OCTOBER, 1940

# THE ULSTER MEDICAL JOURNAL

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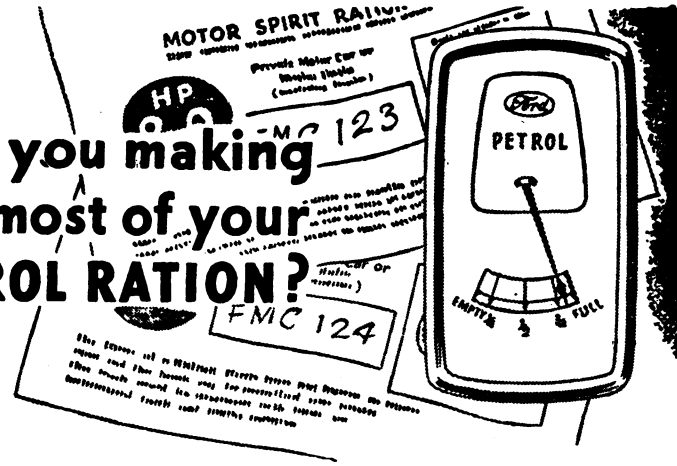


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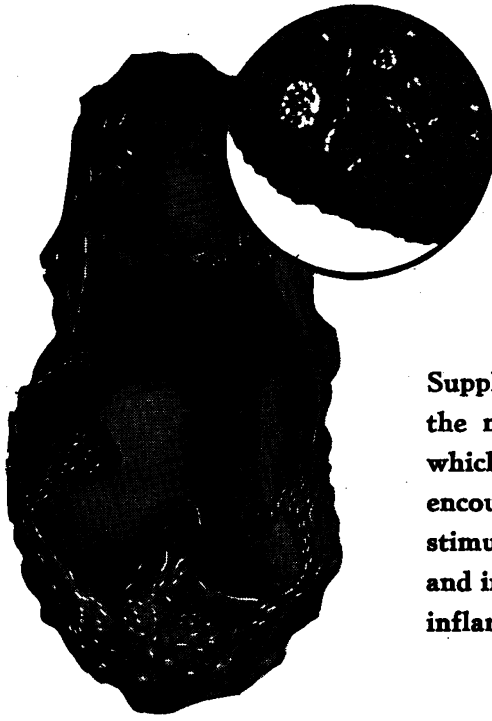

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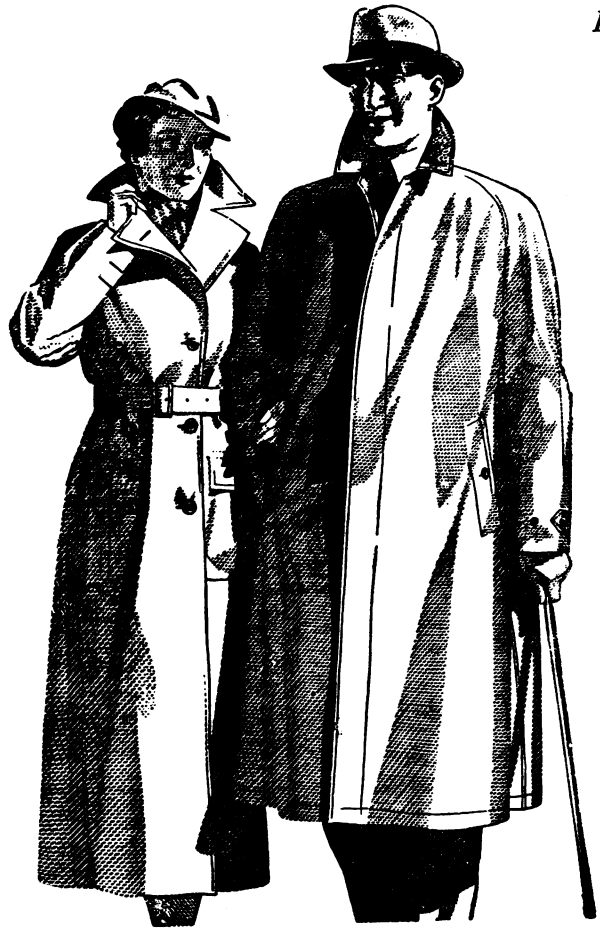

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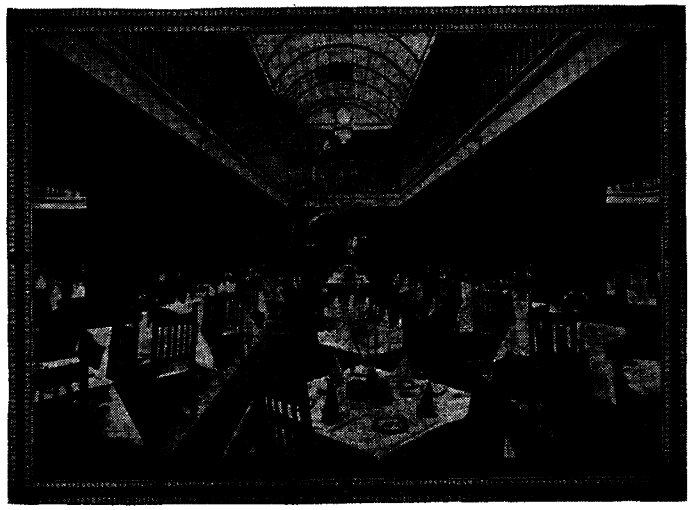

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# CONTENTS






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# THE ULSTER MEDICAL JOURNAL

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1. Manuscript should be typewritten and fully corrected. Contributors will be responsible for the payment of any sum charged for correction of the printer's proof in excess of ten shillings per sheet (16 pages).
2. Illustrations must be in finished form ready for reproduction. They must be properly labelled in type or by hand, with reference pointers if necessary.
3. Line drawings must be sent whenever possible. Illustrations requiring half-tone blocks are costly, and unless printed on special art paper are often unsatisfactory. Authors will be charged for these half-tone blocks at cost price.
4. The legend describing an illustration must be inserted in the appropriate place in the text, and should not be placed on or appended to the drawing.
5. Orders for reprints must be given when the author returns the printer's proof. The cost of these may be obtained from the printers in advance.
6. Editorial communications should be sent direct to the Acting Editor, Dr. Hunter, Queen's University, Belfast.

## ADVERTISEMENTS

First advertising forms go to press thirty days in advance of the date of issue. In forwarding copy, time must be allowed for setting up and submitting proof. All communications for space must be sent direct to the advertisement controllers : Messrs. Geo. A. Stewart & Co., Publicity House, 100 High Street, Belfast. 'Phone : Belfast 23091.

## DATES OF PUBLICATION

For the duration of the present war it is hoped to issue two numbers each year : on 1st April and on 1st October.

tions and are occasionally single figures. Having made the necessary adjustments in the test, it is found that for $n' = 31$ ($n = 30$) the value of $t = 5.12$, the variates being regarded as the differences between the figure "before" and the average "after" multiplied (as theory requires) by $\sqrt{\frac{3}{4}}$, when the average is derived from three observations, $\sqrt{\frac{2}{3}}$ when the average is of two observations, and $\sqrt{\frac{1}{2}}$ when there is but a single observation "after." There is not the faintest doubt of the marked significance of this result. It may be well to add that in this manner of application of this test, it is assumed that, were it not for the treatment, no general improvement in the hæmoglobin figures would have been recorded, i.e., that the "initial findings" might be taken as representative for these persons prior to treatment—if some were below their average on the occasion of that particular test, for instance, they might have been compensated by others which were above their particular average. There is no reason to doubt but that this assumption was justified. If we deliberately selected persons whose hæmoglobin figure was lower on a given occasion than their particular average, and if, without any treatment, we measured them at a later date, we would, of course, find in most cases an increase, to which no significance would attach.

The "after" figures in Table 2A are "average of averages" types of figures, the use of which generally is to be deprecated, but it is hard to see how they could be assembled and digested otherwise.

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*The Editor, "Ulster Medical Journal."*

SIR,—In the April number of your JOURNAL you very kindly published a letter from me, in which I pointed out that 164 subscribers had contributed £193 to the Belfast and County Antrim branch, and in the other counties 124 subscribers had given £112 in the year ending 1st April, 1940; and that 950 Ulster doctors do not subscribe to this, our own charity.

May I again appeal to these hundreds of doctors? I shall be glad to forward banker's order forms (dated 1st January, 1941) to any who apply to me.

It is unnecessary to say that the rising costs of living make our small grants even more inadequate—and we do not subscribe enough even to meet these grants.

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I am, Sir,

Yours faithfully,

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The subscription to the Society is one guinea for Fellows and Members living in the country; two guineas for Fellows living in Belfast; and one guinea for Members living in Belfast who are not qualified more than seven years. The payment of a sum of twenty guineas entitles one to election to Life Membership.

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If you do not wish to become a member of the Society, will you consider entering your name as a subscriber to THE ULSTER MEDICAL JOURNAL? The subscription is five shillings per annum, payable in advance to the Honorary Treasurer.

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THE
ULSTER MEDICAL JOURNAL

:: PUBLISHED ON BEHALF OF THE ULSTER MEDICAL SOCIETY ::

Vol. IX 1st OCTOBER, 1940 No. 2

# Cerebro-Spinal Fever and Meningococci Infection

*By* Sir Thomas Houston, M.D., and J. C. Rankin, M.D.

This contribution consists in a review of work done during the severe epidemic of cerebro-spinal meningitis which occurred in Belfast during 1907 and 1908, together with some additional observations that have been made in France during the Great War and also during the present year in Belfast.

During 1907 and 1908 we devised an application of Sir A. E. Wright's opsonic technique for the laboratory diagnosis of this infection. We found that this technique was not difficult and gave positive results in several hundreds of cases of the disease examined during the epidemic. By means of this test, a number of cases of meningitis not due to the meningococcus could be definitely excluded, and these negative findings were confirmed in a number of instances by post-mortem examination. Sera obtained from cases infected with other micro-organisms or sera from normal individuals never gave this reaction.

One of us, while in France during the Great War, further tested the accuracy of this method, and again during the present epidemic in Belfast has re-applied this test to the diagnosis of the disease and to determine the type of the infecting meningococcus. The points of interest in this serological test are—

(1) Its great value in the diagnosis of meningococcal infection—the first place in diagnosis must of course be given to the isolation of the meningococcus from the cerebro-spinal fluid or the blood, but in a number of cases such examinations may fail to give positive results, and again in so-called meningococcal septicæmia without meningitis blood-culture may be negative.

(2) The reaction to be described occurs in cases treated with Sulphapyridine, and as this reaction is no doubt a reaction of immunity, its presence in such treated cases seems to support the view of Fleming and others that the action of such drugs is bacteriostatic and that the defences of the tissues are also necessary for the cure of the disease.

(3) This method has only differentiated two types of meningococcus, and has not confirmed Gordon's classification into four types.

The details of this technique are as follows : An actively growing meningococcus of the required type is necessary for the test. Mr. Fred Burns, one of the laboratory assistants in the Institute of Pathology, Belfast, has found the following plan a reliable one for keeping the meningococcus alive.

To 1 per cent. agar in ordinary broth is added 20 per cent. serum, and the medium is allowed to set in test-tubes. Three or four stabs are made into this medium with a culture of the meningococcus, and the tubes put in the incubator overnight. The medium is then covered with sterile liquid paraffin and stored in the incubator. By slanting the tube, a small piece of agar can be fished out, and this gives a good growth of the meningococcus on a serum agar slant. In this way the culture remains viable for months.

The meningococcus usually makes a perfect emulsion in saline, but some cultures recently isolated may show some small clumps in saline. Such strains should be cultured daily for several times, when a more uniform emulsion free from clumps will result. In these cultures it is best to use a 3 per cent. agar with serum, as with 1 per cent. agar small pieces are apt to get into the emulsion.

(1) The test emulsion is made in saline or Ringer's fluid, and should be as uniform as possible. It should be freshly prepared, and not kept for more than an hour. It must be made from a rapidly growing meningococcus, and a six- or seven-hours growth should be used. If a twenty-four hours growth is used, the emulsion contains numerous degenerating cocci, which stain badly and act like particles of Indian ink and do not give the specific reaction.

(2) The washed corpuscles are prepared in the usual way for doing an opsonic index, i.e., a few drops of a Type IV (O) blood are put into a centrifuge tube containing citrate solution, and separated by the centrifuge, the supernatant fluid is pipetted off, and the deposit is washed with saline and again separated by the centrifuge and the supernatant saline pipetted off. The deposit furnishes the white cells for the test.

(3) The sera from the patient's blood and the controls are obtained in the usual way.

The test is done as follows :

The technique is that of the opsonic index. A capillary pipette is taken and a fiduciary mark made at a convenient distance from the distal end : Then equal parts of the washed corpuscles, the emulsion, and the serum are drawn into the pipette with a rubber teat, each separated by a bubble of air. The contents are thoroughly mixed on a slide and reaspirated into the pipette, and the distal end sealed in the flame. The pipettes are then incubated for fifteen or twenty minutes at 37°C., preferably in an opsonic incubator.

After incubation the contents are again mixed and films are made on glass slides. The making of suitable films requires a little practice, but one who has done opsonic indexes will find no difficulty. The films are stained by Leishman's stain and examined with an oil immersion lens.

The positive films show marked agglutination and high phagocytosis. The low opsonic effect always found with the control preparations made with normal or

non-infected sera, combined with the uniform distribution and absence of agglutination of the meningococcus, forms a striking contrast to the very high opsonic effect and marked agglutination of the positive films. Opsonic index determinations with other micro-organisms require most careful and accurate counts, but in the case of this reaction such laborious work is usually unnecessary. The picture is so characteristic that an examination of the films is all that is necessary to arrive at a definite diagnosis. The validity of this technique depends on the fact that normal sera or sera from cases infected with other organisms have very little opsonic and no agglutinative effect on the meningococcus.

Another interesting character of the meningococcus developed while we were working with a coccus isolated from one of the first cases of cerebro-spinal fever in Belfast. This coccus had been subcultured about 150 times, and was about five months old. We found that at this time the leucocytes in the preparations made with normal sera phagocytosed more cocci than they had formerly done. Thus whereas in using an emulsion of approximately the same density the earlier preparations showed from twenty-five to fifty cocci in fifty leucocytes—the later preparations showed from two hundred to three hundred cocci in fifty leucocytes. At first this coccus had agglutinated in a marked degree with sera from cases of cerebro-spinal meningitis, but shortly after we had noticed this rise in the ingested cocci in the control preparations we found that this coccus was no longer agglutinated with serum which in preparations containing a more recently isolated coccus gave a high opsonic power and marked agglutination. This observation is exceedingly interesting, as it shows that the meningococcus by prolonged growth may entirely lose these important properties. Various other experiments such as heating the emulsion, growth on unsuitable media, etc., made the meningococci unsuitable for doing opsonic determinations, as these altered cocci were phagocytosed in a non-specific manner. By the examination of sera from several hundreds of cases we found that this technique gave reliable and definite results.

The following table is a synopsis of the results obtained by the examination of 114 cases by this method :—

| Day of Disease | Number of Determinations | Number Giving Positive Reaction | Number Giving Negative Reaction | Percentage of Positives |
|---|---|---|---|---|
| 1st | 1 | 0 | 1 | 0 |
| 2nd | 12 | 3 | 9 | 25 |
| 3rd | 11 | 3 | 8 | 27 |
| 4th | 13 | 2 | 11 | 15 |
| 5th | 5 | 3 | 2 | 60 |
| 6th to 133rd | 130 | 125 | 5 | 96.1 |

Thus of 114 different cases of epidemic cerebro-spinal meningitis, 40 were examined during the first five days of the disease, 10 of these were positive and 30 were negative. Of the 74 cases examined from the 6th day onward, 4 were

convalescent for some time and 70 were suffering from the disease : of these 70, 68 gave a positive result and 2 gave a negative result, that is, 97.1 per cent. gave a positive result. As a rule this reaction quickly disappears when the disease subsides, but it persists longer in cases that have been ill for a prolonged period.

Having satisfied ourselves about the accuracy of this method as a means of diagnosis, the reaction was used—

(1) To contrast the opsonic and agglutinative power of the blood-serum and that of the cerebro-spinal fluid. It was found that the cerebro-spinal fluid had always a much lower opsonic and agglutinative power than that of the blood-serum of the same patient taken at the same time.

(2) To distinguish different cocci.
   (a) Were there different strains of meningococci?
   (b) Was the epidemic which we were investigating always due to the same strain of meningococcus?

The first question (a) was answered in the affirmative through the kindness of the staff of Great Ormond Street Children's Hospital, who sent us sera and meningococci from the cases of meningitis occurring in their hospital. Some of these cases were acute, and resembled clinically cases of epidemic cerebro-spinal fever, while others might be classed as cases of typical posterior basal meningitis.

It was evident from our results that—

(1) The meningococci of the Great Ormond Street cases react with the blood of these cases, but give no reaction with the blood of the epidemic cases in Belfast.

(2) The meningococci from the Belfast cases react with the blood of these cases, but do not react with the blood of the Great Ormond Street cases of meningitis.

These results were confirmed by Dr. Alice Taylor at Great Ormond Street.

The second question, viz., were the epidemic cases which occurred during the years 1907-1908 all due to the same strain of meningococcus? To answer this question we obtained menigococci and sera from the following centres :—

(1) Ruchill Fever Hospital, Glasgow.
(2) City Hospital for Infectious Diseases, Edinburgh.
(3) Hamburg—meningococci sent by Dr. Carnwath and Dr. Trautman.
(4) New York and Municipal Hospital, Philadelphia — through Dr. Simon Flexner.

The evidence derived from these examinations by this technique was sufficient to show that cases of epidemic cerebro-spinal fever which have occurred during 1907-1908 on the Continent, in America, in Glasgow, Edinburgh, and Belfast, were all due to a menigococcus having the same agglutinative and opsonic reactions. This meningococcus was called Type I, while the meningococcus obtained from the Great Ormond Street cases termed Type II.

While at Etaples in France, one of us with the help of Dr. John McCloy had an opportunity of verifying the value of this test on several cases of cerebro-spinal

fever. We also made a study of the meningococci obtained from the naso-pharynx of carriers occurring amongst the Forces stationed there, and we found that a number of these cocci belonged to Type I, while others were Type II, and also that some strains from carriers could not be classified in either type.

Having read the Medical Research Council's Report of the work of Dr. M. Gordon (No. 3) and his colleagues, we endeavoured to classify our strains of meningococci, using the sera and technique recommended in this report, into Gordon's four types. In our hands this investigation was far from satisfactory, often giving indefinite and irregular results. We think it possible that such unsatisfactory results may have been due to the fact that the emulsions for agglutination were prepared from an eighteen- or twenty-four-hour growth of the meningococci, and were always heated before use. We have indicated already that such procedures may destroy the specific properties of the cocci in such a way that they may not give the specific opsonic and agglutinative qualities described in this paper.

We found, however, that the serum of some of the persistent carriers gave the opsonic and agglutinative reaction, although they had no symptoms of meningitis.

As a number of cases of cerebro-spinal meningitis were occurring at the present time in Belfast and the neighbourhood, one of us with the help of Dr. McCoy has re-applied this test to the diagnosis of the disease and to determine the type of the infecting coccus.

We are indebted to Dr. Kane of the Purdysburn Fever Hospital for a number of specimens of blood from infected cases that had been treated with Sulphapyridine; and to Dr. Norman Graham for strains of the meningococcus recently isolated from the cerebro-spinal fluid in the laboratory at the Royal Victoria Hospital.

These recent results have fully confirmed our previous findings of 1907, and have shown that this reaction is almost invariably present in this form of meningitis, and does not seem to be prevented by treatment with Sulphapyridine. The cases examined up to the present have all belonged to Type I, and the meningococci isolated from cases of meningitis here have all belonged to this type.

Within the last month, Major F. B. Smith, B.E.F., has drawn our attention to the fact that cases of meningo-septicæmia are occurring in France. These cases are characterised by attacks of intermittent fever, no symptoms of meningitis, metastatic cutaneous nodes and rash—the intermittent attacks of fever are coincident with the rash. The patients are usually not severely ill.

The following memorandum was sent to pathologists in France :—"Meningo-septicæmia (chronic or subacute), e.g., eight cases from two hospitals: Fever 3-6 weeks, painful muscles and joints, painful raised small nodes in the skin, headache, leucocytosis, two positive blood-cultures of Type I and Type II meningococci. A mild illness easily missed, responds promptly to Sulphapyridine."

The serum from one of these cases that gave a negative blood-culture was sent to Belfast by Major Smith, and gave the characteristic reaction described in this article, with Type I meningococcus.

We are also indebted to Major J. M. Houston, who is pathologist to a military hospital in England, for an account of a similar case with bouts of temperature and rash but no symptoms of meningitis. The meningococcus (Type II) was isolated by blood-culture and the case responded to Sulphapyridine.

We are indebted to Dr. Norman C. Graham for the following observations, which may have some bearing on the preparation of the suspensions used in the test:

"During the recent outbreak of cerebro-spinal fever I was interested in the types of meningococci isolated from the cerebro-spinal fluid of cases admitted to the Royal Victoria Hospital. In the experiments I used recently isolated cultures and type sera supplied by the Medical Research Council. By the use of a dry, dark ground condenser, microscopic observation of the agglutination of the coccus was facilitated and the type rapidly determined. The majority of strains studied were Type I, and this was subsequently confirmed by the usual macroscopic technique.

"It was considered that this method of microscopic observation of agglutination might be applied in studying the agglutinins in the patient's blood during the early stages of the disease. For this purpose a Type I strain was used, and seven specimens of the sera of patients from the eighth to the thirty-ninth day of disease were investigated conjointly with Sir Thomas Houston. All gave a positive result in a dilution of 1 in 10, and no agglutination with the specimens of normal sera investigated. With the majority of specimens a much higher titre could be readily demonstrated, in one specimen in a dilution of 1 in 100. In using this technique it is essential to use a young actively growing culture, incubated for not more than six to eight hours. A small portion of the growth is taken directly from an agar slope and carefully emulsified in an appropriate dilution of the patient's serum in such a way that no visible microscopic clumps occur as shown by a control preparation. A satisfactory way is simply to emulsify the dilution of serum and culture on a cover-slip, and invert over a hollow ground slide, which is then sealed with vaseline. Agglutination usually occurs immediately or within ten minutes in a 1 in 10 dilution in a positive case.

"From preliminary experiments it has been found that suspensions of older cultures (fifteen to eighteen hours) in normal saline are inagglutinable and unsuitable. Similar suspensions prepared from a twelve- to fifteen-hour-old culture are also unsatisfactory unless used immediately. These observations support the view of Flexner (1907) that the salt solution has an injurious action on the meningococcus, but they also may result from antigenic changes in the micro-organism during the later stages of its growth on an artificial medium.

"It is suggested that further investigation of patient's sera by this simple technique may prove useful in the diagnosis of meningococcal infections."

Our original papers on this subject are to be found:—

*Lancet*, 4th May, 1907.

*British Medical Journal*, 16th November, 1907.

*Journal of the Royal Sanitary Institute*, 1911, 32, No. 9.

# "The Effort Syndrome"

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THE effort syndrome has been defined by Grant (1936) as "that condition of ill-health in which symptoms and signs produced in normal subjects by excessive exercise are called forth in the patients by lesser amounts and in which no definite physical signs of structural disease are anywhere discovered." More briefly it may be described as a depressed capacity for exertion without distress in the absence of demonstrable disease.

## "THE SOLDIER'S HEART."

It has elsewhere been wrongly described as having been "invented by the R.A.M.C.," but it is not confined to soldiers, although it was first made the subject of careful clinical observation by Da Costa during the American Civil War. Da Costa's name for it was "irritable heart" (1864 and 1871), an earlier term than "disordered action of the heart," both of which were criticized by Lewis (1939) on the grounds that they "maintain for those who use them the presumption that there is a cardiac malady, and among patients they awaken serious apprehension." His term, effort syndrome, might perhaps be regarded by some patients as the result of undue effort on their part. With transatlantic brevity the Americans have called it "neuro-circulatory asthenia" instead of D.A.H.

While the syndrome is not rare in civilians, as Da Costa himself observed, it is notoriously more common among soldiers. The reasons for this greater frequency are:

(1) In civilian life individuals usually gravitate sooner or later to the occupations for which they are physically suited. Even in manual labour a man can usually perform a given task in his own way and at his own speed. Again, in a gang of men the big fellow will ordinarily take the heavier burden. In the army, on the other hand, there must necessarily be uniformity of effort and equality of achievement: a man may carry his comrade's rifle, but it is essential that the comrade should complete his march. In war, many diverse types, physical and psychical, are bound to a common task.

(2) Communal life in barracks, billets, and camps increases the spread, not only of major infections such as cerebro-spinal fever, but of so-called minor infections. Lewis estimates that "in at least fifty to sixty per cent. of the cases infectious diseases may be held to have played a chief part in promoting the syndrome." Da Costa stressed the importance of insufficient convalescence as a cause. Men are returned to duty and strenuous exercise too soon. Sir Adolphe Abrahams has noted the adverse effect on athletic achievement of septic foci, as in the case of a distinguished athlete whose "times" varied with the adequate discharge of a fistula-in-ano, the radical cure of which restored his high level of performance. Apart from recent minor infections, the stresses of war may discover tendencies, hitherto latent, which have had their origins in some long-past infection. For example, Parkinson (1940) reported a history of rheumatic fever in twelve per cent. of effort-syndrome patients, as compared with five per cent. in one thousand

wounded soldiers. Grant (1925) found a history of rheumatism or chorea in 19.6 per cent of his 665 cases.

The importance of tuberculosis will be discussed in a later paragraph.

(3) "Emotion is motion, hence the name." More cases occur among men on active service than among men in training. Apart from hard labour, infection, and unsuitable food, the strain of waiting for active attack or determined defence makes the pulses of the boldest quicken. (A colleague told me that on 1st July, 1916, when the Ulster Division awaited the signal to go over the top, some of the officers amused themselves by counting pulse-rates; one only was found to be seventy-two. His steady heart still beats, I am glad to say.) Here, as in toxic goitre, age is important. Young hearts endure tachycardia better than the middle-aged.

Herman (1936) says that there are two psychological types of men particularly prone to neuro-circulatory asthenia. These are the very alert, and the subnormal. It is obvious that the former are of high potential value to the state and the latter of little value. By the perversity of war the former must be given an opportunity to serve in some useful category, while the latter are useless to the army, and are relegated to the comparative safety of civilian life and the propagation of their kind.

(4) The diet of troops is frequently very different from that of peace-time and likely to be very deficient in vitamins. For example, adequate vitamin C is necessary in fighting infection.

(5) It is probable that many soldiers smoke too much, although tobacco is not the cause of the syndrome. Indeed, Lewis found that only five per cent. of his cases smoked twenty or more cigarettes daily. "The heaviest smokers are those with the best exercise tolerance, for they are relatively undisturbed by smoking" (Lewis). This does not mean that a medical officer may accept a confession to forty cigarettes a day as a substitute for an exercise tolerance test. I think that tolerance of tobacco varies amongst smokers, and is not always directly proportional to their tolerance of exercise.

In any review of the causes which contribute to the ætiology of effort syndrome, one important but negative point must be made: the syndrome is *not* due to heart strain in the vast majority of cases, and it is extremely rare to find the symptoms arise and persist as the result of an unusual effort on the part of a hitherto healthy man.

## ÆTIOLOGICAL GROUPS.

Sir Thomas Lewis classifies syndrome patients as follows:—

(1) Patients with constitutional weakness, nervous or physical or both.

(2) Those who may be regarded as played out by exposure, hard continuous work, and disturbed sleep.

(3) Those who may be regarded as exhibiting delayed convalescence from acute illnesses.

(4) A not inconsiderable group is that comprising actual though unrecognised infection, including incipient tuberculosis, local pus infections, infections of intestinal tract.

Bramwell's classification is similar :—

(1) Those of subnormal physique and stamina.

(2) Those who are convalescent from a recent acute infection.

(3) Those who are suffering from an anxiety state.

Da Costa found in two hundred cases—

| | | per cent. |
|---|---|---|
| Fevers (typhoid, etc.) | 34 | 17.0 |
| Diarrhœa | 61 | 30.5 |
| Hard field service, particularly excessive marching | 69 | 38.5 |
| Wounds, injuries, rheumatism, scurvy, ordinary duties of soldier life, and doubtful causes | 36 | 18.0 |

Many observers agree the psychical factor is the most important. As a colleague has put it : "It is the only constant factor in causation, and therefore it is probable that the condition is really a psychic one, and treatment which takes no account of the psychical cause can only hurt a relative success."

## SYMPTOMS AND SIGNS.

The circulatory symptoms are in the main "those which are produced in normal subjects by excessive exercise," and may resemble those of organic heart disease, but there are certain distinguishing features.

(1) TACHYCARDIA.

"Tachycardia is present all day long in all cases, but the pulse-rate drops to normal during sleep" (Fraser, 1940). The rate is often 100-120, and the rhythm may be broken by extra systoles. This persistently high pulse-rate is very easily augmented by emotion; after exercise the rate does not return to its former level for at least two minutes. The subjective sensation of palpitation is not directly related to the heart-rate, and extra systoles are often more distressing than the increased rate itself.

In paroxysmal tachycardia there are the characteristic bouts of rapid rate, with their sudden reversal to normal.

(2) DYSPNŒA.

"Breathlessness is always admitted, but seldom the primary complaint"(Parkinson, 1940). Its cause is imperfectly understood, as there is neither demonstrable heart-disease nor significant diminution of vital capacity. It is usually rapid and shallow, but differs from purely hysterical tachypnœa in that it is normal at complete rest. The "unsatisfied breath phenomenon" is common. This is the feeling that "if only one could take a deep breath one would be all right." It is always strongly suggestive of neurosis. Breathlessness due to cardiac failure in young persons is almost invariably accompanied by easily detected signs of valvular disease or cardiac enlargement. There exist cases of myocarditis due to diphtheria or rheumatism, where only an electro-cardiographic and radiographic examination will detect the nature of the myocardial change; but the objective signs of congestive heart failure, distension of veins in the neck and engorgement of the liver, will be demonstrable. The breathlessness of lung disease is proportional to the rate of progress of the disease, rather than to its extent, at least until the disease has become very extensive and its associated toxæmia profound.

(3) Præcordial Distress.

"Left inframammary pain is the commonest symptom volunteered by patients" (Fraser, 1940). Herman is right, I am sure, in saying there are two phases—dull rather persistent "heartache," varied by sudden knife-like stabs. This pain is, as it were, loosely associated with exertion, and may occur at rest. It may occur on exercise one day and be completely absent on another. It may disappear during exercise or may last for hours afterwards. While there is scarcely the imperative halt of true angina, the patient may feel constrained to stop, but rest does not bring the exquisite respite of angina relieved.

In patients who complain of pain there is very commonly hyperæsthesia of skin or tenderness of the pectoral muscles of the left side. This sign is an important one, but one must remember that hypersensitive chest muscles may sometimes be found in organic heart disease.

(4) Exhaustion.

It is this symptom which most clearly shows the psychological aspect of the syndrome. In milder cases it may amount only to the undue fatigue of a sedentary worker "out of training" for exercise, but in established cases "the tired, anxious look, the tremor, the headache, and the mental and physical weariness must be due to a psychological factor" (Fraser, 1940).

Repeated medical examinations directed particularly to the condition of the heart, and those verbal indiscretions in the hearing of the patient of which even senior physicians are too frequently capable, may well have reduced the patient to a state in which he is almost afraid of ordinary movement for fear of imposing further strain on his heart.

Associated symptoms are fainting (often for a mixed physical and psychical stimulus such as a hypodermic needle), dizziness (often of postural type, occasioned by sudden changes of position), headache, and profuse sweating. Like the pulse-rate, the blood-pressure is labile, usually normal at rest, but rising quickly, to fall more slowly, after exercise.

## DIAGNOSIS.

(1) From Organic Heart Disease.

The presence of an apical systolic murmur is insufficient evidence on which to condemn a heart. Sir Thomas Lewis allowed a climber who had such a murmur to take part in the Mount Everest expedition. On the other hand, the absence of recognized rheumatism does not exclude carditis. Crighton Bramwell confirmed my finding that twenty-five per cent. of cases of mitral stenosis in pregnancy had no such history, and mitral stenosis without rheumatic fever is not exclusive to the female sex. Again, coronary lesions reveal little to the stethoscope, and are not unknown under forty years of age.

The desire to serve or to avoid service tends to make an accurate history more than ordinarily difficult to elicit, and it is not always the volunteer who is the optimist and the conscript the pessimist about his own condition, but careful physical examination will usually decide the matter. I have in this Journal in 1933 emphasised the amazing freedom from symptoms in young persons with

rheumatic heart disease which leads them into unsuitable occupations. Of the instrumental methods, X-ray, to determine heart-size, and electro-cardiography are useful, but "a man's *observed* capacity to accomplish work is the only dependable test of such capacity" (Meakins, Parkinson *et al.*, 1916).

(2) From Toxic Goitre.

This condition presents many symptoms found in the effort syndrome. It is well to remember that (a) goitre in male subjects is often larger than one at first suspects, because the swollen lobes tend to spread backwards on either side of the trachea and the full extent of the change may only be fully appreciated at operation; (b) in toxic goitre the sleeping pulse-rate is raised, whereas in effort syndrome it is little if at all above normal; (c) in toxic goitre the skin is uniformly warm, and in effort syndrome the extremities are often cold and even painful; (d) estimation of the basal metabolic rate is useful, but not always necessary.

(3) From Pulmonary Tuberculosis.

Percussion and auscultation of the lungs may be difficult in a recruiting board-room, but sometimes we forget the proper significance of the term medical inspection. Malar flush, a flattened apex, diminished respiratory movement—and the mercury in a thermometer, are all visible phenomena. X-ray examination is invaluable. Blood sedimentation rate is cheaply and easily observed; in the absence of other toxæmias such as those of rheumatism or rheumatoid arthritis, a raised blood sedimentation rate makes one suspect tuberculosis.

## PREVENTION.

(1) One of the most striking of R. T. Grant's (1926) observations on the after-histories of men suffering from the effort syndrome was, that five years after the war of 1914-1918 the incidence of pulmonary tuberculosis among them was eighty per cent. higher than in the general population of London. This surely means one or other of two possibilities: either that tuberculosis was the unrecognized cause of the syndrome, or that the patients had a lessened resistance to tuberculosis. If the former, it is an additional reason for the accurate diagnosis of tuberculosis in recruits and young soldiers.

The examination of all recruits by a board of five doctors is an improvement on the slipshod methods of 1914, when probably the only division to be adequately examined on enlistment by teams of volunteer-doctors was the 36th (Ulster) Division. Stethoscopes are not enough: X-ray examination should be available for every board. The cost to the state of one X-ray picture is less than that of a "less than twenty per cent." disability pension for twelve months, the difference being approximately twenty pounds.

Again, at least one tuberculosis medical officer in England notified the medical officer of any unit into which one of his tuberculous patients had been enlisted, but this obviously desirable practice was not universal, and many tuberculous patients "passed the doctor" and passed on their infection to their comrades. Now, after twelve months of war, and twenty years retrospect, it seems that the authorities are awaking to the danger.

If it is true that tuberculosis has a special relationship to the effort syndrome, and Grant's figures are in accord with other clinical opinion, steps to prevent the spread of the former will lessen the incidence of the latter.

(2) When a nation with a small peace-time army adopts conscription there seems to be a plethora of soldiers. This may subconsciously influence medical boards to a line of least resistance, and to the exclusion of every candidate who presents the slightest departure from a "normal" heart—systolic murmurs, extra systoles, even sinus arrhythmia may find their way to the discard. By this means men capable of rendering valuable service are turned away and are liable to regard themselves as invalids because they have been "rejected by five doctors." The most experienced and careful board must often find cases which are difficult; even with the excellent advice of the confidential instructions (1938), I suggest that there should be a special category for such cases as these: the alert, eager, patriotic type recruited from a sedentary occupation, with a systolic bruit, or subnormal exercise tolerance, or tachycardia or extra-systoles; or the less admirable individual whom one suspects of a desire to avoid military service. These should be classed in grade I (m), the bracketed letter to imply that they will be on probation and under the special observation of the medical officers of their units for at least three months. If a large number of grade I (m) recruits is enlisted they should be posted to command depots on the lines of those created at the suggestion of Colonel Sims Woodhead in the last war, where graduated exercises under medical supervision brought thousands of men convalescent from wounds and sickness back to physical fitness.

"To discharge the large number of cases of functional disorder of the heart which must exist in every army during war, would, I believe, deplete it as much as an engagement, and have on many a soldier, seeing the ease with which a discharge can be obtained, a demoralizing effect" (Da Costa).

(3) When a member of the service develops even a minor infection he should not be returned to duty or training without an adequate period of convalescence.

## TREATMENT.

When the syndrome presents itself, every necessary step must be taken to exclude organic disease *before* the patient is reassured. It destroys confidence to tell a man that his heart is all right one week and to send him to be electro-cardiographed the next week. During this diagnostic period a few days in bed may be necessary, to be followed by a few days during which the patient is encouraged to move about out of doors. Then graduated exercises should be commenced, on the lines laid down by Meakins, Parkinson (1916), and their colleagues at Hampstead in 1916. They evolved seven sets of graduated exercises, which proceeded from fifteen minutes very light exertion to thirty minutes of quite strenuous exercise. At the Command Depot, Tipperary, these exercises were followed by "route marches" at first without rifle or pack, at an easy pace for a mile or so, and increasing, until our best cases could march twelve miles with full equipment. The depot band "played them in" for the last two miles.

A great deal depends on the personalities of the physician and the P.T. instructor, and on the "atmosphere" of the depot. Games and simple recreations must be

provided for those hours when the patient is not actively engaged. In Tipperary the cases were not segregated, but were mixed with the larger number of men recovering from wounds who were receiving massage, electrical treatment, and graduated exercises and marches after many weeks of hospital treatment. These men by their courage, cheerfulness, and determination to get fit, contributed largely to the success of the place.

I have no knowledge of specialised psychological methods of investigation of treatment, but many cases suggest that this is a promising field. There is no drug of any specific value in the treatment of the effort syndrome.

## PROGNOSIS.

Prognosis depends on the origin, duration, and severity of symptoms. As might be expected, the best results are to be found in cases following a transient infection, and in the last war men who broke down overseas had a higher recovery-rate than those who did so under military training at home.

The longer the symptoms have lasted the harder they are to eradicate. Parkinson regards long-standing submammary pain and hyperæsthesia as a symptom of poor prognosis. Grant found age to be important in prognosis. Between the ages of 17 and 20 the recovery-rate was twenty-five per cent., between 41 and 60 years it was 2.1 per cent. (The incidence in these two age-groups was 2.9 per cent. and 16.7 per cent. respectively.) The fact that he found that 56.2 per cent. of his cases had remained stationary, and 3.2 per cent. had become worse five years afterwards, proves how severe and intractable the syndrome may be, but "from the fact that the incidence of definite cardiac disease for the whole group during the period of five years is no more than one per cent., it is felt that incipient cardiac disease cannot be regarded as the underlying cause of the effort syndrome in anything but a negligible proportion of the cases" (Grant, 1926).

Whishaw reviewed the physical condition of 130 returned soldiers suffering from the effort syndrome in 1939. These were men who had taken part in the war of twenty years ago. His findings confirmed Grant's conclusions, and in particular that the effort syndrome does not predispose to organic heart disease. Cardio-vascular disease was discovered in thirteen cases (ten per cent.); of these, coronary disease accounted for six, hypertensive heart disease two, chronic nephritis with hypertension one, chronic rheumatic heart disease one, and specific aortitis three. This incidence does not seem remarkably high, considering that the average age of the men was forty-six years.

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# Notes on the Pharmacology of M.&B. 693 and Uleron

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It is intended here merely to give an outline of the results obtained in a large series of experiments performed in the study of the absorption and excretion of M.&B. 693 and of some of the toxic effects of that drug and Uleron. Experimental detail will not be described.

## ABSORPTION AND EXCRETION OF M.&B. 693.

Various methods have been employed in the estimation of the sulphonamides in the body fluids. The method used in the present investigation was that described by Werner (1939).

M.&B. 693 is absorbed from the gastro-intestinal tract and appears in the blood-stream and urine within half an hour after its ingestion by mouth. The maximum concentration is reached in from two to five hours time, the maximum urinary output being delayed for from half an hour to five hours after the blood peak has been reached. After a single dose of the drug, M.&B. 693 can still be detected in the blood for forty-eight to sixty hours and in the urine for eighty-four hours, whilst, with repeated dosage, it has been recovered from the blood thirty-six hours and from the urine sixty hours after the last dose, a point of importance in view of the toxicity of the drug. The output of the drug varies with diuresis, but large amounts of fluids appear to wash it through the bowel too rapidly for complete absorption from the intestine to take place, and the urinary output is thus considerably less than on a low fluid intake: Baines and Wien (1939) have shown that normally a small amount of the drug is excreted in the fæces, and it is likely that excretion, when large amounts of fluid are administered, is chiefly through the bowel. It will be mentioned later that in treating non-specific urinary infections, a fairly high concentration of the drug in the urine is necessary; where such a condition is being treated with M.&B. 693, therefore, fluids should not be given in excess. Where toxic manifestations appear following absorption of M.&B. 693, forcing fluids will tend to wash the drug out of the body. Increased fluid intake, however, does not appear to accelerate absorption from the gastro-intestinal tract as has been shown by others to occur with sulphanilamide (Marshall, 1939; Lucas, 1939).

A blood concentration of 2.5 milligrammes per cent. has been found to be a reasonably satisfactory level in the treatment of most cases of gonococcal urethritis, and this concentration can be maintained by a dosage of two grammes per day following a heavier initial dose of three grammes during the first day's treatment. The blood level varies with, though not in proportion to, the dosage, a reasonably steady blood level being maintained by repeated doses given at four- to five-hourly intervals during the period of administration of the drug. The concentration of the drug falls during the night, and in urgent cases where a steady blood level is desired, the last dose of the drug should be given late at night and the first dose

early the following morning, or an extra dose should be administered during the night.

The drug appears in the blood and urine partly as a free, active compound and partly as an acetylated, inert derivative. The amount of the free and acetylated drug varies considerably, not only from patient to patient, but in the same patient from time to time. On an average, about twenty per cent. of the drug was found to be in the inactive form in the blood and about forty per cent. in the urine, though a much higher degree of acetylation sometimes occurs, figures rather lower than those recorded by other workers (Stokinger, 1939; Long and Feinstone, 1939).

Clinical failures with M.&B. 693 are sometimes due to inadequate concentration of the drug in the body fluids. This may be due to one of three things :—

(1) Poor absorption, or
(2) A high degree of acetylation, or
(3) A patient who requires a higher concentration of the drug than the average patient.

Where failure to respond to chemotherapy is due to inadequate concentration of the drug, increased dosage will usually result in a satisfactory clinical response.

The concentration of the free drug in the urine is of more importance than that in the blood in the treatment of diseases due to non-specific organisms, a level of at least fifteen to twenty milligrammes per cent. being necessary in these cases—a figure in accord with the experimental findings of Melton and Beck (1939), who demonstrated the marked bactericidal effect of a concentration of M.&B. 693 of fifteen milligrammes per cent. in urine to which varying dilutions of B. coli had been added. This concentration is very often not obtained when fluids are forced (see above).

With poor excretion, accumulation of the drug in the tissues occurs and toxic manifestations, often in proportion to the amount of the drug in the tissues, are seen.

## TOXIC MANIFESTATIONS.

In common with sulphanilamide, both M.&B. 693 and Uleron show a high degree of toxicity. Many "minor" toxic reactions are common with M.&B. 693, especially nausea, flatulence, headache, and (particularly in females) vomiting. These "minor" reactions are much less common with Uleron. The use of both drugs, however, is often followed by more serious toxic manifestations, which are often missed or unrecognised. Of these, the most important are the effects of the drugs on the blood cells of the body and on the kidneys, whilst a less urgent, though often more alarming, toxic effect is the occurrence of skin rashes and drug fever following ingestion, especially of M.&B. 693.

### (1) Effect on the Blood.

Both drugs have a marked effect in reducing the numbers of both the white and red blood cells, the effect on the red blood cells being of a more transient nature than that on the leucocytes. The lowering of the white blood cell count is chiefly the result of a decrease in the numbers of the neutrophils. With a dosage of

M.&B. 693 of three grammes for one day, followed by two grammes daily for a further six days, thirty-two per cent. of cases showed an absolute neutropenia on one or more occasions, whilst a relative neutropenia occurred in no less than eighty-three per cent. in a large series of patients investigated. This phenomenon was seen not only during administration of the drug but for some considerable time afterwards, the maximum lowering of the blood-cell count in the cases examined (in the case of M.&B. 693) occurring nine days after cessation of chemotherapy.

This depressive action of M.&B. 693 on the blood cells does not appear to depend on the concentration of the free drug in the body fluids.

A number of cases of granulocytopenia have been recorded following the use of M.&B. 693, and in several of these cases at least the condition did not develop until several days after withdrawal of the drug (Barnett et al., 1939; Graham et al., 1939; Agranat et al., 1939; and Briggs, 1939). In some of these cases (Briggs, 1939) an atypical response to chemotherapy was witnessed. It would appear to be important, therefore, to keep a close watch on the blood, especially where prolonged chemotherapy, heavy dosage, or atypical response occur, and blood examinations in these cases should be continued periodically for several days (ten to fourteen at least) following the end of chemotherapy.

Uleron has an even more marked effect in reducing the blood-cell counts than M.&B. 693.

Cyanosis occurs occasionally with both M.&B. 693 and Uleron, though methæmoglobin was found once only on spectroscopic examination of the blood of a patient who had had an unusually heavy dosage of M.&B. 693 within a short period of time. Repeated spectroscopic examination of the blood in patients on routine dosage of M.&B. 693 and Uleron failed to reveal either met- or sulphæmoglobin.

(2) Effect on the Kidneys.

Another toxic manifestation of considerable importance, which has been found to complicate therapy with these drugs, is hæmaturia (McCann, 1939). Microscopical hæmaturia has been found in fifty-two per cent. of cases treated with M.&B. 693 (of which thirteen per cent. may have had a traumatic origin) and in twenty-nine per cent. of cases treated with Uleron. Isolated reports have appeared from time to time describing gross hæmaturia occurring with both Uleron and M.&B. 693 (Sommer, 1938; Müller, 1938; Adalja, 1939; and others); these reports included at least one fatal case (Tsao et al., 1939). Experimental hæmaturia has also been produced (Gross and Cooper, 1939; Antopol and Robinson, 1939). The cause of the phenomenon is still a matter of conjecture, but in the more severe cases at least, and in experimental animals, it would appear to be due to the deposit of needle-like crystals of the acetyl derivative of the drug in the urinary tracts of suspectible individuals. In the series of cases analysed personally, hæmaturia was found to be more common in M.&B.-693-treated patients, where the percentage of the acetylated drug in the urine was high. X-ray and blood-urea examinations in a number of cases where hæmaturia was seen, revealed no pathology of the renal tract, but the possibility of renal calculi following chemotherapy with M.&B. 693 and Uleron cannot be overlooked. Time alone will either

prove or disprove this possibility, and it is not suggested that drugs as potent as those now in our possession should be discarded on this account; it is important, however, that they be used with due consideration to their toxic possibilities.

Where gross hæmaturia occurs, as in the case of other severe toxic manifestations, the drugs should be withheld and large amounts of fluids should be given in order to wash the drug out of the tissues.

(3) Effects on the Skin.

The skin reactions observed may follow exposure to artificial or natural sunlight or may occur apart from such exposure. Skin rashes occurred in only four patients treated personally with M.&B. 693, and in only one of these patients was there any suggestion of light-sensitivity. In three cases the dosage was small, the rash appearing on the eighth morning from beginning of chemotherapy in one case and on the tenth morning in two cases. In the fourth case, the rash occurred on the fourteenth day from beginning a second course of the drug. In one case, the dermatitis was accompanied by drug fever, whilst in this case as well as in one other, considerable gastric upset was seen when the drug was being taken. The time factor was of interest in these cases and was similar to that found by Erskine (1939) and Thompson (1939), the skin eruptions occurring in their cases between the eighth and twelfth days of administration of the drug. It has been mentioned that toxic manifestations often result from the accumulation of the drug in the tissues, and such would appear to be a possible explanation of the skin rashes occurring in at least two of the cases noted personally. Again, withdrawal of the drug and forcing fluids are indicated.

No skin reactions were seen in the Uleron-treated cases.

Various methods were tried to combat the less serious though more common "minor" toxic reactions. Some of these are described in another article in this Journal (The Chemotherapeutic Treatment of Gonorrhœa).

## DISCUSSION.

A study of the biochemical response and the toxic manifestations resulting from M.&B. 693 makes it evident, therefore, that whilst a "therapeutic" concentration of the drug in the body fluids is necessary for favourable clinical results, this concentration should be obtained and maintained by minimal effective dosage of the drug. Large doses should be used only when the patient is confined to bed and if possible in hospital, where constant supervision is carried out. The occurrence of the more serious signs of toxicity is usually an indication for immediate cessation of chemotherapy, especially where a study of the absorption and excretion of the drug reveals an accumulation in the tissues. It would seem to be important that repeated blood and urinary examinations be performed, especially where large doses or prolonged chemotherapy is being employed or where atypical response to the drug is manifested, and that the blood examinations especially should be continued for some ten to fourteen days after withdrawal of the drug.

Equally careful control would appear to be indicated where Uleron is the chemotherapeutic agent in use.

I wish to acknowledge my indebtedness to Professor E. B. C. Mayrs for his help and encouragement throughout this work. To Dr. J. C. Rankin and Surgeon-Commander H. E. Hall for permission to work in their department in hospital. To Drs. J. Houston and J. McCoy for pathological reports. To the gynæcological staffs of the Royal Victoria and Royal Maternity Hospitals, and finally, to the nursing staffs of both these hospitals, and especially in the V.D. Clinic at the Royal Victoria and the ante-natal wards of the Royal Maternity.

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# REVIEW

A HOSPITAL PRAYER BOOK. Compiled by M. L. Jacks, D. B. Porter, and G. R. Girdlestone. 1940. Oxford University Press. Price 8d. net.

The Hospital Prayer Book was first published in 1913, compiled by Rev. Verney L. Johnstone, then Chaplain to the Wingfield-Morris Orthopædic Hospital. It received a warm welcome from patients and staff alike, and had an extensive circulation. The 1940 edition is a revised version, incorporating many excellent prayers, suitable for hospitals, which have been written since 1913. It includes some of the older prayers, including the prayer of St. Ignatius: "Teach us, good Lord, to serve Thee as Thou deservest, to give and not to count the cost, to fight and not to ask for any reward, save that of knowing that we do Thy will, through Jesus Christ our Lord." The spirit of the first edition has been retained, and the book should have a wide acceptance amongst the staffs and patients of the great hospitals of our country.

I wish to acknowledge my indebtedness to Professor E. B. C. Mayrs for his help and encouragement throughout this work. To Dr. J. C. Rankin and Surgeon-Commander H. E. Hall for permission to work in their department in hospital. To Drs. J. Houston and J. McCoy for pathological reports. To the gynæcological staffs of the Royal Victoria and Royal Maternity Hospitals, and finally, to the nursing staffs of both these hospitals, and especially in the V.D. Clinic at the Royal Victoria and the ante-natal wards of the Royal Maternity.

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# The Chemotherapeutic Treatment of Gonorrhœa and Its Complications

*By* J. Sydney McCann, M.D.

From the Venereal Diseases Clinic, Royal Victoria Hospital, Belfast

Before the introduction of the sulphonamide group of drugs, the treatment of infections due to the gonococcus was largely confined to the use of urinary antiseptics, irrigations of the urethra, and treatment of complications as they arose. More recently, vaccines and gonococcal antitoxin were added to these time-honoured methods in the hope that possibly a more rapid and successful cure might be attained. Crean (1937) remarks, however, that none of these methods has made any notable change in the length of time it takes to cure an uncomplicated acute case. With the introduction of chemotherapy, however, a new era in the treatment of gonorrhœa was ushered in.

Despite the fact that the sulphonamides have now been in use for some three or four years, there is still considerable doubt on many aspects of the chemotherapeutic treatment of gonococcal infections, this doubt, in some cases, extending even to the question as to which is the most suitable preparation to use in the treatment of these conditions. There is still considerable doubt, too, as to the proper time for commencing chemotherapy: a number of authorities have advocated "delayed therapy," whereby chemotherapeutic treatment in acute gonorrhœa is withheld for some eight to twenty-one days in order to allow the body immunity mechanism to develop; during this waiting period, routine methods of treatment (i.e., urethral irrigations and vaccines) are carried out; other workers, on the other hand, commence chemotherapy as soon as the diagnosis of the disease has been established. Various schemes of dosage have been suggested, whilst difference of opinion still exists as to the total amount of the drug required and as to the total duration of treatment, whilst the vexed question of the advisability or otherwise of combining chemotherapy with routine methods of treatment has not been definitely settled.

Before a satisfactory statement can be made with regard to these points, a number of considerations demand attention, of which not the least important is the choice of the drug itself. There is now little doubt that the most efficient sulphonamide for use in gonococcal infections is M.&B. 693, and the present article is the outcome of an investigation made with that drug in the treatment of gonorrhœa in patients attending the Venereal Diseases Clinic at the Royal Victoria Hospital, Belfast. The cases investigated were mostly males, though the results obtained in a small series of female patients are also recorded. In a few cases, Uleron was the chemotherapeutic agent employed, either per se or before or after the use of M.&B. 693. Whilst the clinical research was being carried out, a study was also made of the absorption and excretion of M.&B. 693, and some of the toxic effects of both M.&B. 693 and Uleron were investigated at the same time. The dosage of the drugs ultimately employed and the duration of treatment decided upon were the result of this combined study, the object being to use what was considered to be a

minimal effective dosage of the drugs given over a minimal effective period of time, taking into consideration the toxic reactions produced by the drugs as well as their absorption and excretion. Some of the results obtained in the more pharmacological aspects of the investigations are described elsewhere in this issue of the Journal.

## PROCEDURE.

The response to treatment in 230 cases of infections due to the gonococcus was studied. These cases consisted of 216 male and 14 female patients: they were divided up as follows:—

(A) MALE:

I. Treated with M.&B. 693—

(a) Uncomplicated cases - - - - 133

(b) Complicated cases - - - - 22

II. Treated with Uleron or Uleron and M.&B. 693 - - 19 (11)

(8 of these cases will be discussed with the M.&B. 693 patients, so that actually there are only 11 additional cases).

III. Controls - - - - - - - 50

(B) FEMALE - - - - - - - 14

The patients were chosen at random. The desire was to get as large and representative a series as possible in all stages of the disease, including a number of patients suffering from a variety of gonococcal complications.

As the use of the drugs and other methods of treatment employed were largely experimental in the early stages of this research, to discuss the various procedures adopted would be to anticipate the results of the investigation about to be described. Such a discussion will be deferred until the various aspects of the clinical results have been considered.

## RESULTS.

### (A) MALE CASES. I. TREATED WITH M.&B. 693.

### (a) UNCOMPLICATED CASES—133 PATIENTS.

In twenty-eight of these patients, symptoms had been present for more than six weeks, in nine others the duration of the disease was doubtful, the remainder were "acute" cases, i.e., patients in whom symptoms had been present for less than six weeks. The actual duration of symptoms before chemotherapy and the number of patients treated were as follows:—

| Duration of symptoms before chemotherapy (days) | No. of Patients |
|---|---|
| 1— 7 | 51 |
| 8—14 | 21 |
| 15—21 | 14 |
| 22— | 38 |
| Doubtful | 9 |

The final results were divided into four groups:—

Group 1.—Cured cases or those who passed tests of cure (T.O.C.), and remained well for a period of two months or longer from the end of chemotherapy.

Group 2.—Probably cured cases or those who passed T.O.C., and remained well up to their default before the end of two months from cessation of chemotherapy, or who have passed T.O.C. and have been under observation for a period greater than one month but less than two months from end of chemotherapy, and are still reporting.

Group 3.—Clinical cures or those who showed a satisfactory response to chemotherapy, but who defaulted before T.O.C. or who passed T.O.C. but defaulted within a month from the end of chemotherapy, or who have passed T.O.C. and are still under observation, but for a shorter period than those still reporting in Group 2.

Group 4.—Failures: those patients who failed to respond to one or more courses of treatment.

T.O.C. were performed at varying intervals after the end of chemotherapy. They consisted of provocative doses of gonococcal vaccine (twenty millions), urethroscopic examination of the anterior urethra, and the passage of a large sound into the bladder, the urethra being massaged against the sound.

Eighty-three patients had adjuvant treatment in addition to M.&B. 693, the remaining fifty having the drug only. The adjuvant treatment consisted of daily urethral irrigations, usually with 1/10,000 potassium permanganate, and in some cases weekly injections of gonococcal vaccine were also given. An alkaline powder was prescribed frequently where nausea following the use of the drug occurred.

A gross analysis of the results reveals the fact that a satisfactory response to chemotherapy was obtained in 128 cases (or over ninety-six per cent.), there were five (or 3.7 per cent.) failures, in eight cases (six per cent.) relapses were seen, and three cases exhibited complications during chemotherapy: the complications were all mild.

The 128 good results were classified as :—

| | |
|---|---|
| Group 1—Cured cases - - - | 69 |
| Group 2—Probably cured cases - - | 20 |
| Group 3—"Clinical cures" - - - | 39 |

Of the sixty-nine cases in Group 1, fifty-five attended for a period varying from three to fifteen months from the end of chemotherapy: as in the other two groups, many of the patients in Group 1 are still reporting at intervals.

The cure-rate was so high in both acute and chronic cases that it seemed evident that neither "delayed therapy" nor adjuvant treatment made the slightest difference to the ultimate outcome. In order to confirm this, the failures, relapsed cases, and cases in whom complications developed during chemotherapy were analysed more fully.

ANALYSIS OF FAILURES.

Five patients failed to respond to chemotherapy with M.&B. 693. Of these, chemotherapy was commenced within two to nine days from the onset of symptoms in two cases, in two others the symptoms were present for six weeks and five and

a half months respectively. The duration of symptoms before chemotherapy in the fifth case was doubtful, as he had had M.&B. 693 at another centre before reporting at our clinic: he stated that his discharge had cleared up but had subsequently recurred. All five cases had adjuvant treatment in addition to chemotherapy. It was evident, therefore, that in these cases at least, neither "delayed therapy" nor adjuvant treatment had made any difference to the ultimate outcome.

The cause of the failure was not always evident. In all cases chemotherapy was more prolonged than usual, whilst in several a larger dose of the drug than usual was employed, when it was seen that the condition was not responding satisfactorily to routine dosage. In one of these cases slight cyanosis developed with the increased dosage; the drug was withheld and the patient put on to routine methods of treatment. Actually, this patient's discharge had cleared up by the second morning on M.&B. 693, but small threads and pus cells continued to be present in the urine: he is still on treatment. When increased dosage failed to cure the condition in a second case, tab. sulphonamide-P (one gramme four times daily) was tried with a similar unsuccessful result, but the patient complained of such severe nausea and upset with the sulphanilamide that the drug had to be withheld on the third day. He too was started on routine measures of treatment, and is still attending the clinic. Whilst chemotherapy in a third case was again responsible for improvement in symptoms, the urine did not become clear, and continued to show considerable numbers of pus cells. The remaining two cases were treated subsequently with Uleron, and it was interesting to note that, as in the second case where a change of sulphonamide failed to produce a satisfactory result, so here a similar unsatisfactory response to the different sulphonamide was observed. Actually the discharge in both cases cleared up (after three "stosses" of Uleron in one case and after two "stosses" in the other), but both cases subsequently defaulted before an adequate follow-up and when considerable numbers of pus cells were still present in the urine. In one patient only could a definite cause be found to explain the chemotherapeutic failure: it was found here that the prostate was slightly enlarged and tender; daily gentle prostatic massage was instituted just before and during Uleron therapy, and his condition showed considerable improvement. The cause of failure in this case was probably due to the prostatitis, a condition to which Cokkinis and McElligott (1938) attributed a number of their failures with sulphanilamide. What the cause of this condition is, is doubtful, but these workers consider that it is a gonococcal prostatitis modified by chemotherapy into an atypical pathology: they have named the condition "sulphonamide prostate."

Apart from the fact that neither "delayed therapy" nor adjuvant treatment had influenced the results in these cases, a number of other points of interest arose. In the first place it became evident that where a rapid response to chemotherapy was not observed, even with increased dosage, continuation of the drug was useless, whilst it was also interesting to note that where M.&B. 693 had failed to bring about a successful issue, other sulphonamides were often no more successful. It has been suggested (Cokkinis and McElligott, 1938) that doses of the sulphonamides which are inadequate to produce a cure may cause abnormal resistance of the

organism to the drug : it is possible that the failures under discussion here may have responded if a higher dosage of M.&B. 693 had been given from the onset, and that the dosage employed had produced a "sulphonamide fast" organism. Even if this could be proved, in the present state of our knowledge it is impossible to forecast which patient is going to show this atypical response, but their number would appear to be so small that it seems to be quite unjustifiable to expose the majority of patients to the dangers of toxicity which large doses of these drugs have been found to cause, for the benefit of this small minority.

ANALYSIS OF RELAPSES.

Relapses occurred in eight of the uncomplicated cases of this series, a figure considerably below that found by other workers (Cokkinis and McElligott, 1939; Assinder and Knight, 1939; Gardner, 1939). Four of these relapsed twice and four (one of whom had relapsed after previous Uleron chemotherapy) relapsed once. Of the four who relapsed twice, two showed an early relapse (symptoms reappearing five and fifteen days respectively after the end of chemotherapy), in addition to a "late" relapse eleven months and two and a half months respectively after the end of all treatment. In the late relapses (i.e., those in whom symptoms reappeared not earlier than approximately three weeks from the end of chemotherapy), the interval between the end of chemotherapy and the reappearance of the symptoms varied from twenty days to eleven months.

The interval between the original onset of symptoms and the first exhibition of M.&B. 693 had varied considerably : in four cases it had varied from 29 to 188 days, whilst in the remaining four, the original chemotherapy had been commenced somewhere between the third and the fourteenth day after the appearance of the symptoms. Three cases had had adjuvant treatment during chemotherapy, whilst a fourth had had urethral irrigations and vaccines for some considerable time before M.&B. 693 had been started. So that here again, neither "delayed therapy" nor adjuvant treatment appeared to play any vital part in the prevention of the relapse. This is rather at variance with the suggestion put forward by Cokkinis and McElligott (1939) that one cause for late relapses is the too early commencement of chemotherapy. These workers also consider that too short chemotherapy may likewise play a part in producing these relapses. In the series under discussion, relapses occurred in three of the early cases treated, when a more prolonged use of the drug as well as a larger dose were being employed than were used subsequently : whilst the maximum duration of the original chemotherapy in these cases was ten days, if too short chemotherapy were responsible for the reappearance of the symptoms, one would have expected a much higher percentage of late relapses in cases treated subsequently.

In three cases, relapses occurred after large amounts of alcohol, whilst in two cases, attendance during chemotherapy had been irregular. Whilst a vigorous denial of re-exposure was almost invariably given, one was suspicious that the reappearance of symptoms in one or two cases at least was the result of a fresh infection.

In these late relapses, the symptoms were often not typical of an acute infection :

usually the patient complained of being damp, and on examination, urethral moisture rather than discharge was seen; this was often gonococcal negative. The urine became slightly hazy again and showed a reappearance of threads and pus cells. Where a copious urethral discharge was seen and where other symptoms typical of an acute attack were present, one was suspicious that the "relapse" was in reality a fresh infection. The symptoms and signs of the early relapse were essentially similar to those of the original attack.

Most of these cases responded satisfactorily to a second course of M.&B. 693, though one case required a much heavier dosage and more prolonged treatment than usual before his symptoms cleared up. Three cases defaulted either in the middle of treatment or before adequate follow-up after chemotherapy: it was interesting to note that these three patients had been irregular attenders during previous chemotherapy.

A point of importance, and one that has been stressed by Cokkinis and McElligott (1939), is the fact that many of the patients in whom symptoms of late relapse occur had passed tests of cure successfully following their first course of treatment. From the facts recorded, it is suggestive that the most rigorous tests of cure in gonorrhœa are indulgence in alcohol by the patient, and a prolonged follow-up after the end of chemotherapy. A prolonged follow-up has been the aim in this investigation, but unfortunately, in many cases, the patients failed to reappear a short time after the end of chemotherapy.

Even allowing for the fact that many patients defaulted before adequate follow-up, it seems evident that the relapse-rate with sulphonamide therapy is very much lower than following routine methods of treatment. An analysis of fifty cases of patients treated by routine methods will be referred to later; suffice it to say here that a relapse-rate of twenty-six per cent. was observed in the controls. That a high percentage of defaulters will report when symptoms reappear is evident from the fact that, of the eight relapsed cases discussed here, no fewer than three had defaulted before adequate follow-up after their first course of treatment. The views of a number of workers, therefore, as to the increased dangers of "gonococcal carriers" being at large as a result of these late sulphonamide relapses, hardly seems to be justified. Rather would it appear evident that the number of relapses is enormously reduced, and the possibilities of gonococcal carriers very much less, than in pre-sulphonamide days.

### Analysis of Cases Developing Complications during Chemotherapy with M.&B. 693.

Complications were seen in three cases only. Two patients developed prostatitis and a third complained of "rheumatism." This last patient had had a previous attack of gonorrhœa some two years earlier, and had suffered from "rheumatism" then, too: the pains in the second attack, when M.&B. 693 was being employed, were much less severe than previously.

Cokkinis and McElligott (1938) had a complication-rate of eight per cent. in their series of cases of gonorrhœa treated by sulphanilamide, and of thirty-six per cent,

in cases treated by routine methods. It will be shown later that in the control cases analysed personally, twenty-four per cent. developed complications during routine treatment : this is rather lower than the figure found by Cokkinis and McElligott (1938), but it is evident that gonococcal complications are greatly reduced with M.&B. 693, not only as compared with complications developing during routine treatment, but also as compared with those developing during sulphanilamide therapy.

(b) COMPLICATED CASES—21 PATIENTS.

In twenty-one male patients treated with M.&B. 693, complications were present before chemotherapy was commenced : these were :—

Group A.—17 cases :—

| | |
|---|---|
| Epididymitis - - - - | 11 cases |
| Prostatitis - - - - | 3 cases |
| Conjunctivitis, periurethral abscess, and retention overflow (each) - - | 1 case |

Group B.—4 cases of arthritis.

It was a significant feature that out of the seventeen patients in Group A, no less than fourteen had had previous treatment by routine methods, whilst in the case of the remaining three patients, previous routine therapy may also have been employed, as the complication was present when these patients first reported at the clinic. In eight of these seventeen cases, chemotherapy was commenced three weeks after the onset of symptoms of the acute attack of gonorrhœa, whilst in the remainder, the interval between the onset of symptoms and the beginning of chemotherapy varied from two to sixteen days. Two cases of arthritis occurred within a few days from the beginning of the acute attack of gonorrhœa, whilst in the remaining two, the symptoms of arthritis had been present for two to three years. It has been mentioned that various workers have recommended a waiting period of from eight to twenty-one days from the onset of the symptoms of gonorrhœa until the beginning of chemotherapy, treatment in this period being confined to urethral irrigations and vaccines. That complications occurred in eight out of the seventeen patients in Group A during this interval, when urethral irrigations and in some cases vaccines were being employed, is a significant reply to those who advocate such a waiting period with adjuvant treatment before chemotherapy.

In discussing delayed therapy in connection with Uleron treatment of gonorrhœa, Marinkovitch (1939) states that some twenty per cent. of his cases developed complications mostly towards the end of the second week of treatment and before chemotherapy was commenced.

Gonococcal Complications—Epididymitis.

In every case, the symptoms of the complication showed an almost dramatic improvement with chemotherapy : this was most marked in the epididymitis cases. Almost always, the pain in these cases had gone by the morning following the beginning of chemotherapy, whilst the tenderness was usually gone by the third morning. Several of these cases still showed some residual thickening of the epididymis at the end of chemotherapy, but this almost invariably disappeared

during the next few weeks, and the organ became perfectly normal. So dramatic was the improvement in one case that the patient actually defaulted in the middle of treatment : he re-attended subsequently when sent for, and reported perfectly fit.

Whilst this gratifying result was observed with the complications, the urethral discharge recurred in a number of cases as the epididymitis subsided or within a short time afterwards : in two cases the task of curing the discharge proved difficult with subsequent treatment : one of the cases not only showed a recurrence of his urethral discharge, but also developed an epididymitis on the opposite side from his original attack, ten days after withdrawal of M.&B. 693. Tab. sulphonamide-P (one gramme four times daily) was administered, but the discharge not only persisted but became more copious, whilst the epididymis increased in size, though the pain and tenderness were considerably eased. This patient defaulted before further adequate treatment.

The second patient showed a continuation of the urethral discharge throughout chemotherapy with M.&B. 693. Response to subsequent treatment with Uleron was also unsatisfactory, but he responded rapidly to a short course of urethral irrigations with 1/10,000 potassium permanganate following chemotherapy. These two cases have been termed chemotherapeutic failures, though it must be remembered that the complication for which the chemotherapy was originally instituted in each case was very greatly improved. It is possible, however, that a focus of infection may still have been present at the site of the complication.

Two other cases showed a "late" relapse, two months and twenty-four days respectively from the end of chemotherapy. One of these patients was showing a satisfactory response to routine treatment when he defaulted, the other case showed a rapid response to a further course of M.&B. 693. The first of these two patients is considered a chemotherapeutic failure, as his response to M.&B. 693 (though the drug caused a rapid improvement in his epididymitis) was unsatisfactory : he continued to complain of morning discharge in the interval between the end of chemotherapy and his relapse. Another patient again showed the same rapid improvement of his epididymitis, but defaulted a few days after the end of chemotherapy and when the urine was still showing threads and some pus cells : he, too, is considered as an M.&B. 693 failure, although his condition probably cleared up satisfactorily.

GONOCOCCAL COMPLICATIONS—VARIOUS.

Of the various complications in Group A, the origin of the conjunctivitis was doubtful, and no gonococci were found in the conjunctival sac : the conjunctivitis and accompanying urethral discharge cleared up rapidly with M.&B. 693, but it is possible that the eye condition would have shown an equally ready response to the adjuvant treatment of argyrol and atropine per se. In the case of the periurethral abscess, incision and drainage were followed by a rapid amelioration in symptoms, whilst the urine became sterile a few days after the first exhibition of M.&B. 693. Twice-daily catheterisation was necessary to relieve the retention overflow during the first two days in the sixth case of this series : this treatment alone in another

hospital, however, had failed to relieve his symptoms : the combination of M.&B. 693, however, appeared to bring about a successful issue within a few days.

GONOCOCCAL COMPLICATIONS—ARTHRITIS.

As in the other complications, the amelioration of symptoms in both acute and chronic gonococcal arthritis was often quite dramatic, and all cases at least showed an improvement.

One case was particularly interesting : this man had had symptoms of arthritis, especially affecting his wrist and hand joints, off and on for two years. M.&B. 693 was started (three grammes daily) and continued for four days, after which time it was withdrawn on account of toxic symptoms. The pains had improved greatly, but recurred slightly following cessation of chemotherapy. A further three grammes per day were given for three more days. He reported at intervals for a further four months. By the end of three months he stated that in the interval he had been able to "go hard at it" from 9 a.m. until 6 p.m. : this was the first time he had been able to work like this since the onset of his complaint.

Dosage of the drug in all these complicated cases was largely experimental, but it was found, as before, that very often an equally good result was obtained by comparatively small doses as that obtained with larger ones, though in the case of arthritis, chemotherapy was usually carried on for a considerably longer period than in the other complications. It again became evident that where a satisfactory response to sulphonamide therapy was not obtained within the first day or two, a failure was almost certainly inevitable. Despite this, the continuation of chemotherapy in the case of complications would appear to be justified, at least for a number of days, as the response of the complication was almost always so gratifying. It again became evident, too, that failure with M.&B. 693 was frequently followed by failure with other sulphonamides.

Adjuvant treatment was employed occasionally. In addition, in almost every case of epididymitis, support for the affected organ was insisted upon.

That failure to respond to chemotherapy is due in part to poor absorption of the drug, became evident from the study of the absorption and excretion of M.&B. 693 in some of those cases where an unsatisfactory response was seen. Apart from the poor absorption of the drug, however, another obvious cause for chemotherapeutic failure and relapse in gonorrhœa becomes evident from the study of these complications. Four out of seventeen (23.5 per cent.) of these cases (excluding the patients suffering from arthritis) were ultimate failures with sulphonamide therapy, despite marked improvement in the complications complained of, whilst two cases (almost twelve per cent.) were "late" relapses. It is possible that some at least of the failures or late relapses recorded by other workers may be due to a slight complication which had been overlooked, and it would appear to be advisable that where a chemotherapeutic failure or relapse is recorded, a thorough examination be made for any possible complication, however slight.

Since failure and relapse are thus more common in complicated than uncomplicated cases, another point in favour of early chemotherapy becomes evident, since it has been shown that gonococcal complications do not usually occur where the

disease is confined to the anterior urethra, but become comparatively frequent when the posterior urethra becomes involved.

II. TREATED WITH ULERON ONLY OR ULERON AND M.&B. 693.

Space does not permit any detailed description of the cases treated by Uleron nor were the results sufficiently encouraging to justify a long report. Several points of interest arose. In the first place, the average cure with Uleron was somewhere between fifty and sixty per cent., a figure very much below that obtained with M.&B. 693, whilst the average total duration of treatment was considerably longer than with that drug. It again became evident that where one drug failed, the results obtained with the other were often no more encouraging, though this was not invariable. "Delayed chemotherapy" and adjuvant treatment gave rather better results when used in conjunction with Uleron than when Uleron was used alone.

III. CONTROLS—50 PATIENTS.

The fifty control patients were chosen at random from those cases who had been treated by routine methods of daily urethral irrigations and weekly injections of gonococcal vaccine. In order to obtain a better general perspective of the results of routine treatment, these cases were chosen from a series who had been treated before the introduction of sulphonamide therapy for gonorrhœa.

The only criteria which were looked for in the cases chosen as controls were that the patients had attended reasonably well during treatment, and that they had been subsequently discharged as cured.

They were analysed, in the main, from three aspects :—

(1) Duration of treatment.

(2) Percentage of relapses occurring.

(3) Percentage of complications arising during treatment.

The average duration of treatment in the fifty cases was just over three months. Actually, several cases attended for treatment for from four and a half to nine months. Thirteen cases, or twenty-six per cent., showed relapses, whilst twelve cases, or twenty-four per cent., developed complications during treatment.

Comment is unnecessary when these figures are compared with the results obtained with chemotherapy.

(B) FEMALE CASES—14 PATIENTS.

Not only is gonorrhœa in the female patient difficult to treat, but the organism, especially in old standing cases, is difficult to isolate and culture. An attempt was made to isolate and culture the organism in most of the cases treated, but this was often unsuccessful, and the condition was treated as the result of the clinical diagnosis of acute or chronic gonorrhœa. Unfortunately, the female is much less tolerant than the male to the sulphonamides, and nausea and vomiting are comparatively frequent, so that co-operation in chemotherapy is often more difficult to obtain than in men. Moreover, the series here considered is rather small for any definite conclusions to be reached as to the appropriate dosage of the drug required, the necessity or otherwise of adjuvant treatment, and the ultimate result following chemotherapy in the female. The results obtained even from this small series leave little doubt that the response of gonococcal conditions to chemotherapy

in the female is as encouraging (given favourable conditions) as in the male.

Whilst most of the cases treated at least showed considerable improvement in their condition (only one failing to do so), several are of special interest.

One was a woman of 33 years of age, who had had a heavy vaginal discharge following a confinement seven years previously : the discharge had become worse during the last three years, during which time she had had conservative treatment off and on. She was started on M.&B. 693 (0.5 grammes four times daily) and chemotherapy was continued for fourteen days. At the beginning of chemotherapy there was pus in the urethra, a heavy vaginal discharge, and the cervix was eroded : when M.&B. 693 was withdrawn, the discharge had ceased and the cervical erosion was greatly improved. The improvement was not only maintained, but became more pronounced, and two months later the patient stated that for the first time for three years she had been able to do without a vulval pad : on examination the only pathology seen was a slight cervical erosion. She subsequently became pregnant after an interval of seven years, during which time she stated that no contraceptive methods had been employed. Unfortunately, she developed a high blood pressure and albuminuria, and the pregnancy had to be terminated at the seventh month : the infant did not live.

Two other cases failed to respond to the oral administration of M.&B. 693, but showed satisfactory progress when intramuscular preparations of the drug were used in conjunction with the tablets. It is probable that oral administration alone was insufficient to give a sufficiently high concentration of the drug in the blood to be really effective in these two cases, and that this was overcome only when the more readily absorbed preparations were used. The second patient was an irregular attender, and that this was also partly responsible for the failure to respond to oral therapy alone is not unlikely, and experience would tend to show that continuous treatment is highly important when chemotherapy is being employed.

Two cases were victims of gonococcal arthritis before chemotherapy. Both responded well to M.&B. 693, though one showed a subsequent relapse; the relapse was accompanied by less severe pain than was experienced at the earlier attack.

## ADMINISTRATION OF THE DRUGS AND ADJUVANT TREATMENT.

### M.&B. 693.

Various schemes of dosage of M.&B. 693 were tried in the early part of this work, and had to be abandoned or modified for one reason or another. A considerably larger dose was used at the beginning than is now employed, but it was found that minor toxic reactions with these larger doses were comparatively frequent and patients complained of headache, nausea, flatulence, and many other unpleasant minor reactions. A number of patients then defaulted in the middle of chemotherapy, after having had a much smaller quantity of M.&B. 693 than the majority of cases : some of these defaulters reported subsequently and were found to have been perfectly well in the interval. In addition, from the study of the toxicity of the drug (a summary of which is described elsewhere in this Journal), it soon became evident that M.&B. 693 was much more toxic than early experimental evidence had promised. A consideration of these facts suggested that not

only was a modified dosage of the drug likely to be as successful as the larger doses being employed, but that such a modification was highly desirable if the possibility of serious toxic reactions was to be reduced to a minimum. Dosage was subsequently reduced, and it was gratifying to find that not only was the frequency of minor toxic reactions much less, but the clinical response was equally good.

The dosage finally decided upon in the treatment of acute and chronic uncomplicated gonorrhœa in the male was 3 gm. of the drug on the first day, the drug being taken in divided doses at intervals which were considered to be sufficient to give a reasonably steady blood concentration, i.e., 1 gm. immediately after examination (about 10 a.m.), 0.5 gm. at 2 p.m., 0.5 gm. at 6 p.m., and 1 gm. at bedtime. The following six days, 0.5 gm. four times daily, was taken at approximately the same time as on the first day. After seven days' treatment the drug was withheld. It was occasionally found that a few small specks were still present in the urine, but these usually cleared up within a few days' time without further treatment. When the specks persisted or when symptoms reappeared (which was seldom), a further seven-day course similar to the first was started.

Where disappearance of the discharge was not seen by the second or third day, the dose was increased (provided no toxic symptoms were seen), as it was considered that the failure to respond to routine dosage was possibly due to poor absorption of the drug. If this procedure was still rewarded by failure (which again was seldom), or where signs of toxicity followed the use of the larger doses, the drug was withheld and other sulphonamides were administered or routine treatment was instituted.

In complicated cases a similar dosage was often found to be equally effective, though treatment was sometimes more prolonged (especially in arthritis cases) than in uncomplicated cases.

Thus dosage and the duration of chemotherapy are considerably less than those recommended by the majority of workers, but the results obtained and the other factors considered would appear to more than justify their continuance.

That the treatment of the female was made more difficult on account of the greater susceptibility to the toxic effects of the drug in this sex than in the male has been mentioned. Unfortunately, decreasing the dosage of the drug in the female was not followed by the same encouraging decrease in "minor" toxic symptoms as was observed in the case of men, and other methods for overcoming these unpleasant effects were adopted. These included giving the tablets suspended in, or in combination with, glucose or alkalis or in giving a smaller dose at more frequent intervals (i.e., half a tablet every two hours rather than a whole tablet every four hours). These methods were followed by success of varying degree in different patients, but no hard and fast rule could be laid down to avoid toxicity in all cases, and in some patients, all efforts resulted in failure to avoid nausea or vomiting or both. In these cases, as in the males, the drug was stopped and another sulphonamide was given or routine measures of treatment adopted. It was found, on the whole, that more prolonged dosage was necessary in the treatment of gonorrhœa in the female than in the male, and that less toxicity was observed

when small doses were given at frequent intervals. The majority of female cases treated were given 0.5 gm. of M.&B. 693 four times daily (or 0.25 gm. two-hourly) for fourteen days where possible.

ULERON.

Uleron was administered in doses of 3 gm. per day for four days, followed by a period of seven to eight days' rest, when a second "stoss" similar to the first was given, and after a further interval of rest as before, a third similar "stoss" was administered. The minor toxic reactions due to this drug were found to be much less common than with M.&B. 693, but the major toxic possibilities were found to be just as serious. In addition, adequate treatment with the drug was found to be much more prolonged and tedious than with M.&B. 693, and the clinical results less convincing. As a result, Uleron has only been used in the treatment of a comparatively few cases.

The broad outline upon which treatment and follow-up were based was as follows :—

With a male patient, on his first appearance at the clinic, the history was taken and a careful note of the clinical condition was made. A smear was taken from the urethral discharge and in a number of cases the discharge was cultured : the smear was stained by the Gram method and examined for the gonococcus. Where a syphilitic infection was suspected as well, a drop of serum from the suspected chancre was examined by darkground illumination : if this was positive, arsenical treatment was at once instituted, and the gonococcal infection was treated by routine methods, as it was considered unwise to employ two drugs together, either of which was capable of causing agranulocytosis per se. In one case only were M.&B. 693 and neoarsphenamine employed together, and no ill-effects resulted. Actually, a rapid response to treatment was observed in both diseases in this patient, though the gonorrhœa was longer in clearing up with M.&B. 693 than usual.

Where chemotherapy was decided upon, the patient was told to avoid all sulphur-containing foods and to use only mild laxatives, when any laxative was necessary, and he was warned to abstain from alcohol and sexual excitement until such times as his condition was cured. The following day chemotherapy was commenced with the chosen drug, and the patient was seen daily during the time the drug was being taken, only one day's supply of tablets being given at each visit. On each visit a smear and, in a number of cases, a culture also were made where possible from the urethral discharge, until such times as the discharge became gonococcal negative : in many cases, however, the discharge had cleared up by the following morning, whilst in others it was very much reduced, and almost always no gonococci were found. Where there was no discharge present, a sample of urine was centrifuged and the centrifuged deposit examined for the organism. At the end of chemotherapy, a further sample of urine was similarly examined, and the patient told to report in three to four days' time, and if everything was satisfactory, to report at weekly intervals for a further period. This follow-up period varied, the aim being to see the patient at intervals for as long a time as possible, and at least for a further

three months from the end of chemotherapy. The weekly visits were extended later to one visit in two weeks and then one visit per month. At varying intervals after the end of chemotherapy, tests of cure (T.O.C.) were performed to see whether or not the condition could reasonably be regarded as cured. In addition to the T.O.C. already described, alcohol was now permitted. The patient was seen twenty-four to forty-eight hours after T.O.C., and a further sample of urine was centrifuged and the deposit examined. If everything was satisfactory, he was told to report as stated above. Frequent urinary examinations were performed during the follow-up period.

T.O.C. are now performed from ten to twenty days from the end of chemotherapy.

With Uleron, the main line of treatment was similar to that for M.&B. 693 except that smears from the urethral discharge or a centrifuged deposit of urine were examined before and after and on the second day of each "stoss," or, where the discharge persisted, a daily smear was examined for the gonococci until the discharge became gonococcal negative.

In the case of females, a careful vaginal and bi-manual examination were performed and smears and culture from the urethra, Bartholin's glands, or the cervix were made. It has been mentioned, however, that these were often negative, and the condition was treated as a result of the clinical diagnosis of acute or chronic gonorrhœa. Follow-up and adequate tests of cure were very much more unsatisfactory than in the male.

The procedures described above are, in the main, those now adopted in the treatment of gonorrhœa at the Venereal Diseases Clinic of the Royal Victoria Hospital, Belfast. Three other things remain to be said.

It has been shown that adjuvant treatment makes little difference to the ultimate outcome of acute cases of gonorrhœa treated by M.&B. 693. Whilst this is true in the majority of cases, one or two patients did show a more rapid response to treatment when urethral irrigations were employed after the first day or two of chemotherapy alone. In addition, it was felt that possibly the use of urethral irrigations might help to prevent the high default-rate which was evident when chemotherapy only was used. As a result, on his first appearance at the clinic and during chemotherapy, the patient is now given urethral irrigations of 1 in 10,000 permanganate potassium in addition to M.&B. 693.

A further point of importance is, that during the follow-up period the patient's blood is examined to exclude the possibility of syphilis. The tests performed are the Wassermann reaction (using the Harrison and Fleming techniques), and, where a doubtful positive result is obtained, a Dreyer flocculation test is also carried out.

Finally, one method suggested by Wilkie (1939) to combat defaulters is that patients should be requested by letter to reattend hospital when they fail to reappear after an interval. The majority of defaulters in the present investigation were requested to reattend for re-examination once, twice, or even three times, but only a very small percentage turned up and frequently they again defaulted. In many cases the communications sent were returned as "not known" or "wrong address"!

## SUMMARY.

(1) The use of M.&B. 693 and Uleron in the treatment of gonococcal infections has been compared with routine methods.

(2) Over ninety-six per cent. of uncomplicated cases of gonorrhœa are cured by M.&B. 693 in one-twelfth the time, and fifty to sixty per cent. are cured by Uleron in one-third the time taken by routine methods of treatment.

(3) Complications with M.&B. 693 are reduced to one-eighth of those developing during routine treatment.

(4) Six per cent. of M.&B. 693 cases showed late relapses : the symptoms of the late relapse are described and their significance discussed. Several of these cases relapsed more than once.

(5) In complicated cases, marked relief from symptoms is observed within a short time from taking M.&B. 693 or Uleron. The ultimate failure and relapse-rate are higher in complicated than in uncomplicated cases.

(6) An analysis of failures, relapses, and complications arising during chemotherapy in uncomplicated cases, together with an analysis of the treatment of complicated cases, showed that with M.&B. 693, adjuvant treatment is unnecessary and "delayed therapy" is not only unnecessary but undesirable. Rather better results are obtained with Uleron where adjuvant treatment and "delayed therapy" are employed.

(7) Some reasons for failure to respond to chemotherapy are suggested.

(8) Failure with one sulphonamide is often followed by failure with another, though this is not invariable.

(9) A plan for the management of gonococcal infections including administration and dosage of M.&B. 693 is described, and the importance of adequate follow-up is stressed.



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# Some Clinical Aspects of Coronary Occlusion

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THE terms "coronary occlusion," "coronary thrombosis," and "cardiac infarction" are often indiscriminately employed as if these expressions were terms synonymous. This is in fact not the case, and differences are well marked between them. Cardiac infarction is the result of the coronary occlusion, and represents the pathological change which has occurred in the myocardium as a result of the arterial block, and may take some hours or even days to develop. It may also be completely absent if the patient should die, after the acute occlusion, before time is allowed for these changes in the muscle to take place.

Coronary thrombosis is often used to denote coronary occlusion, although it is only a special type of it. It presupposes a knowledge of the cause of the occlusion, which from clinical examination it is impossible to have, and which may even be refuted by future pathological examination. Thus, although coronary thrombosis is the commonest cause of the final occlusion, it is by no means the only cause. It is therefore safer to employ the non-specific term, coronary occlusion, for the clinical concept.

The clinical importance of coronary occlusion cannot be overstressed. It is a condition which causes death and much disability in middle age and late adult life, and, as it usually afflicts those of a dynamic, forceful personality, its economic importance is great. It also is a disease of great personal importance to medical men, for it ranks highest as a cause of death in medical men in America and possibly also in this country. There is an opinion also, abroad, that the incidence of the disease is increasing. Although statistical evidence fails to confirm this, it suggests that this increase is more apparent than real, and is due to better diagnosis, the more full investigation of cases of acute thoracic pain, and the recognition of minor coronary episodes and their differentiation from so-called "acute indigestion."

The facts which have been utilised are derived from a personal survey of the case records of 121 cases of coronary occlusion admitted to the Royal Victoria Hospital over a twelve-year period, and all factors were critically analysed. No attempt to discuss ætiology or prognosis will be attempted, but only a presentation made of some aspects of the clinical picture.

Apart from the rare accident of coronary embolism, coronary occlusion seldom occurs except in a heart with diseased coronary vessels, and the predisposing disease of greatest importance is coronary atherosclerosis. Coronary occlusion, therefore, is a condition superimposed on coronary atherosclerosis, and can be considered under two, or at most, three stages in its clinical development :—

1. The stage of coronary atherosclerosis.
2. The pre-occlusive state.
3. The acute coronary occlusion.

1. The Stage of Coronary Atherosclerosis.

This diseased condition of the coronary arteries may not manifest itself in any clinical symptoms whatsoever, and in this series of cases of coronary occlusion some thirty-seven per cent. gave no previous history indicating either general disease or cardiac disorder. All clinicians are familiar with coronary occlusion occurring unheralded. This symptomless period can be present for quite a long time, and clinical examination of the patient during this period will fail to reveal any abnormality, despite the condition of his coronary vessels. Special investigations, X-ray, and electro-cardiography also do not assist in detecting any cardiac abnormality. Such patients would be, and have been, passed as physically fit by insurance doctors, only to be struck down shortly afterwards by an acute coronary occlusion.

A certain number of persons with coronary atherosclerosis do manifest the presence of the underlying coronary disease by certain symptoms, and these symptoms, in descending order of their occurrence, are :—

| | In cases with symptoms. |
|---|---|
| Angina on effort | 53 per cent. |
| Dyspnœa on exertion | 42 ,, |
| Previous occlusion | 30 ,, |
| "Indigestion" | 17 ,, |
| Cardiac asthma | 9 ,, |

The commonest symptom, therefore, is angina on effort, which is found in over one-half of these patients which show symptoms and in one-third of all cases of coronary occlusion. This finding is borne out by other workers, and although the incidence varies somewhat, the finding in this group of cases falls about the general mean. The duration of the angina varied, in some cases being present for a few years prior to the terminal occlusion, while in others it was of more recent onset. The nature in either case was similar.

The angina is produced by a relative coronary insufficiency, caused by a disturbance between demand and supply of blood to the heart muscle. The pathological basis for this symptom is to be found in the diseased condition of the coronary arteries, which are unable, because of morphological vascular changes, to transmit sufficient blood for the myocardium under the stress of increased muscular activity. Effort or emotion or any stimulus which increases the work done by the heart, increases in the myocardium the need for more oxygen to burn up waste products, which can only be supplied by an increased blood-flow. Thus a state of coronary insufficiency is set up, which is manifested as pain of a peculiar nature and distribution. The presence of this pain, therefore, indicates that the coronary blood-flow, although adequate under basal conditions, is not sufficient to meet the needs of an actively-functioning myocardium.

Bourne and Scott (1938) state that "angina of effort should therefore be taken to indicate coronary artery disease unless there is gross anæmia." This generalisation would need some qualification, because angina is a symptom which can be produced by any method which reduces the coronary blood-flow, apart from actual

disease of the coronary vessels. Thus angina occurs in paroxysmal tachycardia, aortic reflux, and aortic stenosis, as well as gross anæmia.

Angina does not in all cases incriminate the coronary vessels, nor do all cases of coronary atherosclerosis terminate in occlusion, and from a review of cases with angina on effort, Bourne and Scott (1938) found that only twenty-nine per cent. suffered at some time or another from a coronary occlusion.

The underlying pathology is not arterial spasm or in all cases arterial disease, but a state of coronary insufficiency, dictated either by an increased demand or a reduced supply of blood to an active myocardium.

Breathlessness on exertion is also a common early symptom in coronary atherosclerosis, and it occurred in forty-two per cent. of those cases showing symptoms. Its presence indicates some lowering of the myocardial reserve, produced mechanically or through some interference with the blood supply to the heart muscle. It is recognised that the heart muscle depends entirely for its proper function on an adequate blood supply, which is supplied via the coronary arteries. Impairment of this blood supply will reduce the functional efficiency of the myocardium. Thus it is evident that a well-functioning myocardium is essentially dependent on an adequate coronary blood-flow. This flow can be impaired in a number of ways; by disease of the coronary vessels, by low blood-pressure, by poor cardiac output, and by peripheral vascular stasis with deficient blood oxygenation. In nineteen per cent. of all the cases (thirty per cent. of those with symptoms), there was history pointing to a previous coronary occlusion. This shows that approximately one patient out of five is subject to more than one attack of acute coronary artery closure. This fact, that multiple attacks of acute occlusion do occur, is not very generally recognised, although it has been often described and is now considered commonplace. It is this fact, that a patient who has had an acute occlusion may be subject to a further attack at some future date and prove fatal, which introduces a very uncertain element into any attempt at prognosis in these cases. Numerous cases have been recorded of recovery from multiple attacks, and a gloomy attitude as regards prognosis is no longer considered justifiable, as considerable recovery of function is possible with adequate treatment.

Quite a number of the patients complained of a group of symptoms referable to the gastro-intestinal tract, which have been placed under the non-committal term, "indigestion." These gastro-intestinal disturbances, consisting of discomfort after meals, were usually associated with flatulence, and the patients often voluntarily stated in their histories that getting rid of the flatulence eased the discomfort felt in the epigastrium and chest. It is suggested that these symptoms are produced in a patient with coronary artery disease by the increased work demanded of the myocardium by reflexes from the stomach during or following a meal. Many of these are cases of attacks of true angina induced by the meal. Others, however, in which the discomfort is relieved by ærophagia, must have some mechanical cause which either acts locally, regionally, or reflexly on the heart. It is doubtful if any of these symptoms would be produced—apart from peptic ulceration or gastritis—

if the coronary vessels were normal. They must be considered an integral part of the clinical picture of coronary atherosclerosis.

Cardiac asthma, or attacks of paroxysmal nocturnal dyspnœa, is one of the less common symptoms. All the cases in this group showing this symptom were hypertensives, and this would suggest that this symptom is an indication of the presence of the underlying hypertension rather than of the diseased coronary vessels. This is, however, an erroneous impression. Coronary atherosclerosis itself, apart from the raised blood-pressure, is capable of giving rise to a reduced nocturnal blood-flow to the left ventricle and thus to transient left ventricular failure, which manifests itself in pulmonary congestion, œdema of the lungs, and, clinically, by sudden nocturnal attacks of breathlessness. It is the coronary artery disease which is the important factor in the development of this condition. As an ætiological factor in the development of this coronary disease, hypertension holds pride of place. Therefore, it is the coronary atherosclerosis which is the cause of the cardiac asthma, and its presence in cases of essential hypertension would indicate a marked degree of coronary artery disease.

The underlying disease, therefore, is coronary atherosclerosis, which has various clinical manifestations or may remain clinically silent. The clinical manifestations can be classified under the following heads :—

1. Disturbances of cardiac mechanism.
   Auricular fibrillation.
   Heart block.
2. Angina pectoris.
3. Acute coronary occlusion.
4. Heart failure,
   which may be first evidenced by shortness of breath on exertion, or paroxysmal nocturnal dyspnœa.

Progressive coronary artery disease usually proceeds to heart failure with or without disturbances of rhythm. During its course, angina pectoris may appear or an acute coronary occlusion occur. It would appear as yet impossible to pick out those cases of coronary atherosclerosis which will eventually suffer from a coronary occlusion, as their symptoms do not differ from the larger group of cases which proceed to cardiac failure or disturbances of rhythm.

2. The Pre-Occlusive State.

Coronary artery disease sets up a state of coronary insufficiency, so that angina pectoris is manifested clinically. Thus, angina often precedes by some months the acute coronary artery occlusion. The usual clinical picture of coronary occlusion is that of the sudden onset of symptoms with intractable substernal pain, dyspnœa, shock, sweating, and a fall in blood-pressure. In a number of cases the onset is ingravescent, and Parkinson and Bedford (1928), etc., have described the occurrence prior to the development of an acute occlusion of premonitory, transitory pain of a nature different from the previous angina. In a number of cases, Feil (1937), Sampson and Eliaser (1937) have described preliminary pain which presents characters different from the previous angina, from which they consider that a

diagnosis of impending acute coronary occlusion could be made. A patient presenting such clinical features has been described as being in the pre-occlusive state. Such a condition does not exist in all cases, most of which present the typical acute onset.

According to Feil, this pain is substernal or epigastric in position, mild in degree, and is not related to effort or emotion. The pain is constant and burning in character, and is not relieved by nitrites. No objective changes can be detected on physical examination, and the electro-cardiogram is normal. As yet no objective methods are available to detect an impending occlusion.

It is suggested by these authors that efforts to improve the coronary artery flow may avert the final thrombosis. They administer fluids, vasodilators, while physical activity is moderately restricted and tobacco severely so.

This series has not been investigated clinically to ascertain if this pain of impending occlusion occurred, but the onset was ingravescent in 15.3 per cent., and was preceded in these cases by a "heavy feeling in the chest" or some such descriptive term, which tended to confirm the opinion that the pain differed from the previous angina. If the onset is heralded in only fifteen per cent. of the cases, prophylactic treatment devised to ward off the final occlusion would fail to reach the majority of potential occlusives. Thus the pre-occlusive state, although it may exist as a rather uncommon clinical manifestation, is of little real value from the prophylactic therapeutic standpoint because of its rarity.

3. Coronary Occlusion.

The symptoms and signs of coronary occlusion are too well known to require repetition.

## SYMPTOMS.

*Pain.*—The main symptom is the sudden onset of pain, which is variously described as severe, gripping, crushing, constricting, or burning. The descriptive ability of this group in conveying a word picture of the pain was not high. No striking descriptions or theatrical similes such as are found in American literature occurred, where such descriptions as "the Empire State Building pressing on my chest," or "like a lassoo round my throat" are commonplace. However, although the pain was in most cases severe in character, many patients described it as mild in degree, and some considered the pain as merely another but more acute attack of angina.

In 7.6 per cent. of the cases there was neither pain nor discomfort in the chest. These patients complained of dyspnœa, with or without collapse, dizziness, and vomiting, or the attack occurred during the course of an acute infection, and dyspnœa appeared when the patient became convalescent. The painless variety of coronary occlusion has been recognised for some time, and was described by Parkinson and Bedford in 1928. Since then, many papers giving the incidence and trying to explain the pathogenesis have been written. The percentage incidence has varied widely, and this has been due to many factors:—

(1) The standard employed. Some include as painless, cases showing chest discomfort, but without actual pain. Others exclude these cases.

(2) The patient's threshold for pain. This is obviously lowered by debilitating diseases or coma, and normally varies in individuals.

(3) Whether it is the first or subsequent attack of acute occlusion. Recent figures give the incidence of painless occlusion as four per cent. among cases where the occlusion was recent, whereas an incidence of twenty-two per cent. was given by Kennedy (1937) for "old attacks" from which the patient had recovered.

The situation of the pain was in most cases characteristically substernal, but the pain did not occur invariably in this position. The epigastrium was the primary seat of the pain in about thirteen per cent. of the cases, and in some other cases it commenced in the shoulder, arms, or gums. From the aspect of differential diagnosis, epigastric coronary occlusion pain presents great difficulties. Such patients have been admitted as surgical emergencies with a diagnosis of acute duodenal perforation because of the sudden onset of pain, shock, rigidity, and tenderness of the abdomen. One of the patients in this series was actually operated on for a duodenal perforation, and closed when none was found. He was subsequently found to have a large posterior cardiac infarct. The clinical differential diagnosis is exceedingly difficult, and the electro-cardiograph cannot be relied upon to exclude perforation so early after the acute occlusion.

The pain may remain localised to the substernal region, but radiation is frequent, and this may occur to many sites, which are by no means invariably the left shoulder or arm (14.3 per cent.). Radiation to both arms and over the whole chest was common, while radiation to epigastrium, neck, and mouth occurred. The pain is constant in nature, with a marked early severity and progressive improvement with rest.

*Dyspnœa.*—With the onset of the pain, breathlessness commonly occurs, and in some cases the sudden onset of breathlessness heralds the acute occlusion and may precede the onset of pain. In cases not complaining of any pain, the sudden onset of breathlessness was the most constant clinical feature.

In this series, breathlessness occurred in sixty-eight per cent. of the cases, and in many instances it was acute in nature and overshadowed all other symptoms.

Other symptoms of which the patient may complain, and which are of less importance, are :—

| | |
|---|---|
| Vomiting | 24.4 per cent. |
| Feeling of constriction | 21.0 ,, |
| Flatulence | 9.2 ,, |
| Dizziness | 7.6 ,, |

The patient who has suffered a recent acute coronary occlusion is usually considerably shocked by the pain, the sudden onset, and the fear, associated with damage, real or suspected, which we all have when we consider our heart to be affected. This is evidenced clinically by the pallor, sweating, and faintness with which a temporary reduction of the blood-pressure is often associated. The more permanent reduction of the blood-pressure in the post-coronary state does not depend on such vasomotor phenomena, but is the result of the altered hæmodynamics induced by an area of myocardial weakening, and therefore a reduction

in cardiac efficiency. The importance of shock is also seen in the experimental production of occlusion in dogs, where the mortality increases greatly when the coronary ligature is performed on an unanæsthetised animal. To determine the presence of shock, it would be necessary to see the patient immediately after he had sustained a recent occlusion, and as these patients were admitted to hospital in many cases some hours, and often a few days, after the occlusion had taken place, any investigation into the presence of shock and its accompaniments would be of no value.

## CLINICAL SIGNS.

The clinical signs associated with a recent occlusion usually include the following :

Signs of congestive heart failure—especially left heart failure—with pulmonary congestion.

Fall in blood-pressure, with a decreased pulse-pressure.

Pyrexia.

Leucocytosis and increased blood sedimentation-rate.

Friction rub.

Faint heart-sounds and occasional gallop-rhythm.

Arrhythmia.

Electro-cardiographic changes.

### Congestive Heart Failure.

The presence of congestive heart failure is quite a common clinical finding following a recent acute coronary occlusion, but it may be of an extremely mild degree and can be entirely absent. The commonest clinical finding is the presence of some fine basal crepitations, which indicate left ventricular failure induced by the myocardial injury. A gross degree of congestive heart failure, with evidence of right as well as left ventricular failure, is not common. It occurred in noticeable form in thirty-one per cent. of this group of cases. Clinically it is manifested by the usual clinical signs of cyanosis, dyspnœa, engorged cervical veins, enlarged liver or œdema.

### Fall in Blood-Pressure.

A fall in blood-pressure is very hard to estimate unless the previous blood-pressure is known, and this is very rarely the case. A reading of the blood-pressure after a recent occlusion may indicate a low figure, a normal figure, or a raised blood-pressure.

A low blood-pressure is not a very common finding and depends on the previous blood-pressure and the degree of shock induced by the occlusion, which is always greater if the occlusion is very sudden and if the patient is older. The blood-pressure was abnormally low in five or six cases, and the lowest recorded is 80/60 on admission.

The presence of a normal blood-pressure reading is not a very uncommon finding, and is due to either—

(a) The fact that the blood-pressure has not fallen appreciably,

(b) The fact that the blood-pressure has fallen to a normal level from a previously raised one.

In the latter case, the diastolic-pressure is rarely reduced proportionately with the systolic, so that the pulse-pressure is low. However, this may not be invariable.

A raised blood-pressure after a coronary occlusion usually indicates a previous state of hypertension, and this was found to be present in forty-two per cent. of this series. In most of the instances in which the pre-occlusive blood-pressure was known, the blood-pressure was reduced following the occlusion.

### Reduction in the Pulse-Pressure.

A reduction in the pulse-pressure is a very common clinical finding, and if the previous blood-pressure is not known, is of far more value in diagnosis. In hypertensive cases, the pulse-pressure may be markedly reduced, and one case showed a pulse-pressure of fourteen and a blood-pressure of 114/100.

### Pyrexia.

Some cases show no pyrexia, especially if the degree of shock is severe and death quickly intervenes. Some degree of pyrexia is common; it occurred in sixty-three per cent. of the cases. The temperature chart has usually a very specific form, with a subnormal temperature on admission, rising to fever height and remaining intermittently high for five or six days, to fall back again to normal by a process of lysis.

### Pulse.

The pulse-rate follows on the whole the temperature, except that the rate is rapid shortly after the onset, while the temperature may be subnormal. A pulse-rate of over ninety on admission was present in sixty-three per cent. of the cases.

### Rhythm.

Twelve per cent. of this series showed some abnormal rhythm of the heart on admission, and in the majority of these cases this abnormality remained permanent. The type of arrhythmia usually consisted of extrasystoles or auricular fibrillation.

### Friction Rub.

The presence of a pericardial friction rub, when present, is of great diagnostic value, but it is far from being a common clinical finding. In only five per cent. of these cases is the presence of a pericardial friction rub mentioned either on admission or during the clinical course. It is stated that, as a general rule a friction rub is only heard when the infarct is located on the anterior aspect of the heart, and when the infarct is posterior no rub is audible. This rule would be true if the pericardial involvement always consisted of a localised pericarditis, but this is not so. A number of cases—about ten per cent.—show the presence of a generalised pericarditis in association with an infarct situated anywhere in the myocardium. With such a finding a pericardial rub can occur, although the infarct be posterior.

### Clinical Examination of the Heart.

Clinical examination of the heart is somewhat disappointing in coronary occlusion. Displacement of the apex beat depends on a previous hypertensive state, and the nature of the cardiac impulse is related to the pulse-pressure and cardiac output.

The presence on auscultation of heart sounds of poor quality or weak intensity is significant taken in conjunction with the history. Only about one-half of these

cases have weak or faint heart sounds. Its presence is not invariable. Murmurs are usually absent, although sometimes a soft systolic murmur appears at the apex. Diastolic gallop-rhythm only rarely occurred.

## CONCLUSIONS.

(1) The previous history of these cases is that of patients suffering from coronary atherosclerosis. The history does not differ from the larger group of patients with this disease who do not suffer from the accident of coronary occlusion.

(2) In fifteen per cent. of the cases, the onset was ingravescent and took some days to develop. The symptoms felt during this period differed from the previous angina, and could be called a pre-occlusive state.

(3) The clinical recognition of a pre-occlusive state is difficult, which renders any attempt at prophylaxis almost impossible.

(4) The clinical history is apparently of more diagnostic value than the clinical signs.

(5) In 7.6 per cent. of the cases, the acute occlusion was painless.

(6) Of the clinical signs the most important are :—

- (a) Signs of left ventricular failure.
- (b) Reduced pulse-pressure.
- (c) Pyrexia.
- (d) Tachycardia.
- (e) Faint heart-sounds.

(7) A pericardial friction rub is a rare clinical finding, and was present in only five per cent. of the cases.

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# THEOGARDENAL IN CARDIO-VASCULAR IRREGULARITY AND ENDOCRINE DISTURBANCES

THEOGARDENAL, which combines the properties of Theobromine and Phenobarbital, has been found valuable in the treatment of high blood-pressure. Its action is similar to that of the nitrites, facilitating cardiac function by dilatation of the coronary arteries, though Theogardenal, as opposed to the nitrites, is comparatively prolonged in its effect.

Disorders of the menopause with their accompanying endocrine disturbances offer a further field for the use of Theogardenal.

Theobromine, of which five grains are contained in each tablet of Theogardenal, resembles caffeine in its action, though its effect upon muscle, kidneys, and heart is more pronounced. Phenobarbital, one half-grain of which is contained in each tablet of Theogardenal, helps to reduce arterial hypertension by its action on unstriated muscle.

A new pamphlet on Theogardenal has been produced by the makers of this drug, Pharmaceutical Specialities (May & Baker) Ltd., Dagenham, from whom members of the medical profession may obtain copies on request.

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# Drugs That Are Requisite: A Plea for More Rational and More Economical Prescribing

*By* James Boyd, M.A., M.D., B.SC., F R.C.P.I., D.P.H.

Chief Medical Officer, Ministry of Labour, Northern Ireland.

SINCE the outbreak of war we have had much valuable instruction and advice on the exercise of economy and the avoidance of extravagance and waste. It is our duty to apply this teaching in our professional as well as in our private life, and to practise the strictest economy in the use of dressings and in prescribing medicines. This does not mean that a drug which is considered necessary in treatment should be withheld simply on grounds of expense; it does mean, however, that before ordering a costly drug a practitioner should satisfy himself that the same therapeutic effect cannot be obtained with a less costly drug.

Over forty per cent. of the population of the United Kingdom are entitled to the services of panel doctors, whose duty it is to order at the expense of the Drug Fund such drugs as are requisite for treatment, and whose responsibility it is to ensure that unnecessary charges are not imposed on the Drug Fund. It follows that a practitioner should never request his panel patients to buy medicine. On the other hand, if a panel patient should be bold enough to ask his doctor to prescribe a particular medicament, such as malt and cod-liver oil, tincture of iodine, olive oil, etc.—and I am told that in some practices this is fairly common—the doctor should, of course, make the patient understand clearly that he must prescribe what in his judgment is necessary, but that he cannot at the cost of public funds pander to a patient's desire by prescribing what in his judgment is unnecessary. It may be that the patient's uninformed faith in such substances and in much advertised drugs will be so strong as to lead him to purchase them himself—and the British public spends some £30,000,000 a year in this way—but the doctor should not make himself a party to such action.

It would appear that in private practice there is no rational method of pricing prescriptions either by chemists or dispensing doctors. Even if the ingredients of a mixture cost but a shilling, the price charged for a bottle of medicine is usually from half a crown to three shillings; and the same charge may be made by the doctor for a bottle of medicine as for a consultation and a bottle of medicine, from which the patient readily deduces that a consultation costs nothing and that what he pays for is the medicine supplied.

In National Health Insurance practice the chemist is paid the cost of the drugs ordered together with a trading profit, and a dispensing fee is added, namely, 5d. for a mixture, lotion, or liniment, 7½d. for seven to twenty-four tablets or pills, etc.

Thus it is seen that there is more scope for protecting the N.H.I. Drug Fund than the private patient's pocket from undue expenditure in the matter of drugs. The decision as to what drugs are requisite must in each case be made by the

practitioner, but his judgment may be questioned by those who pay the bill, that is, in Northern Ireland, the Ministry of Labour.

It is convenient to divide drugs into three classes, namely—

Class I. THOSE FOR WHICH THE INDICATIONS ARE DEFINITE, e.g., iron in hypochromic anæmia; liver extract in Addisonian anæmia; insulin in diabetes mellitus; thyroid extract in myxœdema; thiamin hydrochlorine (vitamin $B_1$) in "alcoholic" polyneuritis; digitalis in auricular fibrillation; quinine in malaria; the arsenobenzenes in syphilis; sulphapyridine in lobar pneumonia; sulphanilamide in hæmolytic streptococcal and some other infections; prostigmin in myasthenia gravis; antitoxic serum in diphtheria, etc.

Class II. THOSE REPUTED TO HAVE THERAPEUTIC VIRTUES, but of whose value we may entertain doubt, e.g., many so-called expectorants; creosote as a "pulmonary antiseptic"; calcium salts for chilblains, urticaria, menorrhagia, certain cases of hæmoptysis, hæmatemesis, etc.; hexamine in large doses combined with alkaline treatment in cholecystitis; liver extract in disseminated sclerosis; alpha-tocopherol (vitamin E) in habitual abortion, the myopathies and many diseases of the central nervous system; chorionic gonadotropin in acne; etc.

Class III. PLACEBOS. This is a very large group. Unfortunately the faith of the public in the bottle of medicine is so great that we are often forced to prescribe medicines for which there is no definite indication. At times this is a crude, but often effective method of practising psychological medicine, and it has the advantage that it may be practised by those with the proper type of personality even if they have little knowledge of psychological medicine. It has the disadvantage, however, that, although it may succeed in restoring the patient's confidence, it leads him to believe that symptoms which originated in an emotional reaction are in reality due to physical illness. These symptoms will be likely to recur and to be misinterpreted in the same way, and the same crude treatment will be expected.

The examples given in Class I will probably be generally admitted to be properly classified. In Class II there will be less general agreement; in fact, some doctors would probably be willing to admit nearly all the examples given under this heading into Class I. It is well, however, to refrain from drawing conclusions too readily, as clinical impressions with regard to the efficacy of drugs are often fallacious. The history of digitalis gives us an excellent example to show that clinical observations, uncontrolled by scientific observations, are liable to lead to error, and that the sanction of tradition, even after half a century, is no guarantee of the value of a drug. Professor A. J. Clark ("Applied Pharmacology", 6th Edition, p. 368) relates the story as follows :—"Digitalis was originally used as a remedy for tuberculosis, but in 1775 Withering showed that it had a powerful diuretic effect and also an action on the heart. . . . After about 1860 it was considered a cardiac tonic, and was believed to raise blood pressure. During the first half of the nineteenth century digitalis was also used for treatment of numerous diseases of the central nervous system, including epilepsy, general paralysis of the insane,

and delirium tremens. The action of digitalis in curing auricular fibrillation of the heart was elucidated by Mackenzie, and in the last twenty years the details of its mode of action have been analysed by means of the electro-cardiograph." Another example is a drug which was formerly used frequently and freely for many years in Addisonian anæmia, and which is still often prescribed with iron in hypochromic anæmia, namely, arsenic; it is probable that it is without value in this disease.

Vaccines should seldom be placed higher than Class II. Their position is summarised in the Introduction to the Medical Annual for 1939 as follows:— "Vaccines have been in use for many years both for curative and preventive purposes. The introduction of typhoid vaccine was brilliantly successful and scientifically controlled. But after many years we have no such evidence for most of the vaccines in common use. Recent investigators of the action of vaccines against influenza and 'common colds' have come to the conclusion that they are quite valueless. Yet their use continues unabated, and it is striking that no attempt is made to rebut the evidence of their inefficacy. Those who employ them seem content to allow matters to rest as they are."

Glycerophosphates and hypophosphites probably belong to Class III, and at the present time there can be little excuse for ordering these preparations, especially in the form of syrups. Much less costly placebos are readily available.

Having decided that a patient requires a drug in Class I, it should seldom be necessary to add drugs from the other classes. Thus in hypochromic anæmia large doses of iron are required, e.g., iron and ammonium citrate, thirty grains three times a day. A solution of this preparation is not unpleasant to take, and there would appear to be little reason for adding such drugs as glycerophosphates or even vitamins. The well-known proprietary preparation, "Syrup Minadex," contains $3\frac{3}{8}$ grains of iron and ammonium citrate in each dessertspoonful, combined, as its name implies, with minerals (in the form of glycerophosphates) and vitamins A and D. Whatever uses such a preparation may have, it cannot be regarded as suitable for iron-deficiency anæmia. Similar reasoning applies in the case of Easton's syrup; syrup, quinine, and strychnine are not needed, and the amount of ferrous phosphate present is not sufficient in hypochromic anæmias.

As medicine is so readily obtainable, and as even patients who are well often think they would benefit by what they and their doctor speak of rather vaguely as a "tonic," the bottle of medicine habit is encouraged under the panel system, especially when the doctor does not possess those qualities necessary for the proper discipline of his patients. It is here in particular that there is ample scope for saving, and patients should be educated as far as possible to do without their placebo. Statistics show that the medicine habit is much more prevalent in Northern Ireland than in Scotland, and in Co. Armagh than in Co. Antrim. Does this mean (1) that the insured are less healthy in Northern Ireland than in Scotland, and in Co. Armagh than in Co. Antrim, or (2) that medicine which is requisite is being refused in Scotland, or (3) that medicine which is not requisite is being prescribed in Northern Ireland? It would be still more difficult to find a reasonable explanation for the remarkable differences to be found in the number and cost of prescriptions

issued by different doctors in the same locality whose practices appear to be approximately of the same type.

Reference has already been made to the irrational methods generally adopted in pricing private prescriptions. The result is that a private patient may often obtain proprietary drugs, attractively packed, at a smaller cost than the corresponding non-proprietary article. In panel practice, however, it may be assumed that proprietary drugs always cost more and their use should therefore be limited to those drugs which cannot be obtained in non-proprietary form, e.g., sulphapyridine tablets, obtainable in the United Kingdom only as "M. & B. 693" : liver extracts for intramuscular injection; prostigmin, etc. Foreign proprietary drugs should seldom be required; thus carbaminoylcholine chloride, formerly prescribed as "doryl," is now manufactured in Britain and sold as "carbachol"; phenyl ethyl methyl malonyl urea, formerly prescribed as "prominal," is now sold as "phemitone"; etc.

A more general adoption of the suggestions already made and of the following further suggestions would help to protect the Drug Fund :—

(1) All cases of alleged constipation should be investigated. Many of them do not require purgative medicines.

(2) Iron has no tonic effect except in hypochromic anæmias, when it should be given in adequate doses, and in these cases it is useless and wasteful to order liver extract. Iron syrups have little place in rational therapy.

(3) In Addisonian anæmia a suitable liver extract should be injected. This is more efficacious and more economical than oral administration. For maintenance therapy periodical blood counts are essential.

(4) The value of gargles in most cases in which they are used is doubtful. At all events there is no need to order expensive preparations, such as compound glycerin of thymol. Solutions of common salt, bicarbonate of soda, etc., are probably as efficacious.

(5) The use of petroleum emulsion for some supposed "tonic" effect is irrational, as liquid paraffin is not absorbed from the bowel.

(6) Most of the polyhormonal preparations on the market, e.g., "hormotone," are of no value apart from any effect produced by their thyroid content; and it costs much less to order tablets containing one-twentieth of a grain of thyroid extract than the same number of "hormotone" tablets. Proprietary glandular preparations, such as ovacoids, testacoids, nephritin, "opocaps" prostatic, etc., have never been shown to have any therapeutic value.

(7) Drug treatment would suffer little if the B.P. infusions were omitted, and the saving would be considerable.

(8) If flavouring agents are considered necessary, they should cost little, e.g., tincture of orange (2s. 4d. an ounce) and syrup of orange (5½d. an ounce) are much too expensive.

(9) Tinctures and B.P. spirits should be ordered sparingly. Liquor ammoniæ aromaticus, B.P.C. costs much less than Spiritus ammoniæ aromaticus.

(10) Rectified spirit (about 2s. an ounce) should not be used for ear drops or external applications. For such purposes the B.P. industrial methylated spirit (½d. an ounce) should be used; this contains ninety-five per cent. of alcohol B.P., and has neither pyridine nor colouring matter. The B.P. industrial spirit is therefore of much greater purity than the ordinary mineralized methylated spirit.

(11) Bismuth carbonate should seldom be necessary. The same therapeutic effect can be obtained in most cases by ordering kaolin, at about one-twentieth of the cost.

(12) The indications for the use of gonadotropic and œstrogenic hormones, synthetic œstrogens (stilbœstrol), progesterone, and testosterone, are by no means clearly defined. Whereas the old unstandardized tablets of ovarian and corpus luteum substance were almost inert, the œstrogens and progesterone, and also testosterone propionate, are potent substances whose dose is measured in milligrams, and which, if improperly used, may do much harm. The advertising literature does not always make this clear.

(13) Vitamin concentrates have a definite use in correcting vitamin deficiencies preliminary to prescribing a properly balanced diet. Although thiamin hydrochloride (vitamin $B_1$) is of value in "alcoholic" polyneuritis, it is probably of no value in fibrositis, e.g., in sciatica due to perineural fibrositis, or in myalgia.

Owing to war-time difficulty in obtaining certain medicaments, the following should be ordered as seldom and as sparingly as is consistent with adequate treatment. (The list is taken from a Memorandum issed by the Chief Medical Officer of the Department of Health for Scotland, July, 1940) :—

(1) dextrose and syrups, (2) glycerin and preparations containing it, e.g., kaolin poultice, (3) liquid paraffin and preparations containing it, e.g., emulsion of liquid paraffin with agar, (4) soft paraffin, (5) olive oil, (6) potassium bromide and iodide, (7) barbiturates, (8) opium and morphine and their related alkaloids and preparations, (9) tinctures and extracts of vegetable drugs, especially those of foreign origin, (10) linseed meal.

Finally it may well be asked—What fraction of the million prescriptions issued annually to panel patients in Northern Ireland is really necessary? Doctors to whom I have put this question have generally given the answer at figures between one-half and two-thirds. If we accept these answers, it follows that prescriptions costing from £20,000 to £30,000 are issued every year in excess of what is necessary. If we add to this the amount spent on unnecessary ingredients in the necessary prescriptions, we realize more fully the extent of the extravagance. A determined effort on the part of our panel doctors would result not only in the saving of a large sum of money annually, but would also have the effect of bringing clinical practice more into line with present-day knowledge.

# Manipulation of the Sacro-Iliac Joint

*By* HUGH J. DUFFIELD, B.A., M.B., B.CH.

As recently as 1937, Horace C. Pitkin in an article in the "Journal of Bone and Joint Surgery" wrote: "Manipulative surgery is a therapeutic waif of lowly origin whose infancy and childhood have been shielded from the light of reason by a congenital veil of empiricism and quackery." Yet in spite of such hereditary handicaps, it continues to thrive wonderfully; and perhaps in no better field than that of the sacro-iliac region has this therapeutic waif justified its existence. It is in an attempt to draw aside this congenital veil in some little measure and shed a little of the light of reason upon this difficult and, I fear, neglected region of the sacro-iliac articulation, that the present article is written.

## ANATOMY.

In a casual review of the literature, the divergence of opinion regarding the classification of this joint at once becomes apparent. Robert Lovett, to whom we owe so much for our knowledge of the anatomy and mechanics of the spine, classifies this joint as a synchondrosis, an immovable joint. Quain improves a little on this, and calls it an amphiarthrosis, that is, a slightly movable joint. This tendency has continued in recent years, and as knowledge has increased, this joint has come to be classified as a diarthrosis, or a freely movable joint. Such authorities as Cunningham, Grey, Morris, and Brooke subscribe to this classification. Steindler tells us that it is a true joint with articular facets, synovial lining, and capsule.

The joint itself is situated between the lateral side of the sacrum and the auricular surface of the ilium. It covers roughly the upper half of the sacrum, and in shape is rather like a side-view of a club-foot. The joint surfaces are said to be covered with fibro-cartilage, and although wave-like in contour, have a smooth surface. When opposed to each other, the slight elevations fit into corresponding shallow depressions. This undoubtedly was one of the reasons for the joint being classified as a synchondrosis.

## LIGAMENTS OF THE JOINT.

The joint is extremely well fortified by strong ligaments. Posteriorly it is covered by the posterior sacro-iliac ligament. This ligament can be divided into three distinct parts: (a) the deep interosseous ligament, connecting by short strong fibres the apposing tuberosities of the ilium and sacrum; (b) the long posterior sacro-iliac ligament, connecting the third transverse tubercle of the sacrum with the posterior superior iliac spine; (c) the short posterior sacro-iliac ligament, connecting the first and second tubercles of the sacrum with the posterior superior iliac spine. (b) and (c) are superficial. In front the joint is covered by the less robust anterior sacro-iliac ligament, connecting the ala of the sacrum to the adjoining part of the ilium.

Three extra-articular ligaments require mention: (1) the iliolumbar, connecting the transverse process of the fifth lumbar vertebra with the crest of the ilium and the ala of the ilium; (2) the sacrotuberous, connecting the posterior iliac spines and

the third, fourth, and fifth transverse tubercles of the sacrum with the tuberosity of the ischium; (3) the sacrospinous, the apex of which is attached to the spine of the ischium, the base being spread over the lateral aspect of the sacrum and coccyx in front of the sacrotuberous.

## FUNCTION.

Having refreshed our memory on the anatomy of this region, we pass on to consider the function of this articulation.

Viewed from the front, the sacrum appears as a wedge mortised between the two ilia, the apex terminating in the coccyx. The area of apposition on either side is the sacro-iliac articulation. In the erect position the full weight of the trunk is transmitted through these articulations; moreover, in transference of weight from one leg to the other, each single joint transmits the full load. From this it is obvious that stability must be the first consideration of this joint. It is, however, not the only consideration—motion also plays its part. Otherwise what would be the use of a diarthrodial joint here? Why not a solid fusion? The answer to this is that the sacro-iliac joint acts as a shock-absorber, and plays an active part in such ordinary movements as walking.

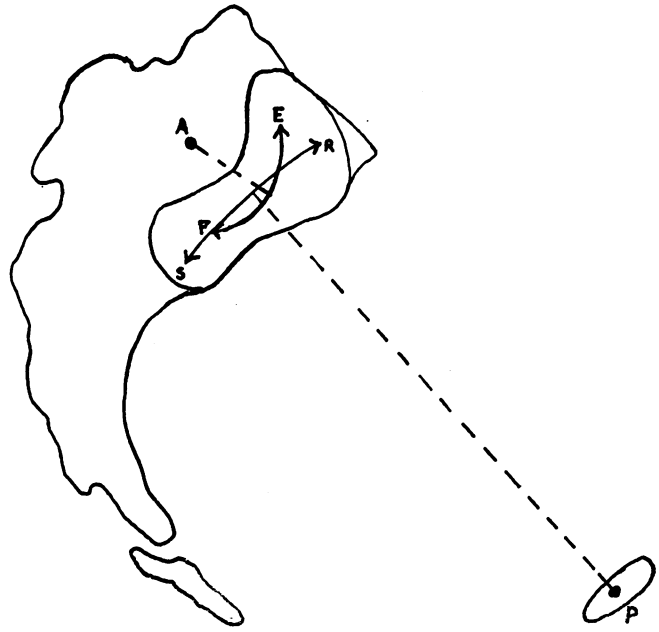
## MOTION IN THE SACRO-ILIAC.

It is now fairly generally acknowledged that some slight movement does occur in the sacro-iliac articulation. Emphasis is always laid upon "slight"—as it were, to nullify this most important physiological fact. We have already stated that stability is the first consideration of this joint. We should not therefore expect a range of movement such as exists in a ball-and-socket joint. But let us not forget that the sacrum is an integral part of the spine and, as such, might be expected to conform to and accompany the normal movements of the spine. These normal movements of the spine are: (1) flexion; (2) extension; (3) a complex movement which may be (a) sidebending-rotation or (b) rotation-sidebending.

The fact that the sacrum does behave in this manner has been fully confirmed by many observers, and not long ago in the "Journal of Bone and Joint Surgery" (see *Sacrarthogenetic Telalgia* by Pheasant and Pitkin, J.B.J.S., 1936-1937). To investigate this thoroughly would take up too much space. Therefore we shall be content to state briefly what has already been thoroughly established.

In flexion and extension the sacrum rotates upon a transverse axis passing through the second piece of the sacrum. This movement is fairly well recognized, and takes place in forward and backward bending of the trunk. What is not so well appreciated is that in unpaired antagonistic movements of the body, as e.g., in walking, the ilia rotate and sidebend upon the sacrum, the axis of this movement being the symphysis pubis. Here the sacrum plays a passive role. To quote from the series of articles mentioned above: "When antagonistic iliac mobility occurs, the sacrum cannot remain suspended in mid-air, but is forced by gravity to follow any downward or forward motion of the ilia. Therefore the articular surface of the sacrum, on the side of the ilium that is rotating forward, accompanies the articular surface of that ilium in its forward and upward movements. The opposite

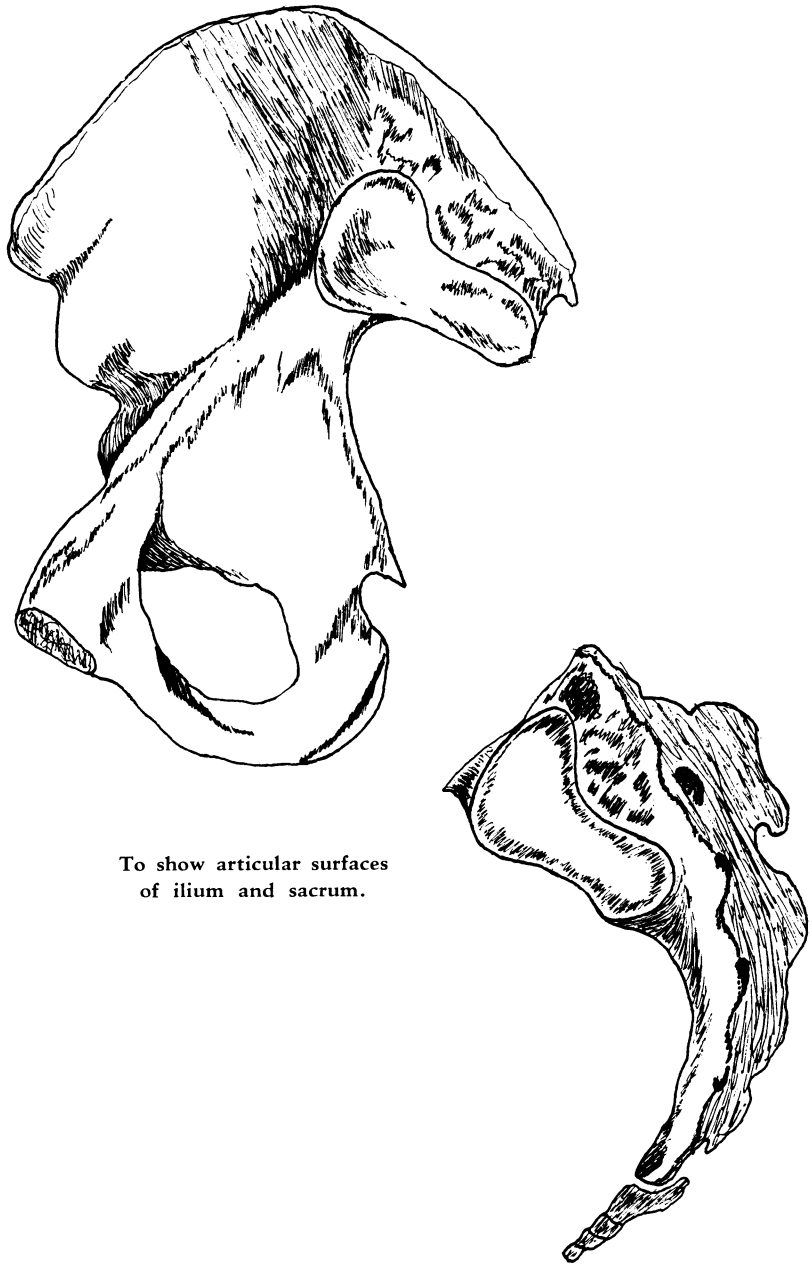
side of the sacrum, in like manner, accompanies the ilium that tends to rotate backwards and downwards." It is important that we should be familiar with these normal movements of the joint in order that we might be able to manipulate it in at least a rational manner. Otherwise we might easily substitute brute force and ignorance for skilful, well-directed effort.



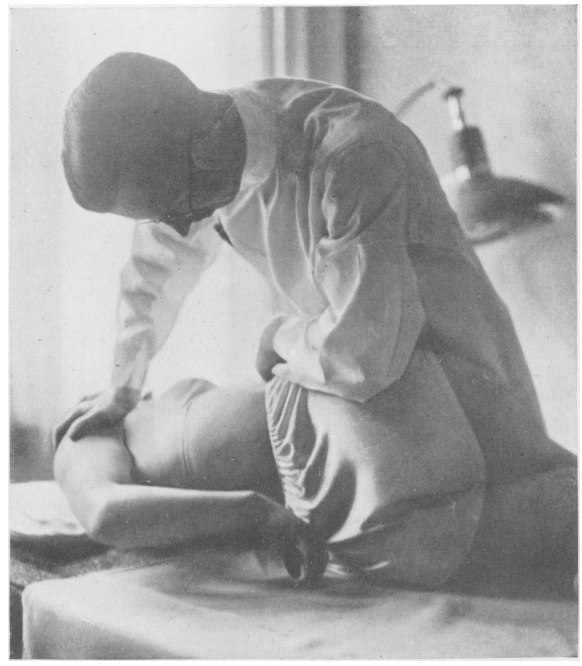

**To show the two types of movement which take place at the sacro-iliac joint. E-F represents the arc of movement in extension and flexion, A being the axis of rotation. In this movement the upper two-thirds of the joint is involved. S-R represents the other type of movement, sidebending rotation. The axis of this movement is the symphysis pubis, the ilium playing the active role, the sacrum the passive. The lower two-thirds of the joint is involved.**

## "SCIATICA."

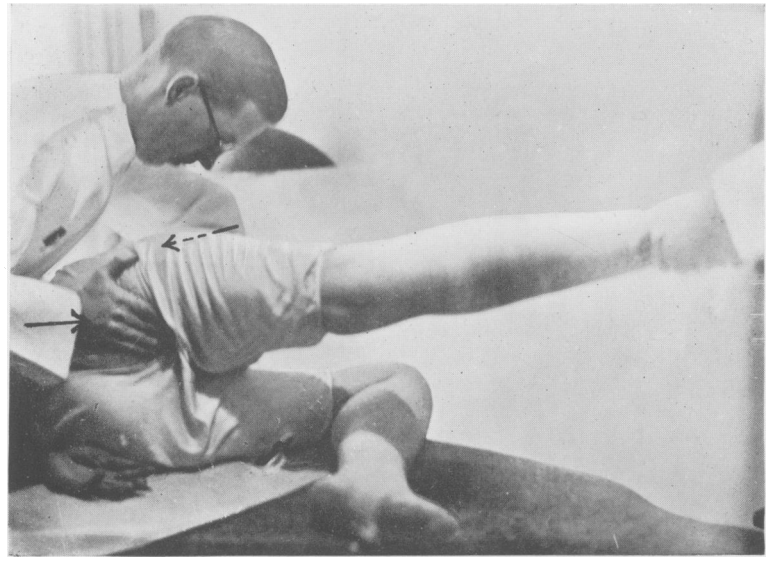
When one (or both) of these joints becomes locked or fails to function in a normal manner, a syndrome develops which is generally labelled "sciatica." Doubtless there are many causes of sciatica; this, certainly, is one of the commonest. The picture has many varying shades, but in outline it is fairly well stereotyped. The patient is stepping out of his bath, when he suddenly feels acute stabbing pain across the lower part of the back. The pain is so severe that it almost causes collapse, and the patient is helped with great gentleness back to bed. Having found the least painful position in bed, he remains there immobile. By this time the pain may have become more localized, and he may be able to say quite definitely on which side he feels it more. Later the distribution of the pain will become more



To show articular surfaces
of ilium and sacrum.



First technique described: for posterior innominate



Second technique described: for anterior innominate

typical, being referred to the ilio-lumbar angle on the affected side, the region of the posterior superior iliac spine, the buttock, frequently round into the groin, the postero-lateral region of the thigh and leg, and sometimes into the outer toes. Two regions consistently escape : the medial side of the leg and the sole of the foot.

The attack does not always develop acutely as in the preceding picture, but may develop insidiously. If we probe sufficiently deeply into the history, we find in most of these cases an account of an injury, direct or indirect, affecting this part of the back. Perhaps it was a fall downstairs, or off a ladder, or a strain when lifting a heavy weight, or trying to lift something from a high shelf. Frequently no obvious cause can be traced, and this is not surprising when we consider the many strains, stresses, and vicissitudes continually affecting these joints.

When the condition has lasted for some time the muscles on the affected side become somewhat atrophied. This is noticeable in the buttock, thigh, and leg. Sometimes fibrillation of the gluteal muscles is seen. The reflexes (the knee-jerk and tendo-achilles) are generally diminished, but there is no nerve degeneration. Scoliosis is almost invariably present. This may be homolateral or heterolateral; occasionally it is alternating.

Sometimes the patient's diagnosis may be "lumbago," and on examination the lumbar muscles may be rigid and tender. This is a frequent accompaniment of a lesion in the sacro-iliac joint; but one has to be on one's guard that the trouble is not higher up in some of the articulations of the lumbar spine. In some cases a differential diagnosis is extremely difficult. The site and distribution of the pain, the palpation of the soft tissues and bony landmarks will help; but above all, the establishment of normal motion in the sacro-iliac joint will exonerate this articulation and incriminate the lumbar spine as the source of trouble.

## EXAMINATION.

The patient is first examined in the standing position with his back to the examiner. When asked where the pain is, the hand generally travels to the region of one or other posterior superior iliac spines, across the buttock and down into the thigh. A scoliosis to one or other side may be noticed, and on the affected side there may be a tendency to bend the knee slightly. If the acute phase has passed, forward bending will be accomplished without much difficulty, although the full range will not be obtained. The extreme of this movement will probably accentuate the pain in the region of the affected joint.

The patient is next examined lying face downward on the couch. The posterior superior iliac spine on the affected side may be found to be a little lower than its neighbour, or the reverse may occur. The former is the case when the ilium rotates backward in relation to the sacrum and becomes locked there; the latter, when the ilium rotates forward. In my experience these are the only two recognizable malpositions of the ilium in relation to the sacrum. When either of these lesions occurs, motion is lost in the joint. It is this fact which is of the greatest importance —because, when this motion is re-established, the excruciating pain which began somewhere in the lower lumbar region and radiated through the buttock, thigh, outer side of the leg and right into the toes, quickly subsides and finally disappears.

The patient is now examined lying on his back. If his legs are anatomically equal in length, we may notice by comparing the internal malleoli that there is an apparent shortness on the affected side. This will be the case if the ilium has rotated back, which is by far the commoner of the two malpositions. The anterior superior iliac spines are now compared and checked with the posterior findings. We now proceed to test the motion of the joint. Beginning with the good leg, we test for leg-shortening. With one hand on the knee and the other gripping the ankle, the leg is flexed at the knee, abducted, and internally rotated. While this is being done, the patient is instructed not to resist the movement, but to relax completely. The leg is now replaced beside its fellow and the internal malleoli compared. From half an inch to three-quarters of an inch of shortening will now appear in the good leg. The patient is now instructed to bend his knees up and, keeping his feet on the couch, raise his hips off the couch. (In a very acute case this movement will cause too much pain and will have to be abandoned.) This will obliterate any apparent shortening, and we shall be back again at the starting position. We now test leg lengthening. The leg is slightly flexed at the knee, adducted over the other leg, and gently externally rotated. The leg is replaced, and again the malleoli are compared. The leg has now apparently lengthened, perhaps half an inch. This is Downing's test, and shows that the sacro-iliac joint on that side is moving normally. On the affected side the internal malleolus shows no variation, or, in comparison with its fellow, a greatly decreased variation, when this test is applied to it.

If any doubt still exists about the diagnosis, a rectal examination is imperative. In the case of a woman a vaginal examination is often necessary.

One might suppose that an X-ray examination of the low back would shed much light on any abnormality of this field. In the case of sacro-iliac subluxation it is singularly disappointing, because of the complex anatomical arrangement of this region and the consequent difficulty of finding a technique which would show both joints clearly. Stereoscopic radiographs give the best help; but even in these too much is left to the imagination.

It is always worth while doing an X-ray examination, if only for the sake of getting a better insight into the patient's body mechanics; and may save us from the pitfall of overlooking an incipient tuberculous or arthritic process in this joint.

## MANIPULATION.

To perform this operation it is seldom necessary to have recourse to a general anæsthetic. There are many good techniques, and one ought to be familiar with as many as possible, because the same technique is not always successful. The following two have been found useful: one, for the condition where the ilium has moved backward; the other, where it has moved forward. No anæsthetic is used. The field of operation is prepared by endeavouring to relax the spastic musculature of the ilio-lumbar region by deep massage. The patient is now placed in position for manipulation. For a posterior ilium, i.e., where the ilium has moved backward, the following technique is adopted. The patient turns on to the unaffected side.

The thighs are fully flexed on the abdomen, the knees being flexed also. By now taking hold of the underarm of the patient, the upper part of the body is rotated fully—into the supine position. The uppermost leg is now extended at the knee and swung over the edge of the couch. The operator is now standing facing the patient, not behind. He places one hand on the patient's far shoulder, and bending over slightly, places the flexed forearm of the other arm on the crest of the ilium which is uppermost. Using the patient's shoulder as a counter-resistance, the ilium is rotated forward and downward (i.e., towards the floor) until all slack is taken up. When the operator senses this condition he pauses slightly; then, still retaining his pressure, he quickly increases his forces, delivering a short sharp thrust. This may or may not be accompanied by a dull audible thud, and frequently the patient immediately experiences a sense of relief. The joint is then tested for motion.

In this technique the spine acts as a lever, being locked in extension and rotation right down to the sacrum : this forms a long lever. A short lever is made use of in the form of the ilium. The long lever is rotating backward, the short one forward. The point of cleavage is the sacro-iliac joint.

In an anterior lesion the following technique may be used. It requires an assistant.

The patient turns on to the unaffected side. The operator, having taken up his position at the foot of the couch, grasps the leg on the affected side at the ankle with both hands. He raises the leg up into a position of mid-abduction. His assistant then takes up his position behind the patient. One hand is placed over the anterior superior iliac spine, the other over the tuberosity of the ischium; the former hand presses backward, the latter forward. The operator at the foot of the table gently rotates the leg until he feels it quite relaxed. A sudden unexpected pull is given, thus piercing the muscle guard and "gapping" the joint. The assistant, waiting for this, increases his forces at the psychological moment and the ilium retraces its path back home.

## CASE REPORTS.

The following two case reports may be of interest, the one an acute case of "lumbago," the other a chronic case of "sciatica."

The first case is that of an agent fifty-five years of age. He had had some mild attacks of lumbago several years ago, for which he took a few veganin tablets. On 10th June last he was stepping out of his bath when he felt a dull aching pain come on across the lower part of his back, which did not yield to veganin. Next morning it had not improved, and after breakfast, while getting up out of an easy chair, he experienced an agonizing pain across the whole of the lower back.

I found him lying in bed flat on his back. He said this was the only position which gave him any relief. With great caution and gentleness I succeeded in getting him on to a portable treating table. A cursory examination revealed a posterior lesion of the left sacro-iliac joint. I spent a little time relaxing the muscles and then manipulated the joint back into position. This operation caused him

surprisingly little inconvenience. I put him back to bed feeling not much better. I saw him on several days following this. Each time he was greatly improved and the soreness was wearing off. After the manipulation he no longer felt the very acute pain. Towards the end of the week he was back at business again.

The other case is of a more chronic nature. The patient was a farmer aged 49. He came to me on the 27th February, 1940. Five weeks previously, while recovering from an attack of influenza, he suddenly experienced severe pain in the left hip and leg. During these five weeks he had tried the usual analgesic remedies with little success, and his doctor welcomed the suggestion of manipulation. His general condition was poor, and he had lost considerable weight. There was obvious pain on movements of the trunk, and this was especially noticeable when getting on to the treating table. The left knee was held slightly flexed, and any attempt to extend it at once elicited pain. There was slight wasting of the muscles of the left buttock, thigh, and leg, and some fibrillation of the glutei was noticed. The knee-jerk and ankle-jerk were slightly diminished. The pain was most marked in the left ilio-lumbar angle, round the crest of the ilium, and radiated into the hip, down the thigh, leg, and into the outer toes.

An anterior lesion of the left innominate was diagnosed. At first it was impossible to manipulate the joint owing to the spasticity of the muscles. During this period we endeavoured to prepare the field by deep muscular massage and heat in the form of infra-red rays. The patient was instructed to apply antiphlogistine at home. On 4th March the joint was successfully manipulated, and treatment continued with steady improvement until 3rd April, when the patient was discharged cured. During this time the patient's general condition had improved wonderfully. He had put on weight, and the muscle atrophy was now almost imperceptible. He received eight treatments altogether. Six weeks later he was reported to be quite well—in fact, doing the laborious work of carting out manure into the fields.

It is with gratitude I acknowledge the help given by Major Howard Crozier, R.A.M.C., in reading over the proofs. Had it not been for his encouragement, the article would not have been written.

For the two photographs I am indebted to Mr. Charles H. Sparrow. His assistance was valuable and very willing.

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# Notes on Infection by Leptospira Icterohæmorrhagiæ

*Weil's disease has appeared recently in a number of districts in Northern Ireland; the following notes have been compiled to draw attention of practitioners to its main characteristics.*

This disease is also known as :—

(1) Weil's spirochætal jaundice.
(2) Leptospirosis icterohæmorrhagiæ.
(3) Spirochætosis icterohæmorrhagica.

INCUBATION PERIOD : Four to nineteen days; usually seven to thirteen days.

PART PLAYED BY RATS : The sewer rat (Rattus norvegicus) is the main carrier of the disease, but shows little if any manifestation of disease. The organism is excreted in the rat's urine, and from this source man is directly or indirectly infected. Moisture appears to be essential for the persistence of the organism outside the rat, and man is usually infected by water or slime in or from places infested by rats, such as *mines, sewers, fish-cleaning premises, farm middens, piggeries, slaughter-houses,* or by *bathing in polluted water.*

HISTORICAL.

The disease was first described by Weil in 1886.

The organism was discovered by two Japanese workers in 1914.

Cases occurred during the Great War, 1914-1918, rat-infested trenches being favourable to infection. Reports were made by Adrian Stokes, J. A. Ryle, Lord Dawson, and others.

The first case reported in Great Britain was by Dr. Manson Bahr in 1922. He isolated the organism from the blood of a seaman who had fallen into the Thames a few days previously.

Up to October, 1939, the grand total of proved cases in Great Britain was 248, of which 108 were in fish-workers. The other workers who were infected included coal-miners, sewer-workers, tripe-workers, farm-workers, canal-workers, and scavengers. In 1939 several cases occurred in Belfast among sewer-workers.

The disease is now regarded as predominantly an occupational disease.

MORTALITY.

Taken as a whole, the case mortality is probably about ten per cent.

MODES OF ACCESS TO THE BODY :

(1) Through skin abrasions, which may be very small. Sewer-workers engaged in repair work and fish-workers engaged in cleaning and filleting fish are specially liable to abrasions of the hand;
(2) Through the alimentary or nasal mucous membrane, either from contaminated food or drink or accidental splashing of sewer slime containing the organism.

Dogs suffer from the infection, and are a possible source of human infection.

The urine of a patient may contain the organism far into convalescence. Infection from man to man is, however, apparently very rare.

CLINICAL COURSE OF THE DISEASE :

(1) The onset is usually sudden with headache, nausea and vomiting, fever, prostration, intense and generalised muscular pain and tenderness.

(2) Congestion of the conjunctiva.

(3) Jaundice, usually fourth to seventh day of the illness, but it is sometimes absent altogether.

(4) Hæmorrhages from the mucous membranes and under the skin usually occur after the periods of jaundice.

ERRONEOUS DIAGNOSES WHICH HAVE BEEN MADE :

(1) Bronchitis,
(2) Pneumonia,
(3) Influenza,
(4) Rheumatism,
(5) Typhoid fever, especially if jaundice is not a symptom.
(6) Meningitis, especially if jaundice is not a symptom.
(7) Catarrhal jaundice, especially if unusually severe.
(8) Acute necrosis of the liver.

LABORATORY TESTS are essential to establish the diagnosis :

(1) During the first week the organism may be found in the blood, either by guinea-pig inoculation or culture.

(2) Later it appears in the urine, but its demonstration is uncertain, as the morphologically identical leptospira biflexa, which is non-pathogenic, may occur in human urine. Moreover, negative animal inoculation results are of little value, as the organism seldom survives in the urine for more than an hour after excretion, and only if the urine is alkaline.

(3) Agglutination Test : This is probably the most convenient routine test after the fifth day of the illness. Varying dilutions of the patient's serum and an equal volume of a young culture of leptospira icterohæmorrhagiæ are allowed to interact for two hours.

Difficulty : In certain dilutions of the serum the leptospiræ may undergo lysis and the result may be masked. This difficulty may be overcome by the use of formolized cultures, but exceptionally the serum gives a flocculation which makes agglutination difficult to observe.

A positive reaction may be expected from serum taken on the sixth day of the disease, and is produced more readily thereafter until about the twentieth day. The reaction may be positive for several years.

Blood samples do not rapidly lose their utility for serological examinations, and can satisfactorily be sent by post.

—J. B.

# Vitamin C and the Menstrual Function

*By* James Deeny, M.D., M.SC., D.P.H., M.R.C.P.I.

*With a statistical analysis and commentary by* R. C. Geary, D.SC.

FOR some years it has been known that the anæmia from which large numbers of women of the industrial classes suffer, is due to the frequent losses of blood in pregnancy or from menorrhagia. This was demonstrated first by Davidson, Fullerton,[1] Orr,[2] and others, in two surveys, carried out in Aberdeen in 1933 and 1935. In the first survey, it was shewn that there was extensive anæmia amongst women in a section of the industrial population of the city. Men and children did not suffer to the same degree. A dietary investigation revealed that a normal blood picture could be maintained on a diet containing much less iron than the amount generally regarded as necessary (fifteen mg. per diem). There was no correlation between the anæmia and the content of iron in the diet, but a definite correlation was found to exist between anæmia, pregnancy, and menorrhagia. In the group of women who exhibited anæmia, an overwhelming number had either one or other of these disabilities. It was considered that since some function of womanhood was responsible for the anæmia, and that blood-loss either from menorrhagia or pregnancy was the deciding factor, then diets capable of maintaining men or children were not sufficiently rich to compensate for the heavier requirements of women. It was not possible to estimate the vitamin content of the diets. In the later survey in 1935, hæmoglobin estimations were carried out on three thousand people. Analysed in groups, it was found that anæmia was most prevalent during the first year of life and during the period of child-bearing. Sixteen per cent. of adolescent and forty-five per cent. of adult women were regarded as anæmic. Anæmia was absent in adolescent and adult males except in association with disease. The more severe cases were treated with iron, and the hæmoglobin content rapidly restored to normal.

Vitamin C also plays a part in regulating the level of hæmoglobin in the blood, and it might be postulated that those who exist on a diet deficient in iron are also likely to be deficient in vitamin C. Deficiency in vitamin C will produce anæmia—such as is seen in scurvy—even on a diet containing sufficient iron. It has been possible to cure persons suffering from anæmia, by a diet containing little iron, but plenty of vitamin C. Leverton and Roberts[3] carried out daily hæmoglobin estimations and red blood cell counts on four women : two for three months and two for four. Complete analysis of diet, excreta, and menstruum was also undertaken during this time. They found that there was no relation between the menstrual flow and the variations which were noted in the Hb. They observed daily variations in the Hb. content as follows :—fifty-seven per cent. were no greater than 0.5 gm. and eighty per cent. were no greater than one gm. In the majority of cases it was not greater than experimental error. The average standard deviation for Hb. was 0.9 gm. The four subjects showed a rise in Hb. content over the period of study. This was a slow upward trend and was not accompanied by any rise in the red cell count. The increases amount in each case to one gm. or more

of hæmoglobin per hundred c.c. of blood. It was accentuated in the case of one of the subjects who received an additional dose of iron in the fourth and fifth cycles. But the rise was also seen in the other three who had not had this supplement, but who were maintained on a very complete diet with a daily iron content of ten to fifteen mgm. On the diet—at that time considered to fulfil normal requirements—the subjects were able to store a measurable quantity of iron.

Apart from its influence on the level of Hb., vitamin C may help to cause "nutritional anæmia" in other ways. Vogt[4] used vitamin C with success in the treatment of "juvenile hæmorrhages." He ascribes its action to a strengthening of the walls of vessels, and found it of especial value in cases of essential thrombopenia. Junghaus[5] treated thirty-five women who suffered from climacteric, pre-climacteric menorrhagia, and other forms of gynæcological hæmorrhages. The treatment was successful in thirty-three cases. Siegert[6] emphasises the clinical significance of Gaethgen's observation, that vitamin C deficiency is common in pregnancy. According to his findings, the vitamin C metabolism of women during pregnancy is always on the border-line of hypovitaminosis. This is most marked in winter, when the diet is poor in the vitamin. In women who were deficient in vitamin C and who suffered from uterine hæmorrhage of unknown origin while pregnant, he was able to obtain prompt healing by giving vitamin C.

Müller[7] achieved good results in the treatment with vitamin C of gynæcological and other hæmorrhages, when these were caused by a C hypovitaminosis. The improvement in the symptoms went parallel with the increase of the reducing property of the urine. If it was found that the greater part of the vitamin C was excreted from the first day onwards, then it showed that the system was supplied with enough vitamin C, so that no retention was necessary. In these the vitamin C therapy was unsuccessful. In the cases treated, the amount of the deficit was ascertained by the usual functional tests, and the dosage regulated accordingly. The results were good in the cases of juvenile, pre-climacteric, and climacteric metrorrhagia, and in cases of hæmorrhage from the myomatous uterus. Gastric hæmorrhage, and one case of bleeding from the nose and lungs, were also influenced. C hypovitaminosis was also shown to be present in a case of apthous stomatitis, and was cured by vitamin C therapy.

Huckel[8] used vitamin C successfully in conjunction with corpus luteum in the treatment of threatened abortion. He suggests the use of vitamin C in the treatment of polymenorrhœa. Kramer, Harmon, and Brill[9] have reported degeneration of both follicles and corpora lutea in scorbutic guinea-pig, as well as a failure to become pregnant or to deliver normal young. Ingier[10] has shown in guinea-pigs that on scorbutic diets in early pregnancy, animals were born dead or prematurely. Bourne,[11] however, has reported that pregnant guinea-pigs remain normal on a scorbutic diet.

Biskind and Glick[12] have shown that the singularly high concentration of vitamin C in certain physiologically-related endocrine organs is striking. Of all animal tissues which they studied, the adrenal cortex, corpus luteum, and the anterior lobe and pars intermedia of the hypophysis are the richest sources; and of these, the

pars intermedia contains vitamin C in the greatest concentration. The correlation between vitamin C concentrations of functionally-related portions of the adrenal and hypophysis may be extended to the corpus luteum, which is physiologically related to the anterior lobe of the hypophysis, and contains vitamin C in approximately the same concentration. They showed that cows' corpus luteum contained 1.4 mgm. of ascorbic acid per gm. of tissue, when the organ was most fully developed; and that the value fell to 0.3 mgm. per gm. of tissue with regression. Biskind and Glick suggested that there may be a connection between the presence of vitamin C and the corpus luteum hormone progesterone. The corpus luteum, in pregnancy of the cow, has a concentration fifty per cent. higher than the mature corpus in the non-pregnant animal. Vitamin C[13 14 15] seems to be unrelated to the female sex-hormone œstrin, but may be related to the hormone pregesterone; as the vitamin[16] content of the corpus luteum seems to be parallel to the pregesterone content. Proper[17] embryo implantation and continuance of gestation depends upon the presence of a corpus luteum, or even more exactly, on the progesterone it produces. When it is recalled that vitamin C deficiency produces degeneration of corpus lutea and failure of normal gestation in guinea-pigs, it would appear at least reasonable to suggest, that the vitamin is necessary for the normal production of the hormone, either by maintaining the integrity of the structures responsible for its formation, or more directly, by influencing the chemical reactions involved in the pregesterone synthesis. Pillay[18] measured the amount of vitamin C excreted in the urine of eleven women, through twenty-four menstrual cycles, and obtained some evidence in support of a theory, that there was decreased excretion of vitamin C at the time of ovulation. Bourne[19] has suggested that vitamin C is associated non-specifically with the production of the corpus luteum hormone. Biskind and Glick used a special technique. They removed pieces of the corpus luteum of cows in different stages of function; cut sections of a certain thickness, and estimated the vitamin C content of the sections.

The knowledge that vitamin C has an effect in preserving the efficiency of the skeletal structures of the blood vessels, and also its relationship to the endocrine organs associated with menstrual function, would lead one to believe that vitamin C deficiency plays a part in the causation of the "nutritional anæmia" present amongst the women of industrial populations, not only in its effect on the hæmoglobin content per se, but also in its effect on the menstrual function, either by the production of an unhealthy condition of the walls of the blood vessels of the endometrium or by a derangement of the mechanics of the menstrual function through the effect of its deficiency on the formation of an essential hormone.

To test the truth of this assumption, a group of women who suffered from menorrhagia, with or without dysmenorrhœa, and who were of a similar social type to that of the Aberdeen sample, were given large doses of vitamin C (Redoxon tablets), and the results observed. Unmarried women were selected, as it was thought that they were less likely to be affected by extrinsic pathological factors. The sample numbered thirty-nine persons, and the ages ranged from fourteen to thirty-two, the average age being 21.6. As the sample was drawn from persons

in my practice, and who underwent the experiment voluntarily, objective tests of the menstrual function were not practicable, or do I know of any satisfactory method applicable to such a work as this. Observations were therefore limited to the duration of the periods and to the subjective clinical conditions associated. Weekly hæmoglobin tests were carried out by means of a Hall-Dare hæmoglobinometer. Comparisons were made between menstrual periods before and after the administration of the ascorbic acid.

Since it was not possible to carry out gynæcological examinations to include pathological conditions, it may be accepted that, as certain of the women may have had gynæcological conditions (pathological) responsible for their menorrhagia, they were not likely to be improved by the vitamin C treatment. The method adopted was to give each woman six thousand mgm. of vitamin C in Redoxon tablets, each of fifty mgm., the daily dose depending on the number of days usual in the cycle, care being taken that there was ample time to consume the whole test amount. Where the experiment was carried on for two months, a similar quantity was given during the second month. As it was considered that two hundred mgm. was the necessary daily quantity of vitamin C to completely saturate the body in the given time, and since the average duration of the cycle might be expected to be thirty days, the total dose was therefore six thousand mgm.

The aim in selecting the sample was to obtain ordinary women of the poorer class, who were suffering from menorrhagia and whose means were such that it might be expected that they were existing upon deficient diets. Many were anæmic and considered themselves run-down. They are a type met with constantly in general practice. During the experiment, one woman became pregnant, and in two other cases there was such irregularity in the menstrual cycle, that consideration of these two cases was not possible. In two other cases, their periods returned within a few days of the commencement of the treatment; the tablets were blamed, and they refused to continue. An unusual feature was, that for the first few days many of the women complained of severe headaches while taking the ascorbic acid, and which in one case was so bad that she was unable to continue. An attempt was made to establish a control group, who were given citric acid tablets, made to imitate the Redoxon ascorbic acid, but this was given up, and reliance placed on control by statistical methods devised for the experiment by Dr. Geary. The results are given in the following tables.

## DISCUSSION.

Although scurvy is now relatively rare, it is evident that sub-clinical scurvy is relatively common. The clearest statement on the matter is that of Orr,[20] who, as a result of a study of diet in relation to income in Britain, proved that fifty per cent. of the population live on diets deficient in vitamin C and minerals. Foodstuffs containing vitamin C, with the exception of potatoes, are relatively expensive. It can therefore be easily understood why the sub-scorbutic condition is so prevalent.

In the account of the literature associated with this experiment, it is seen that vitamin C deficiency may play a part in producing nutritional anæmia: (a) by causing scurvy anæmia, (b) by causing menorrhagia, either by impairing the health

TABLE 1

MENORRHAGIA EXPERIMENT

| Case No. | Duration of Period in Hours: Before taking Ascorbic Acid | After taking Ascorbic Acid | Decrease | Clinical Condition After Treatment: Menorrhagia | Dysmenorrhœa | Associated Symptoms |
|---|---|---|---|---|---|---|
| 1 | 72 | 54 | 18 | 2 | 2 | 2 |
| 2 | 90 | 80 | 10 | 2 | 2 | 2 |
| 3 | 96 | 108 | 12* | 1 | 1 | 1 |
| 4 | 108 | 48 | 60 | 2 | 2 | 2 |
| 5 | 127 | 96 | 31 | 2 | X | 2 |
| 6 | 130 | 96 | 34 | 2 | 2 | 2 |
| 7 | 137 | 144 | 7* | 2 | 2 | 2 |
| 8 | 120 | 132 | 12* | 0 | 2 | 2 |
| 9 | 68 | 63 | 5 | 2 | 0 | 0 |
| 10 | 192 | 96 | 96 | 2 | 2 | 2 |
| 11 | 120 | 48 | 72 | 2 | 2 | 2 |
| 12 | 102 | 72 | 30 | 1 | 2 | 2 |
| 13 | 96 | 93 | 3 | 2 | X | 2 |
| 14 | 180 | 132 | 48 | 1 | 1 | 2 |
| 15 | 170 | 120 | 50 | 2 | 0 | 2 |
| 16 | 72 | 90 | 18* | 0 | 2 | 2 |
| 17 | 132 | 120 | 12 | 2 | 2 | 2 |
| 18 | 120 | 96 | 24 | 2 | 2 | 2 |
| 19 | 95 | 96 | 1* | 2 | 2 | 2 |
| 20 | 90 | 60 | 30 | 2 | 2 | 2 |
| 21 | 138 | 130 | 8 | 1 | 1 | 0 |
| 22 | 120 | 72 | 48 | 2 | 2 | 2 |
| 23 | 120 | 88 | 32 | 1 | 0 | 0 |
| 24 | 112 | 72 | 40 | 2 | 2 | 2 |
| 25 | 96 | 90 | 6 | 2 | 1 | 2 |
| 26 | 60 | 108 | 48* | 2 | 2 | 2 |
| 27 | 168 | 90 | 78 | 1 | 2 | 0 |
| 28 | 96 | 96 | 0 | 0 | 0 | 0 |
| 29 | 114 | 120 | 6* | 1 | 1 | 0 |
| 30 | 192 | 116 | 76 | 2 | 1 | 2 |
| 31 | 98 | 72 | 26 | 1 | 0 | 1 |
| 32 | 48 | 60 | 12* | 0 | X | 0 |

X—Absence of symptoms before and after treatment.
0—No change in symptoms after treatment.
1—Improvement.
2—Completely normal condition.
*—Increase.

"Associated symptoms" are such symptoms as constipation, debility, listlessness, fatigue, loss of appetite, pains related to ovarian dysfunction, but not readily classified as dysmenorrhœa.

Total number of periods observed—110.

of the blood vessels of the endomentrium or affecting the menstrual function in some unexplained way, probably associated with the formation of the hormone progesterone.

Anyone engaged in general practice in a poor area will be familiar with the type of woman of whom the sample was composed. In districts where there is much

## TABLE 2

## HÆMOGLOBIN FIGURES (GRAMMES PER 100 C.C.)

| Case No. | Initial Finding | After Taking Ascorbic Acid. 7th Day | 14th Day | 21st Day | Average Cols. (3)-(5) | After Period 7th Day | 14th Day | 21st Day | Average Cols. (7)-(9) |
|---|---|---|---|---|---|---|---|---|---|
| (1) | (2) | (3) | (4) | (5) | (6) | (7) | (8) | (9) | (10) |
| 1 | 15.2 | 14.6 | 14.4 | 16.0 | 15.0 | 15.2 | 14.8 | 14.8 | 14.9 |
| 2 | 12.8 | 13.0 | 13.6 | 12.4 | 13.0 | — | 12.4 | — | 12.4 |
| 3 | 12.2 | 12.4 | 13.4 | 12.4 | 12.7 | 12.8 | 12.6 | 13.0 | 12.8 |
| 4 | 9.0 | 10.4 | 12.4 | 12.8 | 11.9 | — | — | — | — |
| 5 | 12.8 | 14.6 | — | — | 14.6 | — | — | — | — |
| 6 | 11.0 | 14.0 | 12.4 | — | 13.2 | — | — | — | — |
| 7 | 12.2 | 12.8 | 13.2 | 12.4 | 12.8 | — | — | — | — |
| 8 | 10.8 | 12.6 | 11.8 | — | 12.2 | 10.8 | 12.2 | 12.2 | 11.7 |
| 9 | 13.8 | 13.4 | 13.0 | — | 13.2 | 12.4 | 12.0 | — | 12.2 |
| 10 | 11.6 | 12.4 | 13.2 | — | 12.8 | — | — | — | — |
| 11 | 13.0 | 13.6 | 14.2 | — | 13.9 | — | — | — | — |
| 12 | 12.2 | 13.2 | 15.0 | — | 14.1 | 14.2 | 14.6 | — | 14.4 |
| 13 | 11.6 | 12.8 | 13.2 | — | 13.0 | 12.4 | — | — | 12.4 |
| 14 | 12.8 | 13.6 | 13.2 | 14.4 | 13.7 | 13.0 | 14.6 | 15.0 | 14.2 |
| 15 | 13.0 | 13.4 | 12.4 | 13.2 | 13.0 | 14.0 | 14.6 | 14.6 | 14.5 |
| 16 | 13.2 | 14.0 | 14.8 | — | 14.4 | 13.6 | — | — | — |
| 17 | 10.0 | 10.8 | 10.8 | 12.4 | 11.3 | 11.2 | 11.0 | 10.0 | 10.7 |
| 18 | 12.8 | 13.4 | 14.0 | 14.8 | 14.1 | 12.2 | 13.0 | — | 12.6 |
| 19 | 10.8 | 10.8 | 11.4 | 11.4 | 11.2 | 12.6 | 11.6 | 12.2 | 12.1 |
| 20 | 12.0 | 12.4 | 14.0 | 15.2 | 13.9 | 15.6 | — | — | — |
| 21 | 10.4 | 10.2 | 10.0 | 10.2 | 10.1 | 10.2 | 9.5 | 10.6 | 10.1 |
| 22 | 13.4 | 13.6 | — | — | 13.6 | 12.8 | — | — | 12.8 |
| 24 | 10.4 | 11.4 | — | — | 11.4 | 12.6 | 14.8 | 15.2 | 14.2 |
| 25 | 14.0 | 14.8 | 13.0 | 13.4 | 13.7 | 12.8 | 15.0 | 14.6 | 14.1 |
| 26 | 13.8 | 14.0 | 13.6 | 13.8 | 13.8 | 13.6 | 14.4 | 14.4 | 14.1 |
| 27 | 12.4 | 12.0 | 12.4 | — | 12.2 | 12.4 | 12.6 | — | 12.5 |
| 28 | 14.4 | 14.4 | 14.0 | 13.8 | 14.1 | 14.6 | 15.4 | 13.8 | 14.6 |
| 29 | 13.0 | 13.6 | 14.4 | 15.0 | 14.3 | 15.0 | 14.4 | 15.0 | 14.8 |
| 30 | 12.4 | 12.8 | — | — | 12.8 | 13.0 | — | 15.0 | 14.0 |
| 31 | 12.0 | 12.4 | 11.8 | 13.4 | 12.5 | 13.6 | — | 13.0 | 13.3 |
| 32 | 12.4 | 13.0 | 13.8 | 14.4 | 13.7 | — | 13.6 | — | 13.6 |

The sequence is that immediately following on the hæmoglobin test, known as the initial finding, the subject commences to take the ascorbic acid. The blood is again tested on the seventh, fourteenth, and twenty-first days after. Then follows a menstrual period, and again the blood is tested on the seventh, fourteenth, and twenty-first days after the period has ended.

TABLE 1A

Summary of Menorrhagia Experiment (derived from Table 1) as regards Duration of Period

| Cases in which Duration of Menstruation Prior to Treatment was— | Number of Cases | Average Duration of Period in Hours | | Average Decrease (−) or Increase (+) |
|---|---|---|---|---|
| | | Before Treatment | After Treatment | |
| I. 127 hours or more ... | 10 | 157 | 114 | −43 |
| II. 98 hours to 120 hours ... | 10 | 113 | 82 | −31 |
| III. 96 hours or less ... | 12 | 82 | 84 | + 2 |
| All cases ... ... | 32 | 115 | 92 | −23 |

TABLE 1B

Summary of Menorrhagia Experiment (derived from Table 1) as regards Clinical Conditions after Treatment

| Cases in which After Treatment there was— | Number of Cases | | |
|---|---|---|---|
| | Menorrhagia | Dysmenorrhœa | Associated Symptoms |
| (a) Completely normal condition ... | 20 | 18 | 23 |
| (b) Improvement but not normal condition | 8 | 6 | 2 |
| (c) No change in symptoms ... ... | 4 | 5 | 7 |
| (d) Absence of symptoms (before and after treatment) ... ... ... | — | 3 | — |
| All cases ... ... ... | 32 | 32 | 32 |

TABLE 2A

Summary of Hæmoglobin Experiment (derived from Table 2)

| Initial Hæmoglobin Figures (inclusive) | Number of Cases | Average Hæmoglobin Figures Per Case | | Average Increase |
|---|---|---|---|---|
| | | Before | After | |
| 9.0 to 12.0 ... | 11 | 10.9 | 12.1 | 1.2 |
| 12.2 to 12.8 ... | 10 | 12.4 | 13.4 | 1.0 |
| 13.0 to 15.2 ... | 10 | 13.8 | 13.9 | 0.1 |
| All cases ... | 31 | 12.3 | 13.1 | 0.8 |

female employment, they are particularly common. Such persons are usually pale, thin, and listless. They are easily tired, with poor appetites, are often constipated, and live in constant dread of their monthly ordeal. In the course of the experiment, it was a particular pleasure to observe the improvement, often dramatic, which the ascorbic acid made in their condition. In several of the cases, this was the first period for years in which they had not been forced to leave work and go to bed. Constipation, headaches, and constant perineal pain cleared up in almost every case where such conditions were present. Although it was not possible to transform such clinical observations into figures, these features, together with an improvement in well-being and diminution in blood-loss, were the most noteworthy results of the experiment.

## SUMMARY.

(1) An experiment has been carried out on thirty-two unmarried females of the

industrial class, all of whom were suffering from menorrhagia, to demonstrate the relationship between vitamin C deficiency and nutritional anæmia due to menorrhagia.

(2) After a test dose of ascorbic acid (Redoxon) sufficient to produce saturation, of the thirty-two cases, twenty were restored to a clinically completely normal condition, eight were improved, but not normal, and four had no change in symptoms.

(3) There was a diminution in the duration of the menstrual periods and an increase in hæmoglobin.

(4) Improvement was greatest in the worst cases.

I wish to thank Dr. R. C. Geary, Department of Industry and Commerce, Eire, to whom I am indebted for the statistical analysis and summary. Dr. F. W. Prescott and Professor Harrison for advice and assistance, and Roche Ltd., Welwyn, Herts, for a generous gift of part of the Redoxon tablets used in the experiment.

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# STATISTICAL COMMENT

## *By* R. C. Geary, D.Sc.

Table 1.—The fact that in all but eight cases out of thirty-two a reduction in the duration of period following the use of ascorbic acid establishes a prima facie case of significant relationship. On the average, the reduction amounted to twenty-three

industrial class, all of whom were suffering from menorrhagia, to demonstrate the relationship between vitamin C deficiency and nutritional anæmia due to menorrhagia.

(2) After a test dose of ascorbic acid (Redoxon) sufficient to produce saturation, of the thirty-two cases, twenty were restored to a clinically completely normal condition, eight were improved, but not normal, and four had no change in symptoms.

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# STATISTICAL COMMENT

## *By* R. C. Geary, D.Sc.

Table 1.—The fact that in all but eight cases out of thirty-two a reduction in the duration of period following the use of ascorbic acid establishes a prima facie case of significant relationship. On the average, the reduction amounted to twenty-three

hours (from 115 to 92), and, as Table 1A shows, the reduction was confined to the more serious cases of menorrhagia; there was no significant change induced in the lowest menorrhagic class. (It may be added that the categories in Tables 1A and 2A were devised so as to divide the cases considered into about equal numbers.) Even if there were no relation between the phenomena (menorrhagia and treatment), a somewhat similar relation would be found, since if we arrange in descending order according to the magnitude of one of the phenomena, we must expect to find a greater reduction in the measure of that phenomenon in the highest group. The same reservation attaches to the analogous Table 2A.

Applying the "Student"-Fisher test of significance to the differences in the periods before and after, we find that, in the familiar notation, $t = 3.88$, which, for the number of cases, $n' = 32$ (and hence $n = 31$), gives a value of P near .0002, which approximately represents the probability that a series of deviations greater (in the aggregate) than those found would occur if no improvement were in reality effected by using the treatment; if, in fact, the results found were due to chance. The experiment must be regarded as indicating a most significant relationship between the decline in the duration of period and the use of ascorbic acid.

Table 1B shows that, out of the total of thirty-two, improvement was effected in twenty-eight cases for menorrhagia, twenty-four cases for dysmenorrhœa, and twenty-five cases for associated symptoms. No elaborate test is required to infer the significance of these results. Assuming that if no treatment were given, an infinite series of experiments would show that half the cases would improve and half disimprove, then, on the hypothesis that, even if all the "no change" cases were regarded as unfavourable (and a more plausible assumption would be, that half were favourable and half unfavourable), ratio of actual to standard deviation (i.e., $x - np / \sqrt{npq}$ ; $p = q = \frac{1}{2}$) would be as in the last column following :—

| | No. of Cases | Actual Deviation | S.D. | Ratio |
|---|---|---|---|---|
| Menorrhagia | - 32 ... | 12.0 ... | 2.83 ... | 4.24 |
| Dysmenorrhœa | - 29 ... | 9.5 ... | 2.69 ... | 3.53 |
| Associated Symptoms | - 32 ... | 9.0 ... | 2.83 ... | 3.18 |

The ratios indicate a very small degree of probability that the results were fortuitous.

Table 2.—It must be observed at the outset that, prior to treatment there is no markedly significant relation between the duration of period and the hæmoglobin figures. The coefficient of correlation is $r = -.256$, but the result might have been due to chance—the probability P for $n = 30$ is in excess of 0.1. As Table 2A shows, hæmoglobin increased from 12.3 to 13.1 between the "initial finding" and the average for the subsequent readings—and an increase was recorded in all three hæmoglobin classes, but no deduction with regard to the significance or permanence of the results can be made from these facts alone. In all but six out of thirty cases in which changes were recorded, the hæmoglobin figures increased.

Application of the "Student"-Fisher test of significance in this case is complicated by the fact that the "initial findings" are single observations, and the "after treatment" figures in column (6) of Table 2 are averages of two or three observa-

tions and are occasionally single figures. Having made the necessary adjustments in the test, it is found that for $n' = 31$ ($n = 30$) the value of $t = 5.12$, the variates being regarded as the differences between the figure "before" and the average "after" multiplied (as theory requires) by $\sqrt{\frac{3}{4}}$, when the average is derived from three observations, $\sqrt{\frac{2}{3}}$ when the average is of two observations, and $\sqrt{\frac{1}{2}}$ when there is but a single observation "after." There is not the faintest doubt of the marked significance of this result. It may be well to add that in this manner of application of this test, it is assumed that, were it not for the treatment, no general improvement in the hæmoglobin figures would have been recorded, i.e., that the "initial findings" might be taken as representative for these persons prior to treatment—if some were below their average on the occasion of that particular test, for instance, they might have been compensated by others which were above their particular average. There is no reason to doubt but that this assumption was justified. If we deliberately selected persons whose hæmoglobin figure was lower on a given occasion than their particular average, and if, without any treatment, we measured them at a later date, we would, of course, find in most cases an increase, to which no significance would attach.

The "after" figures in Table 2A are "average of averages" types of figures, the use of which generally is to be deprecated, but it is hard to see how they could be assembled and digested otherwise.

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## .THE ROYAL MEDICAL BENEVOLENT FUND SOCIETY OF IRELAND

*The Editor, "Ulster Medical Journal."*

SIR,—In the April number of your JOURNAL you very kindly published a letter from me, in which I pointed out that 164 subscribers had contributed £193 to the Belfast and County Antrim branch, and in the other counties 124 subscribers had given £112 in the year ending 1st April, 1940; and that 950 Ulster doctors do not subscribe to this, our own charity.

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Surely I do not ask in vain for help for the widowed and the fatherless of our own brothers.

I am, Sir,

Yours faithfully,

9 College Gardens, Belfast. ROBERT MARSHALL.

# Shock and Its Treatment

*By* J. S. LOUGHRIDGE, M.D., B.SC., F.R.C.S.ENG.
Surgeon to Out-Patients, Belfast Hospital for Sick Children

THOUGH shock is due to many different causes, the clinical appearances are more or less constant; they vary only in degree, and are easily recognized in the more severe cases. The symptoms are increased pulse-rate, low blood-pressure, pallor, subnormal temperature, sweating, vomiting, thirst, and dry tongue; the mind is usually quite clear. In addition to the pallor, the skin of the ears and lips may show slight cyanosis. The signs are due to profound changes in the nervous, circulatory, and respiratory systems, and in the temperature-regulating mechanism. The amount of the fall in the blood-pressure and the reduction in volume of the circulating blood vary directly with the clinical condition, and indeed give a good quantitative estimate of the degree of shock present. As a result of study, in the last Great War, of the total blood volume and of the relative volume of red cells and plasma, using the vital red method and the hæmatocrit respectively, Keith[1] has divided shock into three stages according to its severity.

*Group 1.*—Mild shock, in which the condition is good. There is a history of a not too severe injury or of a moderate primary hæmorrhage. On examination, there is some pallor, the pulse is 90-110, the systemic blood-pressure is over 95 mm., and the blood-volume is never below 75 per cent. These may be called compensated cases.

*Group 2.*—The general condition is serious. The extremities are cold and clammy. The pulse is 120-140, the blood-pressure is 70-80 mm., the blood-volume is 65-75 per cent., and the volume of the red cells is increased relatively to that of the plasma. These cases are partially compensated.

*Group 3.*—These cases are dangerously ill. The pulse is almost impalpable, the blood-pressure is below 60 mm., the blood-volume is less than 65 per cent., and on auscultation, the heart-beat is 120-160 per minute. They are not compensated.

It is important to recognize to which group the patient belongs and to treat accordingly. The divisions suggested by these groups are not hard and fast. Intermediate stages occur, and an individual may and often does pass through two or even all three stages in a short time.

Prior to the Great War of 1914-1918, the changes occurring in shock were not fully understood, but observations made then, and much painstaking work by experimental workers carried out since under controlled conditions, have shown many of the factors involved, and have indicated the lines along which rational treatment should lie. It is unnecessary to recapitulate the various theories of shock which have been held, but it may be advantageous to consider briefly how the present conception of shock has been obtained. The great fall in blood-pressure impressed the earlier observers and formed a starting-point for investigation. The fall in pressure might be due either to a loss of peripheral resistance or to a diminished cardiac output. The former, thought to be due to a loss of vaso-constrictor tone, has been shown not to exist. The peripheral vessels are actually in a state of constriction; in other words, the sympathetic nervous system, instead

of being paralysed, is in a state of activity, further proof being afforded by the sweating, the pallor, and the dilated pupils, all of which are due to stimulation of the sympathetic nervous system. The fall in blood-pressure occurring with contraction of the arterioles must then be due to a diminished output from the heart, and this in turn to a reduced intake from the great veins, as the heart itself is normal. However, in time the lowered intake means less blood in the coronary circulation, and the cardiac factor now adds its quota to the reduction in the amount of blood in circulation. The fall in blood-pressure is now therefore accepted as being due to a reduction in the blood-volume, and this reduction is the cause of all the serious symptoms as well as the progressive deterioration in the patient's general condition, which are so characteristic of shock.[2] The restoration of the blood-volume is the fundamental principle of treatment. The loss of blood-volume is due in part to stagnation of blood in capillaries and venules and of muscles and viscera, and also to an actual loss of plasma through the capillary wall. This results in a relative increase of red cells over plasma in the capillaries. The concentration of the corpuscles in the capillaries increases the viscosity of the blood and tends to slow an already sluggish stream, thereby still further reducing the volume of circulating blood. It has been held that the circulatory changes are due to the liberation of histamine from the damaged tissues, but recently Blalock[3] (1934) has brought forward evidence that approximately one-half of the total blood-volume may be lost in an injured extremity, and that this loss is sufficiently great to account by itself for the decline in the blood-pressure. He injected fluid from an animal in a state of shock into another animal, and found that the blood-pressure of the second animal did not fall, but rose.

The vaso-constriction found in cases of shock is evidently nature's attempt to maintain the blood-pressure in the presence of a reduced volume. The vaso-constriction is more or less effective for a fluid loss up to about two pints, but when the loss is greater, the compensation fails and the blood-pressure falls to 60 mm. or less (Keith's third group). The vaso-constriction, the reduced blood-volume, and the low blood-pressure, together produce a totally inadequate circulation to all parts, so that the nervous system, the viscera, and even the endothelium of the blood vessels suffer from severe lack of oxygen and nutritive substances. If continued, this damage is irreparable, hence the importance of instituting early and adequate treatment. Blood or plasma injected after the endothelium has been damaged is not retained in the circulation (except, of course, the cellular elements); transfusion in such a case is therefore of no avail, and may actually be harmful.

## Treatment.

It follows from the above considerations, that the treatment of shock should be started early, preferably before it has become manifest, or at least in its early stages, and that the restoration of blood-volume is the essential step in preventing that worsening of the patient's condition which is such a characteristic feature of shock. In addition to this main requirement of restoring the blood-volume to near a normal figure, attention may be drawn to certain subsidiary factors, each aggravating shock to some degree, and in the aggregate of considerable importance. They are exposure to cold and fatigue, hæmorrhage, pain, lack of

fluid and oxygen, infection, and wounds of special parts of the body. These factors will be considered briefly first of all.

Injuries, and particularly war injuries, often occur under the worst conditions of cold, wet, and fatigue. Wet clothing should be removed and replaced by warm and dry clothing. The patient should then be placed in a bed warmed by jars or an electric blanket and the foot of the bed raised. Apart from the movements necessary for the change of clothes, the patient should be kept as still as possible, and all elaborate examinations or unnecessary manipulations carefully avoided.

A tourniquet should be applied only in cases of severe hæmorrhage, and should not be retained for more than an hour or so—under normal working conditions—unless the limb is obviously beyond saving. For a limb not hopelessly damaged, a firm bandage applied over plenty of wool is preferable to a tourniquet, and is equally effective in preventing blood- and plasma-loss into the damaged tissues.

Pain is a potent factor in maintaining and increasing shock. Its relief is of the first importance, and is easily obtained by the use of morphine. The first dose may be $\frac{1}{4}$ to $\frac{1}{3}$ grain, given preferably subcutaneously or intramuscularly for speed of effect, and repeated every four or six hours as indicated. In bad cases of shock, the circulation may be so poor that morphia given subcutaneously may not be carried to the central nervous system in a reasonable time. An almost immediate action can be produced by giving $\frac{1}{4}$ grain of morphine dissolved in 1 c.c. of sterile water intravenously.[4] One minute or more should be taken for the injection.

Not only do wounded men lose water by perspiration, but they often have less than the normal amount of body fluids before being wounded, particularly if they have undergone much physical exercise in dry weather or hot climates. The loss of water and salt should be made good as soon as possible. The mouth is the natural route for the intake of fluid, and the greatest use must be made of it by encouraging the patient to drink much and often. Water containing half a teaspoonful of salt to the pint, and even normal saline (one teaspoonful to the pint) has a scarcely perceptible salty taste. Haldane found that coal miners in the deep pits at Salford perspired heavily at their work, and when given saline, drank by the quart and asked for more! Warm drinks, for example coffee and tea, may be given as frequently as possible. When fluids cannot be taken by mouth, they should be given by the rectum, subcutaneously, or intravenously. Isotonic saline, glucose, or preferably Ringer-Locke solution warmed to body temperature, may be used. As these fluids soon pass out of the circulation, it is of advantage to give them slowly and over a considerable period by the "continuous drip" method. In bad cases, blood or plasma may be given before or with the saline.

Oxygen is of value in cases where cyanosis can be detected, and particularly in wounds of the chest, in cases with pulmonary œdema, and in poisoning with carbon monoxide. To be effective, the oxygen must be given by an apparatus which will appreciably raise the oxygen tension in the lung alveoli, from the normal fourteen per cent. to seventy per cent. or more. The Boothby, Lovelace, and Bulbulian apparatus is recommended.[4] It consists of a mask, a connecting device, and a reservoir breathing-bag. Raising the carbon dioxide in the inspired air to about five per cent., either by rebreathing or by adding carbon dioxide to the oxygen,

causes deeper breathing, and is an important method of increasing the amount of the tidal air. Carbon dioxide is especially indicated in cases of carbon monoxide poisoning, e.g., from coal-gas or explosions in enclosed spaces.

The degree of shock depends not only on the extent of the injuries received, but also on their nature and on the parts injured. Of special importance in this connection are burns, head injuries, wounds involving the spine and spinal cord, and wounds of the chest, especially open pneumothorax and wounds of the pericardium. Open chest wounds are associated with a high mortality unless quickly sealed; indeed, closure of such wounds should be carried out immediately, even if only by a few interrupted sutures in the skin. Burns, as is well known, cause shock, the degree of which bears a relationship to the area of the burn rather than its depth. Shock from burns is now regarded as identical with that due to wounds, and the treatment is the same.

The question of operation has to be considered in certain cases. When operation can be postponed until shock has been successfully combated, the answer is obvious; but in the remainder it must be left to the judgment of the surgeon in each case how much is to be gained by operating in the presence of shock or by waiting for a time until the shock has been partially or completely treated. This remainder includes depressed fractures of the skull, wounds of the chest, especially if there is an open pneumothorax, and extensive wounds with hæmorrhage or gross infection. Amputation may be considered in hopelessly mutilated limbs; and incision for infection, followed by the administration of drugs of the sulphanilamide group and the appropriate anti-sera. When it has been decided to operate, due consideration should be given to the choice of the anæsthestic. Ether may be given in short cases, but in prolonged anæsthesia it is in itself a potent cause of shock. Nitrous oxide and oxygen is free from this defect, but it requires skill to give good anæsthesia with a minimum of anoxæmia.

Actual experience of recent air-raid casualties has shown the value of determining the degree of shock and instituting the appropriate treatment. Early operation, particularly the amputation of badly mutilated limbs, has been associated with a high mortality. The number of cases requiring prompt operation for excessive hæmorrhage has been surprisingly small, being less than five per cent. of the total injuries.[5]

As follows from the physiological changes occurring in shock, the restoration of the blood-volume is the logical and fundamental element in the treatment of all but the lesser degrees of shock, and should be attempted as soon as the patient is in bed and the general measures have been or are being carried out. The fluid which was originally used intravenously for this purpose was blood. Its use in a large scale in the war of 1914-1918 and since then has been instrumental in saving many lives. It remains the fluid of choice in those cases where shock is due primarily to hæmorrhage. The original routine amount of one pint is usually insufficient, and can be increased advantageously to two, three, or four pints. The blood may be fresh or preserved.[6] In cases of shock not due to bleeding, the red cells are increased relatively to the plasma; and the viscosity of the circulating fluids is increased. The addition of more red cells is therefore undesirable. Gum

saline was introduced for this and other reasons, but its use has been largely discontinued on account of accidents. It was only recently that the obvious and natural fluid for transfusion in such cases has been used, namely, human plasma or serum.[7] Even in hæmorrhage, the restoration of the blood-volume and its maintenance by the osmotic pressure exerted by the proteins of the injected plasma have been found to be of great value. Plasma is produced at the Royal Victoria Hospital from blood which has not been required for use within its normal keeping time. To 150 c.c. of 5 per cent. glucose in doubly distilled water and 50 c.c. of 3.8 per cent. sodium citrate are added 350 c.c. of blood. The citrated blood is stored in the refrigerator for ten or twelve days. If not used within this time the plasma is decanted off, and is capable of being stored indefinitely at four degrees centigrade. The plasma may be dried to the powder state, in which it will keep even longer at room temperature.[8] The powder is prepared again for injection by the addition of sterile distilled water or glucose saline.

The intravenous injection of plasma is of greatest benefit in cases of shock belonging to Keith's group 2 (see above). In group 1 the general measures of rest, heat, morphine, and fluids indicated earlier are usually all that are necessary. Patients in group 3 are practically beyond help from any treatment, because in these people the endothelium of the blood vessels has been so damaged that it is no longer able to retain even the plasma proteins, emphasizing the importance of recognizing shock in its earlier stages and treating energetically.

The clinical course of each case of shock should be checked as frequently as possible, at least hourly. The patient's colour, the temperature of the extremities, the strength and rate of the pulse, and the blood-pressure all give indications of his progress. If facilities are available, red-cell counts and hæmoglobin estimations are also of value. Injection of plasma should be repeated and the general measures maintained until the patient's condition is satisfactory.

In conclusion, stress may be laid on the importance of recognizing shock in its early stages and of starting effective treatment immediately. The essentials of treatment can be summarized as follows:—Rest with a minimum of interference for any reason, dry warmth, morphine for the relief of pain, plenty of fluids by the mouth or other routes, operation in only a few special cases, oxygen for cyanosis, and the intravenous injection of two to four pints of blood or plasma, repeated if necessary, in all cases where the amount of shock is not slight, and if the fall in the blood-pressure and the rise in the pulse-rate is progressive. For details of the technique of injection and a description of the B.L.B. apparatus for the administration of oxygen, the Medical Research Council's War Memorandum No. 1 is recommended.[4]

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# Studies from the Institute of Pathology

## CASE IX.

## A PATIENT WITH MELANOMA. A.2811.

### Clinical History.

The patient was a man of 59 years. His previous history gave no facts of importance. He was admitted to hospital suffering from weakness in the left arm and left leg, which he had first noticed about five weeks previously. This weakness was of gradual onset. During the past two weeks he vomited occasionally, this vomiting showing no relationship to food.

Whilst in hospital several pigmented spots were noted on the front of his chest and also on his back. These appeared to be beneath the skin, and in spite of careful search, no nævus could be discovered. In view of this, and because of his cerebral symptoms, examination of his ocular fundi was carefully carried out. A small tumour was discovered in the left eye.

### Post-Mortem (J. McM.).

The body is that of a poorly nourished elderly male subject. It shows normal male distribution of body hair and subcutaneous fat. There is no jaundice and no œdema. Eyes, ears, and nose appear healthy. Rigor mortis is present. Numerous small spherical nodules are present beneath the skin of the chest and anterior abdominal wall. These are purplish-black in colour, and vary in size from 1 to 10 mm. in diameter.

*Body Cavities.*—The peritoneal cavity contains no free fluid. There are numerous small pigmented nodules in the tissues. Both pleural sacs are partly obliterated by dense fibrous adhesions and contain three ounces of greenish-yellow fluid. The pericardial sac contains four ounces of discoloured fluid, and its surfaces are studded with black nodules of varying size.

*Heart.*—The heart is normal in size and shape. Its surface is covered by numerous greyish-black nodules. Some of these extend up to the aorta. The right auricle is dilated. Its endocardium appears injected, and shows numerous tumour-nodules. The tricuspid valve is thin and slightly dilated. There is extensive replacement of the myocardium of the ventricle by black masses of tumour-tissue. The pulmonary valves and artery appear normal. The left auricle is less extensively involved than the right. The mitral valve is normal. The muscle of the ventricle is pale in colour and is heavily infiltrated by masses of tumour. Some of these nodules appear as small pedunculated nodules on the endocardium, and on the surface of these are small fibrinous thrombi. The aortic valve is normal.

*Lungs.*—The pleura over the right lung shows dense fibrous adhesions. Numerous rather flattened tumour-nodules are present just beneath the pleura. The glands at the hilum are slightly enlarged, and on section are seen to be replaced by tumour-tissue. The bronchi show nothing of note. On section, the lung tissue appears

œdematous, with numerous small reddish-black tumour-nodules scattered throughout.

The left lung presents a similar appearance, but the deposits of tumour-tissue, more especially in the lower lobe, are larger and more numerous.

*Liver.*—This is normal in size. Its capsule is smooth. The common bile-duct is patent. The gall-bladder is thin-walled and contains no stones. On section there are numerous nodules of tumour-tissue. The majority of these are greyish-black in colour, but others appear white. The liver lobules are relatively distinct. The radicles of the portal vein and bile-ducts appear normal.

*Spleen.*—This weighs eight ounces. Its capsule is raised to cover many rather rounded masses, some of which measure 2 cm. in diameter. On section, the malpighian corpuscles are distinct. The pulp is red, but is replaced in part by numerous nodules of tumour-tissue, the great majority of which are deeply pigmented.

*Pancreas.*—This is normal in size. Its ducts are patent. The acinar tissue appears normal, but scattered through it are numerous small pigmented nodules 1 to 3 mm. in diameter.

*Stomach and Intestines.* — The mucosa of the stomach is studded over with sessile, flat, greyish-black nodules, many of which show ulceration. Similar nodules are seen in the first part of the duodenum. Tumour-nodules are also found in the mucosa of the small intestine and appendix. No tumour is seen in the cæcum, ascending or transverse colon, but beginning in the region of the splenic flexure the nodules reappear, and in the descending colon many of these project into the lumen as small pigmented polypi. The rectum and anal canal show no lesions.

*Kidneys.*—Pigmented tumour tissue is present in the perinephric fat. The capsule is easily removed, leaving a smooth surface on which many small black nodules project. On section, several small areas of cortical infarction are present in addition to the masses of tumour. The renal tissue otherwise appears normal. The pelves and ureters are healthy.

*Bladder.*—The bladder is thick-walled. Its mucosa is congested, and shows several polypoid masses of tumour. Pigmented nodules are also seen in the prostate and perivesicular tissues.

*Adrenals.*—These are much enlarged, measuring 2 to 5 cm. in thickness. On section, they appear almost entirely replaced by brownish-black tumour-tissue. A few small islands of yellowish cortical tissue can be distinguished in the periphery of the tumour mass. These glands contain the largest deposit of the tumour.

*Neck Organs.*—The tongue shows deposits of tumour towards its base. There is no ulceration. The pharynx and fauces are congested and show similar nodules. Tumour-tissue is present in the tracheal mucosa, thyroid cartilage, and thyroid gland. The œsophagus appears healthy, but pigmented nodules are present in the lower half.

*Brain.*—The dura is firmly adherent to the skull, and shows on its meningeal surface several tumour-nodules about 1 cm. in diameter. The leptomeninges are

thin, but show pigmentation over the pre-central gyrus on the median aspect of the right hemisphere. There is some flattening of the convolutions. On section, the right pre-central gyrus is partly replaced by a nodule of tumour-tissue 1.5 cm. in greatest diameter. Around this and extending to a depth of 3 cm. into the adjacent white matter is an area of recent hæmorrhage. Small nodules of tumour-tissue, 1 to 3 mm. in diameter, are also seen scattered in various parts of the cortex. The mid-brain and cerebellum show no lesion.

*Hypophysis*.—This is increased in size. On its anterior lobe is a rounded pigmented nodule, 3 mm. in diameter. On section, this is seen to extend deeply into the glandular tissue.

*Eyes*.—The periorbital tissues show many small pigmented areas. The left eye shows three small tumour-nodules in the retina adjacent to the head of the optic nerve.

### Microscopical Examination.

*Heart*.—The myocardium is extensively infiltrated by masses of tumour-cells. These cells are polygonal or cubical in shape, and appear epithelial in character. There is a marked tendency for the development of an alveolar arrangement of the neoplastic cells, and in some areas this simulates acinar formation, but more careful examination shows that the apparent glands are formed by the central breakdown of cells. Mitotic figures are not uncommon. Many of the cells contain granules of a brown pigment. This pigment does not give the prussian-blue reaction, does not stain with any fat-stain, but darkens with silver nitrate (five per cent. solution at 37°C.). These are the commonly accepted histological reactions of the melanin group of pigments. Tumour-cells can be seen invading the walls of tributaries of the coronary veins.

*Lungs*.—Many alveoli are filled with œdema fluid. There are numerous nodules of pigmented tumour-cells, one of which is seen growing as a polypoid mass into the lumen of a medium-sized bronchus. Free tumour-cells are found in many of the alveoli. The peribronchial lymphatics are distended with new growth.

*Liver*.—The tumour-nodules show the pseudo-acinar structure well developed. Some nodules show fine intra-cellular pigment, whilst others show no evidence of pigment formation. Many Kupffer cells are distended with pigment granules. The liver-cells show no abnormality.

*Spleen*.—The tumour-nodules have a similar structure to those already described. In addition to the gross nodules, numerous small groups of neoplastic cells are found in distended sinusoids, and the sinusoidal cells contain melanin pigment.

*Adrenals*.—It is difficult to find any adrenal tissue. The tumour-cells are very deeply pigmented, and are arranged in a pattern very similar to that of the normal adrenal. In the deeper parts of the tumour the pseudo-glandular structure reappears. No medulla is seen.

*Kidneys*.—Secondary deposits are seen in the cortex. Many glomeruli also show tumour emboli composed of clumps of two or more cells, very often only recognised as neoplastic cells by reason of their pigment content. Small deposits are present in the peri-pelvic fat.

*Thyroid.*—The tumour-nodules here tend to be composed of sheets of polygonal cells with a variable melanin content. The tumour-cells tend to invade the thyroid acini, and in the earliest stages of invasion grow around the acinus on the basement membranes. The thyroid tissue is in no way abnormal.

*Brain.*—The tumour-tissue shows a curious tendency to perivascular growth resulting in a papilliform structure. In the perivascular spaces, phagocytic cells containing pigment derived from the breakdown of tumour-cells are seen. The hæmorrhagic area is surrounded by proliferating astrocytes. Numerous small capillary tumour emboli are found in the cortex, and in some areas the tumour-cells are present in the sub-arachnoid space.

*Hypophysis.*—The anterior lobe contains a metastasis occupying about one-fourth of its volume. It is deeply pigmented, and has grown into the colloid-filled spaces of the pars intermedia. A small deposit is also present in the pars nervosa.

### Anatomical Diagnosis.

Melanoma of unknown origin: ? adrenal: metastatic deposits in liver, spleen, heart, lungs, skin, brain, thyroid, hypophysis, kidneys, pancreas, and intestines: Infarcts in kidney: Cerebral hæmorrhage: Terminal œdema of lungs.

### Comment.

From the clinical side this patient presented the appearance of a cerebral lesion resembling in some ways that of a "stroke" due to cerebral thrombosis. However, the history of gradual onset of the left-sided weakness was not suggestive of a cerebral vascular accident, and the more careful examination of the patient revealed the pigmented nodules in the skin and the lesions in the eye. Once these had been noted, the probability was that the nervous symptoms were due to a deposit of tumour-tissue in the path of the motor neurones supplying the left side of the body. From the position of the lesion found at autopsy, it is probable that the weakness of the left leg preceded all other motor symptoms, and that much of the paralysis noted was due to the subsequent development of an intra-neoplastic hæmorrhage.

From the pathological viewpoint this is an interesting case in several ways. Firstly, it is a good example of an extensive dissemination of tumour-cells by the blood-stream. The result of this dissemination is rendered more striking by reason of the pigmentation of the deposits, but in its essential characters a similar process is often seen in many other non-pigmented neoplasms. The evidence in favour of blood dissemination is marked. Thus we have tumour-cells in the coronary veins of the heart, tumour emboli in the renal glomeruli, and pigment phagocytosed by the reticulo-endothelial cells in the liver and spleen. Like most other examples of tumour-spread, evidence for other modes of extension is not wanting. Thus in the lungs there is direct invasion of bronchi and spread by the air passages to the alveoli. The invasion and replacement of the hilum lymph-nodes indicate a lymphatic spread from the nodules in the pulmonary tissue, whilst, finally, there is microscopical evidence of the spread of neoplastic cells by the cerebro-spinal fluid. It is thus obvious that this tumour has utilised practically every preformed pathway in its spread throughout the organs of the body.

The second point of interest arises from the difficulty in establishing the origin

of the tumour. Clinically the primary tumour has produced no symptoms, and the clinical history is merely a résumé of those symptoms resulting from the destruction of a specialised portion of the cerebral nervous system. A breast carcinoma with similar latency of symptoms and signs of the primary tumour has already been studied in this series (Case III). Pathologically, the distribution of the tumour is so extensive that it would be difficult to defend any particular site as its origin. Pigmented tumours usually arise in one of two sites—(1) from pigmented moles in the skin, and (2) from the choroid of the eye. Much more rarely, pigmented tumour may arise in the meninges, and a few examples, by no means generally accepted, have been thought to originate in the adrenals. Pigmented tumours form also in the epidermis, but these differ in structure from those arising in moles.

The most common type of melanoma is that which arises from a congenital mole. Histologically, such moles are seen to consist of peculiar abnormal cells situated in the dermis. These cells have the property of being able to produce the pigment melanin, but whilst it is agreed that they form the starting-point of the neoplastic process, their nature is a matter of much debate. Dawson (1925) derives the nævus cells from the pigment-producing basal layer of the epidermis, and maintains that all forms of melanomata, including those arising from the choroid, are of epithelial origin. Bloch, using dioxyphenylalanin, developed a staining reaction which was positive in those cells capable of producing melanin.

The frequent association of moles with von Recklinhansen's neurofibromatosis led Soldan (1899) and, more recently, Masson (1921, 1926) to re-investigate their origin, and the latter author has produced strong evidence that these malformations are in some way related to the end-apparatus of sensory nerves.

Comparative pathology has only served to make the problem more obscure, as in the lower animals the function of pigment production appears to reside in a specific mesoblastic cell—the chromatophore. In the human, however, the role played by the chromatophore in the origin of the melanoma is by no means clear.

The actual structure of the group of melanomata gives little help in arriving at any opinion as to the true nature of their cells of origin. Apart from the production of pigment, they present very variable histological appearances, at one time simulating sarcomata, at another carcinomata. Indeed, sections from various parts of the same tumour may present appearances completely unlike. Even Bloch's "dopa" reaction is not always of use. It is not positive in tumours of choroidal origin. Indeed, it would appear that it is a mistake to assume that all pigmented tumours arise from a common cell type, and that the group of tumours known as melanomata may include tumours of diverse origin having, however, the common function of pigment production.

In the present case the histological picture is highly suggestive of a carcinoma —a melano-carcinoma. In spite, however, of very careful search, no skin lesion which could be considered the primary source was found. The skin lesions were subcutaneous and did not present the histological structure of a nævus. The eyes too were excluded as the origin. Thus, by virtue of negative incidence, we are forced to consider the possibility of a visceral site for the primary tumour, and

here the most likely organ is the adrenal. Benign melanotic tumours are rarely seen in this organ, but we have seen one, and Luksch has also described their occurrence. The one studied by ourselves was cortical in position and bore no resemblance to medullary tissue. The present case resembles others reported, in that the lesion is bilateral. This fact renders us dubious of the adrenal origin of these tumours, though the occurrence of benign pigmented adrenal tumours convinces us of the possibility of such an origin. Apart from a possible adrenal origin, the study of the morbid anatomical findings precludes the establishment of any other viscus as the primary site of the tumour.

In summary, therefore, a case of widely disseminated melanoma is reported. The common sites of origin of this type of tumour, skin and eye, were eliminated. The evidence suggests an adrenal origin, but the bilateral affection of the adrenal renders this doubtful. The case, however, constitutes an excellent example of blood-spread, air-spread, and lymphatic-spread of a neoplasm.

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# REVIEWS

CLINICAL PRACTICE IN INFECTIOUS DISEASES. By E. H. R. Harries, M.D., M.R.C.P., D.P.H., and M. Mitman, M.D., M.R.C.P., D.P.H., D.M.R.E. With a foreword by W. Allen Daley, M.D., F.R.C.P., D.P.H. 1940. Edinburgh: E. & S. Livingstone. Pp. 468. 17s. 6d. net.

THIS text-book contains 468 pages, divided into thirty-seven chapters, of which the first eleven, comprising ninety pages, are devoted to general principles, e.g., notification, modes of infection, clinical methods of diagnosis with descriptions of rashes, laboratory aids, control and management of and diet in infectious diseases. Although this method of approach obviates a good deal of repetition, it is open to question whether it is the most suitable method for students beginning the subject. Without doubt it has much to commend it in the case of more advanced students, such as hospital residents, D.P.H. students, general practitioners, or even medical officers of health and specialists in fevers.

The authors have included diseases which they consider likely to assume increasing importance under war conditions, e.g., tetanus, typhus, relapsing fever, infection by leptospira icterohæmorrhagiæ (Weil's disease). The last-named has assumed increased importance in the United Kingdom in civilian life during the past few years, and is now listed as an industrial disease under the Workmen's Compensation Act.

On page 38 we read: "Because it is not uncommon in *typhoid fever,* the syndrome associated with a severe toxæmia has been called the *typhoid state.*" This is scarcely correct; surely in this expression the word *typhoid* is used in its literal sense, namely, *"like typhus."* On page 300, in dealing with the differential diagnosis of cerebro-spinal fever, it is stated that in typhus the Wilson-Weil-Felix reaction is positive, but it is not pointed out that it is unlikely to be positive before the end of the first week. In the routine treatment of rubella we may well question the value of a saline purge. Latin inflexions are not always treated seriously; for example, we find morbill*us* bullosi, flagell*æ,* etc.

In spite of these minor criticisms, this book may be warmly recommended, especially to those already in the profession, as a most readable, up-to-date, and sufficiently detailed account of "Clinical Practice in Infectious Diseases." The authors are to be congratulated on such an achievement, and the publishers on the attractive way in which the volume has been produced—and at such a moderate price.

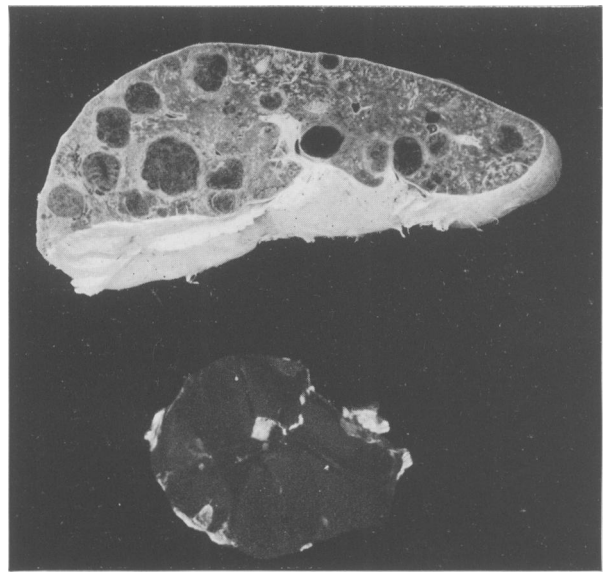

**Fig. 1.**
**To show the number and size of the metastatic deposits in the spleen. The lower organ is the left adrenal, which is almost completely replaced.**

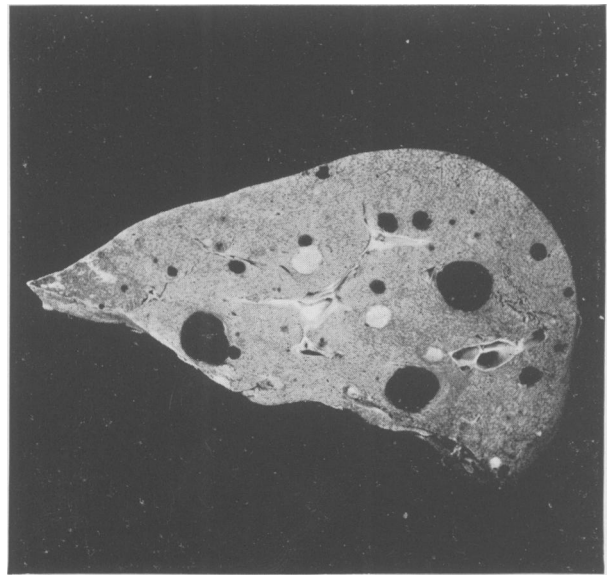

**Fig. 2.**
**To illustrate the involvement of the liver, and the development of both pigmented and non-pigmented nodules.**

*Photographs by Mr. D. McA. Mehaffey.*

Fig. 3.
To show the extensive cardiac involvement. Note the absence of any clinical signs of these lesions.

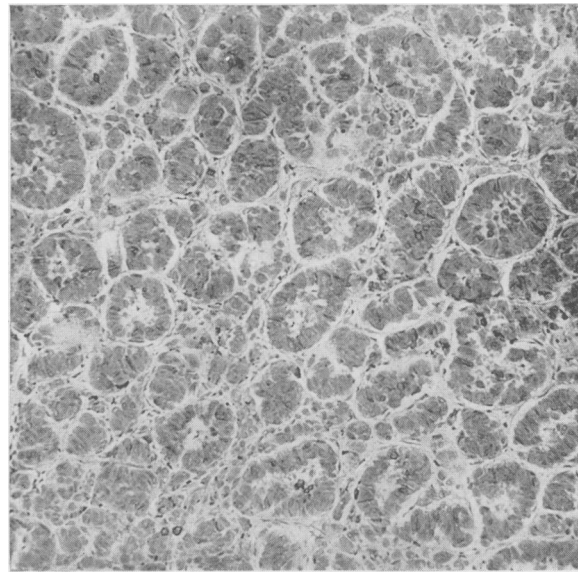

Fig. 4.
A pigmented deposit in the liver showing the epithelial characters of the neoplasm, and its marked tendency to produce pseudo-glandular structures.

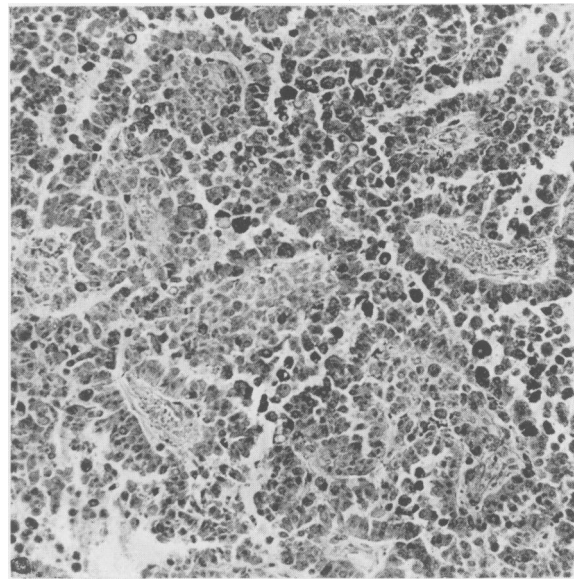

Fig. 5.

The cerebral metastasis, showing the perivascular arrangement of pigmented epithelial cells.

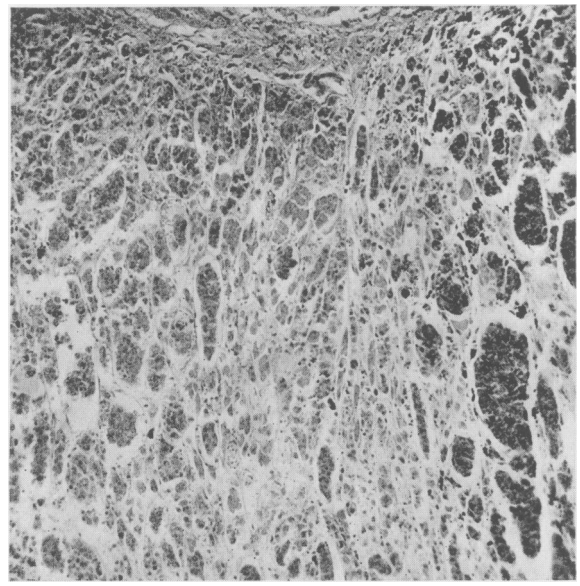

Fig. 6.

A section of the adrenal gland. A pigmented portion of the tumour is seen to the right. The tissue on the left is non-pigmented tumour, and only a few cells of the adrenal cortex survive in the centre of the field.

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## SURGERY OF THE HAND. By R. M. Handfield-Jones, M.C., M.S., F.R.C.S. E. & S. Livingstone, Edinburgh, 1940. Pp. 134, 95 Illustrations. Price 15s. Postage 6d.

THIS work is divided into three parts :—Infections, Injuries, and Other Surgical Lesions.

The first two parts contain detailed accounts of infections and injuries, the essential features of which are clearly shown in many beautiful X-ray plates and diagrams. In fact, much instruction is to be gained by a study of the illustrations alone. The author is to be congratulated on his excellent exposition of the general principles underlying the treatment of these conditions. The methods of treatment are clearly described, and the importance of operating on a hand rendered bloodless by sphygomanometric pressure and under general anæsthesia is stressed on several occasions in various parts of the book.

The chapter on restoration of function is among the best of many good chapters, and throughout there is the tendency, highly to be commended, to write in simple language and with practical detail devoid of unnecessary theory.

The third part of the book has been rather condensed, and, compared with the other sections, appears in the light of a synopsis of rare surgical conditions of the hand. It is to be hoped when a second edition of this work is published, that the third part will be rewritten more fully and with the same attention to detail which characterises the earlier chapters.

Mr. Handfield-Jones is to be congratulated on a book which should soon find its way into the libraries of all practising surgeons.

## DISEASES OF THE NERVOUS SYSTEM described for Practitioners and Students. By F. M. R. Walshe, O.B.E., M.D., D.Sc., F.R.C.P. 1940. Edinburgh : E. & S. Livingstone. Pp. 288. 12s. 6d. net.

THE author states in the preface to this book that he has "tried to deal only with what is possible in general practice in the matter of diagnostic methods and of treatment" and "to strip the subject of unnecessary complexities." For this reason the subject of ventriculography and encephalography is dismissed in a few lines; no account is given of the newer method of electro-encephalography; and many of the rarer diseases, e.g., progressive lenticular degeneration, are not considered.

The book consists of 288 pages and is divided into two parts. Part I contains 41 pages devoted to the general principles of neurological diagnosis, and gives no more anatomical and physiological detail than is considered necessary for diagnosis. The remainder of the book is given up to the more common diseases of the nervous system, and a brief but most useful chapter is included on the psychoneuroses.

Although several workers have reported that vitamin B was found present in normal amounts in the blood plasma in subacute combined degeneration of the cord, disseminated sclerosis, etc., many clinicians still resort to vitamin B therapy in these diseases. It is therefore interesting to note that Dr. Walshe does not even mention this vitamin in the treatment of either "subacute combined" or disseminated sclerosis; and in the case of multiple neuritis he states that "the time has not yet come for a just assessment of the value of this mode of treatment . . . and extravagant claims should be treated with the greatest reserve." Referring to the recent claim made for vitamin E in checking the progress of motor neurone disease, we are reminded that "this claim has not been confirmed, and should be accepted with the greatest reserve."

The author has certainly succeeded in providing the general practitioner with a clear, authoritative, well-balanced practical guide, which should do much to remove that lack of confidence on the part of many practitioners which often results in disinclination to carry out proper neurological examinations.

## SURGERY OF THE HAND. By R. M. Handfield-Jones, M.C., M.S., F.R.C.S. E. & S. Livingstone, Edinburgh, 1940. Pp. 134, 95 Illustrations. Price 15s. Postage 6d.

THIS work is divided into three parts :—Infections, Injuries, and Other Surgical Lesions.

The first two parts contain detailed accounts of infections and injuries, the essential features of which are clearly shown in many beautiful X-ray plates and diagrams. In fact, much instruction is to be gained by a study of the illustrations alone. The author is to be congratulated on his excellent exposition of the general principles underlying the treatment of these conditions. The methods of treatment are clearly described, and the importance of operating on a hand rendered bloodless by sphygomanometric pressure and under general anæsthesia is stressed on several occasions in various parts of the book.

The chapter on restoration of function is among the best of many good chapters, and throughout there is the tendency, highly to be commended, to write in simple language and with practical detail devoid of unnecessary theory.

The third part of the book has been rather condensed, and, compared with the other sections, appears in the light of a synopsis of rare surgical conditions of the hand. It is to be hoped when a second edition of this work is published, that the third part will be rewritten more fully and with the same attention to detail which characterises the earlier chapters.

Mr. Handfield-Jones is to be congratulated on a book which should soon find its way into the libraries of all practising surgeons.

## DISEASES OF THE NERVOUS SYSTEM described for Practitioners and Students. By F. M. R. Walshe, O.B.E., M.D., D.Sc., F.R.C.P. 1940. Edinburgh : E. & S. Livingstone. Pp. 288. 12s. 6d. net.

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# NEW PREPARATIONS

## SONERYL

THE demand for a Soneryl suppository of greater strength than the existing 3-grain product has led to the introduction of a new packing :—5 x 10-grain suppositories.

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Pharmaceutical Specialities (May & Baker) Limited, Dagenham, will be glad to send full details of Soneryl, on request, to any member of the medical profession.

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Soluseptasine, for parenteral administration, is the only colourless sulphonamide available in concentrated aqueous solution. It is widely used in conjunction with Proseptasine for the treatment of erysipelas, puerperal sepsis, and septicæmia.

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# THE ULSTER MEDICAL SOCIETY

## SESSION 1940-41

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LAST year, owing to the war, all activities of the Society were suspended, with the exception of a clinical meeting at the Royal Victoria Hospital. In this session, however, the Council have decided to restart the meetings. At first it was thought that through lack of material these meetings would probably be more infrequent than usual, but the presence of a large number of medical men in the armed forces in Northern Ireland has led to close co-operation between the Ulster Medical Society, the British Medical Association, and these medical services. The result has been that a combined programme has been arranged. This includes papers and clinical meetings. Several changes were made to facilitate a better attendance at meetings. The first was that meetings will be on Wednesday instead of Thursday. The second was that the times of meetings should alternate as far as possible—8 p.m. and 4.30 p.m. Thirdly, meetings will be held at least once per month, and if sufficient material is forthcoming, they will be more frequent.

The opening meeting was held on Wednesday, 9th October, at 8 p.m. In the absence through illness of Dr. McCloy, Sir Thomas Houston presided, and introduced the president for the year, Mr. T. S. S. Holmes, and invested him with the chain of office. Mr. Holmes thanked Sir Thomas Houston for his remarks and the Society for their honour in electing him their president. He then read the names of those who had passed away since the last presidential meeting, and the fellows and members and visitors stood as a token of respect.

Mr. Holmes then delivered a most interesting address on "The Incidence of Abortion in the Jubilee Hospital." He stressed the increase in this condition, saying that fifteen years ago four hundred cases had been admitted to this hospital, while last year the number had increased to one thousand. Mr. Holmes dealt with the causes—criminal, toxic, and pelvic. He emphasised the difficulties in preventing the criminal abortion; the duties of the Government in coping with bad diets and housing as a cause; and the treatment of the pelvic conditions predisposing to abortion.

A hearty vote of thanks was proposed by Professor C. G. Lowry and seconded by Professor W. J. Wilson. Mr. Holmes then suitably replied.

H. HILTON STEWART,

*Hon. Secretary.*

18 Malone Road, Belfast.