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JANUARY

1946

BRANCH OF THE INDIAN MEDICAL ASSOCIATION

Editor: D. SRINIVASAN, L.M.P.

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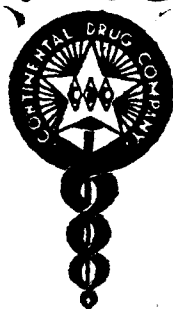


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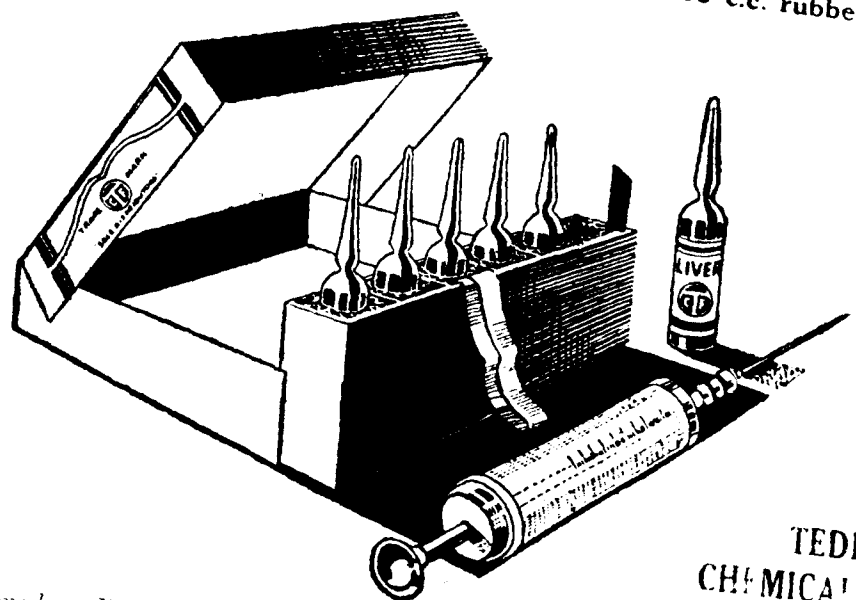
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OF THE

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BRANCH OF THE INDIAN MEDICAL ASSOCIATION (Regd.)

VOL. XIII]

JANUARY 1946

[No. 4

### PSEUDO-PARALYSIS DUE TO SCORBUTIC EPIPHYSITIS

By A. BRAMWELL COOK, M.B. (N.Z.), F.R.C.S. (Edin.)

F.R.A.C.S., M.R.C.P. (London).

The Salvation Army Emery Hospital, Anand.

THE term 'scurvy' brings to one's mind a picture of bleeding gums or purpuric patches on the skin. It is not sufficiently recognised that a state of pronounced vitamin C deficiency may occur without either of these manifestations.

A clinical condition very frequently met with in Gujarat is a 'pseudo-paralysis' of the legs due to scorbutic epiphysitis. The term pseudo-paralysis is used because in nearly every case the diagnosis of paralysis has already been made by the practitioner or parent.

The previous history is usually that the child has suffered from some infectious disease or debilitating malady such as typhoid, measles, dysentery or small-pox. After convalescence it is found that the child refuses to walk or even stand. The child is fretful, crying, loses weight and declines to eat. There may be slight fever.

In typical cases, the attitude of the child is characteristic and almost

pathognomonic, and bearing the condition in mind, one may 'spot' the diagnosis as soon as the parent presents the child for examination. Held up by the armpits, the child keeps its thighs and legs flexed up in mid-air. If an attempt is made to place the child on its feet, it refuses to bear its weight on its legs and withdraws its feet and flexes its legs more. If the legs are straightened, the child cries with pain. The legs are obviously not paralysed, but as the child refuses to walk or even stand, the impression of paralysis is often incorrectly gained by parents and even doctors. Frequently cases are seen, which have been treated as paralysis, rheumatism, tuberculosis or osteomyelitis for weeks or even months on end. The doctors have prescribed every vitamin except vitamin C, with the result that the child has drifted into chronic invalidism and the parents into disconsolate despair.

On being questioned, the parents invariably and emphatically reply that

the child never eats fruits. In most cases, the child seems to have an aversion to fruit and has always obstinately refused to eat any.

One week's treatment with vitamin C has the miraculous effect of converting an apparently hopelessly paralysed child into a practically normal child, able to stand and walk.

The gums are usually normal. In some cases, however, the usual scorbutic changes are seen in the gums, but the striking point is that they are more frequently normal than otherwise. In only 7 cases out of 30 were there scorbutic changes in the gums. The fact that an obvious case of vitamin C deficiency can show epiphysitis and not scorbutic gums is no more remarkable than that an advanced case of rickets can occur with all the usual skeletal deformities and yet have normally developed teeth.

Purpuric hæmorrhages in the skin were not seen in any case of this series. In adults, cases of scorbutic purpura are frequently met with, but none have been encountered in this series of children's cases of pseudo-paralysis. The skin is not hot nor changed in colour, and shows no inflammatory changes.

The knees at the joints are usually affected. They present a diffuse, rounded swollen appearance, tender to palpation and painful on passive movement, especially extension.

Not infrequently, however in cases presenting the characteristic flexed attitude of the knees and with the usual history of deficient intake of vitamin C, the knees appear externally quite normal. A skiagram will, even in such cases reveal that there is scorbutic epiphysitis (vide infra).

Occasionally only one knee joint is affected. The diagnosis is then more obscure. I have seen cases in which only the hip joints have been affected.

I have seen no case in which the upper extremity was affected.

Subperiosteal scorbutic hæmorrhages may occur. In one case, an extravasation of blood under the periosteum of the femur, in a bottle-fed baby of 11 months, led to an incorrect diagnosis of osteomyelitis. In one week with appropriate therapy, the swelling had dramatically subsided. Such an extravasation of blood may occur over the spine, in which case a diagnosis of tuberculosis of the spine may excruciatingly be arrived at.

Three classes of cases may thus be described:—

- (i) Epiphysitis with swollen joints, usually the knees.
- (ii) Epiphysitis complicated subperiosteal extravasation of blood. Such cases present considerable swelling and simulate acute osteomyelitis.
- (iii) Cases with normal appearance of knee joints. The parents complain that the child is always stumbling and falling and is unsteady on his feet. At times the child may even 'go off his feet' and refuse to walk at all. There is no pain in the knees and no swelling. A skiagram will show the changes described below.

#### DIAGNOSIS

(1) The characteristic attitude of the child can be considered of diagnostic value.

(2) Other signs of scurvy, e.g. purpuric spots, bleeding gums, may be looked for.

(3) The skiagram is diagnostic. A dense irregular band, obviously containing an excessive amount of calcium is seen at the end of the diaphysis. This is the provisional bone laid down by the epiphysis, and it is composed

of unorganised calcium phosphate. This appearance is diagnostic of scorbutic epiphysitis. This provisional bone is friable and often breaks, and there may be hæmorrhages in this area and microscopic fractures or dislocations of the epiphysis. The neighbouring zone is greatly decreased in density so that the bone may not be visible. The essential disturbance seems to be failure of the osteoblasts to convert provisional into true bone. The true bone of the shaft is rarefied, in striking contrast to the provisional bone. The shaft looks blurred—the so-called ground-glass appearance.

(4) Failure of the urine to decolorize dichlorophenol-indo-phenol after administration of ascorbic acid. In one child three tablets of ascorbic acid 50 mg. each and one injection of 'Redoxon' 50 mg. were given. The urine subsequently passed did not decolorize dichlorophenol-indo-phenol, indicating a marked deficiency of ascorbic acid.

(5) Improvement on vitamin C therapy, given orally and parenterally, will confirm the diagnosis.

#### Differential Diagnosis

(1) *Infantile paralysis*. Many cases are referred with this diagnosis and have had prolonged therapy with vitamin B, to no advantage. On careful scrutiny, it is obvious that the legs are not paralysed.

(2) *Tuberculosis*. The slightly expanded knee joint may suggest tuberculosis, but the bilateral nature of the condition should cause further reflection.

(3) *Acute rheumatism*. In scorbutic epiphysitis, the condition remains limited to the knee joints, whereas in acute rheumatism the condition shifts from joint to joint.

(4) *Acute osteomyelitis*. If there is an extensive subperiosteal extravasation of blood, acute osteomyelitis may

be thought of, but the leucocyte count will not be raised and the child's condition will not be so critical as in acute osteomyelitis.

(5) *Rickets*. In rickets, the bone ends are expanded at the joints, and the skiagram shows a cup-shaped epiphyseal cartilage, quite distinctive from the radiological appearances in scurvy.

The doctor's note, attached to one case, is given below in full, as it illustrates the common fallacies in diagnosis and treatment.

"The patient has been under the treatment of various doctors since the last 4 months for daily rise of temperature and pain in the lower extremities. Two months back he was referred to me for continuous fever. He had at that time enteric fever complicated with jaundice which condition cleared up in due course. In the meantime my attention was drawn to the localized swelling in the lumbo-sacral region which was tender and bearing relation to the pain in the lower extremities. The relatives are convinced that the spine is affected and the patient is sent for radiogram. He is having Adol drops and osteo-calcium tablets and a mixture containing calcium, iron and bitter tonic. He is advised plaster of paris jacket."

As the child was presented to me by the parents, the diagnosis was obvious. Both knees were flexed acutely in the mid-air and the child screamed as I tried to straighten the legs. The lumbo-sacral swelling was a scorbutic hæmorrhage tender to touch. The gums were bleeding. This point had been overlooked by the doctor. When I questioned the parents as to the child's diet, they admitted that the child obstinately refused to take any fruit at all. The white cell count was normal.

#### Treatment

Ascorbic acid is given in large doses, orally and parenterally.

Local treatment is unnecessary, but frequently lead lotion, belladonna and glycerine are prescribed.

As auxiliary treatment, cod-liver oil and ultra-violet light are given.

Fruit is insisted on as a part of the diet.

**Prognosis.** With the correct diagnosis in mind, it is most gratifying to be able to reassure the parents and predict that, with the proper treatment, the child will be showing distinct improvement within a week.

Cases relapse if correct diet is not given subsequently. Some cases relapse each year.

## DRUG ALLERGY

**A**LLERGY has been defined as a condition of specific reactivity, with characteristic symptoms to the administration of a substance in a quantity which to the majority of persons would be harmless. In other words, allergy is a pathologically altered reaction-capacity of an individual to a particular antigen or allergen. The word "drug" refers to any substance which is used as a medicament. Drug "idiosyncrasy" had been observed and described long before the words "anaphylaxis" and "allergy" were coined. Even after allergy was defined, there was much doubt as to drug idiosyncrasy's being in reality drug allergy. It was known that *proteins* could incite a state of hypersensitivity, but it did not seem possible that drugs of relatively simple molecular weight would be able to exert antigenic activity. Landsteiner produced evidence that simple substances can combine with proteins and thus be converted into antigens. Sulzberger showed that complex molecules are not always necessary and that simple substances can, by themselves, produce allergic reactions in sensitive tissues without the necessity of coupling with larger molecules.

The allergic reaction arising from administration of a drug is not, as a rule, similar to the therapeutic or the toxicologic effect expected from that drug. The symptoms of drug allergy

may be fever, granulocytopenia, rhinopathy, asthma, and a variety of eruptions. In order to distinguish allergic reactions from the therapeutic and toxic effects of drugs, Sulzberger gives the following characteristics of eruptions caused by drug allergy:

"1. Even very minute amounts of a drug which has been well tolerated for weeks, months, or years may suddenly produce severe eruptions.

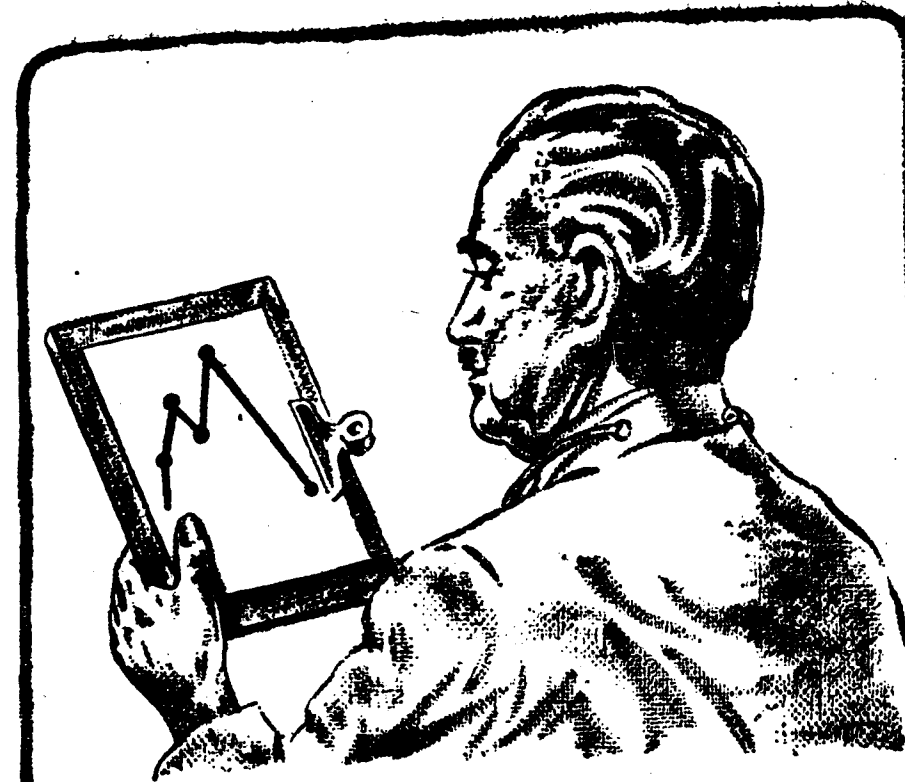
"2. Once such an eruption has occurred, it is likely to recur upon subsequent minute exposures to the offending drug or to a related drug.

"3. As a rule, the cutaneous response is entirely different from that produced by the pharmacologic or toxicologic action of the drug.

"4. Drugs with entirely different pharmacologic actions often produce identical eruptions; and the same drug is often capable of producing radically different manifestations in different individuals - or in the same individual at different times.

"5. The amounts required to elicit eruptions are often much smaller than those necessary to produce pharmacologic or toxicologic effects.

"6. Many drug eruptions occur only in certain predisposed individuals and, regardless of the deliberate increase in dosage, can never be made to appear in the majority of individuals.



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"7. The role of cumulative effects can usually be ruled out. As a general rule, drug eruptions can recur upon re-exposure to small amounts, even years after the last previous exposure... and even when the last demonstrable vestiges of the previously administered drug have been eliminated.

"8. The marked specificity of drug sensitivity can often be demonstrated. Individuals sensitive to one drug are frequently found to show no demonstrable sensitivity to isomers of that drug or to drugs with only slightly altered chemical constitution. But, just as has been demonstrated in sensitivity to living allergens, with drugs also, group specificity and cross reactions may be demonstrable.

"9. The usual form and the general phenomena found in other proven allergic... responses have their exact replicas in many recognized drug eruptions...

"10. It has been shown experimentally that many of the substances producing drug eruptions are capable of sensitizing the skins of human beings and laboratory animals..."

Sulzberger noted that cascara sagrada had never to his knowledge produced a drug eruption, while, at the other extreme, a drug called nirvanol produced drug eruptions in almost 100 per cent. of cases. Between these two extremes, all other drugs could theoretically be graded in terms of the percentage of persons capable of becoming hypersensitive to them.

Abramowitz stated that there are now about 350,000 organic drugs and a few thousand inorganic chemicals used as medicines, and that any drug of therapeutic value probably can produce an eruption or other undesirable effect in some individual with an idiosyncrasy to that particular agent. Yet in spite of the fact that drugs in millions of prescriptions are dispensed yearly, not to mention those used as household remedies, the incidence of

drug eruptions following oral or parenteral use is surprisingly low. Such eruptions are not mentioned among the ten ranking skin diseases, and presumably they are not nearly so frequent as eruptions produced by foods. It might be added that if a given drug is used widely, there will be more reports of allergy to it than if it were used less often.

Leftwich reported an intradermal test for the recognition of hypersensitivity to the sulfonamide drugs. Serum was used which was obtained from patients who were receiving a sulfonamide and whose serum contained 2 to 25 mg. per cent. of the drug. Positive skin tests were obtained in individuals known to be sensitive to the sulfonamides. The author suggested that the sensitizing antigen may be a sulfonamide-plasma-protein combination which occurs in vivo in the circulating blood of patients receiving the drug, the sulfonamide perhaps acting as a haptén.

#### Drug Fever

Fever is probably the most frequent symptom of drug allergy. Urbach observed the interesting fact that allergy to antipyretics can result in fever. There is a considerable resemblance between serum sickness and the fever following drugs of relatively simple composition. Vaughan stated that fever may occur with or without eruption in quinine, iodine, and mercury allergy. The temperature may be as high as 104° to 106° F.

Lyons and Balberor investigated febrile reactions accompanying the administration and re-administration of sulfathiazole. In a series of 200 consecutive hospital cases in which a single course of sulfathiazole was administered, drug fever developed in five, all after the seventh day of treatment. When sulfathiazole was administered for a period of two to eighteen days and then re-administered as a second course after an interval of two to

twenty days, febrile reactions were more frequent and developed shortly after the beginning of the second course. In appropriate cases it was possible to give intermittent courses in such a way as to produce a high degree of hypersensitivity; thus, very small doses of the drug might elicit a febrile response. (In the majority of persons it is apparently impossible to develop allergic hypersensitivity.) Lyons and Balberor observed that if a person who is sensitized to sulfathiazole is given 4 gm. of this drug in the form of a succession of small doses, the febrile response is less severe than if the whole 4 gm. were given at once.

Talbot and Adcock observed febrile reactions to sulfadiazine both in the initial and second courses. Those occurring with re-administration of the drug were frequently accompanied by delirium, chills, and a maculopapular rash.

Green Steckel, and Michener disagreed with reports concerning the re-administration of sulfathiazole, for the side-effects occurred with practically the same frequency and severity as those following the initial administration of the drug.

#### Urticaria: Angioneurotic Edema

Urticaria seems to appear most frequently about the lips, ears, eyelids, and cheeks. Among the drugs which may cause urticaria or angioneurotic edema are: salicylates, phenobarbital, belladonna, iodides, bromides, opium, morphine, phenolphthalein, atropine, aminopyrine, acetophenetidin, arsenicals, cinchophen, dinitrophenol, and a number of others.

#### Eczematous Eruptions

All cases of "eczema" are by no means due to allergy, much less to drug allergy. Nevertheless, eczematous eruptions due to drug hypersensitivity do appear, and patients with this condition should be questioned among other

things about medicaments that are being used. Drugs which have been known to give rise to eczema include: the arsphenamines, ephedrine, mercury, quinine, procaine, formalin and chloral.

#### Erythematous Eruptions

Morbilliform and scarlatiniform erythemas and the dreaded exfoliative dermatitis have been known to follow the use of arsenic, the arsphenamines, the sulfonamides, and belladonna. Other drugs which may cause the condition include aminopyrine, acetophenetidin, acetylsalicylic acid, cinchophen, digitalis, dinitrophenol, ephedrine, emetine, iodides, opium, phenobarbital, quinine, balsams, and various heavy metals.

Erythema-multiforme-like eruptions can result from hypersensitivity to antipyrine, aminopyrine, acetophenetidin, salicylates, sulfonamides, iodides, phenolphthalein, gold, and barbiturates. The self-limited eruption called erythema-multiforme may be the exanthem of a specific infection. Similar eruptions can arise from food allergy.

#### Eruptions Similar to Erythema Nodosum

Urbach described erythema nodosum as a morphologic rather than an etiological entity, which takes the form of painful reddish-purple subcutaneous nodules, usually along the tibia, but occasionally on the extensor and flexor surfaces of the thigh. The disorder may be produced by a number of different agents, including streptococci, tubercle bacilli, fungi, and drugs. The nodules may actually contain bacteria or fungi; in other instances, they are the reaction of a high allergic skin and are to be regarded as the "id" phenomenon. Drugs which are thought capable of causing this condition are iodides, bromides, and salicylates.

#### Pemphigoid Eruptions

Kasselberg described a pemphigus-like reaction which appeared after a

patient had taken only 4 gm. of sulfamerazine over a period of forty-eight hours. Approximately a year previously, the patient had had purulent otitis media which had been treated successfully with sulfathiazole without reaction. The maculopapular eruption involved the entire body; there were many blebs in the nasopharynx; the conjunctiva was edematous and injected.

#### Purpuric Eruptions

Not all purpuric eruptions are a manifestation of allergy, but doubtless some of them are. They may be caused by such drugs as: arsphenamines, iodides, and barbiturates, also acetylsalicylic acid, balsams, ephedrine, mercury, quinine, and the sulfonamides.

#### Fixed Drug Eruptions

Brunsting described the "fixed drug eruption" as being due to focal sensitization of the vascular network underlying a circumscribed site in the skin. On occasions when the offending drug is brought by the circulation to this particular region, a characteristic local flare results, with spreading erythema, edema, pruritus, and finally pigmentation. Bullae may form.

Attention was called by Abramowitz to the fact that the word "fixed" does not indicate that the eruption is permanent or lasting, but that the reaction site is fixed. He named a long list of drugs that have caused fixed eruptions. They include acetanilid, acriflavine, aminopyrine, antimony and potassium tartrate, antipyrine, arsenicals, barbiturates, bismuth salts, cinchophen, eucalyptus oil, iodides, magnesia magna, mercury, phenolphthalein, quinine, salicylates, and the sulfonamides. Fixed eruptions can also be produced by vaccines, alcoholic liquors, foods, karaya gum, auto-toxins, menstrual disturbances, physical exertion, and psychic distress.

Sams and Capland reported on fifty-three patients with various cutane-

ous infections, chiefly impetigo and ecthyma, which had been successfully treated by local application of sulfathiazole powder and sulfathiazole ointment with no detrimental local or systemic effect. Subsequently, they encountered a patient who was treated by insufflation of sulfathiazole powder into the external auditory canals. After an interval, sulfathiazole was again applied locally to one ear, and a dermatitis resulted in the ear. Six weeks later a dose of 15 grains of sulfathiazole was given by mouth, and four hours later edema of the ears was noted. This was followed by acute dermatitis of the face and ears and subsequently by generalized erythematous macular eruption. Patch tests for sulfathiazole had been negative.

Of 1,000 patients treated with sulfonamide compounds applied locally, Livingood and Pillsbury described twelve in whom a sensitivity to sulfathiazole was apparently induced by local application of it to diseased skin, and in whom evidence of sensitivity appeared when the drug was later administered by mouth. They concluded that local sulfathiazole therapy is highly effective when properly applied in frank, superficial pyodermas; but they considered that such therapy should not be employed for prolonged periods (more than five days), since the danger of sensitization is apparently increased thereby. If improvement occurs with local sulfonamide therapy, it does so in a relatively short period of time, and prolonged local application is neither advisable nor necessary.

#### "Idiopathic" Pruritus

Itching is a characteristic of many eruptions due to drug or food allergy. It is thought that pruritus without eruption may in some instances be a manifestation of allergy. This may be the cause of some cases of idiopathic pruritus ani or vulvae. Drugs thought capable of causing this are aminopyrine, acetylsalicylic acid, phenobarbital,

morphine, codeine, belladonna and the sulfonamides.

#### Respiratory Tract Symptoms

Drug allergy may produce asthma. This condition has followed administration of ipecac, quinine, hyoscyamus, and acetylsalicylic acid. Thomas reported an attack of bronchial asthma following the inhalation of powdered neoarsphenamine.

Rhinopathy may result from administration of acetylsalicylic acid, iodides, or quinine.

#### Granulocytopenia

The condition called "agranulocytosis" was first described in 1922, and thereafter efforts were made to discover the agent which caused the reduction in granular white blood cells. In 1934, Madison and Squier incriminated aminopyrine as a frequent cause of agranulocytosis and said: "We believe that the appearance of primary granulocytopenia following the use of such drugs may be the result of an allergic or anaphylactoid drug reaction." In 1936, Dameshek and Colmes investigated eight recovered cases of agranulocytosis. One of these reacted within ninety minutes to the oral administration of 10 grains of aminopyrine with clinical and hematological manifesta-

tions of agranulocytosis. Two of three such patients developed features of agranulocytosis shortly after the intradermal administration of aminopyrine in amounts not in excess of 1/6 grain.

While aminopyrine may have been incriminated most often as a cause of granulocytopenia other drugs, such as dinitrophenol and the sulfonamides, are capable of producing this effect.

#### Diagnosis of Drug Allergy

It would appear that the number of cases of drug allergy is small when compared with the number of patients being treated with drugs capable of producing allergy. It seems evident, too, that certain individuals are quite incapable of becoming allergic to certain drugs. However, in the present state of knowledge, drug allergy is unpredictable. When it does occur, the symptoms may be very puzzling until their cause is realized. It is desirable that drug allergy be identified promptly in order that the use of the drug by that patient may be discontinued promptly and permanently. There is a need for tests which would detect sensitivity to a drug before its use is begun and for methods of desensitization in case the pharmacologic effects of a drug are urgently required by a sensitized patient.

*Adapted from Physician's Bulletin Dec. 1944.*

## MENSTRUATION AND ITS DISORDERS

### Functional Uterine Bleeding—Treatment

A PREVIOUS article (*Physician's Bulletin*, 9: 102 [July-August, 1944]) discussed the causes and physiology of functional uterine bleeding. This article is concerned with therapy.

Obviously, sound treatment of any condition must have two foundations: (a) accurate diagnosis and (b) thorough understanding of the underlying patho-

logic physiology. With regard to functional uterine bleeding, it seems clear that diagnosis is always somewhat tentative because of (1) the hazy border line between pathologic bleeding and the outer limits of normal endometrial bleeding of various kinds, and (2) the difficulty of absolute exclusion of anatomical causes of abnormal bleeding. As to pathologic physiology, four points

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seem worthy of note: (1) The most common immediate cause is relative estrogen excess; (2) the nervous system may affect the coiled arteries without involving the endocrine mechanism (but details are lacking); (3) the thyroid may possibly affect the coiled arteries directly (tentative); and (4) other factors at present unknown may operate in many cases.

If blood loss from the uterus is so great as to require its prompt cessation, two methods are available: curettage or the administration of large doses of estrogen. The latter is usually so effective that the former is now seldom needed. Of the estrogens, diethylstilbestrol is perhaps most commonly used because of its potency and its prompt effectiveness on oral administration. While larger quantities have been given by some, most investigators have found oral doses of 5 mg. at intervals of four to six hours to be effective within a period of hours, seldom more than twenty-four. Smaller doses apparently act more slowly.

### Administration of Estrogen

*In view of the observation that excess estrogen can lead to uterine bleeding, it is not clear why the administration of estrogen will check bleeding.* Such, however, is the case. After cessation of estrogen therapy, withdrawal bleeding may occur, especially after the larger doses. This ordinarily resembles a normal menstrual period and need not alarm the patient if she is told beforehand to expect it.

### Vitamin B Complex

If severe bleeding has been controlled or has not occurred, the only present rational approach to the underlying disturbance must be directed toward correction of the hormonal imbalance or alleviation of the nervous and emotional condition, or both. The possibility of blood dyscrasia and of hypothyroidism must always be considered.

Signs of deficiency of the vitamin B complex should also be searched for. Comprehensive discussion of B-complex deficiency will be found in *Medical Clinics of North America* for March, 1943, in a series of articles edited by Tom D. Spies. Diagnostic criteria occurring in the mouth are described and discussed in the *Physician's Bulletin* 8: 70, 1943. If B-complex deficiency can be established or is suspected, a therapeutic trial is worth while. The Biskinds have found large doses necessary, equivalent to about three Pulvules 'Becotin' (Vitamin B Complex, Lilly) daily by mouth. Parenteral therapy was often used in addition, in the equivalent of up to two Ampoules 'Betalin Complex' (Vitamin B Complex, Lilly) every two or three days. The necessary duration of treatment has not yet been determined. Some patients receiving both oral and parenteral therapy have relapsed when the injections were discontinued; others have been maintained on oral treatment alone. In perhaps the majority of cases large doses had to be continued indefinitely, regardless of route of administration. Small doses will usually be completely ineffective.

In those cases where relative estrogen excess is due to disturbance in the function and relationship of the ovaries and pituitary, a number of considerations must be weighed. Many cases of this type will sooner or later readjust themselves without treatment, especially in adolescents. Therapy may not be necessary unless (1) blood loss is sufficiently large to cause anemia or undue strain on hematopoiesis; (2) the patient or her family is excessively worried or inconvenienced by the situation; or (3) the condition seems to impair a desired fertility.

### Radiation

In choosing among the various types of therapy, one must consider the patient's age and the importance of preserving ovarian function. In the

premenopausal group, when further pregnancies are not desired, Novak reports uniformly and permanently satisfactory results from abolishing ovarian function by radiation therapy. As he points out, it is essential to be certain the bleeding is actually functional, and this requires diagnostic curettage with microscopic examination, in addition to careful and complete pelvic examination. The dose of radiation should be sufficient to assure permanent cessation of ovarian function. Estrogenic therapy may be necessary subsequently to control menopausal symptoms.

### Progestin

In the younger patients it is especially important to insist on an adequate intake of calories, and vitamins and to curtail the excessive physical and emotional stress so common in this age group. Often these measures alone will be followed by return of the menstrual function to normal limits. If more specific therapy seems indicated, it should be limited to those agents which do not permanently impair ovarian function. The administration of progestin would appear the most logical method of restoring the hormonal balance, at least locally, but it has not proved a panacea. Allen and Heckel and others have reported satisfactory results in 50 per cent. or more of patients from the administration of total quantities of at least 30 mg. progestin or much larger amounts of pregnenolone subdivided into four to eight daily doses. Withdrawal bleeding was frequent following the series of injections, but in most cases all bleeding stopped within ten days. In those patients with regular but excessive bleeding, it would seem well to start the treatment at the end of three weeks following the onset of the last previous flow. In about one-third of the cases of Allen and Heckel, normal cycles occurred for four months or more after treatment; in another third, there was recurrence of

abnormal bleeding in less than four months; and in the final third, amenorrhea followed, either immediately or after two or three cycles. No explanation is suggested for this amenorrhea.

At least an equal degree of ultimate success has been achieved by the use of estrogens. When such agents are given as previously outlined for the immediate control of uterine bleeding, the quantity is sufficient to stop temporarily the pituitary output of gonadotropin and thus indirectly check ovarian function. However, the immediate effect of these large doses on bleeding is much too prompt to be due to alteration of pituitary and ovarian activity and must be related directly to the rapid rise in estrogen supply to the endometrial arterioles. In the course of several days, however, pituitary and ovarian function does come to a temporary halt, and especially where smaller doses of estrogen are used, as by Hamblen and co-workers, it is probably the alteration in endocrine function that is responsible for the subsequent return of menstruation to normal.

### Diethylstilbestrol

In the absence of emergency, and when the flow, although excessive, has some degree of regularity. Palmer prefers the following schedule, to be started on the third day of bleeding.

- 1 mg. diethylstilbestrol daily for seven days then
- 5 mg. diethylstilbestrol daily for seven days then
- 0.3 mg. diethylstilbestrol daily for ten days or until bleeding recurs.

In most cases only one such course has been necessary.

Hamblen and co-workers have suggested cyclic therapy with both estrogen and progestin, but the practical advantages of the combined therapy are not clear.

Other agents than estrogen and progestin have been used, including androgens, chorionic gonadotropin, and small doses of x-ray. It seems likely that their mode of action is to stop ovarian function temporarily. A direct action on the endometrium may also occur with androgens. None of these agents, however, appears to have an advantage over estrogen. With androgens, excessive dosage must be avoided because of the possibility of masculinization. Chorionic gonadotropin seems to be contra-indicated when it is desired

to preserve ovarian function, for there is evidence of rather prolonged depression of ovarian function following its use. Ovarian response to x-ray is notably variable, and it is generally thought that radiation therapy should be used in younger women only in otherwise intractable cases.

Many other agents have been advocated in times past, but present evidence suggests that they are less effective than those discussed.

*Adapted from Physician's Bulletin Oct. 1944.*

## SEDATIVES

### An Optimist

A SCRIPT was submitted to a producer. The movie boss took one quick look at the title and handed it back to the author with a sorrowful smile.

The author of the story was puzzled. He hadn't been in Hollywood very long. "But you didn't read it," he said.

The big boss was impatient. "The phooey. You call it. 'THE MIST!'" Me and you know what means, sure, sure, but how many of thick skulls out in front will that it's an eye doctor?"

—*St. Louis Soc. Co. M. Soc. Bull.*

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—*Bull, Sagamon Co. M. Soc.*

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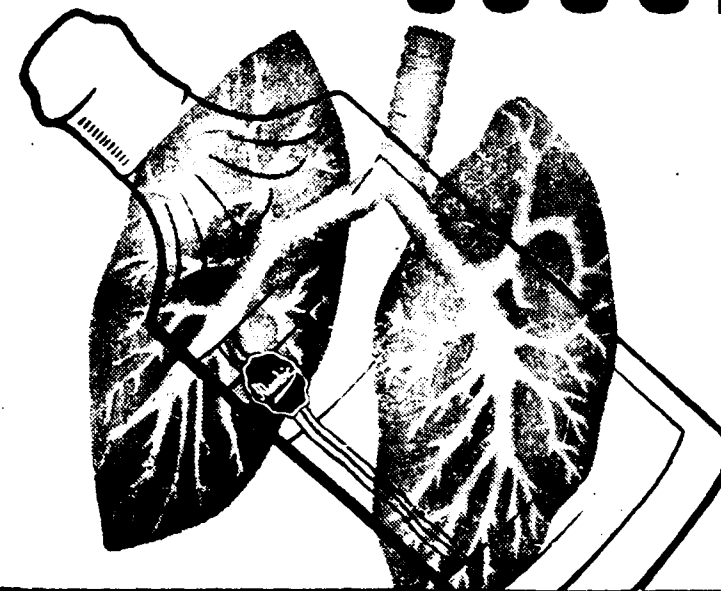
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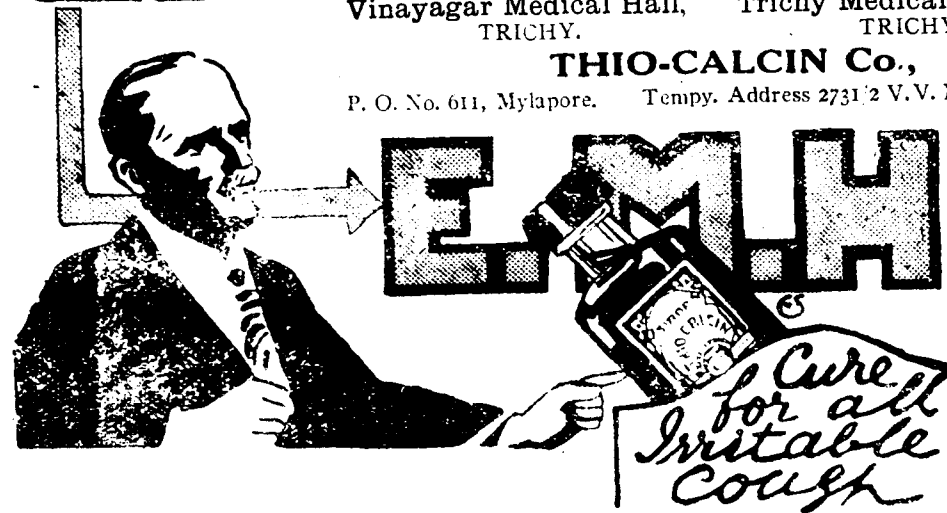
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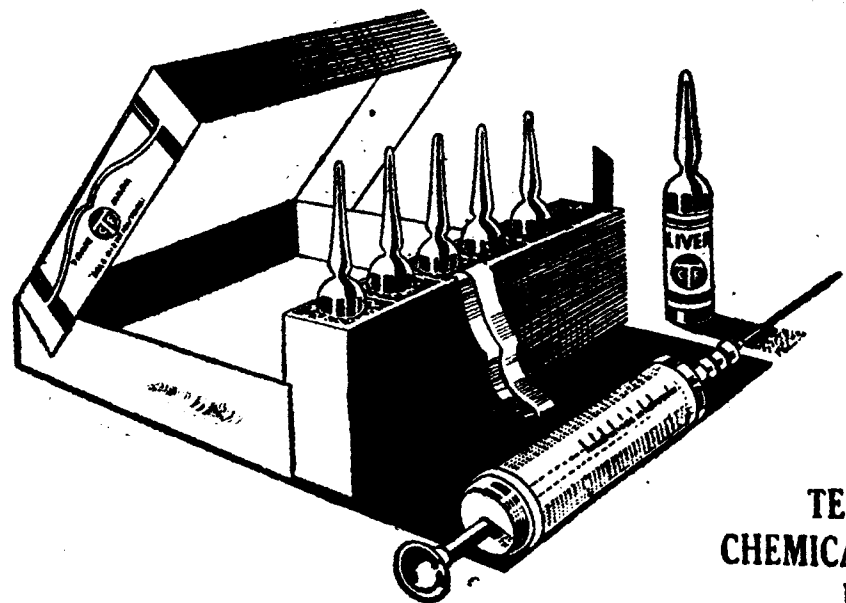
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BRANCH OF THE INDIAN MEDICAL ASSOCIATION (Regd.)

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[No. 5

## MARCH OF SCIENCE IN WAR TIME

(The Role of Scientists in Planning and Development)

SIR S. S. BHATNAGAR,

Director, Scientific and Industrial Research, New Delhi.

IT will take some time before all that science has accomplished during the war gets known to the public. There are, however, several inventions and discoveries which are of such outstanding importance to society as a whole, apart from their use in war, that they have already come before the public eye even during war time.

Perhaps the most fascinating invention of the war is the application of radio to the location of enemy planes and submarines. This great triumph of British enterprise and American production methods popularly known as radio-location of Radar enabled British to put up a magnificent resistance to the onslaught by German aeroplanes and pilotless planes in the period of the blitz and later. It is rightly acclaimed that the credit of winning the Battle of Britain should go to the scientists who perfected and operated the Radar.

It is an interesting coincidence that at the time when the British scientific men were active in developing large scale use of the Radar, the I. C. I. and their scientists were engaged on pro-

ducing an extraordinary plastic material which is now well known as 'polythene.' Polythene is a polymer of ethylene and is composed of a large number of ethylene units, five hundred or more, chemically linked together under the influence of extremely high pressure, some heat and a catalyst. This product has outstanding electrical properties, great toughness and flexibility coupled with lightness and extreme water resistance. It has found immediate uses in telephone, telegraph and submarine cables and more especially in high frequency electric circuits. But for this discovery the large scale use of Radar for aeroplane detection which is rightly acclaimed as having saved Britain during the worst days of the war, could not have been developed so successfully.

Another plastic material which bids for supremacy and which is also a war baby is popularly known as 'Silicone.' This resin is obtained by the replacement of certain carbon atoms by those of the element silicon in compounds usually employed in the laboratory for polymer formation. The element silicon

most abundantly occurs in combination with oxygen as sand. The plastic "Silicone" is used chiefly as an insulating varnish and bids fair to revolutionise the electrical industry. Merely treating the surface of cotton, paper or glass with it, leaves a water repellant film which can withstand washing, dry cleaning and considerable abrasion. Ceramic insulators treated with this varnish are used in aircraft radios as they are not made conducting by the deposition of moisture on them. Silicone oils stay fluids even at very low temperature and are still usable up to 400 to 500° Fahrenheit. Again, made into rubber like materials, silicones are proving valuable as in super-chargers and searchlights, where their heat resistance enables them to perform heavy duty under which other materials break down.

#### Powerful Insecticide

The Japanese war particularly in the tropical jungles created a demand for a powerful insecticide to protect the troops against the mosquito and the lice. This led to the production on a large scale of the famous product DDT and some other products of a similar nature such as Gammexane and Phenoxetol. The discovery of DDT is an interesting story of the fruitful combination of fundamental knowledge of dyestuff chemistry and the new research techniques in the biological laboratories. The first full scale application of DDT in a war section was reported in 1943 when in Naples a whole population of a million and a quarter people were threatened destruction by the typhus epidemic. A dusting powder containing ten per cent. DDT was successfully employed against the louse and the epidemic was brought under control within three weeks. Shirts impregnated with DDT are now issued to the army in Europe which protect the wearer against lice for at least two months even after three or four launderings. The successful fight against the mos-

quito is an epic of achievement. DDT is already used in conjunction with pyrethrum in anti-mosquito sprays.

Another method of fighting the mosquito is by the use of DDT in paraffin oils on the stagnant waters and marshes which are the usual breeding grounds. In combination with coumarin resins DDT has proved a potent flykiller and its further uses in paints and varnishes are likely to be on the increase.

In the Hunter Memorial Lecture, Dr. R. Slade, the I.C.I. Research Controller, described on March 8th, 1945 a new insecticide which has been named Gammexane. This new insecticide which is expected to be even more potent than DDT is one of the isomers of benzene hexachloride, a compound made by the additive chlorination of benzene in the presence of light. Gammexane or 666 as it is popularly called has already captured the imagination of scientific workers and one expects great benefits to the tropical countries by the large scale production of this material.

Mention must be made here of the outstanding discovery of the anti-bacterial action of certain moulds which has culminated in the production of the wonder drug penicillin. The drug has effected miraculous cures in cases of blood poisoning and pneumonia and all sorts of staphylococci infections. Penicillin is unique among anti-bacterial substances as it is more or less free from any toxic effects. Its large scale production, following its discovery by Fleming and Florey in England, has been mostly in America and is a real triumph of biological and chemical research.

#### More Potent Drugs

In the category of promising anti-bacterials may be mentioned the work on phenoxetol conducted by the Department of Pharmaceutics at the College of the Pharmaceutical Society of Great

Britain. This substance is the monophenyl ether of phenoxy ethyl alcohol. In bacteriostatic and bactericidal tests, it was found to be weakest against staphylococci, better against streptococci and strongest against psudomana, pyocynania a gram-negative organism which is the cause of blue pus in wounds. This organism is unaffected even by penicillin and resists the action of sulphonamides, the acridine compounds and the quarternary ammonium compounds. Phenoxetol has yielded excellent clinical results as an ingredient of penicillin cream. Recent announcements show that another product synthidine has been found to be even better than penicillin and one hopes to hear of still more potent drugs in the field.

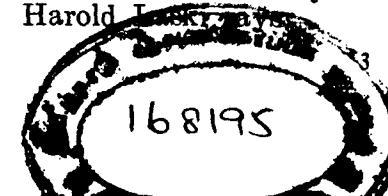
No scientist worth his name will boast of the numerous weapons of destruction which have been invented during the war. If one does mention them as achievements, it is because of the great potentialities they have in being able to promote better standards of living in the future and of their obvious usefulness in the more peaceful occupations of the human kind. It is quite possible that pilotless planes may be used in peace time for quick transport purposes. It is possible that the element of danger involved in such a method of transport may one day be even less than in conveyances piloted by erring human beings. The V 2 may perhaps be harnessed for new scientific conquests on this earth and even on planets. Poisons of most virulent types may help in destroying insect pests and wild beasts and help us forward towards better agriculture and better forestry. The new metal alloys of beryllium, magnesium and aluminium have already provided ways and means of reducing weight of machinery and vehicles and increase the facilities of transport. We were at no time in the world's history nearer success in utilising the energy of the atom than

at this time and when the results of these achievements are made known, they will revolutionise methods of storing and using new sources of energy.

#### New Outlook

Great as the achievements of science are in the fields described above and in such other fields as operational research, new building technique, and new methods of housing, transport and preservation of food, there is no doubt that the greatest achievement of science during the war which will be remembered by posterity is the creation of an entirely new outlook on science by society. The scientist is now definitely acknowledged as a man who seeks to organise the relations between nature and his fellow human beings and to give them power to control nature. In order to achieve this, co-ordination of all sciences has to be attempted on the largest possible scale. The men of science in the future must necessarily understand to control public affairs. At the same time the ordinary citizen and the civil servants must be given an insight into scientific matters. Just as State activities such as post-office, railways and trade and industry must be organised, so must science be organised. There must be a flow of ideas and products in a continuous manner as without such a process the present civilisation which is essentially based on applied science will become rapidly out-of-date, antiquated and inefficient. Such an organisation of science does not contemplate the idea of research made-to-order but a genuine attempt by the State and the people to give science a chance.

No planning and development by any Government of the world will henceforth be undertaken without the fullest consultation and active participation of the scientist. The understanding of Science must be the spinal column of our educational system. Professor Harold I. ...



"We must shape the minds of the post war generations in such a way that administration, at the highest level, can be undertaken by men with a knowledge of scientific methods, instead of treating such men, in the Civil Service, as clerks with special qualifications. Many of our great scientists could hold their own with the best of the Permanent Secretaries of the Treasury."

Whether the scientist likes it or not, he will be called upon to play an important part in the administration of a civilisation which is based on applied sciences.

Perhaps the most outstanding example of the position of science in society is given in a report submitted by Professor P. Kapitza the celebrated Russian Physicist to the U. S. S. R. Academy of Sciences. The following significant sentence occurs in this report:

"In our socialist country science occupies a special place. Of course it is well known and commonly accepted in the other countries too, that science plays a great role in the development of the culture and technology of the country. But in our country science is recognised as one of the essential mainstays of the development of culture and is accorded a leading position in the development of our technology and national economy. For this reason the organisation of science in our country must have a more purposeful character than that to be found in other countries where it is rather accidental and spontaneous. The connection between

science and life must be close and more complete."

That this idea has caught like wild fire is evident from the fact that even a country like the U. S. A. firmly entrenched in the belief that private enterprise is best for applied science and industry, created an office of Science and Research Development under the State during the War and its activities in a slightly modified form will continue after the war. England, her dominions, and India have created departments or offices for scientific and industrial research in close conjunction with plans for post-war reconstruction. These activities will continue to be on the up-grade until Science finds its rightful place in the nation building activities of the State in all its phases.

A. R. Oplin of the U. S. A. have recently made the statement:

"During the war many physicists are learning for the first time that there is as much thrill and satisfaction in applying physical truths as in discovering them."

Some of us in this country who have obtained their initiation in applied research during the present war have had similar experiences. The interesting thing is that even the hard boiled industrialists are now beginning to realise the value of pure research. This happy collaboration between pure and applied research is indeed another great achievement which will have far reaching effects on human progress.

*Adapted from Calcutta Medical Journal, Dec. '45.*



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## THE VALUE OF EARLY CLOSURE OF WOUNDS

EARLY closure of wounds is not a new treatment; it has been practised at various times during the last fifty years. Each time it has been discarded as a dangerous form of treatment. However, the great advantage of the treatment has been missed: if a wound can be closed successfully at an early date, return to functions, and, in many cases, return to full functions, will be assured in minimum time.

Burns and Young point out in their paper on the treatment of femur by closed methods (*Lancet*, 1945 (i), 236):

"In the 'Medical History of the War' Sir Anthony Bowlby quotes details of a series of 211 compound fractures of the femur treated by delayed primary suture, 161 being successful. He observes that the results were greatly improved in proportion as the practice of delayed primary suture increased. Closure diminishes the risk of all kinds of complications and gives rise to much more rapid union. In 1919 Pearson and Drummond were impressed with the importance of obtaining knee movements from the start."

These notes were written on experiences obtained during the last war, before the days of sulphanilamide and before Fleming had discovered the *penicillium notatum*. Such treatment could only be carried out under the most careful supervision because of the possibility of flaring-up of infection in soft tissue and joints.

In the period between the two wars, these valuable observations were forgotten, and no serious work was performed to ascertain the potentialities of this form of treatment in spite of the advances made in chemotherapy. It was considered unsafe to suture a

wound involving a compound fracture after six hours, even if careful excision and wound toilet were performed.

At the beginning of this war, British surgery was greatly influenced by the work of Trueta and his colleagues dealing with Spanish Civil War casualties. The treatment consisted of laying open the wound and surgical debridement, and enclosing the limb in plaster with the wounds left open: partial closure was practised in some cases. Infection was controlled by the administration of sulphonamides, &c. The oedema was reduced by the immobilization and even pressure exerted by the plaster, and subsided with healing of the wound, but this might be slow if at all extensive. This form of treatment undoubtedly saved innumerable limbs which would otherwise have had to be amputated. The great disadvantage was that slow healing of the wound gave rise to massive fibrous tissue formation, bone and tendons were exposed for long periods in the discharging wound with resultant sloughing and necrosis, and joints become stiff from immobilization and fibrosis.

Early closure of wounds is the natural evolution in wound surgery which keeps abreast of the discoveries and acquired knowledge of the properties of sulphanilamide and penicillin. The bacteriostatic properties of these drugs have gone a long way towards removing the danger of septicaemia and wound cellulitis. Infection due to staphylococcus, streptococcus and gas gangrene can be completely controlled in the vast majority of cases. These discoveries combined with new methods of resuscitation and blood transfusion render the patient a far more suitable subject on whom to try the lessons learned by earlier surgeons. This has been proved by

Colonel Jeffries and his co-workers. Up to date these drugs have been used purely as defensive weapons against infection, and, as such, their value has not been exploited to the full.

The use of penicillin and early closure does not obviate full removal of all dead and infected tissue at the primary excision. Many of these wounds, if they reached the base hospital within a few hours of injury can be primarily sutured under penicillin with absolute safety, but when they have been several days in transit without adequate observation and regular administration of penicillin, it is unwise to resort to primary suture. Delayed closure is carried out at the base hospital, ideally between the third and twelfth days. The administration of penicillin is started before the patient goes to the theatre and in case of heavy infection, due to inadequate excision, a massive dose of penicillin or twenty-four hour course may be given first (depending on general condition). The wound is inspected, cleansed with saline or peroxide; any residual recesses examined for retained foreign bodies or completely loose bone, and a swab taken. The skin edges are freshened and freed; they are then sutured without tension. In wounds where the skin edges cannot be brought together without tension, and a large raw surface is left, closure is completed by the application of a Thiersch or split-skin graft, sutured to the periphery, and even pressure applied by flavine emulsion wool and a firm bandage.

By this combined method the complete closure of even the most extensive wound can be obtained. Penicillin is given systemically for five days. Local application of penicillin by means of tubes has been disappointing, the wound frequently breaking down and forming sinuses.

**Advantage of early closure.**—It is well known how indurated and scarred a limb may become around a chronic

varicose ulcer or an extensive burn. The fibrous tissue forming under the granulating surface penetrates deep into the underlying structures. The pain from a raw surface prevents the patient from moving the limb, while contractures further limit joint movement. So also in the extensive soft tissue wound, as healing occurs a large scar will develop adherent to the underlying muscle.

It is practically impossible to keep a large granulating surface free from pathogenic organisms for any length of time. Any secondary infection developing is followed by fresh fibrous tissue formation. The depth to which this fibrous tissue may extend is seen at any operation on a raid casualty treated by the old methods. It may reach to underlying bone, binding skin, deep fascia and tendons down to bone, and make movement impossible.

Complete closure of a soft tissue wound will not only prevent reinfection of the wound but will also reduce the amount of scarred tissue formation to a minimum. Oedema of the tissue will be absorbed rapidly as soon as the source of irritation is removed. The patient's pain will be relieved and of his own volition he will start using his limb and an earlier return to function is assured.

If the tissue can be drawn together by closure, the recesses in the wound will be shut down, thereby preventing the pooling of serum blood or pus. The early movement of the muscles of the limb will help to express any such collection.

The protection of tendons can be assured by closure of the wound by complete suture. Where it is necessary to complete the closure by skin graft, an adherent scar may result, but this can be excised later and a full-thickness graft applied when the tendon has been saved from initial destruction. In the case of compound fractures

early closure of the wound is absolutely essential to prevent secondary infection reaching the bone. If it should be necessary to swing skin flaps or make parallel skin incisions to retain tension on the main incision, these secondary incisions can be Thiersch-grafted.

Burns and Young have shown in cases of fractured femurs treated by control of infection and early closure of wounds that movements can be started immediately, alignment being controlled by weight traction (Tr. of Fractured Femurs, *Lancet*, 1945 (i), 236).

Wounds of the knee-joint demonstrate very clearly the value of early closure. It has been long known that the synovial membrane can look after itself as long as it is not being bombarded by infection from a source within or outside the joint. It is the damage to the soft tissues and bone that determines the ultimate functional result of a knee-joint injury. After

surgical toilet of the wound and removal of the foreign body the synovial membrane is closed. The soft tissues must then be drawn together and the wound completely sutured or grafted.

Early closure by suture and skin graft will ensure minimal extra articular scarring and rapid absorption of oedema and swelling. Throughout, the infection must be controlled by the administration of penicillin and sulph-anilamide systematically. Fluid collecting in the joints is aspirated and penicillin is instilled into the joint to keep up the concentration of penicillin in the synovial fluid.

Failure to obtain a good result in cases of penetrating wounds of skin-joints is usually where there has been excessive bone damage (articular) and where, owing to the soft tissue loss, the wound has not been closed.—Freebody in *P. R. S. M.*

## GOLD TREATMENT IN RHEUMATOID ARTHRITIS

A STUDY has been made of 110 patients, 28 males and 82 females with rheumatoid arthritis, 61 of whom received injections of MYOCRISIN, and 49 an inactive control substance containing the same constituents as the MYOCRISIN, with the exception of the gold radical.

Ten of the patients were aged between 10 and 19, twenty-nine between 20 and 29, fifty-nine between 30 and 39, and twelve, all males, were between 40 and 49. All the patients had had the condition for 2 to 5 years.

Forty-nine of the patients had a history of rheumatic fever, scarlet fever, or tonsillitis. Most of the patients had already had some form of treatment, e.g. eradication of septic foci,

protein shock, salicylates, physiotherapy, with little or no improvement. None had been treated with gold salts.

All the patients, with one exception, received ambulatory treatment and attended the clinic once a week for observation and injections. They also received some form of physiotherapy such as heat and massage. Each patient was given a thorough clinical examination before treatment was started. This included joint measurements, full blood count, blood sedimentation rate, blood uric acid, urine analysis, urea clearance, and radiological examination. The same procedure was adopted at the end of the period of observation (one year) while during treatment weekly urine analyses, fortnightly blood

cell counts and monthly blood sedimentation tests were carried out.

Both the MYOCRISIN and the control substance were administered in the same way. Intramuscular injections were given in the buttocks at weekly intervals in the following doses:  $1 \times 0.01$ ,  $2 \times 0.02$ ,  $1 \times 0.05$  and  $9 \times 0.1$  Gm., giving a total of 1 Gm. in a course. After an interval of 3 months a second course of 1 Gm. was given in the same dosage if required. As the period of observation was for only one year, it was not possible to give more than 2 courses of injections. Treatment was suspended temporarily when the milder forms of toxicity appeared and permanently when the reactions were severe.

The results show that while 82 per cent. of the patients who received myocrisin improved clinically, 45 per cent. of those on the control substance also showed some improvement. There is, however, a considerable difference in the degree of improvement in the 2 groups. Seventy-two per cent. of the control group felt that they had received some benefit from the injections, although only 45 per cent. showed clinical improvement.

Seventy-five per cent. of the 61 patients who received gold injections deve-

loped toxic manifestations, but the majority of these were mild. Seven patients had multiple reactions.

It was found that those patients who developed the more severe toxic reactions (exfoliative dermatitis and colitis) showed a marked alleviation of the joint condition.

Thirty-seven per cent. of the 49 patients who were given the control substance had "toxic reactions" (skin 16, kidney 2, and mouth 1). The improvement shown in some of the control cases was no doubt due to the fact that all the patients received some form of physiotherapy, and also that spontaneous remission must have occurred in a number of the cases. These 2 factors must also be taken into consideration when assessing the value of gold treatment in the other group.

Although the number of patients in this series is small, and the period of observation short, the results indicate that gold salts are of value in the treatment of rheumatoid arthritis, particularly when used in conjunction with general physiotherapeutic and orthopaedic measures. (Fraser. Abstracted from the Annals of the Rheumatic Diseases, Vol. 4, No. 4, June 1945, Page 71.)

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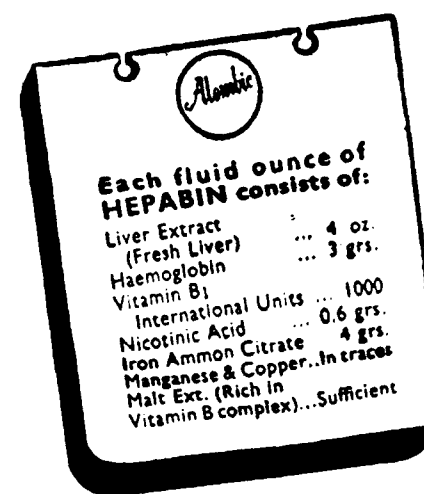
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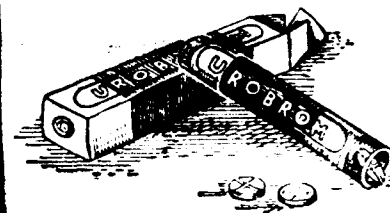
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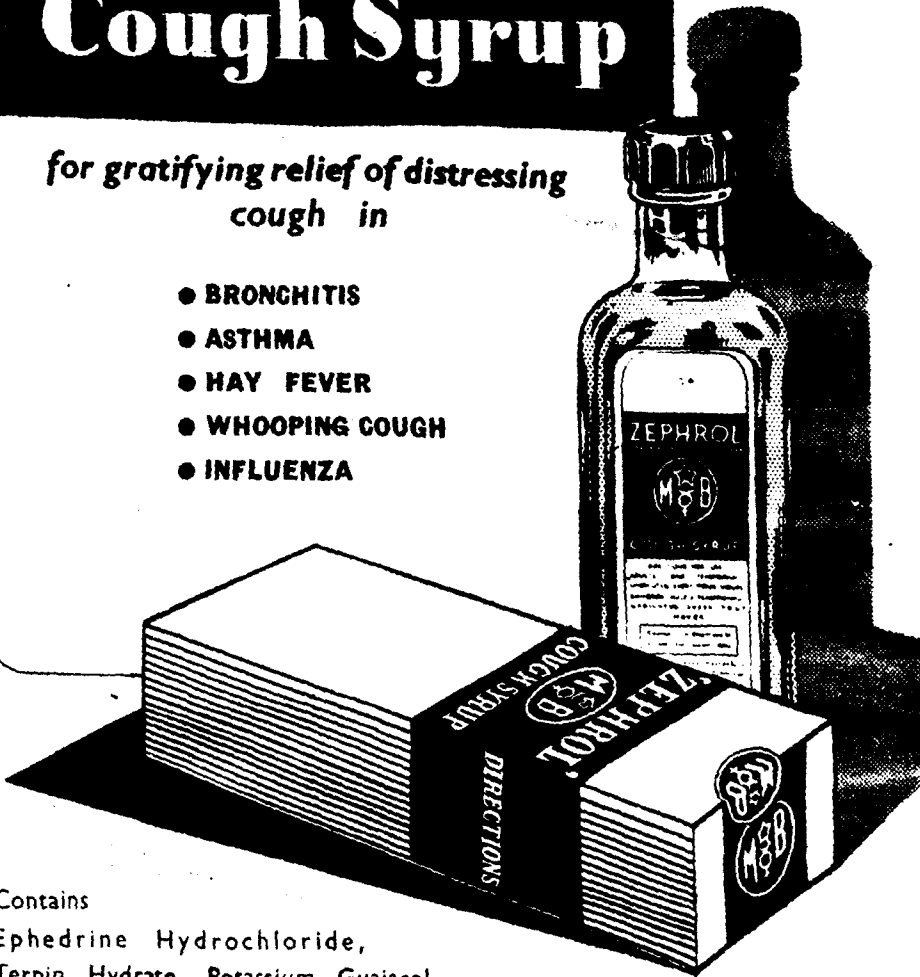
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## Cough Syrup

*for gratifying relief of distressing cough in*

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- ASTHMA
- HAY FEVER
- WHOOPING COUGH
- INFLUENZA



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*Direction:*—15 to 60 drops i. e. 14 to 1 dram 2 or 3 times a day, after food, with an ounce of orange juice or milk or water.

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