without an end. We remember more, that language is not static, but that neologisms continually mark our progress not only in general ideas but in science. We use to-day scores of scientific terms that men who lived as recently as Priestley, Lavoisier, and Darwin would not understand. It is not enough, therefore, to build a machine that could use words (if that were possible), it would have to be able to create concepts and to *find for itself* suitable words in which to express additions to knowledge that it brought about. Otherwise it would be no more than a cleverer parrot, an improvement on the typewriting monkeys which would accidentally in the course of centuries write *Hamlet*. A machine might solve problems in logic, since logic and mathematics are much the same thing. In fact some measures to that end are on foot in my university's department of philosophy. If the machine typewrites its answers, the cry may rise that it has learned to write, when in fact it would be doing no more than telegraphic systems do already.

Nor must we overlook the limitations of the machines. They need very intelligent staffs to feed them with the right problems, and they will attempt the insoluble and continue at it until the current is switched off. Their great advantage is their speed compared with a human mind, and I have given reasons for that. But, it may be asked, is that so very much more marvellous than the crane that can lift so much more than can a man or than an automobile that can move so much quicker?

The great difference in favour of the calculating machine as compared with the crane, and I willingly allow it, is that the means employed are basically so similar to some single nervous lay-outs. As I have said, the schism arises over the use of words and lies above all in the machines' lack of opinions, of creative thinking in verbal concepts. I shall be surprised, indeed, if that gap is bridged, for even supposing that electrical charges could be made to represent words, what then? I cannot see that anything but jargon would result. Not until a machine can write a sonnet or compose a concerto because of thoughts and emotions felt, and not by the chance fall of symbols, could we agree that machine equals brain—that is, not only write it but know that it had written it. No mechanism could feel (and not merely artificially signal, an easy contrivance) pleasure at its successes, grief when its valves fuse, be warmed by flattery, be made miserable by its mistakes, be charmed by sex, be angry or depressed when it cannot get what it wants.

Conclusion

I conclude, therefore, that although electronic apparatus can probably parallel some of the simpler activities of nerve and spinal cord, for we can already see the parallelism between mechanical feed-backs and Sherringtonian integration, and may yet assist us in understanding better the transmission of the special senses, it still does not take us over the blank wall that confronts us when we come to explore thinking, the ultimate in mind. Nor do I believe that it will do so. I am quite sure that the extreme variety, flexibility, and complexity of nervous mechanisms are greatly underestimated by the physicists, who naturally omit everything unfavourable to a point of view. What I fear is that a great many airy theories will arise in the attempt to persuade us against our better judgment. We have had a hard task to dissuade man from reading qualities of human mind into animals. I see a new and greater danger threatening—that of anthropomorphizing the machine. When we hear it said that wireless valves think, we may despair of language. As well say that the cells in the spinal cord below a transverse lesion "think," a heresy that Marshall Hall destroyed 100 years ago. I venture

to predict that the day will never dawn when the gracious premises of the Royal Society have to be turned into garages to house the new Fellows.

I end by ranging myself with the humanist Shakespeare rather than the mechanists, recalling Hamlet's lines: "What a piece of work is a man! How noble in reason! how infinite in faculty; in form, in moving, how express and admirable! in action, how like an angel! in apprehension, how like a god! the beauty of the world! the paragon of animals!" In that conclusion, if not always in my approach to it, I feel confident that I should have won the approval of that bold experimenter and noble character in whose remembrance this oration was founded.

THE USE IN CHILDREN OF PROCAINE PENICILLIN WITH ALUMINIUM MONOSTEARATE

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Frequent intramuscular injections of penicillin preparations to children often cause much pain and unhappiness. There have been many attempts to prolong the therapeutic action of a single injection by using penicillin added to bases relatively insoluble in water. Such preparations are based on the premise that a single injection will introduce into the body a depot of penicillin which will be released slowly, thus achieving a therapeutic concentration in the blood over a prolonged period.

Procaine penicillin G, described by Salivar, Hedger, and Brown (1948) and Sullivan, Symmes, Miller, and Rhodhamel (1948), is a relatively insoluble equimolecular combination of procaine together with the sodium or potassium salts of penicillin G. It is usually prepared as a suspension in a base of refined sesame or arachis oil. The clinical value of procaine penicillin has been described by Herrell, Nichols, and Heilman (1947) and Boger, Oritt, Israel, and Flippin (1948). In adults it is claimed that adequate blood levels can be demonstrated up to 24 hours after one injection of 300,000 units. Similar levels were found after single daily injections in children by Carson, Gerstung, and Mazur (1949). That blood levels in children 24 hours after a single injection may be variable has been shown by Emery, Stewart, and Stone (1949). It is realized, however, that procaine penicillin has considerable advantages over previous preparations.

Buckwater and Dickenson (1947) described a new vehicle for the intramuscular administration of penicillin, in which penicillin salts are suspended in peanut oil combined with aluminium stearate. It would seem that the aluminium ester

produces a unimolecular envelope to the penicillin particles, to some extent preventing solution of the penicillin. (This preparation is not to be confused with the aluminium salt of penicillin, the experimental activity of which was reported by Reid (1947).)

Thomas, Lyons, Romansky, Rein, and Kitchen (1948) studied the effect of a single injection of various penicillin salts in a peanut-oil medium together with 2% (w/v) of aluminium monostearate. They found that the absorption of penicillin from the peanut-oil preparation containing aluminium stearate was delayed as compared with the absorption from the same salts in peanut oil alone or in peanut oil with wax. A single intramuscular injection of procaine penicillin in peanut oil with aluminium monostearate resulted in blood concentrations being maintained over a longer period than after a single injection of similar preparations of sodium or aluminium penicillin. It was further observed that the smaller the size of the individual particles of the preparation the greater the prolongation. The greatest prolongation was when 95% of the particles were under $5\ \mu$ in diameter.

Similar observations on the importance of particulate size have been made with respect to suspensions of procaine penicillin by Dowling *et al.* (1947) and Welch, Hirsh, Taggart, and Smith (1947). Clinical trials of procaine penicillin in an oil and aluminium monostearate gel have confirmed the production of prolonged blood levels. Robinson, Hirsh, Milloff, and Dowling (1948) found that the majority of their patients had assayable blood levels after 24 hours, while one-third had assayable levels after 48 hours.

This paper records an investigation of penicillin levels in the blood of children following the injection of a preparation of procaine penicillin in arachis oil with 2% (w/v) aluminium stearate.

Method

Dosage was graded according to age. Children over the age of 5 were given the usual adult dose of 300,000 units, which is 1 ml. of the emulsion. Children from 1 to 4 years old were given 150,000 units (0.5 ml.). Under the age of 1 year, some were given 75,000 units and others 150,000 units. Injections were made into the vastus lateralis.

Penicillin serum levels were estimated by the capillary-tube method described by Fleming (1943), using whole blood inoculated with Richard's strain of *Streptococcus pyogenes*. The serum used for assay was from capillary blood collected in Wright's capsules. Control specimens were taken before the injection of penicillin. Daily specimens of blood were taken from all patients for 48 hours; in some it was not possible to continue taking specimens beyond this time. In seven out-patients injections were repeated at the end of 48 hours, and in 11 ambulatory children injections were given daily for three days. In 11 in-patients the serum levels were obtained at one, three, and six hours after the first injection to assay the rapidity of absorption.

The particulate size of the procaine penicillin in the suspension of each bottle used was estimated by direct measurement under the microscope. Over 95% of the particles of the preparation were below $5\ \mu$ in diameter, which agreed with the claim made by the makers (Imperial Chemical (Pharmaceuticals), Ltd., Manchester).

Note on Technique of Injection.—The chief disadvantage of this preparation is the difficulty of drawing the suspension into the syringe. A wide serum needle can be used. A more economical method is to pump air into the bottle, using a No. 1 Record needle, thus causing the pressure in the bottle to fill the syringe. If the injection is made at

right-angles to the skin and muscle there is a tendency for the material to leak back along the needle track, particularly if the muscle is held tense. This back leak is almost entirely eliminated by making an oblique injection.

Results

The serum penicillin levels obtained in 11 patients one, three, six, and 24 hours after the injection of procaine penicillin with 2% aluminium stearate are given in Table I.

TABLE I.—*Serum Penicillin Levels in 11 Children in Bed During the 24 Hours Following the Injection of Procaine Penicillin in 2% Aluminium Stearate*

Serum Penicillin Level (u./ml.)	Hours after Injection			
	1	3	6	24
8	..	..	..	..
4	..	..	..	..
2	..	..	..	..
1	..	..	..	..
0.75	..	..	..	..
0.50	..	..	..	..
0.25	..	..	..	..
0.12	..	..	..	..

Dose of penicillin: 0–1 year, 75,000 units; 1–4 years, 150,000 units; 5–12 years, 300,000 units. The figures give the number of patients showing the tabulated levels at the time intervals.

In all patients the serum level was 0.5 u./ml. or higher at one hour and three hours. At six hours the concentration fell a little, but the minimum level was 0.25 u./ml., and at 24 hours the minimum level was 0.12 u./ml.

An analysis of the daily serum penicillin levels in 66 children of varying ages, following the injection of the aluminium procaine penicillin, is given in Table II. All

TABLE II.—*Analysis of the Serum Penicillin Levels in 66 Children after the Injection of Procaine Penicillin with 2% Aluminium Stearate*

Age Group in Years	Dose of Penicillin (Units)	In- or Out-Patients	No. of Patients	No. of Cases Giving Serum Penicillin Levels of 0.06 u./ml. or Over			
				24 Hours	48 Hours	72 Hours	96 Hours
0–1	75,000 150,000	Mixed ..	8 6	8 6	8 3 of 3	4 of 5 2 of 2	2 of 2 —
1–4	150,000 150,000 300,000	I.P. O.P. I.P.	14 11 1	14 10 1	11 of 11 9 of 10 1	7 of 10 — 1	7 of 7 — 1
5–13	300,000 300,000	I.P. O.P.	21 5	21 5	16 of 16 4 of 4	11 of 14 1 of 1	5 of 12 —
0–13	As above	O.P. I.P.	8 3	Reinjection after 48 hours		8 3 of 3	5 of 5 3 of 3

the children under 1 year old gave a serum level of 0.06 u./ml. or over at the end of 48 hours after the injection. Four of five receiving the smaller dose of 75,000 units had a level of 0.06 u./ml. or over at 72 hours.

All the 14 in-patients aged 1–4 who were given 150,000 units had a level at least 0.12 u./ml. at 24 hours and 0.06 u./ml. at 48 hours, and seven of these followed to the end of a fourth day showed levels of 0.06 u./ml. Of 11 out-patients aged 1–4 given 150,000 units, all except one had levels of 0.06 u./ml. or over at 24 and 48 hours after injection. One child aged 4 was given 300,000 units, and he still had a level of 0.06 u./ml. at the end of four days, when he was discharged.

All the 26 patients aged 5 to 13 given 300,000 units had levels of at least 0.06 u./ml. at 24 hours, as did all 20 examined at 48 hours; 12 of 15 examined at the end of three days showed similar levels. Five of 12 patients of this group showed a level of 0.06 u./ml. after four days.

Eight patients given injections on alternate days maintained levels of at least 0.06 u./ml.

The blood penicillin levels of 11 children who received a daily injection of procaine penicillin with aluminium stearate are given in Table III. In the great majority the levels were above 0.12 u./ml. throughout.

TABLE III.—Serum Penicillin Levels in 11 Ambulant Children given Once-daily Injections of Procaine Penicillin with 2% Aluminium Stearate

Serum Penicillin Levels (u./ml.)	Control	No. of Patients Showing Tabulated Levels at the End of		
		1 Day	2 Days	3 Days
4	11	1		
2			1	
1		1		2
0.75			1	1
0.5			2	4
0.25		5	3	3
0.12		2	3	1
0.06		2	1	
0.03				
Nil				

Dose of penicillin: 0-4 years, 150,000 units; 5-12 years, 300,000 units.

No child showed a general reaction to the injection. One parent stated that her child had walked with a limp for 12 hours afterwards, but on examination we could find no localized swelling or tenderness.

Discussion

This investigation was concerned primarily with serum penicillin levels obtained after the injection of procaine penicillin with aluminium stearate, and no attempt has been made to assess accurately the therapeutic value of the preparation; the clinical results, however, were satisfactory.

The high serum penicillin levels obtained during the first three hours after injection suggest that there is more rapid absorption at this period than later. This is possibly due to absorption before the formation of an inflammatory barrier and to the immediate absorption of any free penicillin already present in the preparation.

The results we have obtained with the preparation are considerably better than those obtained with procaine penicillin without aluminium stearate, and agree very well with the findings of Thomas *et al.* (1948) and Robinson *et al.* (1948) in adults. In the doses we have used a level of at least 0.06 u./ml. was obtained after 48 hours in all but one out-patient. Furthermore, a level of at least 0.06 u./ml. was found in 20 of 22 patients whose blood was examined at the end of three days.

From the results we have obtained it would seem theoretically reasonable to give injections on alternate days, and in the eight children in which this was carried out a level of 0.06 u./ml. or over was maintained. Eleven children were, however, given daily injections to ascertain if there was a summation effect and if it was possible to maintain high levels of penicillin in the blood by this means. Daily injections were carried out for three days, as it was thought that from the persistence of levels in ambulant children for three days only a maximum level would be reached by the end of three days and no higher levels could be reasonably expected later. The results shown in Table III indicate that daily injections not only provide a satisfactory level but give a summation effect. It is clear that the blood penicillin levels are maintained in the great majority of cases above 0.1 u./ml., a level which is bacteriostatic for almost all pathogens other than those showing particular resistance, such as particular strains of staphylococci.

A disadvantage of the preparation is its oily nature, which makes it rather more difficult to administer than aqueous preparations of penicillin. There is also the possibility of sensitization, and possibly a skin test with the preparation

may have to precede treatment. We have not seen any reaction, but we have not given the preparation to any child continuously over a very long period. The possibility of the effects of absorbed procaine after conversion to para-aminobenzoic acid interfering with the action of sulphonamides is largely theoretical and extremely difficult to prove. Carson, Gerstung, and Mazur (1949) could obtain no conclusive evidence on this point when using the earlier simple procaine penicillin, in which the rate of absorption is much greater than in this suspension with aluminium stearate.

This preparation of penicillin seems to have advantages over all previous preparations that have been marketed. It gives an almost painless injection site, minimal local and no general reaction, and in our experience an almost stable concentration of penicillin in the blood for at least 48 hours; and one is confronted with the unusual prospect of deciding at what daily intervals injections should be given.

Summary

Blood penicillin levels have been followed in 66 children of varying ages given graded doses of procaine penicillin in arachis oil with 2% aluminium stearate in which over 95% of the particles were below 5 μ in diameter.

The doses given were 75,000 units (0.25 ml.) and 150,000 units (0.5 ml.) to children under 1 year, 150,000 units to children aged 1-4 years, and 300,000 units (1 ml.) to older children.

There is a rapid initial absorption of penicillin, giving a level above 0.2 u./ml. by the end of the first hour, and this level is maintained for at least three hours.

In all but one case a blood penicillin level of 0.06 u./ml. or more was maintained for at least 48 hours after injection.

Children given daily and alternate daily injections maintain a continual penicillin level in the blood, the daily injection producing higher levels than the alternate daily injection.

We conclude that procaine penicillin in arachis oil with 2% aluminium stearate is a suitable preparation for the daily injection of penicillin.

We would like to thank Dr. T. Colver, whose patients were used in these estimations, our nursing and medical colleagues for their co-operation, and Miss Dorothy Lee for laboratory technical assistance. The penicillin preparation was kindly supplied by Imperial Chemical (Pharmaceuticals), Ltd., Manchester.

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According to a report (B.U.P.) the war in China has led to a great increase in the price of menthol. The stock of this substance in Hong Kong is said to be practically exhausted, and it is almost impossible to obtain more from the interior of China under present conditions. During the war, when Far Eastern supplies were cut off, Brazil developed the production of menthol, which is derived from peppermint oil, but this year's output is estimated to be less than 100 tons, and the United States alone uses between 250 and 300 tons a year.