circulation had recovered completely after two hours—i.e., four hours after the blockage—and full use of the legs was regained. His cardiac condition did not improve and he developed a subacute bacterial endocarditis, but he was lost sight of at the time of the forced hospital evacuation in Sept., 1939.

Case 5.—Woman aged 36, admitted April 12, 1939, with auricular fibrillation and slight cardiac failure. She was given small doses of digitalis, and on May 5 developed a right femoral occlusion with the typical signs and slight pain. She was operated on within four hours under spinal anaesthesia, and an embolus together with 8 in. of thrombus was removed. The circulation recovered perfectly and pulsation of the posterior tibial artery at the ankle could be felt after a few hours. She left hospital, and although still fibrillating was doing most of her housework one year later.

I wish to thank Dr. J. Dick, medical superintendent, St. James's Hospital, Leeds, at which hospital I was working, for permission to publish these cases.

REFERENCES

- Deitch, H. I. (1936). *Lancet*, **1**, 475.
Griffiths, D. L. (1938). *Ibid.*, **2**, 1339.
Handley, W. Sampson (1907). *British Medical Journal*, **2**, 712.
Jefferson, G. (1925). *Ibid.*, **2**, 985.
Leriche, R., Fontaine, R., and Frieh, P. (1933). *Bull. Soc. nat. Chir.*, **59**, 386.
Moynihan, B. G. A. (1907). *British Medical Journal*, **2**, 826.
Murray, D. W. G. (1936). *Canad. med. Ass. J.*, **35**, 61.
Riddell, V. H. (1937). *Proc. roy. Soc. Med.*, **30**, 684.
Strömbeck, J. P. (1935). *Acta chir. scand.*, **77**, 229.

GLOBIN-ZINC-INSULIN: SOME EXPERIMENTS

BY

R. D. LAWRENCE, M.D., F.R.C.P.

(From the Diabetic Department, King's College Hospital)

The above new delayed-action insulin—a compound of ox globin, insulin, and a trace of zinc—is already on the market in America, where several articles (see Bibliography) have been published on its action on animals and use in diabetics. These reports seem to have been thought so favourable by the British manufacturers and authorities that I gather it is already licensed and may soon appear for sale. It has received no proper clinical trial in this country (not easy in wartime); but even were it proved to be more useful than protamine-zinc-insulin, it seems doubtful wisdom to introduce another new type of depot insulin without withdrawing the old, as this is sure to confuse clinical practice. Moreover, any real new merit in globin insulin is not apparent to me either from the published works or from the following trials of a supply kindly provided by the courtesy of Burroughs Wellcome and Co.

It is generally agreed that soluble insulin is strong but too short-lived in action, and P.Z.I. weak but prolonged and apt to cause serious hypoglycaemia at night if too large doses are given in an attempt to stop glycosuria after meals. It is hoped that G.Z.I. will be intermediate in action and, with one injection before breakfast, will act strongly and control sugar by day,

lished shows many irregularities and contradictions, and, when one discounts the bias in favour of something new, little real difference. I have substituted 20 to 40 units of G.Z.I. for P.Z.I. in 6 mild cases under hospital control, and my colleague Dr. Wilfrid Oakley has tried other cases, without being able to appreciate any difference on blood and urine tests. I have not compared a series of severe cases in this way, as the results from day to day on any depot insulin are so irregular as to make such a study valueless. But the accompanying table shows the results of what is probably the least erroneous clinical method—the effect of equal doses of different insulins on the fasting blood sugar of a severe diabetic followed for 24 hours without carbohydrate food.

A diabetic man aged 35, on insulin five years, feeble-minded but otherwise organically normal, was the subject. His insulin had varied from 40 to 50 units a day, and was kept at 20 and 16 units during the experimental period. Once a week the evening dose was omitted so that the patient was thoroughly diabetic next morning, and after two fasting blood-sugar estimations at 7 and 8 a.m. (a wise precaution) the same test dose, 32 units, of the different insulins was given. The effect on the blood and urine was followed two-hourly, later three-hourly, for 24 hours, during which time no carbohydrate food was given, but some protein—meat, bacon, etc.—was allowed, which I always find does not affect the blood sugar although it probably increases ketosis. The table shows the blood-sugar results and the ketonuria by Rothera's test—more informative than the glycosuria, which ran strictly parallel. The fasting blood sugars are at a fairly uniform level and the comparisons on the whole satisfactory, although some tests (the blood sugars mostly in duplicate) were lost. Perhaps the contrast would have been clearer with a larger test dose; but any risk of hypoglycaemia had to be avoided, as quite small restorative doses of sugar may raise the blood sugar considerably in such protamine experiments and completely spoil the curves.

It is clear that soluble insulin is much the most active, that neither G.Z.I. nor P.Z.I. gives any very active liberation of insulin during the 24 hours, and that there is no practical difference between the general trend of their action. G.Z.I. seems to come into action more quickly (4 to 6 hours after injection), but its maximum effect is shown at 15 to 18 hours—no different from P.Z.I., and still making the night the most likely time of hypoglycaemia.

There are other points against the present introduction of globin insulin which are more obvious from the clinical than from the laboratory angle. It is clear that its action is weak and that it will have to be supplemented, like P.Z.I., in many cases with soluble insulin. At present a large number of cases are treated with a mixed injection of P.Z.I. and soluble insulin, and we know that some of the soluble is converted by the excess of protamine. We do not know if G.Z.I. contains an excess of globin nor what is the result of mixing G.Z.I. and soluble; but this is of great practical importance, and now is the stage when the initial mistake made with P.Z.I. might be

Time in Hours	Globin Insulin at								P.Z. Insulin				Soluble Insulin			
	I		II		III		IV		V		VI		VII		VIII	
	32 Units Globin		32 Units Globin		32 Units Globin		32 Units Globin		32 Units P.Z.I.		32 Units P.Z.I.		32 Units Soluble		20 Units Soluble	
	Blood Sugar (mg. %)	Urine Ketosis Rothera	Blood Sugar (mg. %)	Urine Ketosis Rothera	Blood Sugar (mg. %)	Urine Ketosis Rothera	Blood Sugar (mg. %)	Urine Ketosis Rothera	Blood Sugar (mg. %)	Urine Ketosis Rothera	Blood Sugar (mg. %)	Urine Ketosis Rothera	Blood Sugar (mg. %)	Urine Ketosis Rothera	Blood Sugar (mg. %)	Urine Ketosis Rothera
7 a.m.	164	0	258	+++	263	+++	282	+++	233	—	278	+++	256	+++	265	+++
8 a.m.	260	Sl. tr.	Lost	—	278	+++	267	+++	233	+++	285	+++	241	+++	256	+++
2 hours	250	+	260	—	285	+++	260	+++	256	+++	282	+++	235	+	222	+++
4 "	260	++	215	—	217	+++	263	+++	256	+++	267	+++	180	++	177	+++
6 "	202	++	190	+++	210	+++	244	+++	250	+++	263	+++	137	+	145	++
8 "	210	—	210	—	Lost	+++	210	+++	256	+++	266	+++	91	Sl. tr.	204	+++
10 "	218	+++	183	+++	210	+++	244	+++	244	+++	278	+++	90	+	—	—
12 "	206	+	183	+++	244	+++	227	+++	250	+++	259	+++	133	++	—	—
15 "	167	Trace	167	+++	241	+++	215	+++	217	+++	218	+++	—	—	—	—
18 "	194	+	194	+++	244	+++	169	+++	170	+++	190	+++	—	—	—	—
21 "	190	0	213	++	244	+++	177	+++	187	+++	198	+++	—	—	—	—
24 "	Not done	—	213	—	238	+++	220	+++	230	+++	200	+++	—	—	—	—

especially in the afternoon, but will tail off and avoid hypoglycaemia at night, though retaining enough action to prevent a serious diabetic relapse before breakfast—a worthy ambition but a tall order for any one preparation. On the whole the publications and opinions expressed in America suggest that G.Z.I. has more action in lowering blood sugar near from 4 to 12 hours after injection and less from 12 to 24 hours than P.Z.I. But a close study of the few detailed protocols pub-

avoided. The manufacturers must know the problem of mixed injections, because I have urged them for years to try to produce a P.Z.I. without an excess of protamine (I gather it contains twice as much protamine as is necessary to precipitate the insulin) so that varying mixtures of P.Z.I. and soluble could be injected with more predictable results. Again, the fact that P.Z.I. is cloudy and soluble insulin clear is a great safeguard against mistakes between delayed-action and quick-

acting insulins; but the new G.Z.I. is a water-clear solution—to my mind, a serious disadvantage. Mistakes between insulins are all too common at present, and I foresee far more if another depot insulin appears on the market, especially if indistinguishable from soluble except for its label. It is difficult for me to understand how a new preparation of such a potent drug as insulin can reach the stage of marketing without serious trial by, and consultation with, the clinicians who will use it. If there is no administrative mechanism for judging and controlling the marketing of new products by their value in practical treatment it ought to be created.

BIBLIOGRAPHY

- Andrews, G. B., Groat, W. A., Wood, A. V., and Jones, M. L. (1940). *N.Y. St. J. Med.*, **40**, 913.
 Bailey, C. C., and Marble, A. (1942). *J. Amer. med. Ass.*, **118**, 683.
 Bauman, L. (1939a). *Proc. Soc. exp. Biol.*, N.Y., **40**, 170.
 — (1939b). *Amer. J. med. Sci.*, **198**, 475.
 Duncan, G. G., and Barnes, C. E. (1941). *Ibid.*, **202**, 553.
 Levitt, A., and Schaus, J. P. (1942). *Med. Times and Long Island med. J.*, **70**, 187.
 Marks, H. E. (1940). *Med. Clin. N. Amer.*, **24**, 649.
 Reiner, L., Searle, D. S., and Lang, E. H. (1939a). *Proc. Soc. exp. Biol.*, N.Y., **40**, 171.
 — (1939b). *J. Pharmacol.*, **67**, 330.

FAUCIAL AND LABIAL DIPHTHERIA

BY

MANUEL ANDERSON, M.D.

Resident Medical Officer, Sheriff Hill Isolation Hospital, Gateshead

Diphtheritic membrane is rarely observed externally on the lip, and the following case, which presents this unusual feature, is deemed worthy of record.

A girl aged 10 was admitted to hospital on Dec. 23, 1942. On the morning of Dec. 21 she had complained of a sore throat and malaise. During the evening of the same day, while chewing a piece of toffee, she inadvertently bit her lower lip. She had no recollection of her lip bleeding. On the morning of the 22nd Dr. Jamieson—her family doctor—was called in. Finding clinical evidence of faucial diphtheria, he took a throat swab, which was reported K.L.B.—

positive next day, when she was sent to hospital. At the time of this examination Dr. Jamieson saw no evidence of labial membrane.

On admission the girl, who was rather undernourished and pale, was moderately ill. There were flea-bites and a few septic spots over her limbs and trunk. Immediately to the left of the midline on her lower lip was a patch of diphtheritic membrane. On eversion of the lip this appeared to be mainly on the upper and internal surfaces. It was quite discrete, oval in shape, and measured about 3/4 in. by 1/2 in. The membrane had a faint yellowish tinge and glistened. It was

thicker in the middle than at the edges. There was a moderate amount of oedema of the underlying portion of the lip, with marked injection of the area immediately surrounding the membrane (see photograph). The tonsils were moderately enlarged and inflamed. Covering the right tonsil was a patch of membrane about 1/2 in. in diameter and a smaller patch was seen on the left tonsil. There was no appreciable fetor, and only moderate bilateral cervical lymphadenitis. An enlarged, slightly tender lymph gland was present in the submental triangle. Examination of the circulatory, respiratory, and central nervous systems revealed nothing abnormal. The left knee-joint was the seat of long-standing tuberculous disease.

Treatment.—50,000 units of diphtheria antitoxin were administered intramuscularly after a serum-sensitivity test which proved negative. Swabs were taken from both lip and throat; from each of these were isolated "gravis" type diphtheria bacilli. The accompanying photograph was taken shortly after her admission to hospital.

Subsequent Progress.—The day following admission the membrane seemed rather thicker, while the edges began to curl away from the lip surface, so that it appeared even more discrete than previously. After this the process of separation continued by a gradual thinning of the membrane as if its surface were being slowly rubbed away, and at the same time by the separation of tiny flakes from the edges, so that the membrane appeared to shrink in extent and thickness simultaneously. That portion of the lip exposed after separation of the membrane was almost "red-raw," and at times a little blood oozed from the surface.

By Dec. 27 separation of faucial membrane was complete, but the labial membrane was still present, although only half its original size. On the 28th a small thin flake of membrane remained on the lower lip, and only slight local oedema was present. On the 31st there was no appreciable diminution in the size of this flake, and it did not disappear entirely until Jan. 2, 1943. The area of the lip affected showed no evidence of injury after complete separation of the membrane. At this time the only abnormalities revealed on clinical examination were occasional extrasystoles. The patient was allowed up on Jan. 12, and was discharged on the 26th.

Comment

In the literature one can find very little reference to labial membrane, apart from direct extension in cases of late severe faucial diphtheria. An authority of such wide experience as Goodall (1928) says: "The writer has twice seen membrane on the tongue, three times on the lips, twice on the floor of the mouth, and once on the gums." Reiche in 1914 (M.R.C., 1923) recorded 49 instances of lesions of the lips among 7,314 fatal cases of diphtheria in Hamburg.

There can be no doubt that in our case the deciding factor was trauma to the lip in the presence of an existing faucial infection. Yet it is evident that, in view of the girl's story that the wound did not bleed, the trauma could only have been slight. It would appear, then, that relatively slight damage to labial mucosa facilitated the inoculation of the bacilli, and it is therefore surprising that labial membrane is not more frequently seen. Carrying the analogy to the fauces, it seems not unreasonable to suppose that Klebs-Löffler bacilli may gain entry to the tonsillar epithelium by virtue of minute traumata—possibly as a result of swallowing solid foods. This supposition may be further borne out by the experience that diphtheria is not often seen in tonsillectomized subjects or even in people with very small tonsils, in whom the lack of prominence would be associated with less possibility of trauma.

Summary

A case of faucial and labial diphtheria is described in which the formation of labial membrane followed a slight injury to the lip. The subsequent progress is recorded. It is suggested, from a consideration of this case, that slight trauma to a tissue may readily facilitate the introduction of Klebs-Löffler bacilli.

I would like to express my gratitude to Detective McHugh of the Gateshead Police for the excellent photograph reproduced herewith; to the bacteriology department of the City Hospital for Infectious Diseases, Newcastle, for "typing" of the causative organisms; and to Dr. James Grant (medical superintendent of this hospital) for granting me permission to publish this case.

REFERENCES

- Goodall, E. W. (1928). *Infectious Diseases*, 3rd ed., p. 168, London.
 M.R.C. (1923). *Diphtheria: Its Bacteriology, Pathology, and Immunology* p. 229, London.