. Most older twins were professional or business people

[1] We are indebted to the Los Angeles *Times* and Mr. Harry Nelson, its Medical Editor.

TABLE 1 THE MEAN AND STANDARD DEVIATION OF A SINGLE DETERMINATION, AND COEFFICIENT OF VARIATION OF LIPID ASSAYS, FROM 26 DETERMINATIONS OF A CONTROL SERUM POOL

| Determination | Mean | SD | C.V. |
|---|---|---|---|
| | *mg/100 ml* | | % |
| Total cholesterol | 200 | 7.1 | 3.5 |
| Free cholesterol | 59 | 3.9 | 6.6 |
| Total phospholipid | 239 | 4.1 | 1.7 |
| | *mg/liter* | | |
| Glyceride glycerol | 209 | 13.3 | 6.4 |

or their wives. All were Caucasians between 16 and 70 years of age. None had diabetes, myxedema, or nephrosis. None was pregnant or was receiving uricosuric or diuretic therapy.

The twins were seen fasting, in a clinic established for the purpose. A history was taken and a physical examination was done. A blood sample was taken at the first visit and another, also fasting, was taken 48 hr later. Blood was typed for blood factors, A, B: $Le^a$, $Le^b$, D, C, E, c, e; M, N; $Fy^a$; K; $P_1$; and Vel. Blood types were determined on specimens taken as whole blood into an equal volume of Alsever's solution. ABO tests were done at room temperature with saline cell suspensions, as were those for the M and N factor. The five standard tests for the Rh–Hr factors were done at 37°, also with saline cell suspensions. Crystalline trypsin treated cells were used in the $Fy^a$ test; this was done at 37° using the indirect antiglobulin technique. The latter technique was also used in tests for the Kell factor. Ficin treated cells incubated at 37° were used in the $Le^a$ tests.

Blood for lipid determination was allowed to clot; serum was separated, and stored at −10°. The serum specimens were assayed later, in random order. Ten assays were performed each laboratory day on nine test sera and one control aliquot of a pooled serum. Total cholesterol was determined by the method of Abell et al. (1), lipid phosphorus by the method of Chen et al. (2), and glyceride glycerol by the method of Blankenhorn, Rouser, and Weimer (3). Free cholesterol was determined by a solvent partition method developed in this laboratory.[2] Lipid phosphorus was multiplied by 25 to express total phospholipid in mg/100 ml. Glyceride glycerol is given in milligrams per liter. The control serum pool was made from samples obtained from hospitalized patients. It was divided into 5-ml aliquots and stored with test samples. During the experiment 26 determinations were made on the control serum to evaluate the precision of each determination. The results are given in Table 1.

[2] H. P. Chin and D. H. Blankenhorn. *Protein–lipid complex formation in extracts of human serum*, to be published.

Serum uric acid was determined in an autoanalyzer by modification of the phosphotungstic acid procedure of Henry et al. (4), modified to employ the sodium cyanide reagent of Brown for color development (5). All analyses were done in one run, which included 11 control aliquots of a single serum pool. The mean uric acid level of pooled serum specimens was 5.87 mg/100 ml, the standard deviation of a single determination being 0.09 mg/100 ml. This method yields results which are on the average 10% higher than when uric acid is determined with uricase (4), a disadvantage outweighed by the speed and precision of automated determination.

## SECTION 1. ANALYSIS OF VARIANCE OF SERUM TOTAL CHOLESTEROL, FREE CHOLESTEROL, TOTAL PHOSPHOLIPID, GLYCERIDE GLYCEROL, AND URIC ACID

The basic assumptions underlying twin studies are:

1. Intrapair differences (differences between twins of the same pair) of MZ twins are caused only by environment, while those between DZ twins reflect both environment and heredity.
2. Interpair differences (differences between pairs of twins) are differences between unrelated individuals and therefore reflect both the variability of genotype and environment.
3. Environmental differences are greater when twins live apart than when twins live together.

Three previous twin studies of blood lipids have been published by Osborne et al. (6), Gedda and Poggi (7), and McDonough et al. (8). Total cholesterol was studied by all. Osborne et al. included esterified cholesterol and total phospholipids. All authors concluded that both genotype and environment are important in determining blood lipid levels. Osborne et al. based this conclusion on the demonstration that average intrapair variances ($S^2$) for total cholesterol were consistently larger in DZ twins than in MZ twins, although these differences were not statistically significant. McDonough et al. based their conclusion on a comparison of intrapair differences in total cholesterol between a group of MZ twins and a group composed of DZ twins and paired siblings. They did not compare MZ with DZ twins alone. Gedda and Poggi reported significant differences between DZ twins and MZ twins, but their published figures have been rounded off, and intrapair agreement in MZ twins appears to be closer than is ordinarily seen with duplicate cholesterol assays of a single serum. Greater differences between twins living apart than between twins living together were demonstrated by McDonough et al. Osborne et al. found these differences to be of borderline significance.

Under these circumstances an additional twin study seemed indicated and is here reported. It includes all

lipid classes and uric acid. No previous study of serum uric acid in human twins has been published. It takes into account day-to-day changes in serum lipids and uric acid. In the work of previous authors the assumption is implied that lipid levels vary so little that one measurement of each twin furnishes a valid estimate of intrapair differences.

*Results*

Complete lipid assay data were obtained upon 48 pairs of twins (14 male MZ, 17 female MZ, 6 male DZ, 7 female DZ, and 4 mixed DZ). The comparison of blood lipids in MZ and DZ twins which follows is based on analysis of data from these 48 pairs. Assay data for the remaining pairs were not complete. Data from these twins were pooled with those from the 48 pairs to establish normal population values of blood lipids.

The total group of twins studied constituted a population with normal serum cholesterol values. This was established by calculating the mean value of total cholesterol levels and the standard deviation. For this purpose, each twin was considered only once and if values for 2 days were available they were averaged. The mean of our twin population determined from 133 cholesterol values was 214 ± 53 mg/100 ml. The mean of 117 normal individuals reported from Copenhagen by Kornerup was 218 ± 47 mg/100 ml (9). The mean of 683 normal individuals reported from Cleveland by Lewis et al. was 242 ± 50 mg/100 ml (10). A more detailed analysis of our data which considers age and sex is given in section 2.

Lipid values from the 48 pairs of twins used for the analysis that follows are given in Table 2. The conventional analysis of twin data was as follows. Twin pairs in each class were considered a homogeneous population and variances were determined by standard techniques. Experimental error and day-to-day $S^2$ was estimated and subtracted from inter- and intrapair $S^2$ using models given by Snedecor (11). The values of $S^2$ used in our analyses therefore reflect differences between twins more accurately than those from data of previous authors. This calculation was possible because we tested each twin twice, while previous authors tested each twin only once. A more detailed description of our method of calculating $S^2$ is given in section 3.

The results of our analysis of variance are given in Tables 3–5. Intrapair $S^2$ of total cholesterol, free cholesterol, total phospholipids, and glyceride glycerol was found to be significantly greater in DZ than in MZ twins (Table 3). When MZ and DZ twins were considered together, those twins who lived apart had a greater intrapair $S^2$ than did those living together (Table 4). The average interpair $S^2$ was greater than the average intrapair $S^2$ in both MZ and DZ twins, in respect to all lipid fractions except glyceride glycerol in DZ twins (Table 5).

Complete uric acid data were obtained for 44 pairs of twins (13 male MZ, 14 female MZ, 6 male DZ, 7 female DZ, and 4 mixed DZ). The comparison of uric acid in MZ and DZ twins which follows is based on analysis of data from these 44 pairs. Assay data for the remaining pairs were not complete. Data from these twins were pooled with those from the 44 pairs to establish normal population values of uric acid.

The total group of twin study subjects constituted a population with normal serum uric acid levels. This was established by calculating the mean value of uric acid and the standard deviation: 5.37 ± 1.23 mg/100 ml, n = 132. This is in satisfactory agreement with findings on normals furnished by Seegmiller et al. (12) and Hauge and Harvald (13), when differences in methods for determination of uric acid are taken into account. A more detailed analysis of our data which considers age and sex is given in section 2 of this paper.

Table 6 gives the uric acid levels of the 44 pairs of twins, and Tables 7–9 the results of the conventional analysis of them. $S^2$ of uric acid was found to be significantly greater in DZ than in MZ twins (Table 7). When MZ and DZ twins are considered together, those twins who lived apart had a greater intrapair $S^2$ than did those living together (Table 8). The average interpair $S^2$ in respect to uric acid was greater than the average intrapair $S^2$ in both MZ and DZ twins (Table 9).

*Discussion*

This study provides more conclusive evidence for genetic control of blood lipids in normal man than has been available previously. It provides the first evidence that the difference in $S^2$ in blood lipids in DZ and MZ twins is of statistical significance. Free cholesterol and total phospholipids exhibit differences significant at the 1% level. Total cholesterol and glyceride glycerol differences are significant at the 5% level. The present study confirms previous reports that interpair $S^2$ of twins is significantly greater than intrapair $S^2$, thereby confirming that serum lipids of relatives resemble each other more closely than serum lipids of unrelated members of the population. The present study also confirms previous reports that twins living apart have greater $S^2$ than twins living together, demonstrating that environmental effects also influence blood lipids. The present experiment does not partition precisely the relative contributions of genotype and environment to determination of blood lipids because this cannot be done by twin studies (14).

The uric acid findings provide clear evidence that genotype exerts a significant effect upon normal uric acid levels in man because $S^2$ between DZ twins is signi-

TABLE 2 DATA ON 31 MZ AND 17 DZ PAIRS OF TWINS. ALL VALUES ARE MG/100 ML EXCEPT GLYCERIDE GLYCEROL, WHICH IS IN MG/LITER

| Twin No. | Age Type | Apart/ Together | Total Cholesterol | Free Cholesterol | Total Phospholipids | Glyceride Glycerol | Twin No. | Age Type | Apart/ Together | Total Cholesterol | Free Cholesterol | Total Phospholipids | Glyceride Glycerol |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 8A | 16 | T | 188* | 51 | 211 | 117 | 12A | 49 | A | 300 | 83 | 294 | 256 |
| | MZM | | 200† | 51 | 222 | 112 | | MZM | | 296 | 83 | 288 | 251 |
| 8B | | | 161* | 47 | 192 | 120 | 12B | | | 234 | 62 | 234 | 294 |
| | | | 172† | 49 | 183 | 93 | | | | 213 | 66 | 236 | 232 |
| 13A | 16 | T | 152 | 40 | 183 | 95 | 42A | 53 | A | 280 | 83 | 290 | 228 |
| | MZM | | 144 | 40 | 156 | 112 | | MZM | | 288 | 81 | 326 | 164 |
| 13B | | | 160 | 41 | 183 | 97 | | | | 292 | 84 | 270 | 128 |
| | | | 150 | 38 | 171 | 142 | | | | 293 | 82 | 284 | 187 |
| 4A | 18 | T | 199 | 61 | 214 | 156 | 17A | 17 | T | 155 | 43 | 222 | 139 |
| | MZM | | 158 | 43 | 171 | 143 | | MZF | | 163 | 44 | 215 | 109 |
| 4B | | | 133 | 39 | 167 | 204 | 17B | | | 159 | 43 | 217 | 113 |
| | | | 153 | 45 | 191 | 212 | | | | 191 | 48 | 244 | 115 |
| 24A | 19 | T | 208 | 59 | 248 | 141 | 9A | 18 | T | 238 | 64 | 245 | 138 |
| | MZM | | 212 | 57 | 214 | ‡ | | MZF | | 224 | 63 | 214 | 106 |
| 24B | | | 196 | 52 | 224 | 114 | 9B | | | 227 | 62 | 214 | 136 |
| | | | 203 | 60 | 208 | 139 | | | | 227 | 62 | 214 | 105 |
| 36A | 19 | T | 175 | 47 | 199 | 140 | 28A | 18 | T | 152 | 45 | 186 | 92 |
| | MZM | | 181 | 52 | 192 | 172 | | MZF | | 145 | 37 | 177 | 81 |
| 36B | | | 173 | 48 | 174 | 110 | 28B | | | 153 | 43 | 189 | 88 |
| | | | 167 | 46 | 182 | 182 | | | | 145 | 40 | 183 | 88 |
| 7A | 29 | A | 175 | 51 | 187 | 145 | 1A | 21 | A | 151 | 41 | 169 | 87 |
| | MZM | | 151 | 42 | 146 | 101 | | MZF | | 140 | 37 | 162 | 93 |
| 7B | | | 184 | 53 | 191 | 110 | 1B | | | 147 | 40 | 167 | 86 |
| | | | 176 | 50 | 175 | 118 | | | | 137 | 39 | 153 | 75 |
| 14A | 33 | A | 165 | 46 | 198 | 125 | 3A | 21 | T | 225 | 67 | 236 | 217 |
| | MZM | | 192 | 52 | 213 | 154 | | MZF | | 255 | 71 | 260 | 212 |
| 14B | | | 206 | 62 | 198 | 163 | 3B | | | 202 | 53 | 214 | 158 |
| | | | 214 | 65 | 223 | 189 | | | | 192 | 54 | 197 | 73 |
| 37A | 36 | A | 203 | 58 | 228 | 333 | 11A | 32 | A | 222 | 65 | 252 | 227 |
| | MZM | | 206 | 59 | 224 | 253 | | MZF | | 200 | 56 | 226 | 141 |
| 37B | | | 195 | 56 | 203 | 139 | 11B | | | 217 | 61 | 255 | 148 |
| | | | 193 | 52 | 208 | 163 | | | | 192 | 58 | 228 | 129 |
| 41A | 36 | A | 141 | 41 | 183 | 143 | 38A | 34 | A | 190 | 49 | 215 | 106 |
| | MZM | | 154 | 45 | 183 | 165 | | MZF | | 195 | 50 | 192 | 92 |
| 41B | | | 228 | 62 | 254 | 211 | 38B | | | 183 | 49 | 183 | 73 |
| | | | 218 | 60 | 236 | 178 | | | | 200 | 48 | 216 | 98 |
| 31A | 39 | A | 206 | 62 | 281 | 455 | 39A | 36 | A | 233 | 63 | 273 | 131 |
| | MZM | | 193 | 57 | 246 | 391 | | MZF | | 214 | 59 | 262 | 108 |
| 31B | | | 224 | 54 | 246 | 263 | 39B | | | 277 | 52 | 306 | 260 |
| | | | 190 | 54 | 208 | 203 | | | | 294 | 61 | 308 | 167 |
| 35A | 42 | T | 233 | 69 | 222 | 181 | 80A | 39 | A | 153 | 48 | 223 | 110 |
| | MZM | | 205 | 59 | 214 | 157 | | MZF | | 161 | 47 | 208 | 111 |
| 35B | | | 304 | 85 | 261 | 164 | 80B | | | 193 | 55 | 240 | 123 |
| | | | 284 | 83 | 246 | 177 | | | | 188 | 55 | 235 | 80 |
| 33A | 45 | A | 263 | 72 | 262 | 258 | 30A | 41 | A | 203 | 63 | 261 | 222 |
| | MZM | | 302 | 87 | 290 | 300 | | MZF | | 195 | 58 | 257 | 242 |
| 33B | | | 316 | 88 | 296 | 276 | 30B | | | 195 | 55 | 239 | 173 |
| | | | 308 | 89 | 289 | 288 | | | | 207 | 59 | 222 | 139 |

(*continued*)

* Tests done on first blood sample.

† Tests done on the blood sample taken 48 hr later.

‡ Twin pair No. 24 was omitted from all glyceride glycerol analyses involving two days' tests. The estimates of significance given in Tables 3–5 take this omission into account.

TABLE 2 *Continued*

| Twin No. | Age Type | Apart/ Together | Total Cholesterol | Free Cholesterol | Total Phospholipids | Glyceride Glycerol | Twin No. | Age Type | Apart/ Together | Total Cholesterol | Free Cholesterol | Total Phospholipids | Glyceride Glycerol |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 32A | 41 | T | 196 | 57 | 242 | 90 | 70A | 49 | T | 243 | 70 | 243 | 205 |
| | MZF | | 200 | 58 | 246 | 85 | | DZM | | 253 | 69 | 252 | 189 |
| 32B | | | 202 | 55 | 252 | 114 | 70B | | | 276 | 74 | 278 | 190 |
| | | | 190 | 56 | 240 | 155 | | | | 286 | 79 | 288 | 213 |
| 5A | 42 | A | 228 | 60 | 271 | 152 | 61A | 26 | A | 112 | 35 | 155 | 95 |
| | MZF | | 226 | 67 | 281 | 171 | | DZF | | 137 | 42 | 167 | 130 |
| 5B | | | 220 | 59 | 249 | 106 | 61B | | | 144 | 42 | 162 | 130 |
| | | | 211 | 56 | 222 | 102 | | | | 145 | 41 | 155 | 87 |
| 22A | 44 | A | 242 | 73 | 282 | 133 | 65A | 36 | A | 200 | 52 | 231 | 107 |
| | MZF | | 223 | 62 | 252 | 180 | | DZF | | 161 | 42 | 200 | 118 |
| 22B | | | 231 | 61 | 270 | 104 | 65B | | | 249 | 64 | 247 | 147 |
| | | | 223 | 60 | 252 | 135 | | | | 224 | 60 | 223 | 119 |
| 34A | 45 | A | 248 | 68 | 261 | 92 | 16A | 48 | T | 298 | 80 | 278 | 153 |
| | MZF | | 246 | 69 | 262 | 119 | | DZF | | 297 | 78 | 280 | 131 |
| 34B | | | 237 | 70 | 263 | 165 | 16B | | | 304 | 84 | 298 | 257 |
| | | | 229 | 63 | 250 | 131 | | | | 310 | 85 | 306 | 228 |
| 43A | 47 | T | 222 | 66 | 238 | 292 | 68A | 49 | A | 302 | 93 | 300 | 161 |
| | MZF | | 224 | 64 | 247 | 201 | | DZF | | 286 | 77 | 319 | 278 |
| 43B | | | 259 | 72 | 257 | 275 | 68B | | | 286 | 80 | 283 | 179 |
| | | | 253 | 72 | 288 | 313 | | | | 345 | 102 | 298 | 164 |
| 6A | 48 | A | 204 | 60 | 261 | 151 | 77A | 49 | A | 252 | 71 | 261 | 85 |
| | MZF | | 171 | 52 | 222 | 136 | | DZF | | 257 | 72 | 263 | 135 |
| 6B | | | 203 | 62 | 257 | 160 | 77B | | | 320 | 100 | 360 | 445 |
| | | | 239 | 68 | 261 | 203 | | | | 266 | 73 | 238 | 372 |
| 81A | 51 | A | 195 | 55 | 261 | 89 | 2A | 52 | A | 237 | 66 | 270 | 96 |
| | MZF | | 194 | 54 | 261 | 137 | | DZF | | 209 | 58 | 235 | 104 |
| 81B | | | 280 | 76 | 308 | 235 | 2B | | | 294 | 83 | 316 | 178 |
| | | | 222 | 63 | 263 | 179 | | | | 319 | 85 | 343 | 170 |
| 69A | 16 | T | 149 | 43 | 161 | 118 | 82A | 70 | A | 336 | 98 | 336 | 165 |
| | DZM | | 124 | 32 | 147 | 93 | | DZF | | 325 | 85 | 326 | 110 |
| 69B | | | 147 | 40 | 175 | 127 | 82B | | | 256 | 66 | 246 | 135 |
| | | | 155 | 40 | 169 | 102 | | | | 223 | 64 | 247 | 165 |
| 64A | 17 | T | 174 | 48 | 197 | 188 | 63A | 17 | T | 162 | 43 | 159 | 80 |
| | DZM | | 165 | 49 | 190 | 123 | | DZM | | 128 | 33 | 148 | 114 |
| 64B | | | 184 | 52 | 197 | 160 | 63B | DZF | | 202 | 52 | 199 | 176 |
| | | | 168 | 47 | 181 | 129 | | | | 165 | 44 | 175 | 100 |
| 67A | 20 | T | 200 | 52 | 191 | 100 | 78A | 34 | A | 197 | 50 | 197 | 100 |
| | DZM | | 174 | 54 | 220 | 229 | | DZF | | 144 | 42 | 143 | 88 |
| 67B | | | 171 | 46 | 191 | 138 | 78B | DZM | | 289 | 76 | 269 | 252 |
| | | | 182 | 48 | 198 | 129 | | | | 267 | 71 | 244 | 153 |
| 60A | 42 | A | 318 | 93 | 302 | 222 | 73A | 56 | A | 296 | 83 | 277 | 233 |
| | DZM | | 339 | 93 | 288 | 248 | | DZM | | 296 | 83 | 298 | 252 |
| 60B | | | 368 | 83 | 278 | 243 | 73B | DZF | | 273 | 80 | 254 | 152 |
| | | | 336 | 73 | 316 | 233 | | | | 242 | 72 | 245 | 139 |
| 83A | 48 | A | 222 | 61 | 257 | 298 | 76A | 56 | A | 248 | 65 | 243 | 216 |
| | DZM | | 162 | 43 | 175 | 237 | | DZM | | 253 | 69 | 244 | 196 |
| 83B | | | 184 | 36 | 183 | 132 | 76B | DZF | | 326 | 89 | 352 | 156 |
| | | | 186 | 38 | 206 | 122 | | | | 352 | 92 | 354 | 135 |

TABLE 3 INTRAPAIR $S^2$ OF DZ VS. MZ TWINS

| | Total Cholesterol | Free Cholesterol | Total Phospho-lipids | Glyceride Glycerol |
|---|---|---|---|---|
| Intrapair $S^2$ of DZ (17)* | 2660 | 309 | 2350 | 9119 |
| Intrapair $S^2$ of MZ (31)* | 1110 | 76 | 702 | 3764 |
| *P* | <0.05 | <0.01 | <0.01 | <0.05 |

* Number of twin pairs in group.

ficantly greater than $S^2$ in MZ twins. It is well known that gout and hyperuricemia are familial. These data indicate that there is also a familial relationship in uric acid levels during health because interpair $S^2$ of both MZ and DZ twins is significantly greater than intrapair $S^2$. Twins living apart have greater $S^2$ than twins living together, which demonstrates that environment also affects serum uric acid levels, but, as with lipids, an exact partition between environmental and hereditary effects upon phenotype cannot be made from these data.

## SECTION 2. CORRELATION OF BLOOD URIC ACID, GLYCERIDE GLYCEROL, AND TOTAL CHOLESTEROL LEVELS

Most previous reports on the relation between uric acid and blood lipids have dealt with abnormal states. Elevated blood uric acid levels have been reported in familial xanthomatous hypercholesterolemia (15), hypercholesterolemia secondary to myxedema (16), and secondary to diabetes (17, 18). Elevated serum cholesterol has been reported in patients with gout and in gouty families (19–21). A recent report indicates that serum uric acid levels may be more closely related to glyceride glycerol than to serum cholesterol in gouty patients (22). Only one previous study reports on the interrelation of uric acid and blood lipids in normal man (23). This study was limited to persons over 65 years of age and demonstrated a correlation between total cholesterol and uric acid in men but not in women.

TABLE 4 INTRAPAIR $S^2$ OF ALL TWINS LIVING APART VS. $S^2$ OF ALL TWINS LIVING TOGETHER

| | Total Cholesterol | Free Cholesterol | Total Phospho-lipids | Glyceride Glycerol |
|---|---|---|---|---|
| Intrapair $S^2$ of all twins apart (30)* | 2185 | 219 | 1745 | 7892 |
| Intrapair $S^2$ of all twins together (18)* | 784 | 58 | 520 | 1834 |
| *P* | <0.05 | <0.01 | <0.01 | <0.01 |

* Number of twin pairs in group.

TABLE 5 INTERPAIR VS. INTRAPAIR $S^2$ OF MZ AND DZ TWINS

| | Total Cholesterol | Free Cholesterol | Total Phospho-lipids | Glyceride Glycerol |
|---|---|---|---|---|
| | *MZ Twins (31)** | | | |
| Interpair $S^2$ | 6074 | 502 | 4959 | 14266 |
| Intrapair $S^2$ | 1110 | 76 | 702 | 3764 |
| *P* | <0.01 | <0.01 | <0.01 | <0.01 |
| | *DZ Twins (17)** | | | |
| Interpair $S^2$ | 16151 | 1144 | 11014 | 7701 |
| Intrapair $S^2$ | 2661 | 309 | 2350 | 9119 |
| *P* | <0.01 | <0.01 | <0.01 | N.S. |

* Number of twin pairs in group.

In addition to providing information about human inheritance, the twin study is a valid method for collecting normal values of attributes unrelated to twinning. Twins constitute about 2% of most populations and, when selected only because they are twins, can provide an unbiased sample of normal individuals. Our twin population was drawn by a call for volunteers and is therefore not a random sample of all twins. However, it is as unbiased a sample as is presently practicable to draw from those who live in usual urban circumstances and who are willing to furnish blood. It has therefore been used to study the interrelation of total serum cholesterol, glyceride glycerol, and uric acid.

### *Results*

Average serum uric acid, total cholesterol, and glyceride glycerol by decades are shown in Table 10. Figures 1 and 2 show the relationship of glyceride glycerol and total cholesterol to uric acid in men; Figs. 3 and 4, similar relationships for women. The slopes of the regression lines for these relationships are shown in Table 11; only those for women were significant.

No significant relationship could be demonstrated in this group of twins between total phospholipid and uric acid.

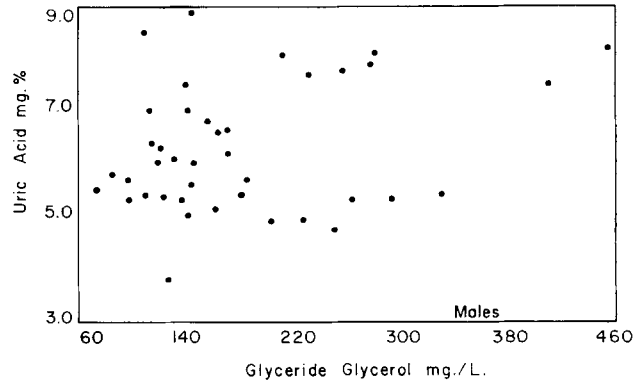


FIG. 1. Interrelation of uric acid and glyceride glycerol in males.

TABLE 6 DATA FOR URIC ACID ON 44 PAIRS OF TWINS

| Twin No. | Age Type | Uric Acid | Twin No. | Age Type | Uric Acid |
|---|---|---|---|---|---|
| 8A | 16 | 6.3* | 49A | 49 | 4.7 |
| | MZM | 7.1† | | MZM | 5.4 |
| 8B | | 6.0 | 49B | | 5.3 |
| | | 6.3 | | | 5.4 |
| 13A | 16 | 5.7 | 42A | 53 | 4.9 |
| | MZM | 5.4 | | MZM | 5.4 |
| 13B | | 5.3 | 42B | | 3.8 |
| | | 5.0 | | | 4.7 |
| 4A | 18 | 6.8 | 17A | 17 | 5.0 |
| | MZM | 5.4 | | MZF | 5.0 |
| 4B | | 4.9 | 17B | | 5.1 |
| | | 5.3 | | | 5.6 |
| 36A | 19 | 7.5 | 9A | 18 | 4.7 |
| | MZM | 6.9 | | MZF | 3.9 |
| 36B | | 8.5 | 9B | | 4.5 |
| | | 6.8 | | | 4.1 |
| 7A | 29 | 6.0 | 28A | 18 | 4.5 |
| | MZM | 4.9 | | MZF | 5.0 |
| 7B | | 5.4 | 28B | | 4.2 |
| | | 6.3 | | | 4.4 |
| 14A | 33 | 5.4 | 11A | 32 | 4.1 |
| | MZM | 5.1 | | MZF | 4.4 |
| 14B | | 5.1 | 11B | | 3.6 |
| | | 5.3 | | | 4.1 |
| 37A | 36 | 5.4 | 38A | 34 | 4.1 |
| | MZM | 6.0 | | MZF | 3.7 |
| 37B | | 5.4 | 38B | | 3.8 |
| | | 5.9 | | | 4.2 |
| 41A | 36 | 9.0 | 39A | 36 | 5.3 |
| | MZM | 9.0 | | MZF | 4.9 |
| 41B | | 8.1 | 39B | | 5.1 |
| | | 7.2 | | | 5.3 |
| 31A | 39 | 8.2 | 80A | 39 | 3.9 |
| | MZM | 7.5 | | MZF | 4.0 |
| 31B | | 5.3 | 80B | | 4.1 |
| | | 4.7 | | | 3.9 |
| 35A | 42 | 5.4 | 30A | 41 | 4.4 |
| | MZM | 5.4 | | MZF | 4.2 |
| 35B | | 6.6 | 30B | | 5.8 |
| | | 6.5 | | | 5.0 |
| 33A | 45 | 7.8 | 32A | 41 | 3.5 |
| | MZM | 7.4 | | MZF | 4.0 |
| 33B | | 8.1 | 32B | | 4.1 |
| | | 6.4 | | | 3.9 |

TABLE 6 *Continued*

| Twin No. | Age Type | Uric Acid | Twin No. | Age Type | Uric Acid |
|---|---|---|---|---|---|
| 22A | 44 | 3.9 | 61A | 26 | 4.1 |
| | MZF | 4.0 | | DZF | 3.9 |
| 22B | | 4.4 | 61B | | 4.5 |
| | | 4.2 | | | 4.6 |
| 34A | 45 | 3.9 | 65A | 36 | 4.1 |
| | MZF | 4.1 | | DZF | 3.2 |
| 34B | | 4.5 | 65B | | 4.4 |
| | | 3.8 | | | 3.7 |
| 43A | 47 | 5.3 | 16A | 48 | 5.0 |
| | MZF | 5.3 | | DZF | 5.5 |
| 43B | | 5.4 | 16B | | 5.5 |
| | | 5.8 | | | 5.3 |
| 6A | 48 | 5.0 | 68A | 49 | 4.7 |
| | MZF | 4.1 | | DZF | 4.3 |
| 6B | | 3.6 | 68B | | 4.5 |
| | | 4.0 | | | 5.3 |
| 81A | 51 | 4.4 | 77A | 49 | 4.7 |
| | MZF | 4.4 | | DZF | 4.8 |
| 81B | | 5.4 | 77B | | 6.2 |
| | | 5.6 | | | 4.6 |
| 69A | 16 | 4.2 | 2A | 52 | 5.5 |
| | DZM | 4.0 | | DZF | 4.9 |
| 69B | | 3.3 | 2B | | 5.6 |
| | | 4.1 | | | 6.2 |
| 64A | 17 | 8.9 | 82A | 70 | 5.2 |
| | DZM | 7.7 | | DZF | 5.4 |
| 64B | | 7.2 | 82B | | 6.7 |
| | | 7.3 | | | 6.4 |
| 67A | 20 | 6.5 | 63A | 17 | 8.5 |
| | DZM | 5.6 | | DZM | 6.6 |
| 67B | | 6.9 | 63B | DZF | 6.4 |
| | | 8.0 | | | 4.7 |
| 60A | 42 | 6.4 | 78A | 34 | 4.4 |
| | DZM | 5.5 | | DZF | 3.6 |
| 60B | | 4.9 | 78B | DZM | 8.1 |
| | | 4.4 | | | 6.9 |
| 83A | 48 | 5.7 | 73A | 56 | 6.4 |
| | DZM | 5.6 | | DZM | 6.2 |
| 83B | | 3.9 | 73B | DZF | 4.2 |
| | | 2.3 | | | 4.0 |
| 70A | 49 | 7.1 | 76A | 56 | 6.0 |
| | DZM | 7.6 | | DZM | 6.0 |
| 70B | | 7.8 | 76B | DZF | 4.5 |
| | | 8.1 | | | 5.2 |

* Tests done on first blood sample.

† Tests done on the blood sample taken 48 hr later. All values are mg/100 ml.

*Discussion*

The data in Table 10 show no apparent increase in uric acid levels with advancing age in men or women. The average values for uric acid of men of each decade are approximately 2 mg/100 ml higher than for women. These data are in accord with published values of uric acid levels in normals (12, 13). The average value of serum glyceride glycerol increases with age and is higher in men of each decade than in women, a finding also in accord with the results of others (24). Total cholesterol levels show an increase with age but do not show a consistent difference between the sexes, a finding in agreement with some, but not all, of the numerous published

studies relating age and sex to changes in total cholesterol levels (25).

Our data show that difference in sex has a greater effect on glyceride glycerol and uric acid than on total cholesterol levels. Because men have higher levels of both glyceride glycerol and uric acid than do women while total cholesterol levels show little if any difference, a comparison of the three variates without regard to sex must show a greater correlation between glyceride glycerol and uric acid than between total cholesterol and uric acid.

More meaningful correlations appear when the sexes are considered separately. Uric acid and glyceride glycerol show significant regression coefficients in women but not in men. Similarly uric acid and total cholesterol show significant regression coefficients in women but not in men. The two regression coefficients in women appear to be of the same magnitude.

Difference in sex has not been taken into account in reports of serum lipid–uric acid interrelations in disease. This may account for some of the conflicts in this growing literature. Our data indicate that uric acid and total cholesterol levels cannot be correlated in men but both are correlated in women. Our data do not show a significant difference in the degree of correlation between total cholesterol, glyceride glycerol, and uric acid levels in women. The difference between our findings and the one previous study of normal subjects (23) may be due to difference in the age of the subjects studied.

TABLE 7 Intrapair $S^2$ of DZ vs. MZ Twins

| | Uric Acid |
|---|---|
| Intrapair $S^2$ of DZ (17)* | 219 |
| Intrapair $S^2$ of MZ (27)* | 66 |
| *P* | <0.01 |

* Number of twin pairs in each group.

TABLE 8 Intrapair $S^2$ of All Twins Living Apart vs. $S^2$ of All Twins Living Together

| | Uric Acid |
|---|---|
| Intrapair $S^2$ of all twins apart (28)* | 157 |
| Intrapair $S^2$ of all twins together (16)* | 69 |
| *P* | <0.05 |

* Number of twin pairs in each group.

TABLE 9 Interpair vs. Intrapair $S^2$ of MZ and DZ Twins

| | MZ Twins Uric Acid (27)* | DZ Twins Uric Acid (17)* |
|---|---|---|
| Interpair $S^2$ | 543 | 544 |
| Intrapair $S^2$ | 66 | 219 |
| *P* | <0.01 | <0.05 |

* Number of twin pairs in each group.

## Section 3. Analysis of Differences Between Monozygotic Twins of the Same Pair

The problem of discordant MZ twins is always present at the core of twin studies but rarely discussed. In early twin studies only similarity of morphologic characteristics could be used to determine zygosity and the problem was obscured by doubt as to the zygosity of twins having dissimilar characteristics. However, Thorndike pointed out that twins sufficiently similar in most respects to be classified as MZ could always be found to differ in some respects if examined closely enough (26). He therefore disputed the concept of monozygosity and dizygosity in twins and proposed instead that they form a continuum of similarity. This viewpoint was attacked by Fisher who used measurements of stature, stem height, weight, and cephalic index to demonstrate that twins of the same sex are not a homogeneous population (27). Fisher's demonstration involved a method which he devised to evaluate the distribution of differences between twins of the same pair. In a homogeneous population these

TABLE 10 Average Uric Acid, Glyceride Glycerol, and Total Cholesterol Concentrations in 132 Twins

| Age | Number | | Uric Acid | | Glyceride Glycerol | | Total Cholesterol | |
|---|---|---|---|---|---|---|---|---|
| | Men | Women | Men | Women | Men | Women | Men | Women |
| | | | *mg/100 ml* | | *mg/liter* | | *mg/100 ml* | |
| 10–19 | 19 | 9 | 6.24 ± 1.21* | 4.34 ± .74 | 130 ± 29.2 | 101 ± 34.0 | 169 ± 22.3 | 181 ± 31.4 |
| 20–29 | 7 | 8 | 6.53 ± 0.84 | 4.66 ± .59 | 131 ± 21.0 | 120 ± 39.9 | 162 ± 29.3 | 174 ± 45.7 |
| 30–39 | 15 | 15 | 6.60 ± 1.18 | 4.19 ± .46 | 201 ± 74.2 | 125 ± 37.1 | 209 ± 33.1 | 200 ± 33.2 |
| 40–49 | 16 | 24 | 6.16 ± 1.43 | 4.61 ± .77 | 226 ± 69.0 | 172 ± 73.0 | 255 ± 56.0 | 211 ± 89.7 |
| 50–59 | 5 | 13 | 5.58 ± 0.83 | 4.67 ± .80 | 230 ± 73.5 | 139 ± 34.4 | 267 ± 36.0 | 253 ± 35.0 |

* Average and SD of a single determination.

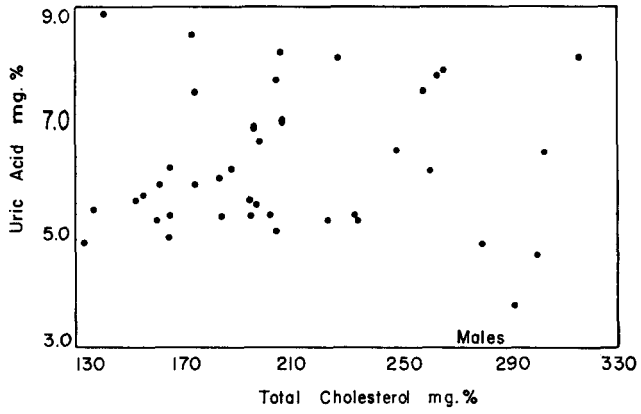


FIG. 2. Interrelation of uric acid and total cholesterol in males.

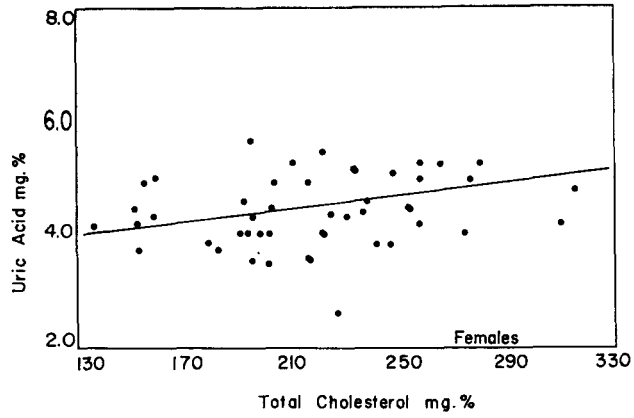


FIG. 4. Interrelation of uric acid and total cholesterol in females.

intrapair differences should be normally distributed and, Fisher reasoned, if this distribution is not normal, twins have been drawn from more than one population. Fisher demonstrated that differences in body measurement of twins of the same sex are not normally distributed. Fisher argued that if like-sexed twins are not a single population, it was because of the effect of mono- and dizygosity. Determination of blood type had not been introduced as an independent method for determination of zygosity at the time of Fisher's study.

Later Osato and Awano showed that twins that were proved by blood type to be MZ exhibit many discordant morphologic characteristics (28). Some, but not all, discordant morphologic characteristics appear to be adequately explained as the results of asymmetry in monozygotic twins. MZ twins have not been carefully examined for concordance and discordance of traits of the sort manifested by blood lipid or uric acid levels, partly because of the lack of adequate methods to classify continuously variable twin differences as concordant or discordant. A first approach to the problem, using Fisher's formula to test twin populations for heterogeneity after selection by blood typing, seems reasonable but has not been attempted.

As described in section 1 our twin experiments differ from those of previous workers in our approach to day-to-day variation. In past twin studies, only one determination of the variate under study has been made for each twin, or if multiple determinations have been made they were averaged before the final calculation of $S^2$. We measured each twin twice and calculated our data differently. The difference in calculation is illustrated for estimation of total $S^2$ of the set of twin pairs $X,X' \ldots Xn,Xn'$. Previous workers have substituted the values $X,X' \ldots Xn,Xn'$ into the equation:

$$S^2 = \frac{\Sigma x^2 - (\Sigma x)^2/n}{n - 1} \quad (\textit{Equation 1}).$$

We calculated total $S^2$ for the same twin set after each twin had been measured twice by constructing a table such as Table 12. The values $X_{\text{day 1}}$, $X'_{\text{day 1}} \ldots Xn_{\text{day 2}}$, $Xn'_{\text{day 2}}$ were substituted into Equation *1* and n was adjusted accordingly to calculate total $S^2$. Interpair and intrapair $S^2$ were calculated from appropriate subtotals according to models given by Snedecor (11).

In the section which follows, an alternative approach has been used: individual 2 × 2 tables of the type shown

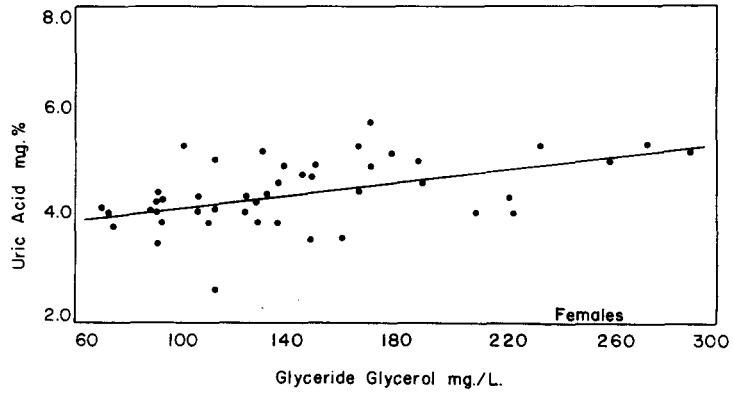


FIG. 3. Interrelation of uric acid and glyceride glycerol in females.

TABLE 11 SLOPE AND STANDARD DEVIATION OF THE SLOPE OF REGRESSION OF GLYCERIDE GLYCEROL AND TOTAL CHOLESTEROL ON URIC ACID IN MEN AND WOMEN

| | Men (n = 40) | | | Women (n = 45) | | |
|---|---|---|---|---|---|---|
| | Slope | SD of Slope | P | Slope | SD of Slope | P |
| Glyceride Glycerol–Uric Acid | 0.038 | ±0.022 | N.S. | 0.059 | ±0.015 | <0.01 |
| Total Cholesterol–Uric Acid | 0.012 | ±0.040 | N.S. | 0.0468 | ±0.021 | <0.05 |

in Table 13 were constructed for each twin pair and $S^2$ was calculated for each pair separately. Total $S^2$ for twin pair $X,X'$ was calculated by substituting $X_{\text{day 1}}$, $X'_{\text{day 2}}$, $X_{\text{day 2}}$, and $X'_{\text{day 2}}$ into Equation *1* and total $S^2$ for twin pair $Xn$ and $Xn'$ by substituting $Xn_{\text{day 1}}$, $Xn'_{\text{day 1}}$, $Xn_{\text{day 2}}$, and $Xn'_{\text{day 2}}$ into Equation *1*. N is now 4 for each twin pair. With this method the $S^2$ associated with differences between days varies greatly in different sets of twins, but is properly pooled with experimental error because the effect of days upon twins is not additive (29). The $S^2$ associated with differences between twins is calculated by subtracting day $S^2$ and residual $S^2$ from total $S^2$.

### *Results*

Two by two tables were constructed for each twin pair, and $S^2$ was analyzed in each table as described above. The results are shown in Fig. 5, which illustrates histograms of interpair $S^2$ of MZ twins arranged in order of ascending magnitude. The $S^2$ values of total cholesterol, free cholesterol, glyceride glycerol, and uric acid appear to fall into at least two populations. The $S^2$ of total phospholipids appears to form a continuum except for two outstanding values.

TABLE 12 THE MANNER OF TABULATING TWIN PAIRS X,X' ... XN,XN' FOR ANALYSIS OF $S^2$ AS USED IN SECTION 1

| | Day 1 | Day 2 |
|---|---|---|
| Twins | $X_{\text{day 1}}$<br>$X'_{\text{day 1}}$<br>.<br>.<br>.<br>.<br>.<br>$Xn_{\text{day 1}}$<br>$Xn'_{\text{day 1}}$ | $X_{\text{day 2}}$<br>$X'_{\text{day 2}}$<br>.<br>.<br>.<br>.<br>.<br>$Xn_{\text{day 2}}$<br>$Xn'_{\text{day 2}}$ |

TABLE 13 THE MANNER OF TABULATING TWIN PAIRS $X,X'$ AND XN,XN' IN 2 × 2 TABLES FOR CALCULATION OF INDIVIDUAL INTRAPAIR $S^2$

| | Day | Day | | Day | Day |
|---|---|---|---|---|---|
| Twins | $X_{\text{day 1}}$<br>$X'_{\text{day 1}}$ | $X_{\text{day 2}}$<br>$X'_{\text{day 2}}$ | Twins | $Xn_{\text{day 1}}$<br>$Xn'_{\text{day 1}}$ | $Xn_{\text{day 2}}$<br>$Xn'_{\text{day 2}}$ |

The formula devised by Fisher and used by him to demonstrate the existence of two populations (DZ and MZ) in randomly selected twins of like sex was next applied to our data. For these calculations values obtained for each twin on each day were averaged and the difference in averages was used. The results shown in Table 14 reveal significant evidence for heterogeneity in the MZ twin population in regard to total cholesterol, free cholesterol, glyceride glycerol, and uric acid. The premise underlying this test for heterogeneity is given below the table.

The chance is small that the phenomenon here described is caused by a wrong diagnosis of zygosity. The histograms in Fig. 5 indicate that the discordant groups of total cholesterol, free cholesterol, and glyceride glycerol are comprised of five, six, and four twin pairs respectively. If the three twin pairs of each group with greatest intrapair $S^2$ are discarded, the evidence of

TABLE 14 TESTS FOR HETEROGENEITY IN MZ TWINS

| | Total Cholesterol | Free Cholesterol | Total Phospholipids | Glyceride Glycerol | Uric Acid |
|---|---|---|---|---|---|
| n | 31 | 31 | 31 | 31 | 27 |
| $\bar{d}$ | 24.12 | 5.9 | 21 | 42 | 5.74 |
| $\bar{d^2}$ | 1115.41 | 71.70 | 704 | 3649 | 67.44 |
| $\bar{d^2} - \frac{\pi}{2}\bar{d}^2$ | 201.45 | 17.01 | −3.8 | 8.78 | 15.68 |
| SD | 55.57 | 6.85 | — | 3.17 | 3.37 |

"If d is the difference of any one pair, found by subtracting the less measurement from the greater, and d stand for the mean difference, $\bar{d^2}$ for the mean of the squared differences, then for a large sample of normally distributed values we should have

$$\bar{d^2} = \frac{\pi}{2}\bar{d}^2$$

whereas, for a mixture of two such populations, with different mean differences, $\bar{d^2} - \frac{\pi}{2}\bar{d}^2$ should be positive. To utilize this fact it is necessary to know the standard error of $\bar{d^2} - \frac{\pi}{2}\bar{d}^2$ and this is found to be

$$\frac{\bar{d^2}}{\sqrt{n}}(2\pi - 6) = 0.5321\frac{\bar{d^2}}{\sqrt{n}}$$ "[Fisher, (27)].

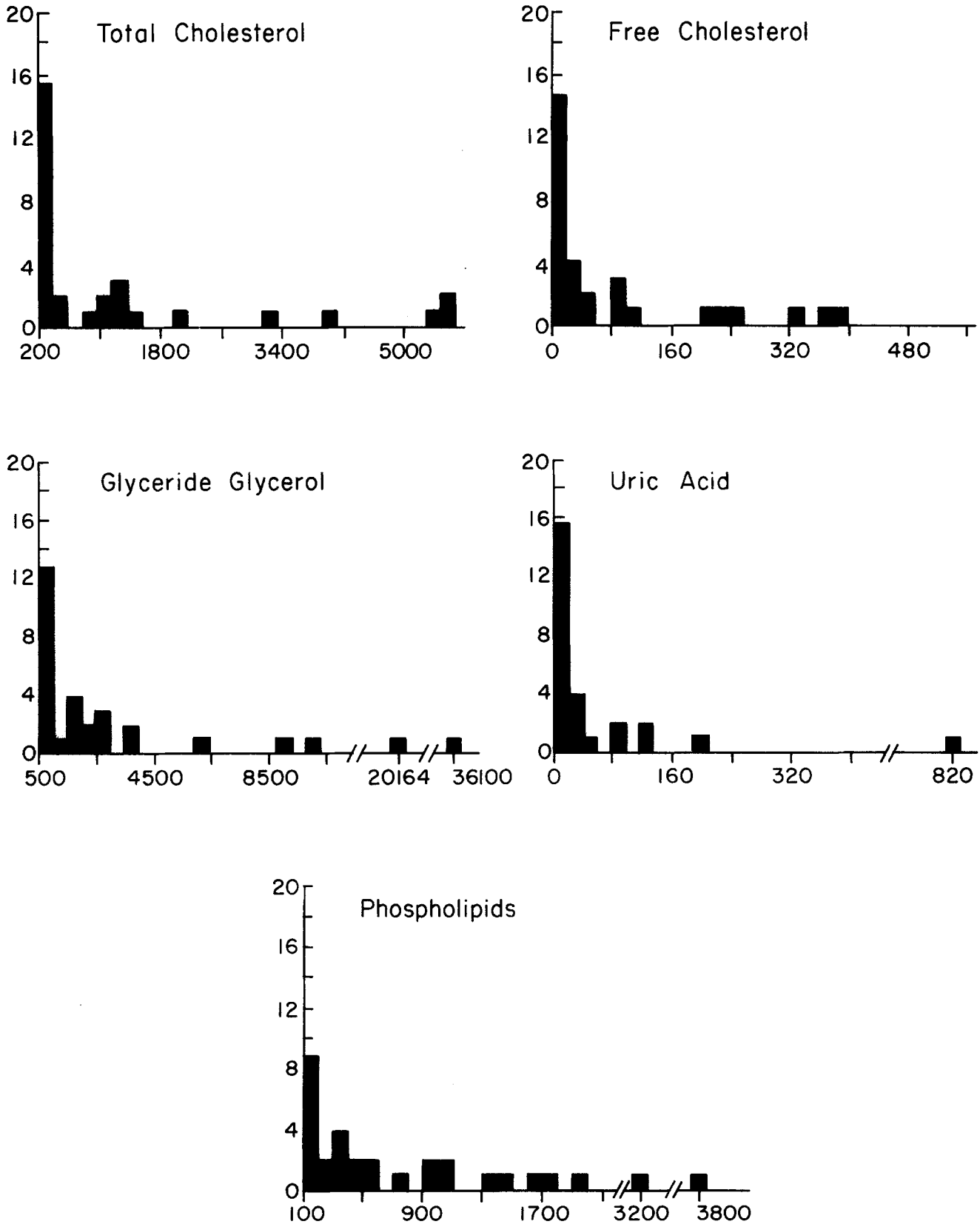


FIG. 5. Intrapair $S^2$ in MZ twins of total cholesterol, free cholesterol, total phospholipids, glyceride glycerol, and uric acid. Magnitude of $S^2$ is shown on abscissa, number of cases on ordinate. Total cholesterol, free cholesterol, glyceride glycerol, and uric acid appear to fall into at least two populations. Total phospholipids form a continuum.

heterogeneity remains significant in all groups. The chance that the three twin pairs discarded from each group are dizygous is less than 0.005 (30). The histogram of uric acid $S^2$ indicates that the discordant group may be only one twin pair, and this argument cannot be applied to the phenomenon as shown by uric acid levels.

*Discussion*

Our data clearly indicate that MZ twins identified by blood typing are not a homogeneous population with respect to intrapair differences in total cholesterol, free cholesterol, glyceride glycerol, and uric acid. The implication of our data is that they constitute more than one population. As a first approach in considering our findings we postulate that there may be two populations which correspond to the concordant and discordant groups observed in morphologic studies of twins whose zygosity is determined by blood typing.

Current concepts regarding the cause of difference in continuously variable polygenic traits between MZ twins attribute this to the effect of environment, which is also a continuous variable (31). Differences between MZ twins should therefore comprise a single population, and our finding does not appear to have any ready explanation in the literature regarding twins. However, MZ twins have not been investigated in a systematic manner for heterogeneity of continuous variables and the implications of more than one population of MZ twins have not been considered in relation to current concepts of the interaction of nature and nurture in twins. One previous twin study of total cholesterol levels applies the term *discordant* to unexpectedly large differences in some twins, but the usage is only a casual adaptation of a term used in morphologic studies (7).

Our argument based on the present data involves difficulties inherent in demonstrating the existence of more than one population in a small group. Evidence for heterogeneity of MZ twins was discovered when we considered various means to take day-to-day variation into account in our calculations. When this evidence came to light, we reviewed the literature on twins and found an approach used by Fisher in 1925 to study the concept of zygosity. This method appears to have received little attention, but when coupled with determination of zygosity by blood typing it is applicable to the problem in our data. It confirms the more laborious calculations we have made.

The phenomenon of heterogeneity in MZ twins has been demonstrated for serum free cholesterol, total cholesterol, glyceride glycerol, and uric acid but not for total phospholipids. The incidence of discordant morphologic characteristics is known to vary greatly, and possibly the incidence of MZ twins discordant for total phospholipids is quite small. Further examination of this question with fractionation of serum phospholipids seems to be necessary.

Although the mechanism underlying discordance of serum lipids and uric acid in MZ twins is not known, the phenomenon has an important bearing on genetic studies of serum lipids and uric acid. Determination of the resemblance between relatives, a basic part of any pedigree analysis, can be greatly affected if discordant twins occur in the family. Our results indicate that approximately 20% of MZ twins may be considered to be discordant with respect to total cholesterol, free cholesterol, and glyceride glycerol and that a smaller percentage may be considered discordant with respect to uric acid. Some factor alters the expression of genotype in these discordant twins to a degree that equals all apparent environmental effects encountered in usual urban living. No known relationship exists between the process of twinning and control of serum lipids and uric acid. It therefore seems reasonable to believe that the same factor which alters the expression of genotype in one or both of discordant MZ twins may also affect the serum lipids and uric acid of some persons who are not twins. Pedigree studies based on small kindreds may be markedly affected by the presence of such individuals.

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