ventricle is perhaps the most frequent cause. Increased bronchial flow in tetralogies and open ductus are other causes.

REFERENCES

- Allen, P., and Lillehei, C. W. (1957). *Minn. Med.*, **40**, 672.
 Burchell, H. B. (1957). *Circulation*, **16**, 976.
 Clark, L. C., jun., Wolf, R., Granger, D., and Taylor, Z. (1953). *J. appl. Physiol.*, **6**, 189.
 Folkman, M. J., and Watkins, E. (1958). *Surg. Forum*, **8**, 331.
 Helmsworth, J. A., Clark, L. C., jun., Kaplan, S., Sherman, R. T., and Largen, T. (1952). *J. thorac. Surg.*, **24**, 117; Discussion, p. 151.
 Ito, I., Faulkner, W. R., and Kolff, W. J. (1957). *Cleveland Clin. Quart.*, **24**, 193.
 ——— Kolff, W. J., and Effler, D. B. (1958). *Ibid.*, **25**, 9.
 Jones, R. E., Donald, D. E., Swan, H. J. C., Harshbarger, H. G., Kirklin, J. W., and Wood, E. H. (1955). *Proc. Mayo Clin.*, **30**, 105.
 Kay, E. B., Zimmerman, H. A., Berne, R. M., Hirose, Y., Jones, R. D., and Cross, F. S. (1956). *J. Amer. med. Ass.*, **162**, 639.
 Kolff, W. J., Effler, D. B., Groves, L. K., Hughes, C. R., and McCormack, L. J. (1958). *Cleveland Clin. Quart.*, **25**, 65.
 ——— and Moraca, P. P. (1957). *J. Amer. med. Ass.*, **164**, 1653.
 ——— Peereboom, G., and Moraca, P. P. (1956). *Cleveland Clin. Quart.*, **23**, 69.
 Lillehei, C. W. (1957). "Present Indications and Contraindications for Open-heart Surgery." Presented at joint meeting of the Cleveland Surgical Society and the Academy of Medicine of Cleveland, Cleveland, Ohio, October 4, 1957.
 Maraist, F. B., and Glenn, W. W. L. (1952). *Surgery*, **31**, 146.
 Melrose, D. G. (1955). *J. Physiol. (Lond.)*, **127**, 51P.
 Muller, W. H., jun., Littlefield, J. B., and Dammann, J. F., jun. (1958). In *Extracorporeal Circulation*, edited by J. G. Allen, p. 336. Thomas, Springfield, Ill.
 Mural, A. von (1954). In *Handbuch der Inneren Medizin*, 4th ed., edited by G. von Bergmann, W. Frey, and H. Schwegk, vol. VI, Pt. 2, p. 310. Springer, Berlin.
 Olmsted, F., Kolff, W. J., and Effler, D. B. (1958a). *Cleveland Clin. Quart.*, **25**, 84.
 ——— (1958b). *Ibid.*, **25**, 169.
 Patrick, R. T. (1957). *Anesthesiology*, **18**, 643.
 Patz, A. (1955). Report of the 16th M and R Pediatric Research Conference, M and R Laboratories, Columbus, Ohio.
 Penido, J. R. F., Swan, H. J. C., and Kirklin, J. W. (1957). *Proc. Mayo Clin.*, **32**, 389.
 Pichotka, J., and Kuhn, H. A. (1947). *Naunyn-Schmiedeberg's Arch. exp. Path. Pharmacol.*, **204**, 336.
 Zoll, P. M., Paul, M. H., Linenthal, A. J., Norman, L. R., and Gibson, W. (1956). *Circulation*, **14**, 745.

INFLUENCE OF THE PITUITARY ON THE ERYTHROPOIETIC PRINCIPLE PRODUCED IN THE KIDNEY

BY

SVERRE OSNES, M.D.

From the Institute of General and Experimental Pathology,
University of Oslo (Director: Professor L. Kreyberg, M.D.)

This study is a continuation of a previous work (Osnes, 1959). The purpose of this report is to demonstrate the stimulating influence of the pituitary on the erythropoietic principle produced in the kidney (K.F.=kidney factor).

It is well accepted that an anaemia develops after hypophysectomy, but opinions differ regarding the mechanism of post-hypophysectomy anaemia.

Flaks *et al.* (1937, 1938) reported that the oral administration of anterior lobe of ox pituitary or extracts of anterior lobe resulted in a significantly increased erythrocyte count in both normal and hypophysectomized rats, and postulated that the anterior lobe of the pituitary contains a specific erythropoietic hormone with the bone-marrow as its target organ. Meyer *et al.* (1940) were unable to obtain the results reported by Flaks *et al.*

White and Dougherty (1945) stated that continued daily injection of pituitary adrenotrophic hormone into

mice resulted in an increase in haemoglobin and in red cells. They concluded that the adrenotrophic hormone, by means of its trophic influence on the adrenal cortex, maintains a physiological control over the number of circulating erythrocytes.

A number of papers which deal with the erythropoietic effect of pituitary extracts and hormones have been published from the Institute of Experimental Biology and the Donner Laboratory, University of California (Garcia *et al.*, 1951; Contopoulos *et al.*, 1953, 1954; Van Dyke *et al.*, 1954, 1957). These investigators reported that normal rats injected with 0.5 mg. of adrenocorticotrophic hormone twice a day for 34 days showed normal haematological values, whereas after 116 days four rats showed a red-cell volume and a haematocrit level above those of normal controls. Oral administration of sheep anterior pituitary repaired the anaemia in hypophysectomized rats, and in adrenalectomized rats brought a 20% increase in circulating red-cell volume above that of either normal or adrenalectomized controls. Hypophysectomized rats injected with "pituitary erythropoietic factor" showed marked increase in red-cell volume, haemoglobin, and haematocrit. "These values were not only brought back to normal but exceeded normal value."

Based on these and other findings, the above authors postulated the existence of a pituitary erythropoietic factor distinct from the well-known pituitary hormones and with the bone-marrow as its target organ. Some of these authors felt that there also was chemical evidence for such an opinion.

Simpson *et al.* (1959), however, presented a re-evaluation of the evidence for a pituitary erythropoietic hormone and stated: "... there is no satisfactory evidence for a pituitary erythropoietic factor distinct from the known pituitary hormones. The adrenocorticotrophic hormone is clearly instrumental in the regulation of red-cell volume, as is thyrotrophic hormone and possibly growth and gonadotrophic hormones. The relative importance and mechanism of action of the several factors remains to be determined."

Several investigators believe that anaemia which follows hypophysectomy does not indicate any specific deficit in erythropoiesis and have claimed that the loss of the pituitary influence on the adrenals, gonads, and especially on the thyroid may be responsible for the developing anaemia. Crafts (1949) reported that in hypophysectomized rats treated with thyroxine, combined with testosterone propionate and high-protein diet, the haematocrit and haemoglobin values were maintained at normal levels and the number of erythrocytes increased above the control level.

The method used in the present work was described earlier (Osnes, 1959). To indicate the variation between the observations, ± 1 standard deviation has been calculated, and plotted in the graphs.

Experimental Findings

Fig. 1 shows the reticulocyte and haemoglobin values in a group of hypophysectomized bled rats and in a group of normal bled rats. It is seen that the reticulocytosis in the hypophysectomized bled rats was only about half the value of that observed in the normal bled controls. Many of the reticulocytes seen in the

hypophysectomized animals were small and deformed cells. After the last bleeding on the sixth day the haemoglobin value rose quickly in the normal rats, whereas the rise in haemoglobin value in the hypophysectomized rats was slight.

FIG. 1.—Hypophysectomized bled rats (6): $\square$ — $\square$, Hb; $\blacksquare$ — $\blacksquare$, reticulocytes. Normal bled rats (6): $\circ$ — $\circ$, Hb; $\bullet$ — $\bullet$, reticulocytes.

The finding that hypophysectomized animals are able to react with reticulocytosis after bleeding has led some authors to conclude that there is no specific deficit in the erythrocyte production in hypophysectomized animals. This, however, may be a premature conclusion. In my experiments bled nephritic mice also have shown a reticulocytosis of nearly the same degree as bled hypophysectomized rats. The nephritic mice, however, are lacking a specific erythropoietic principle (K.F.) (Osnes, 1959).

FIG. 2.—Donors: hypophysectomized bled rats (10). Recipients: —, normal mice (10); ---, nephritic mice (10).

It has previously been demonstrated that serum from normal bled mice has an elevated titre of erythropoietin (produces reticulocytosis when injected into normal mice) as well as of K.F. (produces reticulocytosis when injected into nephritic mice). The titre of these two different erythropoietic principles is also found to be raised in serum from normal bled rats.

FIG. 3.—Adrenalectomized bled mice (7): $\square$ — $\square$, Hb; $\blacksquare$ — $\blacksquare$, reticulocytes. Sham-operated bled mice (6): $\circ$ — $\circ$, Hb; $\bullet$ — $\bullet$, reticulocytes.

Fig. 2 shows an experiment where 10 hypophysectomized rats were bled to a haemoglobin value of about 30%. On the third day serum from each rat was injected into one normal and one nephritic mouse (2% of body weight). Serum from all rats gave reticulocytosis in the normal mice, but in no instance was reticulocytosis found in nephritic mice. This experiment shows that hypophysectomized rats are not able to elevate their titre of K.F. after bleeding, whereas their erythropoietin titre is elevated. These are just the same findings as demonstrated in x-irradiated nephritic mice and in anaemic human patients suffering from nephritis, chronic polyarthritis, and ulcerative colitis (Osnes, 1959). As K.F. is found necessary for the erythropoiesis, the present experiments indicate that the post-hypophysectomy anaemia is related to lack of K.F., and it may be assumed that some pituitary substance has a regulating influence on the secretion or production of K.F.

Fig. 3 shows the reticulocyte values and the haemoglobin values in a group of adrenalectomized mice and in a group of sham-operated mice bled to the same degree. It is seen that the reticulocyte response was the same in both groups. After the mice had been bled for six days the haemoglobin values rose quickly to the same degree in both groups. It is possible that the adrenalectomized mice possessed intact accessory adrenal tissue. The fact, however, that no difference was found in reticulocyte values between the two groups, and that the haemoglobin values rose at the same degree in both groups after bleeding, indicates that the adrenals have no fundamental influence on the erythropoiesis.

Fig. 4 shows the reticulocytosis in normal and nephritic mice after a single injection of serum (2% of body weight) from adrenalectomized bled mice. This serum produced reticulocytosis in normal as well as in nephritic mice. In agreement with the experiments presented in Figs. 3 and 4 we must conclude that the production of erythropoietin as well as of the K.F. may go on in the absence of the adrenals. We must further conclude that the postulated pituitary substance regulating the K.F. does not act via the adrenals.

Fig. 5 shows the reticulocytosis in hypophysectomized rats injected subcutaneously with 4 mg. adrenocorticotrophic hormone twice a day. (The preparation used was "jaton prolongatum." This preparation contains carboxy-methyl cellulose saline of oxycellulose purified corticotrophin. In the following experiments the term A.C.T.H. refers to this preparation.) It is seen that hypophysectomized rats responded with considerable

FIG. 4.—Donors: adrenalectomized bled mice. Recipients: —, normal mice (6); ---, nephritic mice (6).

FIG. 5.—Hypophysectomized rats (6) treated with A.C.T.H.

reticulocytosis after injection of A.C.T.H. Because the anaemia in hypophysectomized rats is found to be related to lack of K.F. (Fig. 2) we must suppose that increased production of K.F. is the cause of the high reticulocyte response seen in these hypophysectomized rats after injection of A.C.T.H.

Increase of reticulocyte counts after injection of A.C.T.H. was found neither in nephritic nor in normal mice when the blood samples were taken at least 24 hours after the last injection. In spite of the finding that injection of A.C.T.H. may stimulate the production of K.F. in hypophysectomized rats, it is not to be expected that injection of A.C.T.H. increases the production of K.F. in nephritic mice, because the impaired production of K.F. in nephritic mice is most probably due to disease in the kidney. In normal mice, however, an elevation of the titre of K.F. without elevation of the titre of erythropoietin would not be expected to cause reticulocytosis.

With the intention of investigating whether A.C.T.H. elevates the titre of K.F. in normal mice the following experiments were done.

Normal mice were injected with A.C.T.H., and serum from these animals was injected into nephritic mice (2% of body weight). The donor group A was injected with 4 mg. of A.C.T.H. eight hours before giving serum to the recipient group A. The donor group B was injected with A.C.T.H. (2 mg. per injection) 24 and 8 hours before giving serum to the recipient group B. The donor group C was injected with A.C.T.H. (2 mg. per injection) 48, 36, 24, and 8 hours before giving serum to the recipient group C. Fig. 6 shows that reticulocytosis developed in all recipient groups. The highest reticulocyte response was seen in group B, which was injected with serum from mice treated with A.C.T.H. for 24 hours. As pointed out above, no reticulocytosis was seen in nephritic mice injected with A.C.T.H. when the blood samples were taken at least 24 hours after A.C.T.H. injection, and there-

FIG. 6.—Donors: normal mice treated with A.C.T.H. at (A) 8 hours, (B) 24 hours, and (C) 48 hours. Recipients: nephritic mice treated with serum from A (4); serum from B (5); and serum from C (4).

fore excludes the possibility that the response seen was due to A.C.T.H. itself. The present experiments clearly demonstrate that injection of A.C.T.H. in normal mice elevates their titre of K.F., because serum from these mice causes marked reticulocyte response in nephritic mice which are lacking the K.F. This observation is of great importance for the problems discussed in this paper and is in complete agreement with the findings presented above, that hypophysectomized rats which are lacking K.F. (Fig. 2) react with considerable reticulocytosis after injection of A.C.T.H. (Fig. 5).

Nephrectomized unbled mice were injected with A.C.T.H. (2 mg. per injection) 24 and 8 hours before their serum was given to nephritic mice. This serum gave no reticulocyte response in the nephritic recipients. In the previous paper it was demonstrated that nephrectomized mice do not elevate their titre of K.F. after bleeding. The present experiment shows that nephrectomized unbled mice do not elevate their titre

of K.F. after injection of A.C.T.H. The latter finding is fresh evidence, added to the former, that the kidney produces an erythropoietic principle (K.F.).

The findings presented above led to the conclusion that some pituitary substance has the kidney as target organ and stimulates the secretion (production) of the erythropoietic principle produced in the kidney (K.F.). One cannot with certainty exclude that the preparation used in these experiments (jaton prolongatum) may contain other active pituitary substances than the adrenocorticotrophic hormone. Therefore it is not possible from the experiments presented to tell whether the active pituitary substance is identical with the adrenocorticotrophic hormone.

If, however, the pituitary substance stimulating the secretion of K.F. is identical with the adrenocorticotrophic hormone, adrenalectomized unbled mice would be expected to have an increased titre of K.F. in their serum owing to their elevated titre of adrenocorticotrophic hormone. That this is the case is demonstrated in Fig. 7, which shows the reticulocyte response in nephritic and normal mice after injection of serum (2% of body weight) from adrenalectomized unbled mice. The adrenalectomy of the donors was performed 32 hours before giving their serum to the recipient groups. This experiment strongly indicates that the active pituitary substance is identical with the adrenocorticotrophic hormone. Serum from mice which had been adrenalectomized 52 hours previously gave only a slight reticulocyte response in nephritic mice.

It is a well-known fact that cortisone counteracts the production of adrenocorticotrophic hormone. If the pituitary substance stimulating the secretion of K.F. is identical with the adrenocorticotrophic hormone, it may be expected that large doses of cortisone will counteract the secretion of K.F. and impair the erythropoiesis. This is also the case. Fig. 8 shows the reticulocyte and haemoglobin values in a group of bled mice treated with cortisone and in a group of bled mice not treated with cortisone. Cortisone was injected subcutaneously twice a day (2 mg. of cortisone acetate in Ringer's solution to 0.2 ml. per injection) and was given two days before the first bleeding. (The preparation used was "cortone.") It is seen that the reticulocyte count in the cortisone-treated group was one quarter of the

FIG. 7.—Donors: adrenalectomized unbled mice. Recipients: normal mice (6); nephritic mice (6).

cortisone-treated group was one quarter of the

FIG. 8.—Cortisone-treated bled mice (7): Hb; reticulocytes. Normal bled mice (6): Hb; reticulocytes.

normal value after injection of cortisone for two days (before the first bleeding). After bleeding, the reticulocytosis in the cortisone-treated group was less than half of that seen in the control group. Many of the reticulocytes seen in the cortisone-treated animals were small and deformed cells, similar to those seen in hypophysectomized bled rats. This experiment clearly shows that the erythropoiesis is impaired in mice injected with large doses of cortisone.

Fig. 9 shows the reticulocyte values in normal and nephritic mice after a single injection of serum from cortisone-treated bled mice. The donors were injected with 2 mg. of cortisone twice a day and were bled on the third and fourth day, and the serum was given to the recipients on the fifth day. This

FIG. 9.—Donors: cortisone-treated bled mice. Recipients: —, normal mice (6); ---, nephritic mice (6).

serum produced reticulocytosis in normal mice, but not in nephritic mice. This experiment shows that mice injected with large doses of cortisone are not able to elevate their titre of K.F. after bleeding, whereas their titre of erythropoietin is increased.

The findings presented in Figs. 7, 8, and 9 have led to the conclusion that the pituitary substance stimulating the secretion of K.F. is identical with the adrenocorticotrophic hormone.

If the kidney is functioning as target organ for adrenocorticotrophic hormone, it may be expected that some demonstrable alteration will take place in the kidney after the influence of the adrenocorticotrophic hormone. This is also the fact. It has been pointed out in this paper that bleeding, A.C.T.H. injection, and adrenalectomy raise the titre of K.F. in mice with intact kidneys. By all these procedures, which raise the titre of adrenocorticotrophic hormone, characteristic changes are seen in the juxtaglomerular cells. It has been suggested that the K.F. is connected with the granules of the juxtaglomerular cells (Osnes, 1958, 1959). Further experiments on the relation between the titre of K.F. and the alteration of the juxtaglomerular cells have corroborated this view and are in good agreement with the assumption that the juxtaglomerular cells function as target organ for adrenocorticotrophic hormone and are the producers of the K.F. or its precursor. The findings related to the juxtaglomerular cells will be documented and discussed in a separate paper.

Discussion

Because hypophysectomized rats show impaired erythrocyte regeneration after bleeding (Fig. 1), and because hypophysectomized rats are unable to elevate their titre of K.F. after bleeding (Fig. 2), it is concluded that some pituitary substance stimulates the secretion (production) of K.F.

The findings that injection of a highly purified adrenocorticotrophic preparation (jaton prolongatum) produces considerable reticulocytosis in hypophysectomized rats (Fig. 5), and, further, that this preparation elevates the titre of K.F. in unbled mice with intact kidneys (Fig. 6), make it most likely that the pituitary substance stimulating the secretion of K.F. is identical with the adrenocorticotrophic hormone.

Because adrenalectomy alone is followed by a raised titre of K.F. (Fig. 7), because injection of cortisone depresses the reticulocytosis in normal as well as in bled mice (Fig. 8), and because cortisone-treated mice are unable to elevate their titre of K.F. after bleeding (Fig. 9), it is concluded that the pituitary substance stimulating the secretion (production) of K.F. is identical with the adrenocorticotrophic hormone.

As pointed out in this paper, adrenalectomy does not decrease the degree of reticulocytosis after bleeding (Fig. 3), and adrenalectomized bled mice as well as adrenalectomized unbled mice have an elevated titre of K.F. in their serum (Figs. 4 and 7). These findings show that the adrenocorticotrophic hormone when regulating the K.F. does not act via the adrenals.

As mentioned above, some authors have reported that they have obtained increased haemoglobin values by oral administration of anterior lobe of the pituitary or by injections of pituitary preparations. I also have found a moderate increase in the haemoglobin value in mice treated with A.C.T.H.

FIG. 10.—Suggested mechanism of production of erythropoietic kidney factor and erythropoietin.

In this paper it is shown that injection of A.C.T.H. into normal mice raises the titre of K.F. The increased haemoglobin values seen in A.C.T.H.-treated mice, however, do not appear to be related to an increased titre of K.F. As pointed out previously (Osnes, 1959), increased amounts of K.F. do not seem to cause increased red-cell production in normal animals. If they did it would be expected that a single injection of A.C.T.H. into normal mice would produce reticulocytosis of about 10 days' duration, due to elevated titre of K.F., and it might be expected that continued injections of A.C.T.H. would produce reticulocytosis of

longer duration. This, however, has not been found. A single injection of A.C.T.H. produced an initial rise in reticulocyte counts from about 2 to about 3% within two hours (outflow), followed by a drop to normal values after about 24 hours. A repeated injection of A.C.T.H., then, gives the same results.

By injection of 1 mg. of A.C.T.H. twice a day into normal mice it has been possible to keep the animals on a raised reticulocyte level for some time. In spite of continued injections of A.C.T.H., however, the reticulocyte counts decrease little by little, and after about 10 days the average reticulocyte counts have reached the normal level.

These findings make it doubtful whether the increased haemoglobin values seen after administration of A.C.T.H. are related to the increased titre of K.F.

The working hypothesis adopted is that the increased haemoglobin values, at least in part, may be related to an increased release of cells from the bone-marrow (outflow) caused by A.C.T.H. This release may act as a stimulus for increased production of erythrocytes. If polycythaemia tended to develop in this way, it might be counteracted by decreased amounts of erythropoiesis-stimulating substances (erythropoietin) in animals with intact mechanism for regulation of erythrocyte and haemoglobin levels. In accordance with this, no marked degree of polycythaemia seems to have been observed in animals after administration of A.C.T.H. Problems related to outflow will be discussed in more detail in another paper.

The mechanism regulating the titre of K.F. has been discussed in this paper. In a preceding paper it was shown that the titre of K.F. increases in cordotomized mice after bleeding, whereas the titre of erythropoietin does not. Two patients with hepatitis showed increased titre of K.F., whereas erythropoietin could not be detected, indicating the liver as a place of formation of erythropoietin. This suggests a mechanism in the production and regulation of K.F. and erythropoietin as shown in Fig. 10.

Summary

Hypophysectomized bled rats show impaired reticulocytosis and their titre of K.F. is not raised as in normal bled rats, whereas their titre of erythropoietin is raised.

Adrenalectomized bled mice show reticulocytosis of the same degree as normal bled mice and their titre of a specific erythropoietic principle (K.F.) as well as of erythropoietin is raised.

Hypophysectomized rats respond with considerable reticulocytosis after injection of adrenocorticotrophic preparation.

Normal mice injected with adrenocorticotrophic preparation have an elevated titre of K.F. in their serum, whereas nephrectomized mice injected with adrenocorticotrophic preparation have no traceable amounts of K.F. in their serum.

Adrenalectomized unbled mice have a raised titre of K.F. in their serum.

Mice injected with large doses of cortisone show impaired reticulocytosis and their titre of K.F. is not elevated as in normal mice after bleeding, whereas their titre of erythropoietin is.

The findings here presented have led to the conclusion that the adrenocorticotrophic hormone, by an extra-

adrenal mechanism, stimulates the secretion (production) of the erythropoietic principle produced in the kidney.

I am indebted to the Norwegian Cancer Society (Landsforeningen mot Kreft) for research grants, and to Professor L. Kreyberg for providing working facilities. I thank Dr. F. Devik for stimulating discussions and for valuable assistance in the presentation of this work. I am grateful to A/S Apothekernes Laboratorium for generously placing the A.C.T.H. preparation *jaton prolongatum* at my disposal, and to Mr. Asbjörn Nilsen for performing the hypophysectomies in the rats used for the experiments kindly provided by Nyegaard et Co. A/S.

REFERENCES

- Contopoulos, A. N., Ellis, S., Simpson, M. E., Lawrence, J. H., and Evans, H. M. (1954). *Endocrinology*, **55**, 808.
 — Van Dyke, D. C., Simpson, M. E., Garcia, J. F., Huff, R. L., Williams, B. S., and Evans, H. M. (1953). *Blood*, **8**, 131.
 Crafts, R. C. (1949). *Endocrinology*, **45**, 159.
 Flaks, J., Himmel, I., and Zlotnik, A. (1937). *Presse méd.*, **45**, 1261.
 — — — (1938). *Ibid.*, **46**, 1506.
 Garcia, J. F., Van Dyke, D. C., Huff, R. L., Elminger, P. J., and Oda, J. M. (1951). *Proc. Soc. exp. Biol. (N.Y.)*, **76**, 707.
 Meyer, O. O., Thewlis, E. W., and Rusch, H. P. (1940). *Endocrinology*, **27**, 932.
 Osnes, S. (1958). *Brit. med. J.*, **2**, 1387.
 — (1959). *Ibid.*, **2**, 650.
 Simpson, M. E., Evans, E. S., and Rosenberg, L. L. (1959). *Endocrinology*, **64**, 592.
 Van Dyke, D. C., Contopoulos, A. N., Williams, B. S., Simpson, M. E., Lawrence, J. H., and Evans, H. M. (1954). *Acta haemat. (Basel)*, **11**, 203.
 — Simpson, M. E., Contopoulos, A. N., and Evans, H. M. (1957). *Blood*, **12**, 539.
 White, A., and Dougherty, T. F. (1945). *Endocrinology*, **36**, 16.

RESPONSE OF CUBAN CHILDREN TO ORAL VACCINATION WITH LIVING ATTENUATED POLIOVIRUS VACCINES

A CLINICAL AND SEROLOGICAL STUDY

BY

JUAN EMBIL, jun., M.D.

Director, Virus Diseases Department, Municipal Children's Hospital, Havana, Cuba

WITH THE COLLABORATION OF

Dr. Agustín Castellanos, Professor of Paediatrics, University of Havana; Dr. Reinaldo Martín Jiménez, Chief Resident, Municipal Children's Hospital, Havana; Dr. Luis Gervais, Assistant to Dr. Juan Embil, jun.

Paralytic poliomyelitis occurs in Cuba as a sporadic disease in early childhood, with periodic relatively small outbreaks. Most of the cases are in children under 5 years of age, and less than 15% are in those over 10 years. In the period 1946 to 1957, with the exception of three years, the annual number of reported cases varied from 10 to 100. In 1946, 1952, and 1955 there were reported respectively 343, 494, and 267 cases (Pan-American Sanitary Bureau, 1958a, 1958b). Paul, Melnick, and Riordan (1952) suggest that perhaps only 50 to 75% of the actual cases occurring in Cuba are recorded. These authors collected 82 sera in a 1950 survey, and demonstrated the presence of Lansing-type poliovirus antibodies in 64% of the children aged 1 to 4 years and in 75% of those aged 5 to 9 years.

Our data indicate that all three types of poliovirus are widespread in the Havana metropolitan districts, and