be controlled by other mechanisms, such as direct or indirect action on tissue metabolism.

Experimental medicine has given us most of our fundamental knowledge of diabetes, and it seems that it will continue to increase this knowledge. It also gives us hope that new methods that will prevent or even cure this disease may be discovered.

BIBLIOGRAPHY

- Barnes, B. O., and Regan, J. F. (1933). *Endocrinology*, **17**, 522.
— and Nelson, W. O. (1933). *J. Amer. med. Ass.*, **101**, 926.
Braun-Menéndez, E., and Martínez, C. (1949-50). *Rev. Soc. argent. Biol.*, **25**, 162, 168; *C.R. Soc. Biol., Paris*, **144**, 415, 417.
Cardeza, A. F. (1950). *Rev. Soc. argent. Biol.*, **26**, 150.
— Mancini, R. E., and Foglia, V. G. (1949-50). *Rev. Soc. argent. Biol.*, **25**, 278; *C.R. Soc. Biol., Paris*, **144**, 425.
— and Rodríguez, R. R. (1949-50). *Rev. Soc. argent. Biol.*, **25**, 178; *C.R. Soc. Biol., Paris*, **144**, 421.
Collip, J. B., Selye, H., and Neufeld, A. (1937). *Amer. J. Physiol.*, **119**, 289.
Del Castillo, E. B., and Sammartino, R. (1937). *Rev. Soc. argent. Biol.*, **13**, 455.
Dolin, G., Joseph, S., and Gaunt, R. (1941). *Endocrinology*, **28**, 840.
Foglia, V. G. (1944). *Rev. Soc. argent. Biol.*, **20**, 21.
— (1945a). *Ibid.*, **21**, 7.
— (1945b). *Ibid.*, **21**, 45.
— (1945c). *Ibid.*, **21**, 360.
— (1949-50). *Ibid.*, **25**, 250; *C.R. Soc. Biol., Paris*, **144**, 424.
— and Cramer, F. K. (1944). *Proc. Soc. exp. Biol., N.Y.*, **55**, 218.
— Mancini, R. E., and Cardeza, A. F. (1950). *Arch. Path.*, **50**, 75.
— Orlas, O., and Sara, J. G. (1944). *Rev. Soc. argent. Biol.*, **20**, 440.
— Schuster, N., and Rodríguez, R. R. (1947). *Endocrinology*, **41**, 428; *Rev. Soc. argent. Biol.*, **23**, 202.
Houssay, B. A. (1937). *Amer. J. med. Sci.*, **193**, 581.
— (1946). *Vitamins and Hormones*, **4**, 187.
— (1948). *Recent Progr. Hormon. Res.*, **2**, 277.
— (1950). *Amer. J. med. Sci.*, **219**, 353.
— Foglia, V. G., and Martínez, C. (1946). *Endocrinology*, **39**, 361.
— Prieto Díaz, H., and Sara, J. G. (1945). *Rev. Soc. argent. Biol.*, **21**, 232.
— Lott, W. A., and Martínez, C. (1950). *Ibid.*, **26**, 335.
— and Martínez, C. (1947). *Science*, **105**, 548.
— (1948). *Rev. Soc. argent. Biol.*, **24**, 63, 123, 242; *C.R. Soc. Biol., Paris*, **142**, 1167, 1573.
— and Mazzocco, P. (1946). *Rev. Soc. argent. Biol.*, **22**, 367.
— and Sara, J. G. (1945). *Ibid.*, **21**, 81.
Ingle, D. J. (1941). *Endocrinology*, **29**, 838.
— (1943). *Amer. J. Physiol.*, **138**, 577.
— and Hogg, J. A. (1947). *Proc. Soc. exp. Biol., N.Y.*, **66**, 244.
— Nezamis, J. E., and Prestrud, M. C. (1947). *Endocrinology*, **41**, 207.
Janes, R. G., and Dawson, H. (1946). *Ibid.*, **38**, 10.
Lewis, J. T., Foglia, V. G., and Rodríguez, R. R. (1949-50). *Rev. Soc. argent. Biol.*, **25**, 67; *Endocrinology*, **46**, 111.
Martínez, C. (1945a). *Rev. Soc. argent. Biol.*, **21**, 254.
— (1945b). *Ibid.*, **21**, 332.
— (1946a). *Ibid.*, **22**, 414.
— (1946b). *Ibid.*, **22**, 135.
— (1946c). *Ibid.*, **22**, 428.
Mering, J. von, and Minkowski, O. (1889). *Versamml. Dtsch. Natur. Aerzte, Heidelberg*, **23**, 393.
Nelson, W. O., and Overholser, M. D. (1936). *Endocrinology*, **20**, 473.
Rodríguez, R. R. (1950a). *Rev. Soc. argent. Biol.*, **26**, 205.
— (1950b). *Ibid.*, **26**, 247.
— (1950c). *Proc. Soc. exp. Biol., N.Y.*, **73**, 317.
— (1950d). Tesis Fac. Med. B. Aires.
— and Martínez, C. (1950). *Rev. Soc. argent. Biol.*, **26**, 127.
Shapiro, R., and Pincus, G. (1936). *Proc. Soc. exp. Biol., N.Y.*, **34**, 416.
Souto-Maior, M. G., and Foglia, V. G. (1944). *Rev. Soc. argent. Biol.*, **20**, 55.
Tejning, S. (1947). *Acta med. scand.*, Suppl. 198.
Young, F. G. (1941). *Lancet*, **1**, 600.

A welfare worker of the Save the Children Fund has been working in Northern Papua since mid-May as part of the disaster relief organized in New Guinea after the volcanic explosion there early this year (*The World's Children*, September, 1951). She remarks that the average Papuan infant is smaller than the European at birth, weighing about 5 lb. Weaning begins at about 6 months old, with hard indigestible taro and rice, but an attempt is being made to teach the mothers cooking of vegetables and the preparation of porridge and other types of infant food.

ORAL TREATMENT OF POLYCYTHAEMIA VERA WITH β -NAPHTHYL-DI-2-CHLOROETHYLAMINE (R48)

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Since Gilman and Philips (1946) and Rhoads (1946) published the first communications on the therapeutic action of nitrogen mustards (methyl bis- β -chloroethylamine and methyl tri- β -chloroethylamine), a number of reports on the use of these substances have appeared. On the whole there seems to be agreement that, given intravenously, nitrogen mustards can produce a distinct, but only temporary, improvement in some cases of malignant lymphogranulomatosis, lymphosarcoma, chronic leukaemia, and polycythaemia vera. As is known, the substances are cell poisons, and their inhibiting effect on bone marrow involves some risk. Thus cases of agranulocytosis have been met with after intravenous treatment with nitrogen mustard (Bjurwill, 1947; Iversen, 1951). There are also other drawbacks, such as the tendency to the formation of thrombi at the site of injection, and nausea and vomiting following the injection, while the intravenous method itself is a disadvantage, particularly as it must be carried out with due observance of various precautionary measures.

R48 by Oral Administration

Continuous work is being done with these fairly simple substances from a chemical standpoint, in order if possible to discover some which act more selectively and are less toxic. For instance, Burchenal (1948) tested two kinds of complex aliphatic nitrogen mustards, but they proved to be too toxic.

Haddow and others (1948) prepared a series of aromatic nitrogen mustards, the action of which they tested on experimentally produced tumours. Some of these substances turned out to be unsuitable for clinical use owing to their toxic effects. One of them, β -naphthyl-di-2-chloroethylamine (R48), however, seemed quite appropriate for a clinical trial. It had the added advantage that it could be administered orally. Clinical investigations were carried out in Oxford, and Matthews (1950) has published a preliminary report on the findings in 17 patients with various grave blood diseases. He found some improvement in five cases of Hodgkin's disease, but not more than has been observed to follow treatment with methyl-bis- β -chloroethylamine. At any rate R48 was unsuitable for the treatment of patients with localized masses of glands; x-ray treatment produced far better results. In two cases of reticulosarcoma and two cases of acute leukaemia there was no effect. In two out of four cases of chronic myeloid leukaemia a surprisingly good remission occurred which lasted for 11-28 weeks. These remissions could be reproduced without toxic effects. But the observation period for all these patients is still too short. The best result was observed in a patient with polycythaemia vera

in whom the remission had so far persisted for one year without any toxic effects supervening during the treatment. Matthews concludes that, on the whole, the action is basically the same as with methyl-bis- β -chloroethylamine, but it occurs more slowly and is more easily controlled.

With regard to the method of administration and dosage it is stated that the drug was given by mouth in tablets of 100 mg. The tablets are chewed, but they are tasteless. The drug is partially inactivated by light, which fact should be kept in mind. The daily dose was 300–400 mg.—at the most 600 mg. (two tablets three times a day). The original intention was to keep the disease in check with small repeated doses, but this was found to be impossible. It was therefore given for periods alternating with free intervals. No scheme for the treatment was adopted. The course of the disease in each patient was followed at first with weekly blood counts, but less frequently later on.

Like methyl-bis- β -chloroethylamine, the drug is toxic to the bone marrow, and therefore a fall in the leucocytes was observed in most cases. Apart from cases of leukaemia, this is not the object in view, nor is it desirable, but the fall sets in gradually and slowly during a period of a few weeks, and it evidently can be easily estimated. It must, however, be clearly recognized that the fall in granulocytes often continues for one to two weeks after the drug is discontinued, only to rise again spontaneously. Matthews (1950) has seen a case of granulocytopenia (550 per c.mm.) in a patient in the final stage of a reticulo-sarcoma; after stopping the drug the granulocyte count returned to normal. The thrombocyte figure also generally fell, and a case is described with a drop in the blood platelets to 55,000 per c.mm. a fortnight after the drug was discontinued. Here, again, there was a spontaneous and complete rise in the number of platelets. On the other hand, the haemoglobin percentage and the number of erythrocytes remained fairly constant.

Gastro-intestinal symptoms in the form of vomiting and diarrhoea were only exceptionally observed after R48: at most there was a little nausea in the first week. Haddow and others (1948) even met with haemorrhagic cystitis in two patients; this was possibly due to the aromatic radicle in the R48 complex, since β -naphthylamine is known in industry as a toxic substance which can cause haematuria.

Present Investigations

After having employed intravenous injections of nitrogen mustards for a year or two in various blood diseases, the attendant risks of which, as mentioned, are conspicuous in the form of nausea and vomiting after the injection and a tendency to thrombosis at the site of the injection, we felt inclined to pass on to oral medication with the related substance β -naphthyl-di-2-chloroethylamine, which we had heard about at second hand. On applying to Professor Haddow, of the Royal Cancer Hospital in London, we obtained some of the substance for our use under the name "preparation R48," and at first the treatment was carried out only with this preparation. Later we used a Danish preparation, "aleukon," prepared and placed at our disposal by the Danish Medicinal and Chemical Company, Medicinalco.

The therapeutic investigations were concerned only with polycythaemia vera. This relatively benign disease, with its rather long course, would seem to be a particularly appropriate one for a treatment which is of a

compensatory nature. We have treated six patients. Only patients whose disease was of several years' standing were chosen. Most of them had already received other treatment such as x rays, intravenous nitrogen mustards, or repeated venesection. None of the patients had had any treatment within the nine months before the administration of β -naphthyl-di-2-chloroethylamine was begun.

The clinical histories are concisely recorded because the emphasis is on the haematological changes.

Case 1

A man aged 69 was known to have had polycythaemia for five years, with the red cells around 7,500,000 per c.mm. He received three series of nitrogen-mustard injections intravenously (methyl-bis- β -chloroethylamine), with good results subjectively and objectively. The remissions lasted four to six months after the first two series of injections, but 16–18 months after the third.

FIG. 1.—Case 1. The dotted line represents leucocytes, the continuous line haemoglobin, and the broken line erythrocytes in this and later figures.

In May, 1949, oral administration of β -naphthyl-di-2-chloroethylamine was begun in doses of 100 mg. four times daily, which each time produced a considerable remission in the blood picture (Fig. 1), and there was an improvement subjectively and a decline in the polycythaemic appearance. A moderate degree of spleen enlargement also disappeared at the same time.

Case 2

A woman aged 49 was known to have had polycythaemia for five years. When the disease was diagnosed the red cells were 7,700,000 per c.mm. She had earlier been treated unsuccessfully with urethane, but later nitrogen mustard intravenously produced a good result, the remission lasting for 15 months.

FIG. 2.—Case 2.

As it was impossible to penetrate into her veins, oral administration was started in March, 1949, with β -naphthyl-di-2-chloroethylamine, 100 mg. three times daily, which she received for 126 days. The redness and lassitude disappeared concurrently with a marked fall in the red-cell count and haemoglobin value (see Fig. 2), which have so far remained normal for 15 months since the termination of the treatment.

Case 3

A man aged 51 was known to have had polycythaemia for nine years. He had previously received x-ray treatment alternating with venesection, with temporary good effect. In April and May, 1947, he was treated with two series of intravenous injections of nitrogen mustard, which had a good subjective effect but only a slight effect on the blood.

After a lapse of nine months treatment was resumed in November, 1948, with β -naphthyl-di-2-chloroethylamine, 100 mg. thrice daily by mouth. It could be given for only 48 days, as the supply of the drug gave out. Except

FIG. 3.—Case 3.

for a fall in the leucocytes no haematological changes occurred after this dosage, though the spleen enlargement disappeared and the redness was somewhat less.

From July, 1949, the patient has been treated continuously with β -naphthyl-di-2-chloroethylamine. For the first three months 500 mg. daily was given, then 600 mg. for two months, and after that 200 mg. daily, on which dose the patient has been kept for 10 months; it is planned to keep him on continuous treatment. In addition to marked haematological improvement (see Fig. 3) his appearance has altered much, the redness having decreased quite considerably.

Case 4

A man aged 61 was known to have had polycythaemia for four years. He has had four series of intravenous injections of nitrogen mustard with temporary benefit. The remissions lasted two to five months.

FIG. 4.—Case 4.

After a lapse of ten months treatment was started again in October, 1948, with β -naphthyl-di-2-chloroethylamine, 100 mg. twice daily. This low dosage was given for only 21 days because of short supplies, and no definite effect followed. Later he received 400 mg. daily for four months, but the haematological improvement was only minimal (see Fig. 4), although he himself felt well in the year following the last series of the treatment. A rather considerable enlargement of the spleen persisted unchanged during the treatment.

Case 5

A woman aged 68 was known to have had polycythaemia for four years. She has twice been treated with intravenous injections of nitrogen mustard. The remissions lasted for only five and four months respectively.

In February, 1950, treatment was begun with β -naphthyl-di-2-chloroethylamine, 400 mg. and, later, 600 mg. daily. The treatment was discontinued after 67 days on account

FIG. 5.—Case 5.

of leucopenia (1,200 leucocytes per cmm. with 82% granulocytes). There was a continued fall in the haemoglobin percentage and red-cell counts, accompanied by a distinct diminution in the patient's polycythaemic appearance, and her dyspnoea and lassitude improved. So far the remission has continued for six months.

Case 6

A man aged 53 was known to have had polycythaemia for three years. He has had intravenous injections of nitrogen mustard four times, with distinct but temporary remissions of up to five months' duration.

In January, 1950, treatment with β -naphthyl-di-2-chloroethylamine was begun at a time when he was greatly troubled by his complaint and had a red-cell count of 9,800,000. To start with he received 300 mg. daily, and later 600 mg. daily for four months, after which the dose was reduced to 200

FIG. 6.—Case 6.

mg. daily; we shall try to keep this patient on this dosage continuously.

Fig. 6 shows a marked remission in a haematological respect. A change in the patient's polycythaemic appearance could also be clearly seen.

Comment

The short clinical histories and the diagrams show that a distinct remission occurred in at least five out of six polycythaemic patients in response to the oral administration of β -naphthyl-di-2-chloroethylamine for periods varying from a few weeks up to a few months. At first we were cautious with the dosage; 500–600 mg. might be given daily to start with for a few months, after which the dose should be reduced. An attempt was made to keep two patients stable on a small continuous dose (200 mg. daily), so far with good result.

We have also seen a fall in the leucocyte values during the treatment: in one case a fall to as low as 1,200 leucocytes per c.mm. occurred, but a spontaneous and rapid rise set in 12–14 days after the drug was discontinued.

It appears from this and what was earlier stated that the substance is a potential bone-marrow poison inherent in which is the risk of damage to the bone marrow, with aplastic anaemia or perhaps rather granulocytosis as a result. It is therefore necessary that these patients should be carefully and constantly followed with blood counts during treatment. As is known, polycythaemia is in itself a relatively benign disease and usually the patients have a fairly long expectation of life (cf. Dameshek (1950) and Videbæk (1950), amongst whose groups of patients there were several with a history of over 20 years), and therefore emphasis must be placed on caution during the treatment.

Summary

Six patients with long-continued polycythaemia were treated orally with β -naphthyl-di-2-chloroethylamine. The dosage was between 300 and 600 mg. daily. Treatments were given in series; in only two patients was it possible to give the drug continuously. In five out of the six cases a marked fall in the percentage of haemoglobin and red-cell counts occurred, and, parallel with this, a decrease in the redness and a subjective improvement. In one of the patients the remission has so far lasted for 15 months.

Attention is directed to the toxic effect of the substance on the bone marrow, which necessitates careful and constant control by blood examinations. Gastro-intestinal symptoms were not observed during our tests with the substance.

ADDENDUM

Follow-up, April, 1951

Case 1.—Hb, 106%; erythrocytes, 4,710,000; leucocytes, 8,000. The patient feels well. No erythrosis of the face. Has been without treatment for seven months.

Case 2.—Hb, 106%; erythrocytes, 4,590,000; leucocytes, 5,300. The patient feels well. No erythrosis of the face. Has been without treatment for 19 months.

Case 3.—Hb, 135%; erythrocytes, 5,620,000; leucocytes, 12,900. The patient feels well. Face less erythrotic. Is under permanent treatment with 300 mg. daily, and has been so for 14 months.

Case 4.—Hb, 113%; erythrocytes, 6,020,000; leucocytes, 10,900. The patient feels well. Face less erythrotic. Has

been without treatment for 20 months, but because of the enlarged spleen the treatment will be continued.

Case 5.—Hb, 107%; erythrocytes, 5,160,000; leucocytes, 4,400. The patient feels well. No erythrosis of the face. Has been without treatment for 10 months.

Case 6.—Hb, 126%; erythrocytes, 5,850,000; leucocytes, 5,700. The patient feels well. Has been without treatment for five months, but because of the rise of haemoglobin the treatment will be continued.

REFERENCES

- Bjurwill, B. (1947). *Nord. Med.*, **36**, 2059.
Burchenal, J. H. (1948). *Radiology*, **50**, 494.
Dameshek, W. (1950). *J. Amer. med. Ass.*, **142**, 790.
Gilman, A., and Philips, F. S. (1946). *Science*, **103**, 409.
Haddow, A., Kon, G. A. R., and Ross, W. C. J. (1948). *Nature, Lond.*, **162**, 824.
Iversen, K. (1951). In press.
Matthews, W. B. (1950). *Lancet*, **1**, 896.
Rhoads, C. P. (1946). *J. Amer. med. Ass.*, **131**, 656.
Videbæk, Aa. (1950). *Acta med. scand.*, **138**, 179.

OBSERVATIONS ON ALL BIRTHS (23,970) IN BIRMINGHAM, 1947*

IV. "PREMATURE BIRTH"

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Our objects in this communication are, first, to present evidence on the mortality experience of a large series of births, and, secondly, against the background of this information to comment on the current conception of "prematurity." The use of weight as an index of maturity is so firmly rooted in contemporary practice that the strongest of reasons would be needed for changing it. We shall suggest reasons for reconsidering it, recognizing that on a matter of this kind the last word is not with the research worker but with the practising obstetrician and paediatrician.

It may be useful to recall briefly the circumstances in which the word "premature" was given a precise meaning. Ylppö (1920) suggested that births of infants less than 2,500 g. in weight should be considered not mature, in the sense that they had not remained long enough in the uterus. He justified the use of weight as an index of maturity on the grounds that it was as good as or better than any single alternative, and explained that the limit of 2,500 g, though quite arbitrary, was one below which most births were not fully developed. He recognized that the word "premature" was unsatisfactory, but thought that as it was well established in the literature it would be wise to retain it.

It should be noted that these views were not based on information about a large series of births; Ylppö himself reported on only 670 individuals. Nevertheless had his proposal been seriously in error it seems certain

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