straight as possible, a plaster jacket is applied over stockinette, the prominences being padded with felt. Two metal bows with studs and two hinges are incorporated in the plaster (fig. 1). When the plaster has set, the

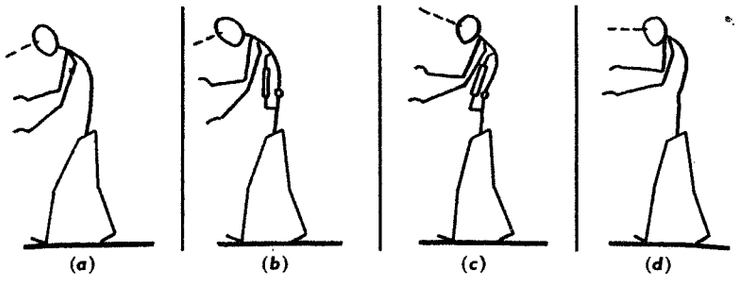

Fig. 3—Stages in progress of illustrative case: (a) on first examination in 1940; (b) jacket fitted in 1943; (c) 2½ months later, visual axis (represented by interrupted line) raised 12° and height 3 cm. taller; (d) 6 months after application of jacket, visual axis 9° higher, and height 2 cm. taller, than on first examination.

jacket is divided into two by cutting out a narrow segment on a level with the umbilicus; and the turnbuckle is placed between both transverse bows by means of the studs fixed to them. By rotating the turnbuckle, the patient controls the extending force acting on the spine. When the curve reaches the upper thoracic region, the jacket can be taken up under the chin (fig. 2) so that the fulcrum is situated at a higher level in the column. And with the plaster jacket as a model, the correction jacket can be made out of strong leather.

By measuring the increase in height and the alteration of the level of vision, it is possible to express the results of treatment numerically. During treatment the patient should have small frequent meals, as gastric over-distension causes a feeling of oppression. During the day he is up and about as usual and can, after the jacket has been applied and inspected in the clinic, give the turnbuckle at home a few more turns every day, but under regular observation.

ILLUSTRATIVE CASE-RECORD

A man, aged 24, was first seen in 1940 with a 5-year history of symptoms. A typical ankylosing spondylitis had developed with much spinal deformity, stiffness of the neck, and restriction of movement in the left hip; thoracic excursion very slight. Pain and stiffness were severe, in spite of his taking 'Pyramidon' gr. 2 daily. There have been 8 attacks of iritis and scleritis. Sedimentation-rate 21 (Westergren). Radiography showed a "bamboo spine," obliteration of the sacro-iliac joints, and a secondary arthritis of the left hip.

The patient received X-ray therapy according to the usual programme, and after the first course the pain considerably lessened, anodynes were no longer necessary, and the stiffness somewhat diminished. Sedimentation-rate 25 mm. in 1 hr. After an interval of 6 weeks another course of X-ray therapy was administered, after which the pain disappeared completely, except in the left hip, which responded, however, to short-wave diathermy and massage.

After 6 months the patient was bicycling again, and able to continue the university courses. Sedimentation-rate 13. During 1941 there was slight pain in muscle-groups, which responded favourably to liniment and a single short-wave treatment; sedimentation-rate unchanged. In the middle of 1942 the patient had pain in neck and hips, which reacted well to a short course of X-ray therapy. In 1943 there were no special features, and the monthly sedimentation-rate remained at 10.

At the end of 1943, for psychological and social reasons (the patient needing social rehabilitation), the correction jacket was applied as described above, the left hip having first been mobilised under anæsthesia. This jacket was applied for a month, during which it was possible to extend the turnbuckle fully; analgesics were necessary only the first night, and there were no other difficulties.

When the first jacket was removed, the muscles of the loin were very painful, and the patient was ordered a week's rest. The pains were relieved with mustard plasters in a few days, and the second jacket was applied. The maximal extension possible of the spine was accomplished by turnbuckle in a month, and the patient was left in this position for another fortnight. He was 3 cm. taller, and his visual axis was raised by 12°, values which remained unchanged after removal of the jacket (fig. 3c).

During the last few days of wearing the jacket, after having had only a week's respite in 2½ months, there was considerable fatigue; and the flank muscles were painful and weak after its removal. After massage and mobilisation the patient was symptom-free after 3 weeks, and a month later he started work. Sedimentation-rate constant at 10.

A follow-up 6 months after application of the jacket, during which time he had to do much walking in connexion with his work, trams and bicycles not being available in wartime, showed an increase in height of 2 cm., and a raising of visual axis by 9° (fig. 3d). The fact that these values were not so good as before (fig. 3c) is probably due to fatigue. He did Swedish gymnastics to maintain these results.

It is our opinion that, even in this long-standing case with obvious secondary structural adaptation, it would have been possible by means of another jacket to correct still further the present spinal deformity, as the turnbuckles of the first two had been opened up to their maximum.

LOUSE-BORNE RELAPSING FEVER
TREATED WITH CALCIUM GOLD KERATINATE

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THE treatment of spirochætal diseases with gold preparations was apparently introduced simultaneously by Levaditi and Nicolau (1925) and by Feldt (1941). Their results were confirmed and amplified by subsequent experimenters. Thus, Steiner and Fischl (1929) found two gold compounds, 'Solganal' and 'A. 69,' more effective than 'Neosalvarsan' and of a higher chemotherapeutic index. Rothermundt and Wichmann (1932) found that, whereas certain strains of spirochætes were more sensitive to gold treatment, others were more sensitive to arsenicals. Feldt (1941) reported that gold keratinates were superior to former gold preparations, as their chemotherapeutic index was higher; calcium-gold keratinate ('Neosolganal') was said to be the best in the series, because of the anti-allergic action of the Ca-ion.

The action of solganal and neosolganal in curing laboratory infections with relapsing fever spirochætes was studied further at the National Institute for Medical Research, London, by Hawking (1944 unpublished). A strain of *Treponema recurrentis* from the Liverpool School of Tropical Medicine was used. Mice were treated on the first day of patent infection, a single dose being given intraperitoneally in 0·5–1·0 c.cm. water. The response was judged by the presence or absence of spirochætes in the blood one day later. Results were as follows:

	Dose clearing half the mice (*mg. per* 20 *g.*)	Dose killing half the mice (*mg. per* 20 *g.*)	Chemotherapeutic index*
Neosolganal	0·5	26	52
Solganal B	1·3	>80	>60
Neoarsphenamine	1·0	8·5 or less	8

*Lethal dose / Therapeutic dose.

The neosolganal was taken from two samples prepared in this country. These results indicated that neosolganal had a much more favourable chemotherapeutic index than neoarsphenamine. Larger batches of neosolganal were accordingly prepared by Dr. D. H. Hey, of British Schering, Ltd., who devised new methods of synthesis, since the original process of manufacture had been kept secret in Germany. The material and biological results were forwarded by the Medical Research Council to the Director of Pathology, War Office, who encouraged the clinical trials here described. No clinical trials of neosolganal during an epidemic of relapsing fever have previously been reported.

It has been our combined experience (Wolman 1944, Dr. Ramli—of the Imbaba Hospital—not yet published) that the treatment of louse-borne relapsing fever with arsenicals is rather disappointing. The testing of other chemotherapeutic agents in this disease was therefore very desirable.

MATERIAL AND METHODS

The experiment was conducted at the Imbaba Fever Hospital in Cairo. The patients were all Egyptians, usually villagers living near to Cairo, and belonging to a low social-economic class. The epidemic was a rather mild one of louse-borne relapsing fever, occurring in a number of villages in the vicinity of Cairo. Lice were occasionally found to harbour spirochætes. The mortality of this epidemic in consecutive groups of 100 varied between 0% and 9% and averaged 2·6% (private communication by Dr. A. M. Ramli).

Patients were usually admitted in the evening. A thick film was taken on admission, stained with Giemsa, and examined next morning. Only patients who had pyrexia at the time and whose blood was positive for spirochætes were included in the experiment and were given a serial number. Even numbers (experimental group) were given intravenous injections of 0·5 g. neosolganal (British Schering) in 5 c.cm. of distilled water. Odd numbers (control group) were not given any drug. Each of these series consisted of 80 patients.

Besides these two series, there were two other smaller series of 20 patients each, one of which was given 1 g. of neosolganal in 5 c.cm. of water, and the other 1 g. of neosolganal dissolved in 5 c.cm. of 'Ametox' (10% solution of calcium-thiosulphate, May and Baker). These last two groups are too small to be of any statistical significance, and a full record of them would therefore be superfluous, although they will be mentioned later.

TABLE I—DISTRIBUTION OF PATIENTS BY SEX, AGE, AND DURATION OF ILLNESS BEFORE ADMISSION

Sex	Number of patients		Duration of illness before admission (days)	Number of patients	
	Experimental group	Control group		Experimental group	Control group
Male	43	48	1	4	7
Female	37	32	2	15	14
			3	29	16
Age (years)			4	11	15
			5	14	13
1–10	9	11	6	2	1
11–20	25	23	7	1	5
21–30	28	32	8	2	5
31–40	13	6	9	2	2
41–50	3	4	10	0	2
51–60	2	1			
61–70	0	3			

Patients were put into one group or the other according to their serial number, no attention being paid to their condition, age, or sex. Children below the age of 4 years were excluded altogether owing to the difficulties of intravenous therapy in small children. Those above this age were given a dose of neosolganal of approximately 0·01 g. per kg. of body-weight.

All patients had as little as possible symptomatic treatment, which was standardised and parallel in all groups. Patients were also given 2 lemons daily to keep a good level of vitamin C in their blood, a point recommended by the makers of neosolganal.

Slides were taken and examined twice daily for almost the whole duration of the experiment. Towards the end, technical difficulties forbade us to continue this routine, and slides were then examined near the beginning and end of each attack.

The age- and sex-distribution of the patients in both groups, and the duration of sickness before admission to hospital are shown in table I.

Some patients gave a history of possible, or probable, former attacks at home. There were 7 patients in each group who had had a recent previous period of illness, which was probably not an original attack of relapsing fever. There were 3 patients in the experimental group, and 4 in the control group who had had a former period of illness which most probably was the first attack of the disease. Since these numbers are almost equal, they do not affect our results.

Some patients had intercurrent diseases and complications as shown in table II.

TABLE II—INTERCURRENT DISEASES (EXCLUDING BILHARZIASIS)

Disease	Number of patients	
	Experimental group	Control group
Bronchitis	2	2
Pneumonia and pleurisy	1	1
Parotitis	1	1
Pyelitis	1	..
Abscesses	..	2
Malaria	1	1
Smallpox	1	..

TOXIC EFFECTS OF NEOSOLGANAL

We were on the lookout for toxic reactions due to the drug. This entailed observation of the patient after the injection was given, and repeated examinations of the urine and white-cell counts.

(1) 60% of the patients had no ill effects from the injections. The other 40% had reactions as follows.

Immediate reactions (within 1 hour of the injection):

15 patients had rigor and/or sweating, possibly due to the rapid destruction of the spirochætes.

6 patients vomited.

7 patients had rigor and sweating and vomited.

1 patient had a severe reaction with loss of consciousness, delirium, and incontinence of urine and fæces. This patient had malignant tertian malaria at the same time, and the reaction might well have been due to the malaria, or to the effect of the drug on it, or to the combination of both diseases.

Delayed reactions :

3 patients had late reactions, vomiting within 6–12 hr after the injection.

(2) Toxic effects of the drug, as expressed in changes of the white-cell count and urine, have been estimated in comparison with the control group. Table III shows that there was no significant difference between the two groups. In compiling this table two facts had to be considered : (*a*) the albuminuria, hæmaturia, and high leucocyte count might possibly be caused by the disease itself ; and (*b*) the fact that more than half our patients had a bilharzial infection.

TABLE III—CHANGES IN URINE AND WHITE-CELL COUNTS 7–10 DAYS LATER COMPARED WITH STATE ON ADMISSION

	No. of patients	
	Experimental group	Control group
Urine :		
Albumin same or decreased	65	68
,, increased	4	5
Sediment same or improved	44	41
,, deteriorated	1	1
White-cell count :		
Same or more than half original value	74	74
Less than half original value	1	2
Less than 4000 per c.mm.	..	..

This table does not include all the patients, because certain investigations were omitted in some cases.

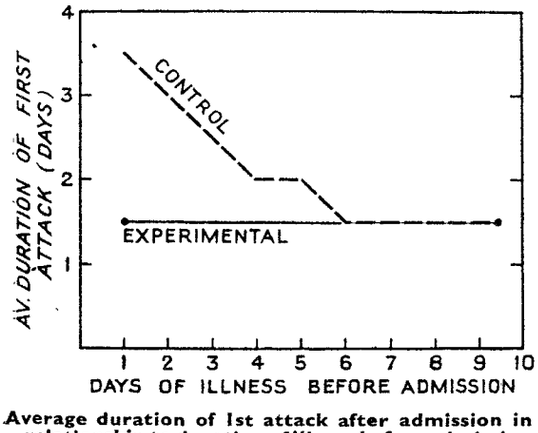
There was no statistically significant difference between the toxic reactions to the drug in the experimental group, who were given neosolganal 0·5 g. in water, and the other two groups, who were given neosolganal 1 g. in water and neosolganal 1 g. in calcium thiosulphate, although these showed slightly more immediate toxic reactions. The last two groups did not differ in the number or severity of toxic effects. It seems, therefore, that calcium thiosulphate does not reduce the incidence of toxic effects from neosolganal.

We conclude that the therapeutic administration of neosolganal does not constitute a hazard to the patient.

RESULTS

Duration of first attack.—The injection of the drug caused the disappearance of spirochætes from the patient's blood within 24 hours in all cases ; therefore, the earlier treatment was initiated the shorter was the initial attack. Since the slides were examined twice daily, the exact time of the disappearance of spirochætes from the peripheral blood could not usually be determined. In some cases the spirochætes disappeared as early as 2 hours after the injection, whereas in others they were found after 10 hours, but the next blood-slide to be examined, 12 hours later, did not show any spirochætes.

In almost all cases the temperature came down within 24 hours of the injection—in all within 30 hours. Usually it came down a few hours after the spirochætes had disappeared from the blood, but in a few cases the temperature came down first.



Average duration of 1st attack after admission in relationship to duration of illness before admission (calculated to the nearest ½ day).

The accompanying figure shows the difference between the average duration of the first attack in the hospital in the experimental and control groups. The number of cases from which the average was calculated can be seen in table I. It will be seen from the figure that there is an apparent relationship between the average duration of the attack (total, in hospital, and at home) and the day of the disease on which the patient was admitted. This is really a fallacy, because patients admitted in the later stages of the attack do not represent a random sample of those affected. Patients arriving after 7 days' illness, for example, are not a random sample, and the average duration of the attack in these cases must, of course, exceed 7 days.

Relapses and non-specific rises of temperature.—We defined a relapse as the reappearance of spirochætes in the peripheral blood-stream after the end of the first attack. This was always accompanied by a rise in temperature above normal (37° C), although in one case a relapse lasting one day had a maximum recorded temperature of 37° only.

A number of cases had rises of temperature after the end of the first attack, with no spirochætes found in the blood, and no complication to explain the rise. These were termed " non-specific rises," as their cause was unknown, although we are inclined to consider them as equivalent to relapses.

Table IV shows the incidence of relapses and non-specific rises in both groups. The difference between the relapse-rates is statistically significant, and that between the non-specific rises is not, while the difference of the sum of both is significant.

The same table shows that neosolganal lengthens the interval between the first and second attack. Two patients in the experimental group and none in the control group had a third attack. The average duration of the second attack was longer in the experimental group than in the controls. Neither of these observations is, however, statistically significant.

Mortality.—In our series 3 patients of the experimental group and one of the control group died. This difference is not statistically significant. All 4 patients were seriously ill and not expected to live when first admitted.

DISCUSSION

We have obviously in our hands a potent non-dangerous chemotherapeutic agent. Its administration seems to be safe, and the immediate effects good. As a rule the spirochætes disappear from the blood and the temperature falls within a day (usually less) of the drug being given. It seems clear that the drug is more useful when given early, simply because the disease will be shortened.

In this experiment neosolganal was observed to have a well-marked effect on the relapse-rate, reducing it from 65% to 17·5% ; it also lengthened the interval between the two attacks. On the other hand, the small size of the samples allows no useful deduction to be made as to the efficacy of neosolganal in reducing mortality in seriously ill cases.

The results of treatment in the two additional groups—given 1 g. of neosolganal in water, and 1 g. in calcium thiosulphate—showed no appreciable difference ; this seems to indicate that the substitution of calcium thiosulphate for water as solvent for neosolganal does not serve any useful purpose. There was no statistically significant difference between either of these two groups and the experimental group receiving 0·5 g. as regards curative effect, though the incidence of toxic reactions was slightly higher in the group with higher dosage ; we therefore consider that 0·5 g. is an adequate dose.

Neosolganal seems to be a valuable therapeutic weapon against louse-borne relapsing fever ; but since it did not prevent 3 deaths nor eliminate relapses altogether it is not the ideal chemotherapeutic agent in this disease.

TABLE IV—INFLUENCE OF NEOSOLGANAL ON RELAPSE-RATE, RELAPSE LENGTH, INTERVAL, AND NON-SPECIFIC RISES OF TEMPERATURE

A—*Rates of relapses and non-specific rises*

	Experimental group		Control group		Difference in percentage	SE of both groups considered together	Difference SE
	No.	%	No.	%			
Relapses ..	14	17·5	52	65	47·5	7·73	6·14 (sig.)
Non-specific rises ..	4	5	9	11·2	6·2	4·30	1·44 (not sig.)
Both ..	18	22·5	61	76·2	53·7	7·86	6·82 (sig.)

B—*Length of interval between attacks, and length of relapses*

	Experimental group		Control group		Difference of means
	Mean length	SD	Mean length	SD	SE of difference
Length of interval (days)	10·0	2·10	7·73	1·73	3·84 (sig.)
Length of relapse (days)	2·785	1·042	2·610	1·350	0·52 (not sig.)

SUMMARY

Alternate patients (80 of a total of 160) with louse-borne relapsing fever were treated with neosolganal 0·5 g.

The drug caused frequent but mild reactions.

Patients were free from spirochætes and apyrexial within a short time (usually 24 hours or less) of the injection.

The incidence of relapses in the treated group was significantly reduced.

Three patients in the experimental group and one in the control group died. This difference is considered to be due to chance.

We are indebted to Colonel H. T. Findlay, DDP, MEF, for his initiative and interest in this work ; Dr. A. M. Ramli, director of the Imbaba fever hospital, for his help in the execution of the experiment ; the staff of the Central Pathological Laboratory, and of the Imbaba Hospital for the valuable assistance rendered ; and Lieut.-Colonel B. W. Lacey, RAMC, ADP, for his help in the mathematical elaboration of the statistical data. The neosolganal was kindly supplied by British Schering, Ltd., through Dr. D. H. Hey.

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