and I venture to hope that we—medical biologists and chemists alike—shall be able to resist the temptation to simplify the problem unduly and to accept too easily as a solution a correspondence which may be no more than an indication; though a most valuable one, of the nature of one of the factors involved in a much more complex mode of action. Meanwhile any hint is of value which will give chemistry a rational clue to follow in this quest.

Penicillin

Hard on the heels of the revolution in the chemotherapy of the bacterial infections came that due to the renewed investigation by Florey, Chain, and their co-workers on penicillin, the existence of which had been made clear by Fleming's observations ten years earlier, and which had then dropped almost out of memory after a tentative chemical investigation by Raistrick had revealed its acidic nature and solubilities, but had suggested a baffling instability under conventional procedures for its separation. The story of how such difficulties were overcome, of the extraordinary potency and harmlessness of penicillin revealed by freeing it from undesirable concomitants, of large-scale manufacture rushed ahead to meet war's needs, the constitution of the now several penicillins determined by a great co-operative effort of British and American chemists and even confirmed in one case by an artificial synthesis (De Vigneaud)—all this is one of the almost romantic scientific achievements of chemistry, working in close alliance with medical biology, attained under the stimulus of the needs of armies in the recent war. And the magnitude of the opportunity now open to chemistry in this new field of antibiotics can as yet be no more than a matter of hopeful speculation.

Symptomatic Treatment

In the time at my disposal, even one aspect of the rapidly expanding service of chemistry to scientific therapeutics which I have chosen for special mention can only be presented thus in selective sketches with but little detail and with no attempt to make the presentation inclusive. There is only time left to me, before I conclude my lecture, to make it clear that, while I have specially dealt with the elimination of the causes of disease as a relatively novel aim and achievement of therapeutics, made brilliantly selective by an alliance of growing intimacy with chemistry, I am by no means depreciating the importance of the alleviation of symptoms. In this direction, also, chemistry has been furnishing a wealth, even in some directions an embarrassing excess, of alternatives—competitive ranges of hypnotics, analgesics, local anaesthetics, diuretics, laxatives, and so forth. And if anybody should doubt the real value, on balance, of the service which chemistry, with intelligent medical use of its gifts, has thus rendered to the ease and the safety of afflicted humanity let him go, for an impression of contrast, to any friend who has had the experience of anaesthesia for operation two or three decades ago and again in recent years. Nor, I think, can it be doubted that in this field of symptomatic treatment again a strengthening collaboration is enabling both chemistry and pharmacology to replace a shallow empiricism by an ever stronger foundation of scientific understanding. If I may be allowed to mention two examples, which have caught my special interest as having some relation to physiological studies of my own, we have recently seen the emergence of a series of synthetic pharmacological antagonists to histamine for the treatment of asthma and other allergic manifestations, and, even more recently, the use of D.F.P. (di-isopropyl-fluorophosphonate), a potent and permanent antagonist of cholinesterase, to relieve the dangerous post-operative paresis of the intestines.

ANOMALOUS MANIFESTATIONS OF MALNUTRITION IN JAPANESE PRISON CAMPS

BY

R. G. S. WHITFIELD, M.R.C.S., L.R.C.P.

Late Surgeon Lieutenant-Commander, R.N.V.R.

In a leading article in the *British Medical Journal* of June 22, 1946 (p. 958), the following passage appeared: "But in the Tropics and in war-stricken European countries field workers have demonstrated repeatedly that the clinical picture shown by malnourished or starved populations may often differ widely from textbook descriptions. As Stannus has pointed out, unknown or ill-defined deficiency diseases probably far outnumber those whose characteristics are already plainly established." Nearly four years in eight Japanese prison camps convinced me of the truth of these remarks, and three clinical conditions are described as illustrations.

Diet

Dietetically the period falls into two divisions:

1. *White Rice Period (January to October, 1942).*—Rice (polished), about 10 oz. (280 g.) daily; wheat flour (white), about 8 oz. (230 g.) daily; sugar, about 1 oz. (28 g.) daily; taro root and sweet potatoes, 4 oz. (115 g.) sometimes; vegetable soups of spinach, turnip tops, chrysanthemum leaves, onions, cabbage, about 8 oz. (uncooked); vegetable oil, about 1 oz. daily for frying; meat, fish, whale, approximately 3 oz. (85 g.) three times weekly until June, then diminishing. The daily diet is summarized approximately in Table I. There were almost certainly deficiencies

TABLE I

	Calories	Protein (g.)	Fat (g.)	Vit. A (I.U.)	Vit. C (mg.)	Thiamine (I.U.)	Nicotinic Acid (I.U.)	Riboflavin (I.U.)
Normal requirements	3,000–4,000	100	100	5,000	75	2,000	23,000	1,600
Probable minimum requirements	2,000	30–40	20–30	2,000	15	900	10,000	1,000
1942 diet	1,800	40–45	30	3,400	35	500	250	700

in pantothenic acid and pyridoxine (vitamin B₆), and possibly in biotin, vitamin E, and folic acid.

2. *Barley and Bean Period (November, 1942, to August, 1945).*—Whole-grain barley and millet were substituted in the rough proportion of three parts barley, one part millet, and one part polished rice. Meat—usually rancid pork—2 oz. (57 g.) monthly; fish, 4 oz. (115 g.) monthly; seaweed, 40 g. daily. Other foods according to season were the usual Western vegetables, plus daikon (a sort of giant radish-turnip), daikon tops, soya-bean paste and curd, sweet potatoes and tops, taro roots, egg-plant, pea-pods, bracken stalks in brine, dried octopus, snakes, wasp grubs, and the pupae of silkworms ("1 pupa = 2 hen's eggs"—any Japanese). Soya beans were issued fairly regularly and were our most valuable food. Deprivation always produced an increase of sickness. The calorie value varied from about 3,000 (1943) to 1,500 (1944). Thefts of food by the Japanese and the prisoners, and the unbelievable trading in food that went on, made it impossible to know how much was being eaten; and because of the intermittent and, in many cases, constant diarrhoea, together with the unexplained nocturnal diuresis, we could not estimate what was being absorbed. The unreliability of Japanese vitamin B injections (prepared from yeast or rice

polishings—the thiamine content was stated by only one manufacturer), too, made it impossible to decide what therapy was being given.

The "Painful Feet" or Gopalan Syndrome

(Hong Kong and Shinagawa, Tokyo, 1942-3)

On the white-rice diet the expected loss of weight, accompanied by weakness, bradycardia, hypotension, and constant "black-outs" on change of posture, soon became universal, and pellagrous dermatitis was not uncommon. After about five months men began to report with painful feet. I met many P.O.W. and Japanese doctors, but none had seen such cases before. The existence of a new syndrome, however, cannot be denied. It occurred in the Philippines, Malaya, Hong Kong, and Japan, and has been described by Stannus (in 1936), Jackson (1946), Page (1946), and others, and elucidated as a deficiency of pantothenic acid by Gopalan (1946). It appears probable that at least some of the cases reported by Ekblom and by Purdon Martin (1946) and described under the name of "jittery legs" in an annotation in the *B.M.J.* (1946) were early cases of pantothenic acid deficiency; for in England a non-bread-eater who disliked liver, kidneys, mushrooms, and peas might well be on the threshold of such a deficiency. It may therefore be worth while to describe the syndrome again.

A feeling of tiredness in the feet develops in a week or so to a vague discomfort mainly at night time. In about a month three symptoms appear: (1) a deep ache starting from the ball of the foot and spreading to the toes and instep, which is described as "like a toothache"; (2) a superficial burning sensation starting in the sole of the foot, quickly reaching the toes, and gradually involving the whole foot; (3) "pins-and-needles"—difficult for the patient to locate in the foot, and varying from "funny-bone" sensation to electric shocks. Occasionally an early case would get relief from heat, but developed cases unanimously sought cold. The pain was worse at night, and most men slept with their feet outside the blankets either because they could not bear the weight of them or, more commonly, because they craved the cold, despite indoor temperatures of 12° F. (−11° C.). The third symptom soon progressed to excruciating bouts of shooting pains up and down the feet and calves. The syndrome took about four months to develop fully.

I cannot exaggerate the sufferings of these men. By December, 1942, out of a total of 300 prisoners there were over 40 cases, and these were driven almost out of their minds. Two very dour tough Scotsmen used to spend every night sitting with their legs in a tub of water in which lumps of ice were floating, their bodies swathed in blankets and coats; and every evening some pain-wracked skeletons would beg for morphine to give them enough rest to carry on for a few nights. Unable to get any treatment for them except 0.5 mg. of vitamin B a week, I sent some twenty patients to a Japanese military hospital, where they were given lumbar punctures by medical students and received beatings on the feet. Several lost their toes through gangrene, and two had leg amputations. One committed suicide, and seven died from neglect.

Physical Signs

Soon after the onset a sharply delimited hyperhidrosis of the affected parts appeared, and the intense hyperaesthesia of the feet was gradually replaced by an ascending skin analgesia with complete insensitivity to pin-prick and cotton-wool, often to above the knee. First the ankle-jerks and then the knee-jerks, after some increase, slowly diminished, but complete absence was rare and occurred

only after a year or so. Advanced cases showed loss of passive movement sensation, and the finger-nose and toe-knee tests became mildly inaccurate. These neurological findings, also recorded by Jackson and Page, contradict those of Gopalan, who specifically differentiates this syndrome as showing brisk knee-jerks, with no loss of sensation or of muscle power and no wasting or foot-drop. It is my opinion that these signs were produced by a concurrent deficiency, perhaps of thiamine, causing a peripheral neuritis (Gopalan's cases were on parboiled rice, which ensured an adequate thiamine intake), and do not in any way invalidate his description. With Gopalan's negative findings I am in entire agreement: there was no muscle-wasting or loss of power (apart from general emaciation), no foot-drop, no Rombergism, no ataxic gait (except that caused by the pain of putting the foot to the ground), no tenderness of the calf muscles, no spasticity, and no loss of superficial reflexes.

Page mentions that definite circulatory impairment was present. This was a late finding, which I feel should be attributed to the prolonged inactivity due to pain, the universal freezing therapy, and the generally impaired circulatory state rather than be considered as an organic part of the syndrome. And Graves (1946) said of the Singapore cases: "I submit that the later signs [in Page's cases] were dependent upon climatic conditions. Our chronic cases continued in the same state for many weeks or months, perhaps developing other of the deficiency syndromes such as retrobulbar neuritis or a spastic paraplegia, but never cyanosis of the limbs, gangrene, etc."

During the second half of 1943 most cases in Shinagawa camp started to improve slowly, both because of the quantities of stolen food brought into the camp and because soya beans and barley have the high pantothenic acid content of 18 and 20 µg. per gramme respectively. Also "refection" may have been occurring.

Associated Ariboflavinosis.—As with Gopalan, nearly every case showed or had shown an eczematous dermatitis of the scrotum, a painful tongue, angular stomatitis, and, less commonly, cheilosis in the form of dry crusting and fissuring of the vermilion of the lips (angular blepharitis was rare). Photophobia of bright sunlight with lacrimation and a feeling of grit in the eye, and conjunctival injection, were common every summer. Seborrhoeic dermatitis of the alae nasi, eyelids, and ears was not seen, nor was there any loss or greying of the hair.

Associated Oedema.—A common but not invariable association was oedema of the ankles or face, or both, without ascites or pleural effusion. One interesting case was that of a most reliable uncomplaining man who was suffering from severe painful feet. Overnight he developed considerable oedema of the feet and ankles and the pain left him entirely. His was a unique case, and I can suggest no explanation. This oedema was generally considered, despite a very small salt intake, to be due to hypoproteinaemia, and was contrasted with the oedema of wet beriberi, which, supposedly caused by lowered tone of the arterial walls and increased tension in the capillaries, is associated with warm extremities, flushed colour, and a feeling of firmness to the fingers (Bicknell and Prescott, 1946). But often cases would respond to injections of Japanese vitamin B coupled with oral yeast, while extra protein in the shape of meat, fish, or a Red Cross parcel did not seem to help. I never felt capable of differentiating between the oedema of beriberi and that of hypoproteinaemia (if there are two kinds), and it is interesting to note that Keys *et al.* (1946), investigating a group of thirty-four men on a "famine" diet with an average of 49 g. of protein, found that, although oedema appeared in all of them, the decline in the plasma protein concentration

averaged only 0.73 g. per 100 ml. (normal 7–8% ; believed critical level for oedema 5%). They believe that famine oedema is not due simply to hypoproteinaemia or to renal or cardiac failure but probably to an abnormality of the capillary wall. Meanwhile Selby and Golberg (1946) have reported successful treatment with folic acid (which was probably deficient in our diet).

Many men developed loss of vision with a retrobulbar neuritis. It is noteworthy that the thirty worst cardiac cases (Table II) did not show very pronounced visual

TABLE II.—*Details of the Worst 30 Cardiac Cases, Mitsushima Camp*

Diarrhoea	T.T.	30
Peacetime alcohol consumption ..	Moderate	18
	Heavy	6
Average weight loss since capture ..		32 lb. (14.5 kg.)
Precordial pain	Yes	22
	No	8
Audible murmurs		3
Pulmonary second sound increased		10
Pistol-shot murmurs over femoral artery		0
Ectopic beats	Yes	15
	No	15
	40–50	1
	50–60	8
	60–70	6
	70–100	8
	100–120	3
	120–140	3
	140–150	1
	None	10
Oedema on admission (i.e., ambulatory)	Face and feet	18
	Feet only	1
	Face only	1
Average number of weeks since cutting	Toe-nails	14
	Finger-nails	10
	0	7
	1	11
Pain on pressing calves	2	9
	3	3
	4	0
	5	18
Analgesia of legs to pin-prick ..	Stocking type	11
	Patchy	1
	Nil	6
	Increased	9
Knee-jerks	Normal	12
	Diminished	3
	Nil	11
Ankle-jerks	Normal	14
	Diminished	5
	Nil	9
	6/5	11
	6/6	2
	6/18	2
	6/24	1
	6/36	1
	6/60	0
Visual acuity	Worse than 6/60	0

deterioration, and none of the worse cases of visual loss were included among them. The causative factor was plainly not identical with those producing the Gopalan syndrome, oedema, pellagra, or beriberi.

A Cardiac Epidemic

(Mitsushima; Winter, 1944)

In June, 1944, Mitsushima camp was emptied and refilled with 100 British direct from the infamous Thailand Railway (all were emaciated and most had malaria) and 100 Americans from a copper mine, near Tokyo in moderate condition. The Japanese immediately cut the food, increased the work, and embarked on a campaign of systematic brutality. The health of the camp deteriorated rapidly. By September weakness, especially of the legs, was general, oedema was common, and complaints of painful feet were starting. Of 213 men, 60 were suffering from evident malnutrition by the beginning of October, 74 by November, 90 by December, and 142 by the beginning of January. In December a survey of the entire camp was made (Table III).

From Dec. 20 to 30, 1944, with an astonishing unanimity of timing, 30 cases of severe cardiac involvement reported—21 British and 9 American. Following two sudden deaths we were allowed to send over 60 men to hospital. Certain features are worthy of comment.

TABLE III.—*General Survey of Mitsushima Camp at end of December, 1944*

No. of men in the camp	213
Failure of vision (81 cases)	
Mild (up to 6/18)	9
Severe (up to 6/60)	26
Very severe (letters visible only a foot or so distant; all with other signs of malnutrition)	3
Oro-genital syndrome (12 cases)	37
Painful feet (124 cases)	6
Some anaesthesia to pin-prick	7
Oedema	5
Diminution of leg reflexes	104
Complaining of shortness of breath	20
	0
	74
	77
	50
	74

1. All the cardiac cases except one appeared in the space of ten days, despite the better physical condition of the Americans.

2. The paucity of physical signs made it difficult to assess the clinical condition. Pain in the feet was in no case as severe as in the 1941–2 period, and the oro-genital syndrome was much rarer. No textbook case of beriberi was seen, but a peripheral neuritis developed similar to that at Shinagawa, except that the skin anaesthesia was markedly patchier and less “stocking” in type, and tenderness of the calves was fairly common. There was no obvious correlation between severity of the neuritis and the cardiac condition. We tried to assess the cardiac condition by means of an exercise-tolerance test of twelve full knee-bends—where it seemed safe. Surprisingly, all the men did well at it, and the pulse rate was nearly always back to normal after two minutes, even though many were too weak in their thigh muscles to manage the full number. As there was no infallible herald of approaching cardiac crisis the prognosis of each case had to be modified frequently. To give or withhold our limited American thiamine was a heart-breaking decision, made on clinical intuition rather than on physical signs.

3. The symptoms were unvaried: sudden weakness of the legs, causing the astonished patient to sit; generalized exhaustion; a consciousness of palpitation and often irregular beats; breathlessness on exertion; and nocturnal attacks of palpitation which woke up the patient sometimes with pain and always with intense anxiety and dyspnoea, partially relieved by sitting up, as in cardiac asthma.

4. All except one case showed delay in nail growth (not found in Shinagawa). Hair growth was affected in only one man who had very severe neuritic signs, and his beard grew at one-third the normal rate. One common finding was the loss of hair on friction areas on the legs. This seems to contradict the findings of Castellani, quoted by Sutton and Sutton, of hypertrichosis of malnutrition affecting especially the legs of boys and girls and returning to normal on adequate diet. Two cases had perforating trophic ulcers of their toes, unknown to themselves.

The treatment of all cases was the same: 12 American “multivite” tablets by mouth a day, each containing 1 mg. of thiamine. Intravenous vitamin B was reserved for emergencies and those with severe diarrhoea. All cases received these until apparently out of danger, and many took 300 to 400 tablets. Yet the response was disappointingly slow, even allowing for poor absorption. Two deaths occurred on Dec. 27 with the usual signs of right-sided failure. American thiamine, 50 mg., was given intravenously, venesection was performed, and digitalization was attempted. On March 17 the Japanese forced a group of light-duty cardiac cases out to work. At lunch-time they were exhausted, and we were allowed to put them in hospital. At tea-time one of them, who had been resting uncomplainingly, died in three minutes. Six days later another died of general weakness, with low-grade bronchopneumonia. One more death occurred in July—that of a man doing normal work, with no symptoms other than a chronic oedema. He returned to camp one mid-morning with dyspnoea. Intravenous thiamine was started, but he died three hours later, his apex beat having moved 1½ in. (3.8 cm.) outward in that time.

The thiamine content of the diet at this period was around 1.5 mg. daily and the calorie intake about 2,000. According to Cowgill's formula the daily requirement would be only just over 0.5 mg. But against this must be balanced the low protein and the low or absent fat intake, the poor absorption due to diarrhoea, the very hard work, and the fact that many workers consider his formula an underestimate.

Was thiamine deficiency responsible for these cases? The experiments of Williams *et al.* (1940, 1942, 1943) on women volunteers in controlled thiamine deficiency are strikingly parallel. These women lost weight, were fatigued and giddy, and had faint heart sounds and lowered blood pressures, with tachycardia and sinus arrhythmia on exertion. Their calves were tender and the squatting test was impaired. But two findings which these authors emphasized were absent. The first was anorexia. In their cases this started after thirty days, developed into nausea and epigastric distress with occasional vomiting in fifty days, and by seventy days there was constant nausea. At Mitsushima vomiting was seen only in acute food-poisoning, while hunger was so constant that scavenging of the kitchen refuse was a grave problem. Epigastric distress did not occur. His second finding was mental changes suggestive of neurasthenia, the subjects becoming depressed, quarrelsome, and fearful. They lost interest in reading, were confused in thought, and lacked manual dexterity. All these symptoms, except perhaps a slight impairment of memory, were conspicuously absent in Mitsushima. One cardiac case developed thickness and slowness of speech and mental retardation, but recovered slowly on treatment. These cases, then, can hardly have been pure thiamine deficiencies. Clinically they resembled cardiac beriberi, except that they responded poorly to vitamin B and had none of the typical nervous lesions. (Anorexia and memory defects are quite common but not invariable in beriberi.)

A Visitation of "Fits"

(Mitsushima; Spring, 1945)

Epileptiform seizures affected four men in the course of six weeks. Three were pyknic in build, powerfully muscled, and well covered with fat. The fourth, mentioned before as having delay in beard growth and marked neuritis, was tall and extremely emaciated. In common they all had insatiable appetites, the thin one being a thief and garbage scavenger. Table IV summarizes the physical condition of these men.

TABLE IV.—*Epileptic Cases*

Case No.	Nationality	Build	Vision		Oedema	Knee- and Ankle-jerks	Anaesthesia	Other Evidence of Malnutrition
			L.	R.				
1	American	Thin	6/18	6/18	Nil	Nil	Marked; patchy up to knee	A severe cardiac case, in bed for weeks. Quite fit
2	"	Fat	6/36	6/24	Face, slight	Normal	Nil	
3	"	"	6/18	6/24	Nil	V. slight diminution	Slight, patchy, offset	Complained of great tiredness
4	British	"	6/18	6/9	Face and ankles, slight	Normal	Nil	Scrotal dermatitis

Case 1.—On April 17, 1945, while the patient was lying down after a copious vomit, tonic convulsions started without warning. He was deeply cyanosed, with trismus; the back was arched in opisthotonos and the pulse was almost impalpable and about 40. The pupils were widely dilated and equal, and the hands were in tetanic spasm. He voided urine but not faeces, and did not bite his tongue. The plantar response was

normal. The tonic stage lasted so long that death seemed inevitable, but it was succeeded by a short clonic phase which lapsed into profound slumber with hissing respiration suggestive of "air hunger." He could not be roused. The urine was strongly acid to litmus, but when tested with some Japanese reagent was negative for sugar. As the nature of this reagent remained a mystery the presence of ketone bodies in the urine must remain open to question. There was no history of epilepsy for the preceding three years. The enormous black liquid vomit turned out to be an infusion made from sarsaparilla gathered outside the camp, but as there was no rubber tubing it was not possible to wash out the stomach. It seemed unlike a Stokes-Adams attack and the pulse rate started rising slowly. There was no history of malaria or nephritis, and the urine contained no albumin. Then a powerful smell of acetone was drawn to my attention (I am anosmic), and it seemed that we had a case of ketosis, perhaps due to starvation. Glucose, calcium, and dried plasma were given intravenously. Three hours later another and equally severe attack occurred and morphine was given. Six hours later there was a third attack, and his condition seemed hopeless. However, after twelve hours' sleep he awoke and seemed none the worse, except for feeling shaky.

Cases 2, 3, and 4.—Within six weeks the three fat men were affected with exactly similar attacks, all occurring while at rest or asleep. One had seven fits in twenty-four hours. Treatment was unchanged except for some sterile bicarbonate solution which we had made meanwhile. All recovered quickly once they emerged from their coma-like slumber, and felt fit for work again in forty-eight hours. There was no residual mental impairment. Only Case 2 had a recurrence—about three weeks after his initial attack.

Contrary to our expectations the heat of the summer failed to produce any more cases, and the little "epidemic" passed off as mysteriously as it had appeared. Why were only four out of 213 men affected in the period of six weeks? They had all received multivite tablets and seemed in no way different from the rest of the camp. Chick *et al.* (1938) produced epileptiform fits in pigs and rats by depriving them of pyridoxine (vitamin B₆), but it is difficult to see why these four men alone should suffer such a deficiency. It seems most likely that they were caused by a sudden ketosis with the formation of aceto-acetic acid. This could not have been exogenous, as there was no fat in the diet; but, in starvation, as the liver glycogen is depleted fat is converted in the liver to ketone bodies, which may be formed faster than the tissues can utilize them. There seem to be two objections to this: first, that except for the one thin man the patients were by no means starving; secondly, it is difficult to conceive of ketone bodies appearing too rapidly in the blood for premonitory symptoms to be felt as in diabetes. All four men started their attacks by copious vomit, so that perhaps fundal pressure on the heart produced vagal stimulation. But such a trigger mechanism could hardly have played any part in the successive seizures, as the distension had been relieved. The possibility that lack of vitamin B complex reduces sugar tolerance in diabetes may be relevant, although Wade (1947) has failed to confirm this in the particular case of nicotinamide.

Summary

Three conditions arising from malnutrition are described which did not behave in the manner laid down in textbooks.

On a diet of polished white rice, pantothenic acid deficiency with an accompanying peripheral neuritis was the chief trouble.

On a barley and bean diet, cardiac beriberi occurred with some pantothenic acid deficiency and a slightly different neuritis.

At no time was a typical case of dry beriberi seen.

A series of four cases of epileptiform seizures of unknown causation is described.

The wise humility of such authorities on deficiency diseases as Stannus is supported by clinical observations.

I wish to thank Dr. Wrigley, of Messrs. Roche Products, for procuring a copy of Gopalan's article and sending it out to me in Greece; and Dr. A. A. Weinstein, of Atlanta, Ga., for refreshing my memory of details of the "fits" episode. The food figures are taken from the "Nutritive Values of Wartime Foods," No. 14 of the M.R.C. war memoranda, or from Bicknell and Prescott.

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TEMPORAL OR GIANT-CELL ARTERITIS

BY

KENNETH ROBERTSON, M.D., F.R.C.P.

Honorary Physician, Royal Hants County Hospital,
 Winchester, and Royal South Hants Hospital, Southampton

Since 1932 reports have been published from time to time describing what appears to be an unusual form of arterial inflammation. This condition seems to have a particular predilection for the superficial cranial arteries, and so frequently have the temporal arteries been involved that it has been known as "temporal arteritis." More recently Cooke *et al.* (1946), in a masterly review of the condition and its literature which includes a full description of seven of their own cases, suggest that the condition is probably less rare than the literature suggests—only forty cases had been described up to 1946—and that its effects are not confined to the cranial vessels but may be widespread throughout the body.

Their histopathological findings differed little from those of other writers, and they describe a subacute inflammatory process which, starting in the adventitia, subsequently spreads axially to the media, and is accompanied by areas of necrosis in the media and interna elastica of such a nature as to suggest an obliterative process in the vasa vasorum. They confirm the finding of giant cells, which give to the condition one of its names. The appearance of these follows necrosis, differing in this respect from tuberculosis, in which they precede necrosis. There is nothing to support a tuberculous hypothesis when considering aetiology.

My observations support the thesis, so ably presented by these workers, that the condition is by no means rare and that its recognition is difficult unless the possibility is borne in mind, but easy when once seen or the clinical picture appreciated. I believe that the diagnosis will be made with ever-increasing frequency and that neurologists particularly may find it useful in answering a number of baffling problems. For these reasons I feel that at the present time reports should be made of cases as they appear, even if only individual cases can be recorded.

Case I

In July, 1945, I was asked to see a man aged 65 who had shown an unexplained temperature for over a month. Two years previously he had suffered from intermittent claudication in the left leg. This had not been severe, and had been in abeyance for over a year. Apart from this the patient, who

had been an Army instructor in physical training, presented an excellent medical record. About six weeks before I saw him he had begun to experience lassitude, depression, and widespread pains about his body. He had lost his appetite, and after ten days retired to bed. His condition deteriorated, and sweating at night became pronounced, while severe headache made its appearance. At this stage he asked his doctor to visit him. Physical examination was negative, but it was found that fever up to 101° F. (38.3° C.) was present. This condition continued, and headache became very severe, preventing sleep. The Widal reactions were investigated and were found to be negative.

When first seen on July 29 his appearance was striking. He appeared ill and looked older than his age. His face was expressionless and suggested profound dejection, which was confirmed in conversation. Physical examination was unproductive, but it was noted that there was no pulsation in the left dorsalis pedis artery and that the left temporal artery and both facial arteries were thrombosed. Furthermore, they were exceedingly tender to the touch, as was the right temporal artery though it was pulsating. There was, in addition, tenderness in the occipital region and the patient explained that his head had been so sore that it was sometimes impossible to lay it on the pillow. The only other findings were an absence of the abdominal reflexes and exaggerated deep reflexes. The plantar responses were flexor. Heart and lungs seemed normal and the blood pressure was 150/90. The fundi were within normal limits. A tentative diagnosis of periarteritis nodosa was suggested and he was admitted next day to hospital.

In hospital further investigations were carried out. A skiagram of the chest showed no abnormality in the heart or lungs. Electrocardiograms were normal. The urine showed a trace of albumin, a few red cells and epithelial casts, and was sterile. The blood count revealed 5,000,000 red cells, 80% haemoglobin, and 6,600 white cells, with a normal differential count apart from an eosinophilia of 7%. The blood sedimentation rate showed a fall of 40 mm. in the first hour when estimated by Wintrobe's method. The blood urea was 42 mg. per 100 ml.; the Wassermann reaction was negative. Agglutinations for enteric and *Br. abortus* were negative. The cerebrospinal fluid was normal, except that 5 cells per c.mm. were present; the Wassermann reaction and the gold-sol curve were negative. Blood culture was sterile.

An inch (2.5 cm.) of the anterior branch of the right temporal artery was removed under local analgesia, and the microscopical appearances here were consistent with a diagnosis of temporal arteritis. The operation produced a remarkable alleviation of headache in this part of the head. During his stay in hospital the fever persisted, but there was a gradual improvement in his general condition. Headache was reduced, sweating became less severe, appetite improved, and he became rather less depressed. His haemoglobin level fell to 63% and his sedimentation rate continued high. Apart from symptomatic treatment he was given nicotinamide by mouth. He was discharged home to bed, where his improvement was maintained.

He was readmitted to the surgical ward at the end of November with gangrene of a toe on the left foot. I did not see him then, but the fact that his sedimentation rate was still high, though falling, suggests that the condition was active. He was apyrexial. A left femoral periarterial sympathectomy was carried out in an attempt to save the toe, but it was not successful and amputation became necessary later. Though no sections were cut off the arteries at the site of the operation, it seems likely that the gangrene was due to arteriosclerosis obliterans and not to giant-cell arteritis. It will be recalled that he had suffered from intermittent claudication two years previously and that there had been no tenderness of the dorsalis pedis artery.

By June, 1946, the patient seemed perfectly well, and his wife assured us that he had suffered no ill effects as a result of his long illness. Furthermore, his blood picture was normal and the sedimentation rate only 4 mm. During his convalescence from the operative treatment there had been a period of mental confusion lasting several days. We did not see him in this state, and it is difficult to be sure whether or not this was