butazolidin was a poor analgesic, and he thought that there was some specificity for "rheumatic" pain. In a series of some 1,200 cases not only was the incidence of toxicity extremely low, but even mild side-effects were rarely seen.

It was known that toxicity was increased by the simultaneous administration of amidopyrine and barbiturates, and in Glasgow they were very careful to stop all other drugs during the administration of butazolidin. He suggested that the high incidence of toxic effects encountered by other observers might be due to the fact that phenobarbitone was so extensively used. The potency of pyrazol derivatives in relieving the symptoms of rheumatoid arthritis appeared to be proportionate to their experimental trauma-protective effect, and it was suggested that further screening of pyrazol compounds should make use of this association.

Dr. G. R. NEWNS (Sheffield) discussed the results obtained in 197 cases treated with phenylbutazone. There was sustained relief of pain in 65% of patients, but the drug did not affect the course of the rheumatoid process. Toxic effects occurred in 25% of cases, and included gastro-intestinal disorders, skin rashes, agranulocytosis (with one death), and oedema. In spite of the high incidence of toxicity he considered the use of butazolidin in rheumatoid disease was justifiable and that it was particularly useful in the rehabilitation of the more long-standing cases.

### Blood Concentrations and Toxicity

Drs. ENA BRUCK, M. E. FEARNLEY, and R. I. MEANOCK (London) reported that the incidence of toxic effects increased considerably with increasing blood concentrations of phenylbutazone. When the blood concentration rose above 10 mg./100 ml., 85% of patients developed toxic effects, as against 37% with blood concentrations between 5 and 9 mg. and 12% between 0 and 4 mg. Maximum relief of symptoms occurred with blood concentrations between 5 and 10 mg./100 ml. Increasing the blood concentration to above 10 mg. did not produce further relief of symptoms. In view of the marked variations in absorption of the drug in different individuals they considered it was impossible to formulate a rigid dosage schedule which would prove satisfactory in the majority of patients.

The discussion was opened by Dr. F. DUDLEY-HART (London), who agreed that butazolidin was a powerful analgesic without specific antirheumatic effects. Its value, he thought, was greater in osteoarthritis than in rheumatoid arthritis and he had found it effective in Paget's disease and metastatic carcinomatosis.

Dr. JOHN GLYN said that they had treated 11 cases of rheumatic fever at the Bellevue Hospital, New York, and found that the results were comparable with those produced by salicylates. The constant and dramatic response of the joint inflammation as well as the immediate effect on pyrexia and tachycardia provided some evidence that in this condition butazolidin had more than a purely analgesic effect.

Professor R. DOMENJOS (Saarbrucken) said that he and his colleagues had found that the effect of butazolidin in inhibiting formalin-induced inflammatory oedema in rats was significantly greater than that of A.C.T.H. or cortisone. They were unable to demonstrate any correlation between the adrenal ascorbic-acid-depleting effect of various drugs, including phenylbutazone, and their anti-inflammatory effect. He considered this lack of correlation indicated that butazolidin did not act via the pituitary–adrenal axis. Experiments in rats showed that the effects of phenylbutazone were not influenced by adrenalectomy and that renal excretion of various substances, including P.A.S. and penicillin, was appreciably delayed by butazolidin.

Dr. R. M. MASON (London) presented observations he had made on uric acid metabolism in four patients with gout and one patient with Paget's disease who was treated as a control. These patients took 600 mg. of butazolidin daily by mouth, and in all but one, who developed congestive heart failure, there was a persistent though slight increase in uric acid excretion and a corresponding fall in blood levels. He believed that the explanation for the differing results reported by other observers lay in the variable preponderance of water-retaining and uricosuric effects in individual patients.

### Effect on Clotting Time

Dr. J. G. HUMBLE (Westminster Hospital) reported that in 44 patients treated with butazolidin the clotting time was significantly increased in six cases and in 14 cases the prothrombin times were prolonged. Experiments showed that butazolidin plasma would correct the deficit in "tromexan" plasma and in "aged" normal plasma. It would not correct that in patients suffering from liver disease and obstructive jaundice. He considered, therefore, that the cause of the clotting effect was due to deficiency of prothrombin. This was confirmed by the two-stage prothrombin assay. The oral administration of vitamin $K_1$ resulted in a prompt return to normal of both prothrombin and clotting times.

Drs. A. HILL and M. S. GOOD (Aylesbury) had studied the effect of butazolidin on C-reactive protein, but the number of cases was too small to enable them to reach any definite conclusions. Their preliminary observations, however, led them to believe that further studies in this field would be amply justified.

Dr. P. O. WILLIAMS (London) reported that butazolidin caused retention of sodium and water during the first few days of treatment, but with continued administration of the drug both water and salt excretion returned to normal. In 13 patients who developed oedema while on treatment with butazolidin all except one had some demonstrable cardiac or renal lesion. He suggested, therefore, that oedema did not develop during therapy unless there was some other pre-existing defect in the control of salt-and-water balance. Since oedema occurred only under these circumstances he did not favour the routine prescription of the low sodium diet. When oedema does develop it should be regarded as more than a simple side-effect of the drug.

## SIR RICKARD CHRISTOPHERS, 80

One of the leading malariologists of the century, Sir Rickard Christophers, celebrated his eightieth birthday this week (on November 27). Colleagues who have worked with him in recent years may find it hard to believe that he is anything like that age, though anyone familiar with the extent of his work—work still in progress, needless to say—will wonder how one man can have found time to accomplish so much. He graduated in medicine in 1896, and his first contact with the disease with which his name will always be associated was in 1898, when with J. W. W. Stephens and C. W. Daniels he was appointed a member of the Malaria Commission of the Royal Society. The investigations conducted in 1899–1900 by the Commission in Central and West Africa laid the foundation of the study of malarial epidemiology. For the first time the conceptions of endemicity in malaria as now understood were set out, and for the first time the principle of segregation of the susceptible immigrant from indigenous infection was laid down as a major antimalarial measure. The connexion between blackwater fever and malignant tertian malaria was also established.

A year or two later Christophers and Stephens carried out researches in India which had a profound effect on the future of malariology in that country, for they stimulated general interest in the study of malaria problems. One important discovery was that different species of anopheles are very selective in their choice of breeding-place and vary widely in their capacity for transmitting malaria—the foundation of the modern concept of species sanitation. Christophers entered the Indian Medical Service in 1902, and during the next few years he was busy studying the life cycle of

various blood parasites—notably *Hepatozoon canis, H. gerbilli,* and *Babesia canis* in both their mammalian and insect hosts—the anatomy and histology of the tick, and the newly discovered parasite of kala-azar. In 1909 he founded the Central Malaria Bureau at Kasauli and started the collections which formed the basis for systematic study of the mosquito fauna of India. He returned to this work after military duty during the first world war in Mesopotamia, where, as might be expected, he made important observations on the anopheline fauna of that country.

In 1924 he published his classic paper on the mechanism of immunity against malaria in communities living under hyperendemic conditions. In the same year he described a new technique for the accurate measurement of the spleen, which has been used as a standard method in India for malaria surveys ever since. Before retiring from the I.M.S. in 1932 Christophers was director of the Kala-azar Commission in Assam in 1924–5 and of the Central Research Institute in Kasauli from 1925 to 1932. His volume on Anophelini in the "Fauna of British India" series appeared in 1933.

[Walter Stoneman, London

From 1932 to 1938 Christophers was professor of malarial studies at London University with his headquarters at the London School of Hygiene and Tropical Medicine. Strains of monkey malaria had recently become available for study, and he was quick to realize the importance of this new field of research. In collaboration with J. D. Fulton he conducted a series of comparative studies of the respiratory metabolism of *Plasmodium knowlesi* and *Trypanosoma rhodesiense,* the first observations of their kind in this field. After six years he left London and settled in Cambridge, where he now lives and works. During the second world war he was in charge of the mosquito repellent inquiry. During his investigation of the repellent properties of several hundred substances he devised new methods for breeding large numbers of mosquitoes in the laboratory and techniques for the testing of repellency. When hostilities ceased he found himself at last free to return to his first love, the mosquito. He is at present engaged on a study of the natural history and structure of *Aedes aegypti,* and this, we understand, is nearing completion. Recently he delivered the Manson Lecture on "Malaria in the Field" before a large and enthusiastic audience at the London School of Hygiene.

A list of all the honours Sir Rickard has received would be a lengthy one. He was appointed C.I.E. in 1915, made Honorary Physician to the King from 1927 to 1930, and knighted in 1931. He has received numerous medals, among them being the Queen Wilhelmina Jubilee Foundation Medal in 1928 and, this year, the Buchanan Medal of the Royal Society, to which he was elected in 1926. His presidency of the Royal Society of Tropical Medicine and Hygiene ran from 1939 to 1943.

His work continues, and he still maintains an interest in a side-line study, that of geology. His many friends, not least those in India, will join in extending their heartiest good wishes to him and to Lady Christophers on this occasion.

# Correspondence

*Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.*

## Seven Insulins in Britain

SIR,—Since Monday, November 16, seven insulin preparations are available on the British market, three old and four completely new, to the medical profession and the diabetics of this country. The whole question of these new insulins was discussed by interested doctors at the annual meeting of the Diabetic Association last July, and it was felt most strongly that the introduction of all these little-known new preparations at once would be most confusing to doctors and hence even dangerous to patients. It was unanimously agreed to advise the authorities that one only, the least unknown and most generally promising, should be introduced first. This opinion was immediately forwarded both to the Ministry of Health and to the British Insulin Manufacturers. Events have shown that this expert medical opinion has been completely ignored. And, after all, several diabetic centres have worked intensively at testing these new products for the British Insulin Manufacturers, and the neglect of our known opinion has been our reward.

I feel that the above should be made public in your columns in the hope of preventing a similar occurrence again, because I think there will be further modifications of insulin within the next few years. I should like to know what other steps, apart from raising the matter in Parliament, we might take to ensure that the considered opinion of those deeply concerned with the best treatment of diabetics in this country should not again be ignored.—I am, etc.,

London, W.1. R. D. LAWRENCE.

## Insulin Zinc Suspensions

SIR,—We feel that the series of papers on the new insulins (*Journal,* November 7) require comment. We have been using "lente" insulin for the treatment of diabetic outpatients, selecting only patients requiring high doses of insulin or those in whom satisfactory control had not been achieved with other insulins. So far lente insulin has been tried in 15 cases, all of whom have been at work. In general, we agree with the authors of the several papers that in such patients lente insulin will frequently achieve satisfactory control with a single daily dose. In some respects, however, our impressions differ from those conveyed by some of the papers and by your leading article.

Drs. J. D. N. Nabarro and J. M. Stowers (p. 1027) suggest that the present mixture of lente insulin is not suitable for the British dietary habit, and your leading article (p. 1037) supports their suggestion that the proportions of crystalline suspension and amorphous insulin should be altered. This would add yet another mixture to the many available, which seems quite unnecessary. The bulk and carbohydrate content of a meal can be varied independently by any dietitian, and in this way the dietary habits of the patient can be adjusted to the type of insulin. In our experience there is no characteristic dietary habit, for, while many patients are accustomed to take their main carbohydrate meal at midday in the form of sandwiches, others habitually have it at night. It seems to us unjustifiable on the experience of some 30 cases to suggest that a mixture of insulin which has been found suitable for some 500 patients in Denmark is unsuitable in this country. Like Drs. I. Murray and R. B. Wilson (p. 1023), we have found patients who have not been as well controlled on lente insulin as on globin or a mixture of soluble and zinc protamine. We do not agree, therefore, with the suggestion of Dr. Wilfrid Oakley