with about 20% of bloods (St-negative), all of which must therefore be homozygous RhRh and represent about half the Rh-positive homozygotes—about 38% of the population. Race and Taylor pointed out that the extent of any preponderance of homozygotes among the fathers of erythroblastotic children should be indicated by the proportion found to be St-negative. In 46 families in which the disease occurred and in which all the mothers were Rh-negative and had anti-Rh agglutinins in their sera, 18 of the fathers have been St-negative and 28 St-positive. If about half of the homozygotes are St-negative, then it appears that of 46 fathers about 36 were homozygous; these frequencies, compared with those expected in the general population, are:

46 fathers	Observed St - 18	Observed St + 28	Estimated Homozygotes 36	Estimated Heterozygotes 10
46 random Rh+ men	Expected St - 10-11	Expected St + 35-36	Expected Homozygotes 20	Expected Heterozygotes 26

and in that case the homozygous fathers would be $\frac{36}{10} \times \frac{26}{10}$ —i.e., 4.68—times more dangerous than the heterozygous. The difference in distribution among the fathers and the normal population is highly significant statistically. Again, in a normal population of 46 Rh-positive persons 10 or 11 are expected to be St-negative and about 35 St-positive: that 18 fathers were St-negative and 28 St-positive is statistically significant.

Further evidence of the preponderance of homozygous fathers in affected families is given by the results of more recently discovered tests which determine certain Rh genotypes. The inheritance of the Rh groups is determined by a series of multiple allelomorphs, and by the use of different sera from the mothers of erythroblastotic babies the genotypes of about 80% of persons can be recognized. (See Race and Taylor, 1943; Race, Taylor, Boorman, and Dodd, 1943; Race, Taylor, Cappell, and McFarlane, 1944.)

Of the 46 fathers 38 were examined by tests which recognize the Rh₁rh and Rh₂Rh₁ genotypes. In the general population the frequency of Rh₁rh is about 33%—that is, about 40% of Rh-positives. Of 38 Rh-positive fathers, therefore, 15 would be expected to be Rh₁rh and 23 not Rh₁rh. But only 5 fathers were Rh₁rh—a highly significant departure from expectation, which shows a marked shortage of this commonest type of heterozygote. Thus:

	Rh ₁ rh	Not Rh ₁ rh
38 fathers: observed	5	33
38 random Rh+ men: expected	15	23

In 435 unselected donors the ratio of the genotype Rh₁Rh₁ to Rh₁rh was almost exactly 1 to 2; but of these 38 fathers 14 were Rh₁Rh₁ and 5 Rh₁rh—again a highly significant shortage of Rh₁rh.

The tests on the last 18 of the 46 fathers made it possible to recognize the following genotypes:

	Rh ₁ Rh ₁	Rh ₁ Rh ₂	(Homo- zygotes)	Rh ₁ rh	Rh ₂ rh or Rh ₂ Rh ₁	(Hetero- zygotes)
Observed	7	6	(13)	3	2	(5)
Expected	4	3	(7)	8	3	(11)

The serological tests do not yet differentiate between the genotypes Rh₁rh and Rh₂Rh₁, but, assuming the two fathers in this group are heterozygotes, then there are 13 homozygotes and 5 heterozygotes, whereas 7 and 11 would be expected in the general population: the discrepancy is on the verge of statistical significance. The 18 fathers have 23 Rh₁ genes to 8 Rh₂ genes—practically the same ratio, 41 to 15, found in the general population. This suggests that both genes are equally effective in producing the disease.

It may be thought that the manner of ascertainment has been responsible for the high proportion of homozygous fathers found in our sample, and that the diagnostic support given by a history of more than one jaundiced baby may make a doctor the more likely to send us blood samples and thus

prejudice our series in favour of homozygous fathers. This difficulty can be overcome if we consider fathers of families in which only one child is erythroblastotic. There are 26 such; 9 of them are St-negative—a proportion not very different from that found in the remaining families with 9 St-negative fathers out of 20. Twenty of the fathers of families with a single affected child were examined by the tests which recognize Rh₁rh and Rh₂Rh₁, and they show a significant shortage of Rh₁rh, there being only 2 instead of the expected 8, while the ratio of Rh₁rh to Rh₂Rh₁ is 2 to 7 instead of the expected 6 to 3.

Conclusions and Summary

The findings reported prove that there is a marked preponderance of homozygous fathers in families affected by haemolytic disease of the newborn; the homozygote appears to be about four or five times more dangerous than the heterozygote. This predominance of homozygotes affects enormously the chances of Rh-negative, and therefore unaffected, children being born. The genotype of about three-quarters of Rh-positive people can be determined serologically, and unless it can be shown that the father is heterozygous in this way, or by his having an Rh-negative child or an Rh-negative parent, the prognosis is entirely unfavourable.

REFERENCES

- Race, R. R., and Taylor, G. L. (1943). *Nature*, **152**, 300.
 ——— Boorman, K. E., and Dodd, B. E. (1943). *Ibid.*, **152**, 563.
 ——— Cappell, D. F., and McFarlane, M. N. (1943). *British Medical Journal*, **2**, 289.
 ——— (1944). *Nature*, **153**, 52.

Medical Memoranda

Latent Malaria presenting as Anaemia

Anaemia is a well-known feature of malaria, both during the acute phase of the disease and in convalescence. Treatment by iron is not by any means always necessary, but in most cases is quickly curative. An anaemia, nevertheless, may occur which is both iron-resistant and susceptible to antimalarial therapy, at a time when the parasite would not normally have been suspected as the causative factor. Two such cases of anaemia are here reported. Response to antimalarial treatment was immediate and satisfactory in both cases.

CASE I

During Oct., 1942, this man had a first attack of clinical malaria which was apparently successfully cured by the usual course of treatment (quinine-mepacrine-pamaquin), but ever since then he had complained of general weakness, occasional cough, pains in the joints, and loss of weight. There were no rigors or sweats, and he was apyrexial. He was seen as an out-patient on Dec. 30—two months after his initial illness—when his condition suggested a blood count. This showed: R.B.C., 3,170,000; Hb, 70% (Sahli); C.I., 1.1; W.B.C., 5,100—polymorphs 38%, lymphocytes 56%, monocytes 6%.

He was admitted to hospital five days later. Detailed physical examination revealed a young man in poor condition and with marked pallor. Temperature 99°; pulse 80. Tongue furred; throat clear. Heart normal in size and position; rhythm regular. On auscultation there was a widespread systolic murmur, best heard along the left border of the sternum. B.P. 120/60. The lungs showed no abnormality. The liver was palpable and tender. The spleen was not palpable. Blood films for malaria parasites were persistently negative.

X-ray films of the chest showed no abnormality. On Jan. 1, 1943, a blood count gave: R.B.C., 3,640,000; Hb, 90% (Sahli); C.I., 1.2; W.B.C., 6,000 (polymorphs 53%, lymphocytes 42%, monocytes 3%, eosinophils 2%). Intensive iron therapy was instituted (ferri et ammon. cit. gr. 120 per diem). After one week the red cells had diminished by 20,000 and the Hb by 10%. Symptoms were not diminished, and his condition was unchanged. Some days later he suddenly developed an acute pyrexial illness, during which M.T. parasites were found in the blood film. Iron was discontinued and antimalarial treatment given. At the end of the treatment the red cell count had risen to 4,390,000, and when the patient was discharged fit and symptom-free a few days later this number had reached 5,500,000, with 96% Hb and 12,200 white cells, although anti-anemic treatment by iron had not been reinstituted.

CASE II

A prisoner of war, 42 years old, admitted to hospital on May 11, 1943, complained of weakness, headache, and slight diarrhoea. There was a history of ten attacks of malaria in the previous five years.

On examination the patient was found to be pale but not icteric. Temperature normal; tongue coated. Some petechial spots were

present on gums and palate. The chest was normal. The spleen was palpable and tender. Pathological examination of the stools showed no evidence of dysentery. In four days the stools were repeatedly normal and the blood count was: R.B.C., 2,900,000; Hb, 57%; C.I., 1.0; W.B.C., 13,000. Intensive iron therapy and liver diet for 16 days produced no beneficial effects—in fact, there was a diminution of 490,000 in the red cell count and 8% in the Hb estimation. His temperature remained normal, his spleen was palpable, and no malaria parasites were found in the blood films. Since neither symptoms nor anaemia had been improved by iron therapy and liver diet this was stopped, and replaced by a full course of antimalarial treatment. The response was immediate. By the end of the course he was symptom-free; the spleen was not palpable; and the blood count was: R.B.C., 4,350,000; Hb, 82%; C.I., 0.9; W.B.C., 5,800 (P. 69%, L. 22%, M. 6%, E. 3%).

British Military Hospital, Khartum.

G. BAUM, Lieut., R.A.M.C.

Two Cases of Imperforate Anus

In view of the comparative rarity of the condition, perhaps the two cases here reported may be of interest in that they illustrate two of the different varieties of the condition.

CASE I

The baby had been born precipitately 48 hours before I was called to see it by a district midwife, who informed me that it had vomited repeatedly and had passed no meconium since birth. On examination it was an apparently normal full-term child, weighing 5 lb. 7 oz., but obviously an ill one. Its temperature and pulse were normal, but the abdomen was somewhat distended and the child vomited every feed that was given. It was admitted to hospital the same day, and x-ray photographs confirmed the clinical diagnosis of imperforate anus. Operation was undertaken that evening and an attempt made to divide the septum which had been shown to separate the rectum from the anal canal. This, however, proved impossible owing to the narrowness of the orifice and the distance of the septum from the anus, so an iliac colostomy was performed. A considerable amount of fluid was found in the peritoneal cavity. There was a recurrence of vomiting later the same night and the stomach was washed out, but the child died in the early hours of the morning.

CASE II

This child, with its mother, was transferred to the Northern Hospital from the hospital in which the birth had taken place; transference was for the mother's convalescence. Birth had been by forceps delivery, and the infant had apparently been considered quite normal and its condition satisfactory. It was apparently a 40-weeks baby, and weighed 8 lb. 1 oz. at birth. It was receiving three-hourly feeds at the breast. The day after arrival at this hospital the infant was obviously ill. Its weight had fallen to 7 lb. 5 oz., its colour was poor, and the abdomen was distended. On examination it was at once seen that no anal orifice existed. This fact had apparently been missed previously owing to the napkins having been stained with meconium, which, it now appeared, was being passed via the urethra.

Immediate operation was performed under ether anaesthesia and an attempt made to find the lower end of the bowel through a cruciform perineal incision, but it soon became evident that no rectum existed at all. While on the operating table meconium was passed from the penis. An iliac colostomy was therefore performed, but the child's condition continued to deteriorate and it died the same night.

At the necropsy there was complete absence of the rectum, and a fistula existed between the lower end of the bowel and the membranous urethra. A dissection of the affected organs was made and mounted, and subsequently accepted by the museum of the Royal College of Surgeons.

COMMENT

The first of these cases illustrates the type of imperforate anus in which a complete membranous septum persists between the post-allantoic gut and the proctodaeum. Case II belongs to the group in which the original communication with the cloaca persists—associated, as is usually the case, with non-development of the post-allantoic gut.

I wish to record my thanks to Dr. A. G. Wilkinson for permission to publish Case I: to Dr. Björckgren, under whose care Case II was admitted to this hospital and who diagnosed the condition; to Mr. W. Rothwell, who performed the operation and made the post-mortem dissection; and to Dr. G. A. Borthwick, medical superintendent, Northern Hospital.

Northern Hospital, N.21.

IAN A. J. MCCREADY, M.R.C.S.

It is reported from Berlin that a single fruit of a specific Bulgarian white rose contains about 4,000 to 5,000 mg. vitamin C. This (according to *Svenska*, Aug. 24, 1943) is a sensational discovery, as hitherto the quantity of vitamin C in vitamin-bearing plants ranged from 400 to 1,000 mg. At the same time, a new method of vitamin extraction has been introduced in Bulgaria, and it is expected that this industry will revolutionize the economic life of that country. The dried seeds are to be compressed into tablets, each of which will contain 20 mg. vitamin C.

Reviews

MODERN STATISTICS

The Advanced Theory of Statistics. By Maurice G. Kendall, M.A. Volume I. (Pp. 457. 42s.) London: Charles Griffin and Co. 1943.

The 457 quarto pages of vol. I of Maurice G. Kendall's book bring back vivid memories to a reader whose statistical education began more than 40 years ago. Even at that time the mathematical literature of the theory of probability was already large; a good deal had been written which those whose formal education in mathematics had been elementary found difficult reading. But textbooks in the titles of which the words "statistics" or "statistical" appeared were descriptive and arithmetical rather than algebraical. In the 40 years general mathematical education has been improved. A youth who has reached the standard of a Higher School Certificate in mathematics may not have much more difficulty in reading Mr. Kendall's book than his father, or grandfather, with equivalent training, had with Todhunter's *History of the Mathematical Theory of Probability* and—this is the essential difference—will cover a much wider field of practically important knowledge.

The columns of a medical journal are not the proper place, even were the reviewer a proper person, for a critical analysis of a primarily mathematical treatise. But as the medical profession numbers in its ranks men of varied non-professional learning, and as statistical analysis has become an orthodox method of medical research, it is proper to indicate the scope of the book and the change in the intellectual attitude of statisticians which it illustrates. A reader of a mathematical book has two difficulties: the writer may assume knowledge of methods and results the reader does not have; he may use a notation or a calculus which is unfamiliar. In this book the difficulties are rather of the second than the first class. We think that an amateur who reads carefully a pamphlet by the late H. E. Soper entitled *Frequency Arrays* (published by the Cambridge University Press in 1922) would find Mr. Kendall's exposition easier to follow. We should add that Mr. Kendall follows the admirable example of Karl Pearson—viz., provides arithmetical examples wherever possible.

Comparing past with present, summarily, we may note that the great pioneers of half a century ago, particularly Karl Pearson, were empiricists in the best sense of the term. Their new methods were powerful instruments, but their logical justification of them was much less complete than we, their pupils, or perhaps they themselves, supposed. It is indeed certain that Karl Pearson did not suppose he had placed the method of moments upon a wholly satisfactory basis of mathematical logic, but his pupils were often free from doubts. A comparison of Pearson's article in *Biometrika* (1902, 1, 265) with Mr. Kendall's 4th chapter, especially pp. 105 *et seq.*, shows how far we have travelled since 1902.

But that does not mean the debt to Karl Pearson is small and that those medical biometricians who "fit" by moments are wasting their time. A natural association of ideas leads one to compare the editorial on probable errors of frequency constants in the second volume of *Biometrika* (1903, p. 273), which was the model we admired 40 years ago, with Mr. Kendall's 9th, 10th, and 11th chapters. We know now, among other things, that it is not quite so easy to evaluate sampling moments as we had thought, and that moments are not the most useful functions to study. Here we might remark that a reader coming fresh to *k*-statistics would find a little book by the late P. A. Macmahon (*An Introduction to Combinatory Analysis*, C.U.P., 1920) helpful. Macmahon wrote this booklet (71 pages) as an introduction to his large treatise; the modern history of statistics shows how wise was Macmahon's own remark that "the theory of probabilities is to a large extent concerned with and dependent upon the enumeration of combinations subject to conditions, and almost every theorem in combinatory analysis has its application to that theory" (*Combinatory Analysis*, vol. I, p. vi). We are, however, diverging from the general to the particular. The remaining chapters of Mr. Kendall's book, treating of association