CLINICAL RESEARCH

Rationalisation of regimens of treatment of kala-azar with sodium stibogluconate in India: a randomised study

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Abstract

The efficacy and safety of six regimens of treatment for kala-azar (visceral leishmaniasis) with sodium stibogluconate were evaluated in a prospective randomised study to ascertain the optimal treatment for Indian patients. Altogether 371 patients with kala-azar were randomised to receive sodium stibogluconate intramuscularly at a dose of 10 mg/kg body weight/day for 20 or 40 days (groups A and A1, respectively), 15 mg/kg body weight/day for 20 or 40 days (groups B and B1, respectively), or 20 mg/kg body weight/day for 20 or 40 days (groups C and C1, respectively). Patients were examined blind before and at the end of treatment and every month for six months. The number of patients who were apparently cured—that is, those whose temperature had returned to normal at the end of their regimen of treatment—was 45 (78%) in group A, 53 (87%) in group A1, 50 (81%) in group B, 60 (95%) in group B1, 58 (92%) in group C, and 62 (97%) in group C1.

At six months 62 patients (97%) in group C1, 51 (81%) in group C, 54 (86%) in group B1, 42 (68%) in group B, 45 (74%) in group A1, and 33 (57%) in group A had not relapsed and were cured as confirmed by a bone marrow aspirate free of parasites. The differences between groups C1 and C, B1 and B, and A1 and A were significant. Logistic regression of the proportion cured with the dose and length of treatment showed that both factors were significant in improving the rate of cure; the highest dose for the longer time (group C1) had the best rate of cure. One patient in group C1, 12 in group C, nine in group B1, 18 in group B, 15 in group A1, and 23 in group A were cured with extended courses of 20 mg sodium stibogluconate. One patient in each of groups C1, B, A1, and A became unresponsive to antimony and were cured

with pentamidine. One patient in each of groups C1, B, and A became unresponsive to both antimony and pentamidine. The patients tolerated the longer duration of treatment safely, and side effects were minor.

Sodium stibogluconate should be given intramuscularly in the dosage of 20 mg/kg for at least 40 days, when patients should be assessed for further treatment if necessary. Such a regimen should achieve the highest rate of cure with low toxicity and low rates of relapse and unresponsiveness.

Introduction

Manson-Bahr's regimen of six days' treatment with 6 ml sodium stibogluconate given intramuscularly or intravenously for kala-azar (visceral leishmaniasis) has largely been followed in India.¹ With this regimen the rate of relapse was about 30% in the current epidemic in Bihar, which started in the 1970s.² Increasing the duration of treatment to 20 days or more, if necessary, greatly reduced the rate of relapse and unresponsiveness.^{3,4} The World Health Organisation suggested that the optimal regimen of treatment should be established for each geographical region.⁵ This encouraged us to find out through a randomised trial the most effective and safe of the six regimens of treatment for kala-azar with sodium stibogluconate that we had designed. We report the outcome of the trial.

Patients and methods

We undertook this trial to rationalise the dosage of antimony according to body weight and to determine the regimen of treatment that would reduce the rate of relapse and unresponsiveness and achieve the highest rate of cure. We also wanted to assess whether Indian patients could tolerate longer treatment and a higher dose of drug than have so far been used in India. We needed a sample of at least 60 based on past experience and assuming a rate of drop out and spontaneous cure of zero and a difference in the rate of cure between the standard treatment and the new treatment of 20%.⁶

The study was conducted from June 1984 to March 1987. All patients with kala-azar, confirmed by the finding of leishmania amastigotes (figure) in a smear of bone marrow or spleen stained with Giemsa, were included in the study. Patients were excluded if they had a haemoglobin concentration below 30 g/l; had complications such as pneumonia, jaundice, tuberculosis,

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and renal or cardiac disease; or had received treatment with antimony or pentamidine for kala-azar. Parasitological infections with hookworm, roundworm, and *Entamoeba histolytica* are so common in this region that patients with these infections were not excluded, and the infections were treated concurrently. A total of 371 patients (282 men and 89 women, ratio 3:2:1) were entered into the trial.

Leishman-Donovan bodies inside and outside macrophages in smear of aspirate of bone marrow (Giemsa stain).

The clinical state of each patient was thoroughly assessed before the start of treatment according to the recommendations of the World Health Organisation.⁷ The duration of illness was noted. The spleen was measured in the anterior axillary line from the costal margin to its tips, and the liver was measured in the mid-clavicular line from the costal margin to its margin. Patients' weights were noted. Total and differential white cell counts, haemoglobin and serum protein concentrations, and serum alanine transaminase and aspartate transaminase activities were measured. Urine was analysed and chest radiography and electrocardiography performed in each patient. Samples of bone marrow and spleen were also aspirated and stained with Giemsa for parasites.

REGIMENS OF TREATMENT, ASSESSMENT, AND FOLLOW UP

The patients were randomly allocated to six treatment groups. Sodium stibogluconate was given to all patients intramuscularly in the buttocks. Patients in group A were given the drug for 20 days at a dosage of 10 mg/kg body weight/day; patients in group A1 received the drug at this same dosage for 40 days. Patients in group B received the drug at a dosage of 15 mg/kg body weight/day for 20 days and patients in group B1 this dose for 40 days. Patients in group C received the drug at a dosage of 20 mg/kg body weight/day for 20 days and patients in group C1 this dose for 40 days. The drug was given in full dosage from the first day of treatment^{3,4}; the previous practice of building up the dosage from 0.5 to 5.6 ml was not followed. The preparations of sodium stibogluconate used were manufactured in India. Samples of sodium stibogluconate manufactured by different pharmaceutical companies were selected randomly and sent to the World Health Organisation for estimation of the content of antimony. All the locally manufactured drugs were found to be comparable (R A Neal, personal communication).

Electrocardiography was performed and urine analysed, and patients were asked to attend for follow up irrespective of the presence or absence of parasites on examination of the smear. Patients were asked to report immediately if they developed a fever. Patients in groups A, B, and C who were not afebrile after 20 days of treatment were classified as not cured by that regimen of treatment. Such unresponsive patients and all those patients who relapsed after treatment was stopped were treated firstly with the 20 mg regimen of sodium stibogluconate. If they did not respond the antimony was combined with allopurinol in the dosage of 20 mg/kg body weight for six weeks. If they did not respond even with this combination pentamidine at a dosage of 4 mg/kg was given intramuscularly three times a week for 15 injections.

The patients in groups A1, B1, and C1 were assessed clinically with the patients in groups A, B, and C after 20 days, although their treatment was

continued for another 20 days. After 40 days of treatment the clinical assessment and investigations were repeated, the drug was stopped, and patients were asked to come for follow up. If the patients had not become afebrile after 40 days of treatment they were classified as not cured by that regimen. All the patients who relapsed and those who were not cured continued taking the drug at a dosage of 20 mg/kg body weight for a further 40 days, or more if necessary. If applicable the treatment for unresponsive patients was started: firstly, the combination of antimony and allopurinol and, secondly, pentamidine.

The criteria for withdrawal from the study were fixed before the start of the trial: if the condition of patients started to deteriorate or they experienced any serious side effect of the drug they were to be withdrawn from the trial. In fact, no one dropped out of or was withdrawn from the study. All the patients were examined blind by one of us, who noted the responses to treatment. Patients were asked to describe any toxic effects such as anorexia, rashes, muscle pain, hypersensitivity reactions, and jaundice. Electrocardiographic changes were particularly noted because patients with kala-azar have shown such changes and died when treated with higher dosages of sodium stibogluconate.⁷

Apparent cure was indicated by the return of the temperature to normal, a decrease in the size of the spleen, and an improvement in general condition. Parasitological cure was indicated by the absence of parasites in the smear taken after treatment. Ultimate cure was defined as clinical and parasitological cure with no relapse during six months of follow up. The World Health Organisation defined primary unresponsiveness as no clinical or parasitological improvement during or after the first course of treatment; secondary unresponsiveness was defined as relapse after one or more courses of seemingly successful treatment.

The patients were followed up every month for six months and were called to each follow up examination by card or messenger. A further card or messenger was sent if a patient did not turn up on the correct day. On each occasion patients were examined and routine investigations performed. At the final follow up examination a sample of bone marrow was aspirated and examined for parasites.

ANALYSIS OF DATA

Data were analysed by χ^2 and Fisher's exact test with Armitage's modification for two tailed tests. Thereafter the data were subjected to logit analysis, which allowed us to test the significance of an increase in dose and duration of treatment on the rate of cure.⁸

Results

The six groups were comparable. The main clinical features were intermittent fever, shivering or rigor, loss of weight, diminution or loss of appetite, dark coloration of skin, leucopenia with monocytosis, anaemia, and a high rate of positive results for parasites in the splenic aspirates (table I). No patient in any of the groups had lymphadenopathy. Table II shows the apparent rates of cure in patients after they had received the six regimens of treatment.

FOLLOW UP AT SIX MONTHS

Table III shows the numbers of patients who did not relapse during the six months of follow up—that is, the ultimate rates of cure. Table IV shows the outcome of patients who were not cured at six months after they had been treated with further regimens of sodium stibogluconate or the other drugs. Sixty two patients in group C1 and 51 in group C were cured at six months, this difference being significant ($p < 0.01$). One of the two patients in group C1 who were not cured became afebrile after 45 days of treatment; his splenic aspirate was positive for parasites on the 60th day and became negative on the 80th day of treatment, when treatment was stopped. At the first follow up examination after one month he was well. At the next follow up examination he complained that his spleen had enlarged (it had been only 4 cm when treatment was stopped); initially it had measured 16 cm. A sample aspirated from the spleen was found to be positive for parasites. He was treated with allopurinol and antimony with no appreciable change. He was eventually cured with pentamidine. The other patient became afebrile after 50 days and was finally cured after 80 days of treatment. Twelve patients in group C were slow responders, eight being cured after 60 days of treatment and four after 80.

Fifty four patients in group B1 and 42 in group B were cured, this difference being significant ($p < 0.01$). Seven patients in group B1 and 14 in group B were cured with a further 40 days of treatment with 20 mg of sodium stibogluconate. Two patients in group B1 and four in group B were cured

TABLE I—Initial clinical findings in six groups of patients with kala-azar

	Group (daily treatment regimen with sodium stibogluconate)					
	A (10 mg; 20 days)	A1 (10 mg; 40 days)	B (15 mg; 20 days)	B1 (15 mg; 40 days)	C (20 mg; 20 days)	C1 (20 mg; 40 days)
No in group	58	61	62	63	63	64
No of men	45	46	48	49	47	47
No of women	13	15	14	14	16	17
Mean (median) age (years)	25.8 (16.6)	26.2 (18.5)	24.8 (16.7)	25.2 (16.9)	24.8 (17.8)	25.2 (16.4)
Age range (years)	6-40	8-41	9-38	8-45	10-45	6-42
Mean (SD) duration of symptoms (months)	5.6 (1.2)	4.2 (1.4)	5.8 (1.8)	6.2 (1.4)	5.7 (1.9)	5.8 (1.8)
No of patients with intermittent fever	56	61	57	60	62	62
No of patients with remitting fever	2		5	1	1	2
No of patients with shivering	56	57	60	61	58	59
No of patients with rigor	2	4	2		5	4
No of patients with diminution or loss of appetite	57	58	58	57	57	57
No of patients with normal appetite*	1	3	4	4	6	7
No of patients with pigmentation of skin	48	52	36	49	56	52
No of patients who had lost weight	57	56	59	56	58	62
Mean (SD) weight (kg)	40.2 (16.2)	46.2 (11.8)	38.2 (15.4)	40.4 (11.2)	42.8 (14.8)	40.2 (10.8)
Mean (SD) splenic size (cm)	11.8 (4.2)	10.8 (5.1)	11.6 (4.2)	10.8 (5.1)	11.2 (5.6)	10.9 (4.9)
Mean (SD) white cell count ($\times 10^9/l$)	4.5 (1.6)	4.6 (1.3)	5.2 (1.8)	3.9 (1.2)		4.2 (1.2)
Mean (SD) haemoglobin concentration (g/l)	72 (12)	76 (19)	82 (18)	68 (12)	67 (12)	61 (16)
No of patients with bone marrow aspirate positive for parasites	55	57	57	58	62	60
No of patients with splenic aspirate positive for parasites	59	61	62	61	63	64

*No patient in any groups had a voracious appetite.

TABLE II—Apparent rate of cure at end of six regimens of treatment with sodium stibogluconate. Values are numbers (percentages) of patients who were afebrile

Dose of sodium stibogluconate (mg)	Days of treatment	
	20	40
10	45 (78)	53 (87)
15	50 (81)	60 (95)
20	58 (92)	62 (97)

TABLE III—Ultimate rates of cure at six months' follow up and significance between different regimens of treatment. Values are numbers (percentages) of patients who did not relapse within six months

Dose of sodium stibogluconate (mg)	Days of treatment	
	20	40
10	33 (57)	45 (74)
15	42 (68)	54 (86)
20	51 (81)	62 (92)

Significance of differences between regimens: A v A1 $p < 0.05$, B v B1 $p < 0.01$, C v C1 $p < 0.01$, A v B $p < 0.1$, A1 v B1 $p < 0.1$, B v C $p < 0.1$, B1 v C $p < 0.002$, A v C $p < 0.01$, A1 v C1 $p < 0.001$.

with 60 days of treatment with the 20 mg sodium stibogluconate of regimen. One patient in group B became unresponsive to antimony and was cured with pentamidine. One patient in group B became unresponsive to all three drugs (table IV).

Forty five patients in group A1 and 33 in group A were cured, and this difference was significant ($p < 0.05$). Fourteen patients in group A1 and 12 in group A were cured with a further 60 days of treatment with the 20 mg regimen. One patient in group A1 and four in group A needed treatment for 80 days. Two patients in group A became unresponsive to antimony; one was cured with pentamidine and the other became unresponsive to both (table IV). Logistic regression of the proportion cured according to dose and length of treatment showed that both factors were significant in improving the rate of cure. The highest dose for the longer time (regimen of group C1) had the best rate of cure (table V).

The response to treatment varied. Some patients became afebrile after just one injection of the drug and some during the first week of treatment; they were the fast responders. Slow responders took as long as four or five weeks to respond. All the patients who were slow responders had had their illness for a long time (about six months or more) and their spleens were more than 15 cm. In fast responders the spleen's size regressed quickly and became impalpable by the 30th or 40th day. In slow responders the spleen's size regressed slowly. Allopurinol was not effective in unresponsive patients in our study. Anaemia improved without any iron supplements.

As our patients were selected so that they did not have a haemoglobin concentration of less than 30 g/l no blood transfusion was required for any patient. No supplement of protein was required for any patient. The associated hookworm, roundworm, and amoebic infections were treated concurrently with the kala-azar with an appropriate drug.

SIDE EFFECTS AND TOLERANCE

Table VI shows the side effects with the different regimens of treatment with sodium stibogluconate. No patient developed an allergic reaction to the drug. Arthralgia in three patients improved with treatment with an anti-inflammatory drug. Pain at the site of injection, swelling like an abscess, and neuralgic pain improved with treatment. A metallic taste in the mouth did not require any treatment. Electrocardiographic changes developed after 40 days of treatment and improved after the drug was stopped for 10 days in one patient in group C1; the drug was continued again and the patient improved. All the patients tolerated the longer duration and higher dosage of the drug without any major side effect.

Discussion

DOSAGE

Our study compared six regimens of treatment of kala-azar with sodium stibogluconate. The highest rate of cure was achieved with the 20 mg regimen given for 40 days ($p < 0.001$). Increasing the dosage from 10 to 15 mg a day for 20 days increased the number of patients cured, but the difference was not significant ($p < 0.10$). The increase in the number of patients cured, however, became significant when the 10 mg regimen for 20 days was compared with the 20 mg regimen for 20 days ($p < 0.01$).

With the 40 day regimen, also, a higher rate of cure was achieved by increasing the dose of antimony. The rate of cure increased when the dose was increased from 10 to 15 mg but the difference became significant when the 10 mg regimen was compared with the 20 mg regimen ($p < 0.001$). Even the difference between the 15 mg regimen and the 20 mg regimen was significant ($p = 0.02$). This showed that the 20 mg regimen was better than the 10 and 15 mg regimens.

Gupta found that 13% of patients relapsed when treated with sodium stibogluconate in the dosage of 9-11 mg/kg body weight,⁹ which is a higher rate than we found. Chulay *et al* showed that increasing the dosage to 10 mg/kg body weight every eight hours—that is, 30 mg/kg body weight—was more effective against the parasites than 10 mg/kg body weight daily for 31 days without being more toxic.¹⁰ When we used this regimen of 10 mg/kg body weight every eight hours three of the four patients died of heart failure.⁹ The results of this and our previous study showed that the 20 mg regimen was optimal for Indian patients.

DURATION OF TREATMENT

In Bihar the rate of relapse with the traditional six day course of sodium stibogluconate was about 30%.² In our previous study we found 7.5% of patients to be unresponsive to antimony; when we increased the duration of treatment the rates of relapse and unresponsiveness declined further.⁴ We showed that by increasing the dosage and duration of treatment the need for another drug—that is, pentamidine, which is more toxic and has caused sudden deaths³—declined.¹¹ Regarding the duration of treatment required

tartrate) and pentavalent antimonial drugs. Some of our patients responded to just one injection of the drug and others responded after four or five weeks of treatment. Certainly, the duration of treatment varied for these two types of patients: the earlier the response the shorter the duration of treatment. Many slow responders were cured with an extended course of treatment with sodium stibogluconate. Jha and Sharma also reported better results with 30 days' treatment in new patients, 60 days in those who relapsed, and 42 days in slow responders.¹⁶ Kager *et al* found better results with an extended course of treatment with antimony in

TABLE IV—Outcome of treatment with antimony, antimony with allopurinol, and pentamidine in patients who were not cured at six months' follow up

Group	No of patients who were not cured (n=84)	No of patients cured with extended course of antimony	No of patients cured with antimony with allopurinol	No of patients cured with pentamidine	No of patients not cured with antimony, pentamidine, or allopurinol
C1	2	1		1	
C	12	12			
B1	9	9			
B	20	18		1	1
A1	16	14		1	1
A	25	23		1	1
Total (% of patients who were not cured)		77 (92)		4 (5)	3 (4)
% Of all 371 patients		21		1	<1

TABLE V—Results of logit analysis of duration and dose of treatment on rate of cure

Regimen	Rate of cure (P _i)	Logit (L _i)	Explanatory variables		
			Duration of treatment (days) (x ₁)	Dosage (mg/kg body weight/day) (x ₂)	Estimated rate of cure
A	0.568	0.023	20	10	0.097
A1	0.737	1.281	40	10	0.939
B	0.677	0.636	20	15	0.868
B1	0.857	1.894	40	15	0.992
C	0.809	1.798	20	20	0.981
C1	0.968	3.055	40	20	0.999

For a constant, estimate = -3.100, SE = 0.806, *t* = -3.84; for x₁, estimate = 0.062, SE = 0.016, *t* = 3.78; for x₂, estimate = 0.177, SE = 0.041, *t* = 4.35 (for significance at 5% level and df = 3, *t* = 3.18).
Regression equation: L = -3.100 + 0.062 x₁ + 0.177 x₂.
R² = 0.917, df = 3.

TABLE VI—Side effects and tolerance of regimens of treatment with sodium stibogluconate. Values are numbers (percentages) of patients

Side effect	Group						Total
	A	A1	B	B1	C	C1	
Pain at site of injection	1	3	2	1	2	4	13
Swelling at site of injection but no abscess		1	2		1	2	6
Arthralgia				2		3	5
Neuralgic pain		1				1	2
Electrocardiographic changes						1*	1

*Occurred when treatment was continued beyond 40 days.

to achieve cure in Indian patients with kala-azar, Napier said long ago that one of the most difficult problems for doctors is knowing when patients are cured and treatment with antimony can be stopped.¹² Rogers suggested that injections should be continued until patients showed noticeable general improvement and their temperature had been normal for at least a month; subsequently he increased this time to two months.¹³ Muir suggested four months' treatment to achieve a cure.¹⁴ Napier and Muir modified this regimen and suggested that, if the temperature became normal within the first two weeks after the start of treatment, treatment should be continued for two months; if the temperature returned to normal in three or four weeks treatment should be continued for three or four months, respectively.

These were the recommendations for trivalent (antimony sodium

Kenya.¹⁷ Anabwani *et al* showed that Kenyan patients who had relapsed responded to a high dosage given for longer.¹⁸ Logit analysis of our data clearly showed that higher doses and longer duration were important factors in achieving a higher rate of cure. Patients in group C1—that is, those given 20 mg for 40 days—had the best rate of cure.

TOXICITY AND UNRESPONSIVENESS

The fear of severe toxicity with higher dosage and longer duration of treatment has been dispelled by the results of our study. Obsessed with this fear of toxicity, Indian experts suggested two periods of treatment of 10 days each separated by a gap of 10 days.¹⁹ Rees *et al* showed that the drug is excreted quickly in the urine and the fear of cumulative toxicity has been exaggerated.²⁰ The toxicity of the drug in this study was small. We monitored electrocardiographic changes carefully as all the patients in our previous study who died after they had been given high doses of the drug developed heart failure after showing these changes.⁷ In Kenya one patient died, presumably of cardiotoxicity, when sodium stibogluconate was given intramuscularly at a dosage of 20 mg/kg body weight every eight hours.²¹

Our results show that the assumption that patients who have not responded to treatment for 20 days are unresponsive to antimony is not true.^{5,22} Some of our patients responded after 20 days and were cured with antimony. Such patients respond late and require a longer duration of treatment. Certainly, we found no case of

primary unresponsiveness among our patients. This might be due to our changed approach of pursuing treatment for longer, even up to 45 days, to get a response. The emergence of secondary unresponsiveness while the patients were receiving an adequate dose of the drug was, however, puzzling. Seven out of 371 patients became unresponsive to antimony, and three were unresponsive to all of the three drugs used. These three patients posed a problem; the only drug that could have been given to them was amphotericin, which was not available. Why a patient with a large spleen or longer duration of illness should respond slowly or became unresponsive to antimony requires further study. Ours was a selected series, but in general practice many patients with kala-azar are still seen who are unresponsive to both antimony and pentamidine. Effective treatment has been prevented in these patients by the prescription of short courses of either drug because of fear of the toxicity of a longer course. The inefficacy of allopurinol in our series was surprising, though this drug was found to be useful in Kenyan patients.

CONCLUSIONS

We suggest that sodium stibogluconate at a dose of 20 mg/kg body weight daily should be given intramuscularly to Indian patients with kala-azar for at least 40 days. In slow responders a longer course of treatment should be given without any fear of severe toxicity. Electrocardiographic changes should be monitored. The longer duration of treatment with an adequate dose will minimise relapses and unresponsiveness, and thus the reservoir of infection will indirectly be reduced. The relation between unresponsiveness and longer duration of illness and the size of the spleen requires further study. A safe and effective drug that can prevent the emergence of secondary unresponsiveness is also needed.

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ONE HUNDRED YEARS AGO

CONSEQUENT on the promotion of Dr. F. X. Maccabe to the Local Government Board, Dr. G. B. O'Farrell has been appointed medical member of the Prisons Board, Ireland. The salary is £800 a year, and as the duties of inspecting reformatory and industrial schools are temporarily added, the annual income from both offices will be about £1,000.

We have no objection to make to Dr. O'Farrell on any personal grounds. He has had three years' service as a Local Government Board Inspector, and before his appointment to that service he enjoyed a large private practice. He is a gentleman of considerable ability, and he has fulfilled the promise which he gave in a distinguished university career. But there his claims end, and we are not surprised to hear that grave dissatisfaction exists as to the appointment. In writing on the subject of the public medical service last week, we referred to the great weight which personal influence has in the filling of offices, and to the necessity that exists for more discrimination on the part of the Government officials who are entrusted with patronage. Here is a case of distinct hardship. The whole affair was "managed." Dr. O'Farrell was a candidate for the Local Government Board Commissionership. He had most powerful friends, but as he could not be given the best thing he was given the next best—he was made member of the Prisons Board *vice* Dr. Maccabe. No vacancy was declared, and even the chance of a vacancy was not known until the appointment was declared.

Dr. O'Farrell has no special knowledge of prison work—he never, we are informed, held a prison appointment—and it is not a pleasant thing to hear it openly stated that he owes his good fortune to the friendship of a Parliamentary official. In Ireland there is a large body of medical men employed in the prison service. They have to perform arduous duties,

especially in these times; they are badly paid, and they not unnaturally look forward to winning the only prize open to them. There are plenty of them who are men of marked ability; they are trained in the work; but twice in succession they have been passed over in the interest of outsiders. When Mr. Forster was Chief Secretary the prison medical officers were promised payment for the increased duties; but his successor and the Treasury repudiated any liability, and declined to pay. They are compelled to provide substitutes at their own cost, even when absent on official duty. To find themselves "dished" in this cool way, in addition to suffering other wrongs, is rather hard for their human nature. Were Dr. O'Farrell's abilities even far superior to those of all or any of the prison medical officers—which it is not derogatory to him to say they are not—his appointment to the Prisons Board would be no less an insult to the prison surgeons of Ireland, and would be no less marked by the smartness of a political job. No one for a moment thinks that such appointments shall of necessity be vested in the service always to the exclusion of others. But, *ceteris paribus*, promotion ought not to be retained in a department, and not given outside of it. We do not wish to give the least pain to Dr. O'Farrell, who is a most popular officer and a cultivated gentleman, nor do we blame him for having taken advantage of any special circumstances to secure the position. But we do blame the system which in all political parties tolerates this kind of thing. Public appointments—the more valuable they are, the better—seem to be fair game with both sides to bestow upon their friends, and we can only hope that repeated protests may in the end serve to break down what has become a public scandal.

(*British Medical Journal* 1888;ii:653)