Only in details do we diverge. My older cases, contrary to Keynes's general assessment, have done fully as well as the cases of brief duration. I have deliberately avoided operating upon mild cases, or those fully maintained under oral medication. Good remissions may often be provoked by judicious treatment with neostigmine alone. Some, in my hands, are complete and of long duration; indeed, equal to those seen after thymectomy. I would consider less than half of 300 patients seen since 1935 as proper candidates for thymectomy, based on our present knowledge of the variable course of the disease. Patients with few symptoms, those responding in a balanced manner to neostigmine, no matter what the dose, most patients over 40 years of age, and particularly those having wide swings of remission and relapse, are not, as I view the problem to-day, best treated by thymectomy.

Secondly, I have not seen "myasthenic crises" characterized by excessive bronchial secretion. Patients may drown in their own secretions, but this, in my experience, is due to excessive or ill-considered use of neostigmine, not to the myasthenia gravis. Before the era of neostigmine, patients died a "dry death," except for pharyngeal accumulation due to dysphagia and inability to cough. Controlled neostigmine, intravenously, has largely removed this hazard during operation.

Finally, my patients do not "hold on" to neostigmine when the need for it is not present. The drug, a powerful stimulant of the parasympathetic system, is poorly tolerated by the non-myasthenic or the myasthenic in full remission. Tolerance to neostigmine, moreover, does not develop. Patients who have been taking the drug since 1935 still find it as effective to-day as when the first tablet or injection was given. That is why it is so valuable over the "long pull"; few other forms of medication can equal it in this respect.

Keynes's experience with 155 patients and his careful analysis of his results have set a pattern traditionally expected of British surgery. Others can only follow and report their results until such a time as general conclusions are justified. That time has not yet come. The key has been fitted to the lock and even partially turned, but the door is not open and what lies behind has not been even disclosed.

I acknowledge with thanks the co-operation received from Edward D. Churchill, Oliver Cope, and Richard H. Sweet, surgeons to the Massachusetts General Hospital; from Benjamin Castleman, pathologist, and my associate in the Myasthenia Gravis Clinic, Robert S. Schwab; as well as the continued support of Hoffmann-LaRoche, Inc., its president, medical director, and other officers.

REFERENCES

- Castleman, B., and Norris, E. H. (1949). *Medicine*, **38**, 27.
 Keynes, G. (1949). *British Medical Journal*, **2**, 611.
 Mattis, R. D. (1941). *Arch. Ophthalmol.*, **26**, 969.
 Schwab, R. S., and Viets, H. R. (1938). *New Engl. J. Med.*, **219**, 226.
 — (1941). *Amer. J. Roentgenol.*, **45**, 357.
 Viets, H. R. (1945). *J. Amer. med. Ass.*, **127**, 1089.
 — Schwab, R. S., and Brazier, M. A. B. (1942). *Ibid.*, **119**, 236.

An article in the *Ministry of Labour Gazette* (December 29, 1949) describes the Ministry's efforts to recruit more nurses and midwives. The situation is said to be improving steadily, though there is still urgent need for more recruits to these professions. During the twelve months ended September 30, 1949, 42,000 interviews were given and 15,000 vacancies were filled. Of these, 3,000 were for trained nurses and midwives, 6,300 were for students, and 6,100 were for unqualified nursing staff. Since the war there has been a general improvement in the staffing of hospitals and the health services. During the year ended June 30, 1949, the number of nursing and midwifery staff employed in hospitals rose by about 15,000, and the number of occupied beds rose by 10,000. The number of students training to be nurses has greatly increased in recent years. In 1943 there were about 43,300 students training to be nurses or midwives; in 1949 the number was 57,800. The demand for nurses continues to increase, and there are still no fewer than 30,000 vacancies on the books of the nursing appointments offices.

PROGUANIL-RESISTANT FALCIPARUM MALARIA IN MALAYA

BY

J. F. B. EDESON, M.B., Ch.B.

AND

J. W. FIELD, M.D.

From the Institute for Medical Research, Federation of Malaya

Some of the earliest and still the most complete trials of proguanil ("paludrine") in falciparum malaria were made in 1946 by the Australian Medical Research Team directed by Fairley in Queensland (Fairley *et al.*, 1946). The results seemed decisive: strains of *Plasmodium falciparum* of South-West Pacific origin were sensitive to proguanil at important strategic points in their life history. The pre-erythrocytic forms were destroyed by a single minute dose appropriately timed to the infecting bites; and persons bitten many times were fully protected by 100 mg. given every day. The asexual blood forms were equally sensitive: acute infections were relieved by a single dose of 100 mg. and cured by a 10-day course of 300 mg. a day. Exposure of the gametocytes to therapeutic doses of proguanil arrested sporogony in the mosquito.

The wide range, the high potency, and the low toxicity of proguanil in falciparum malaria excited much interest, and as supplies became available clinical trials began in other parts of the world. The results in South-East Asia were generally good: the clinical response in acute attacks of malaria was perhaps slower than with quinine or mepacrine, but the suppressive activity of a weekly dose of 300 mg. or even 100 mg. was high. Elsewhere the results were equivocal—particularly in Africa and Southern Europe, where the tendency to a slow clinical response and the failure to cure seemed to demand reinforcement with a more active schizonticide, and where a daily dosage of 100 mg. was needed for efficient suppression (Bettini, 1948; Walls, 1948; Abbott, 1949; Covell *et al.*, 1949). Geographical strains, it seemed, showed differences in the proguanil sensitivity of the asexual blood forms.

Experimental evidence had shown in the meantime that proguanil sensitivity in malaria is not constant for a given species or strain, but tends to wane with prolonged exposure to the drug. Resistance could be produced experimentally in *P. gallinaceum*, a malaria parasite which infects the domestic chicken, *P. lophurae*, a parasite of ducks, and *P. cynomolgi* in monkeys; a resistance so marked in *P. gallinaceum* that the parasites became less sensitive to the proguanil than were the chicks themselves, and so persistent that it survived passage through the mosquito (Bishop and Birkett, 1947, 1948; Williamson *et al.*, 1947; Rollo *et al.*, 1948; Hawking and Perry, 1948). Still more significant was the experimental production of proguanil resistance in *P. falciparum* and *P. vivax* (Adams and Seaton, 1949; Seaton and Adams, 1949).

Proguanil Resistance in Naturally Acquired Falciparum Infections of Malayan Origin

Experimental trials of proguanil, sponsored by the Colonial Medical Research Committee, began in this institute early in 1947. They were planned to give information on the therapeutic and suppressive activity of the drug in acute malarial infection. The therapeutic tests were made on subjects with naturally acquired malaria admitted from neighbouring rubber estates and kampongs to the Tampin Malaria Branch of the institute.

FIG. 1.—Monthly incidence of failure with single-dose proguanil therapy in acute falciparum infection.

TABLE I.—Incidence of Failure with Single-dose Proguanil Therapy in Acute Falciparum Infection

Single Dose	1947		1948		1949	
	Cases	Failures	Cases	Failures	Cases	Failures
100 mg.	6	0	20	0	—	—
250 mg.	—	—	15	4	45	10
300 mg.	33	0	26	0	27	7
Total	39	0	61	4	72	17

The Rising Incidence of Failure with Single-dose Proguanil Therapy.—The therapeutic dosage of proguanil covered a considerable range, but many subjects received only a single dose of 100 to 300 mg.—a deliberate test of minimal dosage designed to confirm, for Malayan strains, the high sensitivity to proguanil reported by Fairley *et al.* (1946) in New Guinea strains. During 1947 the clinical response to single-dose proguanil therapy in acute falciparum infection was good. There was, in fact, little to choose between a single proguanil dose of 100–300 mg. and a course of 300 mg. daily for five days: the fever and parasitaemia cleared at about the same rate. The first intimation of resistance,

slight but definite, was in October, 1948, when a patient treated with a single dose of 250 mg. failed to respond; there have been 20 failures* since—one out of every four cases treated by this method (Table I and Fig. 1).

The mean daily parasitaemia in the cases treated in 1947, 1948, and 1949 is shown in Figs. 2 and 3. The mean parasite count on the first day in the 19 cases which, at the time when Fig. 3 was prepared, had failed to respond to the single proguanil dose was 18,000 per c.mm. of blood, with a range from 2,000 to 71,000 per c.mm.: the mean initial count in 76 cases treated between February, 1947, and October, 1948, when resistance first appeared, was 16,500 per c.mm., with a range of 100 to 80,000.

The Sudden Emergence of Failure with Standard Proguanil Therapy.—The apparent proguanil resistance in falciparum infections observed at the end of 1948 and in the early months of 1949 was a resistance to a single small dose. It was disappointing that this safe and easy method of clinical cure, so hopeful in 1947, was beginning to fail, but the efficiency of a standard proguanil course of 300 mg. daily for 7–10 days was not, as yet, seriously questioned. The clinical response was slow, but it seemed sure. In April, 1949, came our first failure with a standard therapeutic proguanil dosage; and in May and June, 1949, there

FIG. 4.—Chart of Case 1.

were six more in each month. The clinical and parasitological records of five of these cases are given below. (The body weight of the adult Indian is about two-thirds that of the European adult: this difference should be taken into account in assessing the proguanil response.) The drugs were given by one of us. Thick blood films were examined morning and evening, and daily parasite counts were made by the Dreyer-Sinton fowl-cell technique. Daily examination of the urine for proguanil was made to check absorption of the drug.

Case Reports

Case 1.—An Indian woman aged 20 was admitted on June 1, 1949, to accompany her child. She developed fever with mild falciparum parasitaemia while in hospital, and was treated with a single dose of 250 mg. of proguanil without significant effect on the fever or parasitaemia. She was then given a therapeutic course of proguanil, which began on the fifth day at 300 mg. daily and rose to 800 mg. daily on the twentieth day. On the twenty-third day she complained of loss of appetite—an indication, perhaps, that her tolerance for proguanil was being strained. There was patent parasitaemia on most days throughout an observation period of 61 days, with continuous fever for 20 days. Her general condition throughout remained good. The total proguanil dosage over the period of 49 days' irregular parasitaemia was 14.3 g. (Fig. 4).

Case 2.—An Indian man aged 25 was treated in April, 1948, for an acute falciparum infection with a single dose of 100 mg.

FIG. 2.—Mean daily parasitaemia in 26 cases of acute falciparum malaria receiving a single proguanil dose of 100 mg.

FIG. 3.—Mean daily parasitaemia in 133 cases of acute falciparum malaria receiving a single proguanil dose of 250 or 300 mg.

*“Failure” in this context means that there was still parasitaemia on the seventh day, or that therapeutic intervention was necessary before the seventh day.

of proguanil; parasitaemia and fever disappeared within three and a half days. The patient was readmitted on May 5, 1949, again with falciparum infection, and treated with a single proguanil dose of 250 mg., which failed to control the parasitaemia, though he became afebrile on the sixth day. The later history is shown in Fig. 5. During an observation period of 102 days he received five therapeutic courses of proguanil totalling 22.5 g.: he is on his sixth course at the time of writing and becoming somewhat restive. During the fifth course of 500 mg. daily for 14 days he complained of abdominal pain, and this dose may have been near his limit of tolerance.

Case 3.—An Indian boy aged 12 was admitted on May 18, 1949, with an acute falciparum infection and treated with a

FIG. 5.—Chart of Case 2.

the parasite count was 268,000 per c.mm. with a few segmenting forms. He stated that he had taken 200 mg. of proguanil daily for three days before he came to hospital; the urine gave a

FIG. 6.—Chart of Case 3.

single dose of 200 mg. of proguanil. For the next 10 days there was parasitaemia every other day, apparently from a single-brood infection. Thereafter four separate courses of proguanil of 200 or 300 mg. daily failed to clear the blood of parasites. He remained remarkably free from symptoms. The total proguanil dosage over 59 days' observation was 9.7 g. (Fig. 6).

Case 4.—An Indian man aged 29 was admitted on June 8, 1949, with light falciparum parasitaemia, fever, and cough. No parasite count was made, as the infection seemed to be complicated and unsuitable for observation. He was given 300 mg. of proguanil daily for 10 days. The parasitaemia remained and an increased dosage was given. There was irregular parasitaemia through 28 days' observation and irregular fever for 22 days. The total proguanil dosage over 27 days was 7.6 g. (Fig. 7).

Case 5.—An Indian man aged 28 was admitted on June 3, 1949, with a fairly severe falciparum infection;

FIG. 7.—Chart of Case 4.

250 mg. of proguanil daily. Fever and parasitaemia continued; the parasite count on the sixth day was 47,000 per c.mm. and the temperature 104° F. (40° C.); at this point there was therapeutic intervention with chloroquine. He was discharged on June 16. The course of two later proguanil-treated falciparum attacks, probably relapses, is shown in Fig. 8.

By way of contrast with Cases 1 to 5 is the dramatic response of a grave falciparum infection in the following case.

positive proguanil reaction. He was given 500 mg. of proguanil on the first day. The temperature on the second day had fallen to 98° F. (36.7° C.) and the parasitaemia to 25,000 per c.mm. From the second to the fifth day he received

CHLOROQUINE

FIG. 8.—Chart of Case 5.

FIG. 9.—Response to proguanil therapy of an extremely heavy falciparum infection (Case 6).

Case 6.—A male Indian child aged 1 year had been ill for five days when admitted to hospital on June 18, 1949, with an extremely heavy falciparum infection. The parasite count was 710,000 per c.m.m.; 20% of the red cells were infected. The child made an uninterrupted recovery on a proguanil dosage of 100 mg. daily. The rapid fall in parasitaemia is shown in Fig. 9.

This is the heaviest non-fatal infection recorded in the Malaria Division of this institute during experimental observations, over nearly twenty years, of about 2,500 acute falciparum infections.

Comment

Most of the evidence of proguanil resistance in malaria is experimental. Resistance appears when the parasites are exposed to sublethal doses of the drug and passed by blood inoculation from host to host, the increase in resistance being assessed by the relation of the least dose originally active to the least active dose after exposure to the drug. Some of this evidence is summarized in Table II.

Resistance to proguanil seems to be essentially—we cannot yet say exclusively—a resistance of the asexual blood forms, transmissible through the gametocyte and sporozoite. Whether in human malaria the sporogonic forms may become resistant is not known; nor is it known whether the pre-erythrocytic parasites in falciparum malaria are liable to lose their normal sensitivity. Rollo *et al.* (1948) discuss the mechanism of proguanil resistance. They show that resistance appears in *P. gallinaceum* when

the full impact of treatment falls on large numbers of asexual blood forms, but not when the small numbers of parasites present in latent infections are exposed to the drug. A likely explanation, they suggest, is that resistant

parasites occur spontaneously as rare mutants in a normally sensitive strain; and, as a result of selective survival of these resistant mutants when the parasites are exposed to the drug, a stable resistant strain emerges. The impetus towards proguanil resistance would thus be greater when overt malaria is treated and parasites are many than in suppressed malaria when parasites are few.

The rubber estates from which most of our patients were drawn have used proguanil for malaria suppression for many months, some for two years or more. Cases 1 to 5 all came from estates where there was mass suppression with proguanil at a dosage ranging from 100 mg. once a week to 200 mg. twice a week. Case 6 lived on an estate where proguanil was not used—a coincidence, perhaps, for the proportion of successes and failures with single-dose therapy since October, 1948, when resistance first appeared, has been about equal in proguanil-protected and non-protected areas. It is unfortunate that we cannot assess the complex interchange of human and anopheline populations in neighbouring protected and non-protected areas; but the significant fact, we suggest, is the widespread use of proguanil in the Tampin district for the past two years. This fact, we believe, is related to the emergence of the resistant strains of *P. falciparum* which we are beginning to meet in our Tampin centre.

The appearance of drug resistance after mass treatment is no new phenomenon. Van Hoof (1947) reports a marked increase in the incidence of arsenic-resistant trypanosome infections after methodical treatment with tryparsamide: resistant infections in the Leopoldville district of the Belgian Congo increased from 7% to more than 50% between 1938 and 1947. Will there be a like trend in the mass suppression of malaria with proguanil? Proguanil resistance has not yet become a serious embarrassment in Malaya. The drug is used with confidence and success by the medical services, the Army, and rubber companies; and foci where proguanil-resistant malaria has appeared are probably few and scattered. But will they remain scattered?

TABLE II.—Experimental Proguanil Resistance in Malaria

Author	Species	Host	Months to Acquire Degree of Resistance Indicated	Blood Passage at which Resistance Appeared	Degree of Resistance	Persisting Resistance After Mosquito Passage
Bishop and Birkett (1947, 1948)	<i>P. gallinaceum</i>	Chick	4½	23rd	+++ × 20-40	Yes
Williamson <i>et al.</i> (1947)	"	"	7	60th	× 4	"
Thompson <i>et al.</i> (1948)	<i>P. lophurae</i>	Duck	14	Same animal	+++ × 2,000	Yes
Hawking and Perry (1948)	<i>P. cynomolgi</i>	Monkey	20	3rd	× 80	"
Schmidt <i>et al.</i> (1949)	<i>P. vivax</i>	Man	10	27th	+++	"
Seaton and Lourie (1949)	<i>P. falciparum</i>	"		10th	+++	"
Adams and Seaton (1949); Seaton and Adams (1949)	"	"			+++	"

+++ Dose resisted by parasite approaches limit of tolerance of host.

or will they spread, and will resistance increase, until the drug ceases to be a useful schizonticide?

Proguanil resistance in malaria seems most likely to arise when the drug is used to treat acute infections without curing them, and when sporadic bursts of parasitaemia occur during haphazard suppression. We may discourage the emergence of resistant strains by raising the standards of treatment. Covell *et al.* (1949) have already proposed that proguanil therapy in acute falciparum malaria should be reinforced with mepacrine to raise the cure rate. This danger of proguanil resistance lends further support to their recommendation. Regular suppression is theoretically a safeguard against the spread of resistant strains, for proguanil not only arrests the development of *P. falciparum* in the mosquito (Fairley *et al.*, 1946; Mackerras and Ercole, 1948; Covell *et al.*, 1949) but also destroys the parasite in the human host at the pre-erythrocytic stage, which is not known to become resistant (Fairley *et al.*, 1946). But haphazard proguanil suppression is a potential menace, and we may have to consider whether, if we cannot use proguanil efficiently, we should use the drug at all for this purpose, or whether, if we cannot guarantee regular administration, it would be advantageous to alternate proguanil suppression with suppressive measures based on mepacrine or chloroquine, which are not known to produce resistant strains. These are problems which demand attention if proguanil is to retain the important role in the treatment and prevention of malaria which its outstanding merits have so deservedly won.

Summary

Acute falciparum infections treated in the Tampin district of the Federation of Malaya with a single dose of 100–300 mg. of proguanil do not respond as they did two years ago. There were no failures in 1947: now about one infection in every four fails to respond.

Until May, 1949, no falciparum infection treated by us had resisted full therapeutic doses of proguanil: seven infections observed between May and July, 1949, resisted proguanil doses as great as, or greater than, the standard therapeutic course. The daily parasitaemia in five of these infections is recorded.

Proguanil has been used widely but probably sporadically for the past two years throughout the Tampin district, whence the patients were drawn.

The implications of these observations are briefly discussed.

REFERENCES

- Abbott, P. H. (1949). *British Medical Journal*, **1**, 413.
 Adams, A. R. D., and Seaton, D. R. (1949). *Trans. R. Soc. trop. Med. Hyg.*, **42**, 314.
 Bettini, S. (1948). *Riv. Parasit.*, **9**, 107. Cited by Covell *et al.* (1949).
 Bishop, Ann, and Birkett, Betty (1947). *Nature, Lond.*, **159**, 884.
 — (1948). *Parasitology*, **39**, 125.
 Covell, G., Nicol, W. D., Shute, P. G., and Maryon, M. (1949). *British Medical Journal*, **1**, 88.
 Fairley, N. H., *et al.* (1946). *Trans. R. Soc. trop. Med. Hyg.*, **40**, 105.
 Hawking, F., and Perry, W. L. M. (1948). *Lancet*, **2**, 850.
 Mackerras, M. J., and Ercole, Q. N. (1948). *Ibid.*, **41**, 365.
 Rollo, I. M., Williamson, J., and Lourie, E. M. (1948). *Ann. trop. Med. Parasit.*, **42**, 241.
 Schmidt, L. H., Genter, Clara S., Fradkin, R., and Squires, Wanda (1949). *J. Pharmacol.*, **95**, 397.
 Seaton, D. R., and Adams, A. R. D. (1949). *Lancet*, **2**, 323.
 — and Lourie, E. M. (1949). *Ibid.*, **1**, 394.
 Thompson, P. E., *et al.* (1948). *J. infect. Dis.*, **83**, 250.
 Van Hoof, L. M. J. J. (1947). *Trans. R. Soc. trop. Med. Hyg.*, **40**, 728.
 Walls, E. S. (1948). *British Medical Journal*, **2**, 225.
 Williamson, J., Bertram, D. S., and Lourie, E. M. (1947). *Nature, Lond.*, **159**, 885.
 — and Lourie, E. M. (1947). *Ann. trop. Med. Parasit.*, **41**, 278.

HIRSCHSPRUNG'S DISEASE IN INFANCY

BY

E. D. BURNARD, M.B.N.Z., M.R.C.P.

Registrar, Children's Department, Newcastle-upon-Tyne
General Hospital

From the work of Bodian *et al.* (1949) emerges a clear picture of the problem of megacolon in childhood without obvious organic cause. In the condition which they denote true Hirschsprung's disease the colonic dilatation and hypertrophy end at some level above the rectum. Over the length of apparently normal bowel below the dilated portion ganglion cells of the myenteric plexus are absent, though they are present in normal numbers in the megacolon itself. By careful radiography, with oblique and lateral views, the functional obstruction can be demonstrated as a narrowing of the lower sigmoid which communicates with a small rectum. The above-named writers have applied with good results the two-stage operation, devised by Swenson and Bill (1948), of rectosigmoidectomy with restoration of bowel continuity.

It is commonly accepted that symptoms may date from birth. Von Reus (1920) fully describes the clinical picture in the newborn. Ehrenpreis (1946) traces the development of megacolon from the neonatal period, and Zuelzer and Wilson (1948) give the clinical findings in a number of young infants in whom they discovered the histological lesion already referred to. The present report is concerned with symptoms and prognosis in the neonatal period and early infancy, and with other aspects of the problem as they bear on the management of the neonatal group. Seven cases have been followed up for eight months from a few days of birth, and the records of 23 others are available. Survivors in the latter group have been re-examined.

Clinical Features

Of seven neonates (4 male and 3 female), three were observed from birth in a maternity department, three were seen on the third day, and one was seen on the eighteenth day. Vomiting was the first symptom—in four babies within 24 hours of the first feed. Its frequency increased and the vomits soon contained bile. Delay in the passage of meconium and distension were then noted. Six days was the longest initial period of complete constipation. Two of the infants passed meconium in the first 24 hours and thereafter in small amounts for three days. As the distension increased, small-intestine ladder patterning was seen twice and visible gastric peristalsis once. More common was the finding of one or more greatly distended loops of gut standing out on the abdominal wall, along which infrequent peristaltic waves could be traced. After digital examination or an enema a great deal of flatus and meconium was passed, vomiting settled, and further meconium stools and then faeces were passed normally for a few days. The baby was sent home with its mother after the usual puerperium or was promptly discharged when it had been admitted from the district.

Readmission to hospital followed in a few days with a relapse of the vomiting, distension, and constipation. Three of the babies were now seriously underweight and somewhat dehydrated, and a fourth was desperately ill with faecal vomiting. In this baby (Case 5) the relapsed state persisted up to death at 3 weeks, on the evening of a