TETANUS PROPHYLAXIS AND SERUM SENSITIVITY TESTS

BY

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"Every hospital should have written rules making it clear on whom the responsibility rests for giving antitoxic serum; and newcomers to the hospital should ask what the rules are."—(Rock Carling, 1950).

In a review of the incidence of tetanus among civilians in England and Wales from 1931 to 1948, Conybeare and Logan (1951) showed that the number of fatal cases dropped from an average of 100 a year up to 1944 to an average of 74 in the period 1944–8. Since then the average has dropped still further to 71 in the years 1949–53. As Cole (1951) has pointed out, exact data about the incidence of the disease are hard to obtain, since tetanus is not a notifiable disease. It is estimated, however, that there are on an average about 200 cases annually in England and Wales (Parish, 1954b), the average mortality rate varying between 40 and 70% in different case series. Comparison of the total of 23 deaths from diphtheria in 1953 with 61 from tetanus in the same year would, however, seem to indicate that the problem of adequate tetanus prophylaxis is still not fully solved, although provisional figures for 1954 show that both these fatality figures are again reduced.

There is, indeed, a wide variation in practice among general practitioners and in different hospitals concerning when and in what circumstances antitetanus serum should be administered. Some hospitals follow the practice that all cases with a break in the skin, however slight, should receive a prophylactic dose; others leave it to the discretion of the casualty officer or houseman whether this course should be adopted. In this latter category, the regulations are almost invariably either extremely vague on the subject or non-existent. In these present times when, unfortunately, so much emphasis has to be laid on the medico-legal consequences which may follow medical practice, especially in hospitals, there is little doubt that circumstances could quite easily arise under such a system where failure to administer tetanus prophylaxis might place an inexperienced house officer in serious jeopardy. Indeed, the medico-legal societies have had to settle a number of claims in the past few years involving instances where there was failure to give antitetanus protection (French, 1955; Robinson, 1955).

Consultation of the literature shows no evidence of unanimity or of clear guidance in this matter. Generally speaking, the American authorities are in favour of giving prophylaxis in any case where there is a break in the skin. Newell and McVea (1940), discussing the problem of reactions to antitetanus serum injection, state that these complications should not in any way influence the administration of serum to any patient with a break in the skin unless it was felt, as was rarely the case, that contamination by the tetanus bacillus was practically impossible. Abstracts of the reported discussion which followed the reading of their paper show that most of their colleagues agreed with them. The same conclusion was reached by Rackemann (1942) and many other authorities.

In this country very few writers commit themselves on what rules should be laid down to ensure passive immunization. Parish (1954a) comments that there are considerable differences in procedure and that some doctors are reluctant to use any serum in prophylaxis so as to avoid possible sensitization. Cole (1954), however, in reply to a direct question on the subject states that "prophylactic antitoxin for passive immunization should only be given after wounds in which there is a reasonable possibility of tetanus infection. A needle prick in the finger is very unlikely to cause tetanus if it is kept clean, but if it becomes infected and leads, for example, to a whitlow, it may do so. A clean cut sustained in the home is unlikely to cause it, provided that it is kept clean, but every case must finally be judged on its merits."

Analysing 50 consecutive civilian cases seen between 1928 and 1945, Cole (1951) found that passive immunization should have been given to and would have prevented about half the number, and particularly those with severe infected wounds, most of the whitlows (which were 10 in number, 20% of the total—a surprisingly high figure), and some of the penetrating wounds. He added his opinion that, even if practitioners were more alert to the possibility of tetanus and gave prophylactic antitoxin more frequently, it is doubtful if, in practice, the present incidence of the disease could be reduced by more than another 20%.

Prophylaxis

There can be no doubt whatever that the method of deciding whether or not to give prophylaxis on the merits of each case assures that adequate protection will be afforded in a high percentage of cases seen in casualty departments and surgeries. Nevertheless, both from the purely medical and from the medico-legal aspect of the matter, it is perhaps worth while—bearing in mind the weight of the authority from which it emanates—examining the statement that the decision to give prophylaxis or to omit it should depend on the apparent merits of each case as judged by the practitioner or the house officer, the latter being often of only recent qualification.

Press (1948), analysing 982 cases in the United States in connexion with the civilian use of toxoid in peacetime, showed that 15% of these tetanus cases followed a "trivial" injury and that in 34.5% the cause and nature of the injury was unknown. Press goes on to comment that "recently evidence has become more prevalent that tetanus very frequently is preceded by non-penetrating wounds and that often a trivial injury results in the disease." He deduces, from the moderately large proportion of those cases in which no history of any injury could be obtained, the implication that any wound sustained was so slight that it escaped notice, and he gives a detailed analysis of such cases. Stafford *et al.* (1954), in a review of 169 cases, comment that most of these patients had what they regarded as trivial injuries for which they did not seek medical attention. Indeed, Cole and Spooner (1935), in a series of cases from the rural districts of Cambridge, showed how slight may be the initiating injury.

In reviewing two cases of tetanus at the West Kent General Hospital and all cases recorded at St. Thomas's Hospital over a twenty-year period (Moynihan, 1954), I found that in seven out of the fourteen cases recorded the injury was of such a nature that it is more than probable that, on the above criteria, any doctor seeing it before the onset of the disease would not have given prophylactic cover. Three out of these seven cases were in fact initially seen, and in each it was not thought necessary to give antitetanus serum. In two other cases no primary lesion was found (although in one the patient had hit his thumb with

a hammer ten days before the onset of the tetanus). The remaining two cases in this category were not seen until the disease had developed, but the nature of the wound was exceedingly trivial in both.

Other series do not emphasize such a high percentage of causation by trivial injury, but in the series of 10 cases in twenty years reported from Guy's Hospital by Macrae-Gibson (1950) there is again a high percentage of trivial wounds for which, on their merits, prophylaxis would probably not have been given.

It must therefore be finally deduced from the history of individual cases, from the nature of the wounds in cases where tetanus has developed, and from the number of whitlows from which tetanus does not develop in spite of the lack of antitetanus serum cover, that it is almost impossible accurately to differentiate those cases which can be ignored from the prophylactic point of view. It would therefore seem only logical, if it is aimed to give complete passive immunization, to give all cases with breaks in the skin or wounds that have developed whitlows an injection of antitoxin serum. Since, however, this may not always be possible in practice and it may be felt that cuts sustained in the home or in clean surroundings are usually safely dealt with without antitetanus precautions, every casualty department should have rules laid down for A.T.S. administration, which must be carried out by the casualty officers. They should form the policy regarding this matter in that particular hospital. General practitioners will, of course, use their own judgment.

Cole (1951), however, states that such wholesale prophylaxis is undesirable because tetanus antitoxin itself is not entirely harmless and certain subjects may die or develop very severe reactions within a few minutes of a prophylactic injection. A study of the figures in the Registrar-General's Statistical Review, 1953, however, shows that there were only six deaths in England and Wales from this cause in the ten years 1944-53, as against 725 deaths from tetanus in that period. Moreover, a recent survey of all reactions, both general and local, in a series of 7,580 injections of antitetanus serum (Moynihan, 1955) showed that the incidence of serum sickness (as defined by von Pirquet and Schick in 1905) was 2.5% and of localized reactions 2.7%. There were only two "anaphylactic" protein-shock reactions in this series over a two-year period, neither of which was fatal. It is felt that this low incidence, together with a total reaction rate of 5.29%, is not in itself a sufficient deterrent to a complete prophylactic cover in casualty departments.

Test Doses: Lack of Prophylactic Cover

The question of the necessity for guarding against such anaphylactic or protein-shock reactions and the methods which should be used is comprehensively discussed by Laurent and Parish (1952). The unreliability of the intradermal, conjunctival, and scratch tests is clearly pointed out and the *trial dose* method described. Yet, in a recent visit to 37 hospitals situated in widely separated parts of the country, it was found that 31 were still using the intradermal skin-sensitivity tests as a guide to general or constitutional sensitivity; this number included most of the London teaching hospitals. This may perhaps be understood when it is realized that many authorities—for example, the latest edition of such a widely used handbook as *Pye's Surgical Handicraft* (Mills, 1950)—still describe this discredited test.

In order to study the effect of this widespread procedure on the effectiveness of tetanus prophylaxis, it was decided to investigate the methods used at three hospitals in a really large series of cases.

The survey covers all patients to whom it was thought necessary to administer tetanus prophylaxis in the casualty departments (a) during two years in a county-town hospital in a rural district where tetanus is relatively prevalent (Conybeare and Logan, 1951); (b) during two years in a general hospital in an industrial borough; and (c) during

one year in a London teaching hospital. The number of such patients totalled 8,900 (5,698 males and 3,202 females), with ages ranging from 6½ months to 84 years, the majority, however, being young adults.

In the first two hospitals it was understood, though not specifically laid down by regulations, that all patients with wounds which involved a break in the skin were to receive a prophylactic dose of antitetanus serum. At the third, though once again no written rules on the subject existed, the matter was left to the discretion of the casualty officers, who judged each case on its merits. In all three hospitals there was no routine or occasional prophylaxis for whitlows, and the method of using intradermal skin-sensitivity tests for general or constitutional sensitivity to serum was (and still is) in use.

The number of such skin-sensitivity tests, the number of such tests judged by casualty officers, sisters, or nurses in varying circumstances to be "positive," and the number of persons actually given prophylaxis are shown in Table I.

TABLE I

Hospital	Casualty Patients	A.T.S. Injections	Positive Skin Injection (Full Serum Prophylactic Dose Not Given)	Full Serum Prophylactic Dose Not Given for Other Reasons			
				Previous Injection	Allergic states	Refusal of Patient	General Reaction to Test
West Kent General Hospital, Maidstone: Jan.-Dec., 1953	8,915	1,510	308	41	18	21	3
" " " 1954	9,274	1,818	270	33	16	18	2
St. Nicholas, Plumstead: Jan.-Dec., 1953	7,201	1,263	179	30	19	11	11
" " " 1954	7,800	1,560	168	26	14	4	5
St. Thomas's Hospital: Jan.-Dec., 1954	21,054 (surgical casualties only)	1,429	102	10	3	5	3
Totals		7,580	1,027	140	70	59	24

The total number of patients who were thought to require A.T.S. prophylaxis was 8,900. The total number who did not receive it for the various reasons listed was 1,320 (14.8%). The number who had so-called "positive" skin tests was 11.5%.

Those persons judged to be "positive" did not receive a prophylactic injection. It will be seen that, over the whole series, this number reached the startling figure of 11.5% of all persons who were thought to require prophylactic injection—1,027 out of 8,900 patients.

The number of cases of tetanus recorded at each hospital during the period 1953-4 and over a ten-year period, including those actually seen initially in the casualty departments and seen outside by a doctor, is shown in Table II. Fortunately, none of these cases arose from any of the

TABLE II.—Cases of Tetanus at Each Hospital at Which the Series was Conducted

Hospital	1953-4					In 10-year Period, 1945-54				
	Seen by Outside Doctor		Seen in Casualty Dept.		Not Seen Before Admission to Hospital	Seen by Outside Doctor		Seen in Casualty Dept.		Not Seen Before Admission to Hospital
	Given A.T.S.	Not Given A.T.S.	Given A.T.S.	Not Given A.T.S.		Given A.T.S.	Not Given A.T.S.	Given A.T.S.	Not Given A.T.S.	
West Kent General Hospital	—	1	—	—	—	—	1	—	—	1
St. Nicholas, Plumstead	—	—	1*	—	—	—	—	1*	—	—
St. Thomas's Hospital	—	—	—	—	2	—	—	—	—	5

* Doubtful.

patients who showed "positive" skin-sensitivity tests. In the case of the teaching hospital, four out of the five cases seen were sent from rural districts outside London.

When it was found that the so-called positive skin tests formed such a high percentage of the total tests it was decided to carry out two investigations using normal physiological saline and tap-water as controls against the test dose of antitoxic serum. The results of these investigations on 100 patients with each control are shown in Table III. The 200 patients all had a positive flare with a weal of

TABLE III.—*Comparison of 200 Cases of So-called "Positive" Skin Tests to A.T.S. With Their Reaction to Saline and Water*

Comparison of Positive Skin Test Reactions with	Similar Skin Reaction	Smaller Reaction	Negligible Reaction
(a) N 10 saline (100 cases) ..	47	11	42
(b) Tap-water (100 " ") ..	28	39	33

diameter not less than $\frac{1}{2}$ in. (1.3 cm.). It will be seen that saline induced the same reaction in 47% of the first group and a small reaction in 11%, having no effect in the remainder. Tap-water induced the same result in 28% of the second group and a small reaction in 39%, having no effect in the remainder. All of the 200 patients were given the full dosage of antitetanus serum without any ill effect whatever except that 9 (4.5%) later developed a generalized serum sickness reaction and 11 (5.5%) a localized reaction at the site of injection. This is a slightly higher reaction than the average for the whole of a group of 7,580 injections (Moynihan, 1955).

Other Causes of Lack of Prophylactic Cover

In addition to those who did not receive prophylaxis because of this erroneous idea of the value of the skin-sensitivity test, a number of patients, 293 in all, did not receive the prophylactic dose because of other reasons (Table I). These may be summarized as follows:

(a) Previous Injection of Antitoxic Serum

Lowden (1955) states that "more frequent injections than once in six months are not necessary." In this series, 140 patients were not given prophylaxis because the casualty officer, having elicited the fact that the patient had had a previous injection within a period which varied from three weeks to eighteen months, recorded the fact that this was sufficient for safety and sent the patient away. Since 28 doctors in this series recorded their impression that immunity persisted at least up to a three-months period, and others used the phrases "recently" and "within the last few months," it should be stressed that *effective protection following a dose of 1,500 units does not last even for four weeks*. This was first demonstrated in a series by Bigler and Werner (1951), who showed that the fall of antitoxin titre after injection of 1,500 units of antitetanus serum reached a minimum protective level in three weeks. It was later confirmed by Hartley *et al.* (1950). Parish (1954a) summarized the matter by stating that "the protection is usually at its maximum two or three days after a subcutaneous or intramuscular injection and then slowly diminishes as the serum is eliminated. Occasionally, however, the duration of adequate immunity may be only a few days in some sensitive persons who have had previous injections of horse serum."

In this latter connexion, it has been shown that there is evidence that previous experience of a soluble antigen leads to a much accelerated removal from the circulating blood on a second or subsequent injection and consequently to a curtailment of any effectiveness that it may possess as a passive prophylactic agent (Littlewood *et al.*, 1954). This is obviously important, since of the 7,580 patients who actually received prophylactic injections of antitetanus serum in this series 362 were known definitely to have received one or more previous similar injections and a further 547 stated that they thought they had had such prophylaxis. Little-

wood *et al.* stated: "One important practical conclusion emerges from the present discussion. Once a person has received an injection of any horse-serum antitoxin, irrespective of the disease for which it may have been given, that person should be promptly immunized against diphtheria and tetanus with the appropriate toxoid. By thus creating the state of active immunity, which can be effected without any unpleasant side-effects, any future need for passive protection against these diseases with horse-serum antitoxin is rendered unnecessary." Theoretically, this may well be important. Practically, it is extremely doubtful whether it is ever considered, let alone carried out, in any hospital in the country, and this was certainly so in 36 of the 37 hospitals visited.

(b) Allergic History, Either Personal or Familial

In this series, 70 persons were not given prophylaxis because of such a history. Laurent and Parish (1952) lay down in detail the method whereby such patients should be given a prophylactic dose of serum, and the reasons are fully discussed by Parish (1954a). These methods are seldom adopted in casualty departments, usually through ignorance—a fact elicited in the visits to the 37 hospitals previously mentioned. This procedure should be incorporated in written instructions in every casualty department.

(c) General Reaction Noted to a Sensitivity Test Dose

The method of test-dosing for serum sensitivity has been fully described by Laurent and Parish (1952), and consists in preliminary *subcutaneous* injection of small doses which are not given with the purpose of observing a local reaction of any kind. They are meant to be absorbed slowly into the general circulation with a view to testing the patient's general reaction to a small dose of serum before giving him a large dose. Laurent has used this method for over twenty-five years in daily practice, and has found it safe and valuable, and this is also the experience of many of his colleagues and others. In the present series 7 patients given such a test dose and 17 others given the intradermal dose to test for skin sensitivity showed signs of generalized reaction within a twenty-minute period. These consisted in malaise, headache, and flushing. Since the conception that the patient can be desensitized by numerous graduated small injections, given either intradermally or subcutaneously at short intervals, without causing a reaction is probably illusory, and in practice probably impossible (Laurent and Parish, 1952), none of these 24 patients were, in fact, given prophylaxis.

In addition to these 24, two persons who had given no signs of reaction to a skin-sensitivity test, either generally or locally, developed symptoms of protein shock or so-called "anaphylaxis." One occurred immediately after injection of the full prophylactic dose; the other, a milder reaction, occurred about an hour later. These cases again demonstrate the unreliability of the skin-sensitivity test.

(d) Refusal of the Patient to have an Injection

Fifty-nine patients refused to have an injection of prophylactic serum. Sixteen had had such an injection before, and five of these had had reactions, three being of the generalized serum-sickness type. (It is usually ensured that the patient signs a note to the effect that he has decided to dispense with the prophylaxis; the rules regarding serum administration should include a reminder that this precaution should always be carried out in such circumstances.)

Indications of the Survey

Thus, out of 8,900 patients to whom it was thought necessary to give passive immunization on account of their injuries, 1,320 (14.8%) did not receive prophylaxis, although a small number of these, 59 in all, refused such treatment. It is clear from these figures that there is sufficient indication that the present methods of providing immunization

against tetanus infection leave much to be desired. The survey of other hospitals previously mentioned confirms that this state of affairs is not limited to the hospitals in which this investigation was carried out.

Discussion

Cole (1951, 1953) stated that Service experience has shown that active immunization could eradicate the disease if it were applied to the whole population, in the same way in which diphtheria has been conquered. He adds, however, that this would be a "heavy undertaking" to prevent the comparatively small number of cases which occur and that its implementation is partly an economic question. Conybeare and Logan (1951) also mention the financial cost of widespread active immunization, but have suggested that, in view of the relatively high death rate in the disease among children in the age groups up to 15, such prophylaxis would be justifiable, especially on a topographical basis. Boyd (1951), on the other hand, recommended selective active immunization on an occupational basis.

Stafford *et al.* (1954) state that the actively immunized group of the population of the United States may now amount to some twenty millions, constituting a major health asset to the nation. In discussing the value of active as against passive immunization, they cite the experience of the United States Army in the second world war: out of 2,734,819 admissions to hospitals for wounds and injuries there were, as justification of the value of the former method, only 12 cases of tetanus, of which only one had received active immunization (Long and Sartwell, 1947). As against this experience those authors record the investigation of 169 cases of clinical tetanus in the city of Baltimore from 1928 to 1953, which showed that 25 of these patients, including 13 who died, developed the disease in spite of passive immunization given when the wound was sustained. These writers go on to cast some doubts on the value of tetanus antitoxin as an adequate prophylactic agent in every case, and urge that every effort should be made continuously to enlarge the portion of the population enjoying basic immunity to tetanus. This question of the doubtful prophylactic value of tetanus antitoxin serum is further discussed by Stafford (1955).

Many other American workers believe that everyone should be actively immunized against tetanus (McGuinness, 1952), and immunization with triple toxoid (diphtheria-tetanus-pertussis) is widely used in America (Dyer, 1951), in France (Ramon, 1950), elsewhere in Europe (Payling Wright, 1954), and in Canada. Such combined prophylactics have the obvious advantage of reducing the number of injections required (North and Patterson, 1953a), although, as Parish emphasized, it would be necessary to give the usual booster doses as in the present diphtheria programme. Given at the age of 12 to 15 months, at school entry, and at 9 to 10 years, such booster doses would carry the child past the danger age emphasized by Conybeare and Logan.

Miller *et al.* (1949) showed that if more than four years has elapsed since basic immunization against tetanus or since a booster dose has been given, the rate of recall is lengthened, and McGuinness (1952) suggests, therefore, that booster doses should be given routinely at three-year intervals and whenever a contaminated wound is sustained, these later doses acting also, of course, as boosters.

In the most recent works on this subject, however (Stafford *et al.*, 1954; Turner *et al.*, 1954), it has been shown that, in a series of serum antitoxin level in 175 individuals, most of the subjects maintained a protective level of antitoxin despite intervals of five to eleven years since their last booster toxoid injection, and with an interval of less than five years 93% enjoyed a protective level. Booster doses produced a response starting in four days, with a rapid and large rise in the level of circulating antitoxin within seven days. It was suggested, as Boyd (1946) had earlier postulated, that the growth of tetanus bacilli in an immunized person might well constitute a sufficient booster in itself and set up a prophylactic mechanism. Stafford (1955)

urged the administration of a booster dose of tetanus toxoid at least every ten years in immunized persons, and also called attention to the availability of tetanus antitoxin in the serum of actively immunized persons in the treatment of clinical tetanus in patients sensitive to horse serum. Perhaps a satisfactory compromise between opposing viewpoints would be to give a boosting dose of toxoid every five years: this interval seems to be gaining general acceptance in many countries.

Toxoid immunization has the advantage over the anti-tetanus serum used in passive immunization in that it is not associated with the risk of allergy or other complications. Rare cases of such complications as encephalopathy associated with combined diphtheria-pertussis inoculation have been reported from time to time (*British Medical Journal*, 1950; Anderson and Morris, 1950), but there have been no reports of this complication following the use of tetanus toxoid or the triple prophylactic. The reactions which follow the triple toxoid prophylactic injection were the subject of a recent survey (Barr *et al.*, 1955), and it was shown that, whereas the adsorbed triple toxoid caused severe reactions with unsatisfactory diphtheria titres at the age of 12 months, the use of a fluid combined diphtheria-tetanus-pertussis prophylactic caused a few mild local reactions and a low general reaction rate with satisfactory diphtheria titres above that usually regarded as the Schick level at the age of 12 months. All tetanus toxoid used in England has been trouble-free since Witte peptone has been excluded (Parish, 1954a). Weiner *et al.* (1955) encountered 12 reactions in 1,000 injections of combined diphtheria and tetanus prophylactics, none of which was serious. It is clear, therefore, that the administration of tetanus toxoid, whether singly or in the combined form, should give rise to little difficulty from the point of view of reactions.

In any case in which tetanus infection seems highly likely a further booster dose of toxoid would be given. It is here that trouble might arise were active immunization with triple toxoid to be widely introduced, since it might prove difficult in a casualty department to know exactly when such immunization had been given. Parish (1955) has stressed the necessity for a record card of inoculations and has deprecated haphazard and unrecorded immunizations. As a long-term policy, there seems to be no valid reason why a small space should not be utilized on page 1 of the patient's National Health Medical Card (Form F.C.4), so that all toxoid immunizations and booster doses, particularly diphtheria and tetanus, would be automatically recorded when conferred. Stafford (1955), in America, and North and Patterson (1953b), in Australia, also urge that public health authorities should record individual immunizations so that essential information could be readily available in an emergency.

Conclusions and Summary

There is evidence that the present method of conferring passive immunization to tetanus is unsatisfactory in its scope. It has recently been suggested that it may also be unsatisfactory in its nature.

The system of intradermal testing for sensitivity to horse serum in many hospitals is quite unreliable and should be replaced by the subcutaneous "trial dose" method.

In view of the possibility of medico-legal problems arising from failure to give passive prophylaxis, every casualty department should have written rules for the guidance of house officers. These should set out the regulations for administrations of antitoxin and toxoid and the methods to be adopted when immunizing both normal patients and those sensitive to serum.

The present position of the use of active immunization against tetanus is discussed. It is suggested that recent evidence shows no valid reason why this method

of prophylaxis should not be practised universally so that it will eventually supersede the less satisfactory method of horse-serum administration.

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The Royal Society of Health held a sessional meeting in London last November at which a number of papers were read on the subject of "The Design of Health Buildings." In an introductory paper Dr. CHRISTIE W. GORDON stated that the National Health Service is founded upon the family and its doctor, and suggested that in the future development of hospital services out-patient departments should be considered as an extension of the facilities available to the general practitioner in his surgery. The in-patient departments of the hospital might be organized into an admission unit and special departments, supported by neighbourhood homes and a country annexe. The neighbourhood homes would receive patients from the special departments of the hospital as soon as they could be moved, and there they would be cared for by their general practitioner. A trained nurse would be in charge of the homes, which would so far as possible be maintained by the patients themselves, members of their family, and voluntary workers.

CARDIOVASCULAR ACTIONS OF CHLORPROMAZINE

WITH PARTICULAR REFERENCE TO PERIPHERAL VASCULAR DISEASE

BY

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Since its introduction by Laborit and Huguenard (1951) chlorpromazine has been found to have a variety of interesting actions. It is a powerful anti-emetic and produces hypothermia. It has been used in the treatment of various psychiatric conditions and as an adjuvant in general anaesthesia to combat the shock syndrome.

Despite much experimentation with laboratory animals certain of its pharmacological effects in man have not yet been fully elucidated. It has been shown to cause profound circulatory changes in the hands, forearms, and calves of healthy subjects (Foster *et al.*, 1954) as a result of both central and peripheral actions. The present paper concerns the effects of intravenous chlorpromazine on the general circulation and on the blood vessels of hands, feet, and forearms of both healthy subjects and patients with peripheral vascular disease.

Methods

Throughout each experiment the subject reclined comfortably on a couch in a laboratory in which the ambient temperature was kept between 22° and 24° C.

FIG. 1.—Effect of intravenous infusion of 25 mg. of chlorpromazine on blood flow in the left hand and right foot of a healthy man.